Clinical Study Protocol

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

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Abstract – Study 19766N

Title: Early Value of Eptinezumab in the Community (EVEC) Study: An exploratory, prospective, randomized, pragmatic, open-label, cohort study to assess the comparative effectiveness of eptinezumab in the United States

Rationale and Background

Migraine is a debilitating disorder with an estimated prevalence of self-reported migraine or severe headache in the United States (US) among adults at 15.3% (95% confidence interval [CI]: 14.75, 15.85. In the US, it is estimated that there are 36 million people with migraine. Eptinezumab (Vyepti®) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to the calcitonin gene-related peptide (CGRP) ligand and blocks its binding to CGRP receptors. It is indicated for the prevention of migraine in adults. Randomized controlled trials have shown that eptinezumab is efficacious in reducing mean monthly migraine days (MMD) versus placebo. However, there is a need to determine the comparative effectiveness of eptinezumab relative to other advanced preventive medications (i.e., subcutaneous [SC] anti-CGRP injectables and onabotulinumtoxinA [Botox]) used routinely in clinical practice. This type of evidence will further assist clinicians, payers and patients in making informed decisions in migraine preventive care.

Study Aim

This exploratory study has multiple objectives within the overall aim to examine how eptinezumab compares to other advanced preventive medications in a real-world community setting. These objectives include exploring the comparative effectiveness on patient reported outcomes including participant-identified most bothersome symptoms (PI-MBS), good days and bad days, quality of life (QOL), and healthcare resource utilization (HRU). The impact of mediating factors including monthly migraine days, early prevention and perceived stress on these outcomes will be evaluated in this process. Finally, we will assess participant preferences for shared decision making, patient satisfaction with their treatment and confidence in managing their own health.

Study Design

This is an exploratory, prospective, randomized, cohort study to be conducted in adult participants with episodic migraine (EM) or chronic migraine (CM). Participants will be recruited from sites that can offer all therapeutic options. A total of 200 participants will be enrolled in the study. Participants will be classified as living with either EM or CM based upon their medical history. Within these strata, the participants living with EM will be randomized to eptinezumab or other advanced preventive medication (i.e., erenumab, fremanezumab or galcanezumab) in a 1:1 manner. Those experiencing chronic migraine will be randomized to eptinezumab, subcutaneous (SC) CGRPs, or Botox in a 3:2:1 manner. Participants who are randomized to a SC CGRP will be permitted to select treatment with the injectable of their choice (i.e., erenumab, fremanezumab or galcanezumab). Participant data will be collected at multiple time points throughout the study. The daily migraine status,

symptom data, and acute migraine medication usage will be collected daily via a study-specific smartphone application (app). QOL data and HRU data will be collected two ways, via the smartphone application and the site staff. QOL assessments include the EuroQol-5 Dimension-5 Level (EQ-5D-5L), Headache Impact Test (HIT-6), Good Day/Bad Day scale and the Migraine Disability Assessment (MIDAS). All PROs will be completed directly by the participants via the app, with the exception of the Infusion Satisfaction Survey (ISS), that will be completed via paper questionnaire. 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. HRU will be tracked via participant input into the app and site staff led interviews.

Participants will be trained to report any healthcare interactions into the app (e.g., office visits, urgent care visits, picking up prescription medication). In addition, the site staff will interview participants monthly to determine if any healthcare system interactions occurred. Several additional measures are planned to assess participant preferences regarding shared decision making and satisfaction with their treatment.

Study Objectives

The outcomes in this exploratory study will be the following:

1. **Patient-identified most bothersome symptom (PI-MBS):** This will be measured daily using the PI-MBS. Participant will select the symptom that they find most impairs her or him at the time of reporting and rate the severity of that symptom. The difference between randomization groups evaluated at 4-, 12- and 24-weeks following randomization
2. **Good day/Bad Day scale:** The participant will report the number of "good days" and "bad days" they had in the previous week on a weekly basis using the Good Day/Bad Day scale. The difference between randomization groups evaluated at 4, 12, and 24 weeks.
3. **EuroQol 5-Dimension, 5-Level Quality of life Scale (EQ-5D-5L)**: The participant will complete the EQ-5D questionnaire on a weekly basis to indicate their preference for their current health state. The difference between randomization groups evaluated at 4, 12, and 24 weeks.
4. **Health resource utilization:** The participant will report their use of health services and medications on a daily basis using the smartphone app. The difference over time between the randomization groups will be evaluated at 4, 12, and 24 weeks.
5. **6-item Headache Impact Test (HIT-6)**: The participant will report the impact of headache on their quality of life using the six-item HIT-6 scale. This will be done each month. The difference in change over time between randomization groups will be evaluated at 4, 12, and 24 weeks.
6. **Migraine Disability Assessment (MIDAS)**: The participant's perception of their degree of disability will be evaluated by the MIDAS scale. This will be measured quarterly. The difference in change over time between randomization groups will be evaluated at 12 and 24 weeks.
7. **Treatment Satisfaction Questionnaire for Medication (TSQM)**: The participant's reported satisfaction with treatment will be evaluated at the study closeout visit (i.e., visit #9). This will be compared between randomization groups at week 24.

8. **Medication Switching:** The frequency of switching of migraine preventive medication from the medication administered at baseline will be compared between the randomization groups from baseline to week 24.

Additional Outcomes (not between group comparisons)

1. **9-item Shared Decision-Making Questionnaire (SDM-Q-9)**: The participant will report their satisfaction with shared decision-making using SDM-Q-9 following education on treatment options. This will be evaluated at screening and week 24.
2. **SURE Scale**: The participant will report their readiness to decide or determine whether their comfort with their treatment decision using the SURE scale. This will be evaluated at screening.
3. **10-item Patient Activation Measure (PAM-10)**: The participant will report their knowledge, skills, and confidence to manage his or her health condition via the PAM-10. This will be evaluated at screening and weeks 12 and 24.
4. **Infusion Satisfaction Survey (ISS)**: Participants initiating therapy on eptinezumab will describe the satisfaction with care with the ISS at baseline and week 12.

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List of Abbreviations and Definitions of Terms

ADR	adverse drug reaction
AE	adverse event
AHS	American Headache Society
AUC	area under curve
Botox	onabotulinumtoxinA
CGRP	calcitonin gene-related peptide
CI	Confidence interval
CM	chronic migraine
CRF/eCRF	case report form/electronic Case Report Form
CRO	clinical research organization
eDiary	electronic diary
EM	episodic migraine
EQ-5D-5L	EuroQol-5 Dimension – 5 Level
EVEC	Early Value of Eptinezumab in the Community
HIT-6	Headache Impact Test
ICSR	individual case safety report
ICHD 3rd ed	International Classification of Headache Disorders 3rd edition
IgG1	immunoglobulin G1
IV	Intravenous
mAb	monoclonal antibody
MBS	Most Bothersome Symptom questionnaire
MIDAS	Migraine Disability Assessment questionnaire
MMD	monthly migraine days
MOH	medication overuse headache
ORC	Observational Research Committee
OTC	over-the-counter
PAM-10	Patient Activation Measure – 10 items
PI-MBS	Patient Identified-Most Bothersome Symptom
QOL	quality of life
SADR	serious adverse drug reaction
SAE	serious adverse event
SOC	standard of care
SDM-Q-9	Shared Decision-making Questionnaire
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States
Advanced preventive medications	The collective term used to describe the non-eptinezumab treatment arms in EVEC consisting of onabotulinumtoxinA and subcutaneous anti-CGRP injectables (i.e., erenumab, fremanezumab and galcanezumab)

Major Changes Since Last Edition

The following summarizes the major changes since the last edition of this CSP.

Chapter/ Section Number	Chapter/Section Title	Change
Abstract	Section 1. 2	*Deleted*: Monthly migraine days (MMD) removed as an outcome
Abstract	Section 1.3	*Deleted*: Monthly migraine days (MMD) removed as an outcome
Section 2	Objectives	*Deleted*: Monthly migraine days (MMD) removed as an outcome *Added*: Final sentence of section revised to note that MMD will be considered as a mediating factor
Section 5.3	Exclusion Criteria	*Updated*: Exclusion criteria #4 revised to note that participants who have taken gepant medications for prevention are excluded. This was added with the recent approval of these medications for prevention by the FDA.
Section 8.2	Screening Visit (Visit 1)	*Updated*: Increased interval allowed between screening to the baseline visit from 14 to 21 days to allow more flexibility for participants
Section 8.3	Baseline Visit (Visit 2)	*Updated:* Increased interval allowed between screening to baseline visit from 14 to 21 days to allow more flexibility for participants. Change made in first and second paragraphs.
Section 8.6	Visit 5 (Day 84± 3 days)	*Added:* Following was added to encourage in-person visits and maintain equal treatment between the study arms: "*To maintain equivalence with the those receiving eptinezuamab and Botox it is preferable that this visit occur in person for those receiving the subcutaneous anti-CGRP as well, however, it is acceptable to conduct this visit via telephone or videoconference.*"
Section 8.10	Safety Follow-up Visit	*Deleted:* Removed reference to adverse drug reaction (ADR) as all adverse events will be recorded.
Section 9.3.2	Adverse Drug Reactions	*Deleted:* Entire section removed since all adverse events will be collected
Section 10	Adverse Events and Adverse Drug Reactions	*Updated:* Minor changes made to section to make it consistent with interventional study SOP.
Section 10.1.1	Adverse Event Definitions	*Deleted:* Removed definition of adverse drug reactions *Added:* Added definition of "Suspected unexpected serious adverse reaction" (SUSAR) consistent with interventional study SOP
Section 10.2	Pregnancy	*Added:* Added language to third paragraph to address data collection for pregnant persons who do not choose to enroll in the Lundbeck data collection.
Section 10.5	Treatment and Follow-up of Adverse Events	*Updated:* Corrected name of department receiving reports.
Section 10.6	Compilation of Safety Information	*Deleted:* No longer required as all adverse events will be collected

1 Introduction

1.1 Background

1.1.1 Overview

Vyepti® (eptinezumab-jjmr) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to the calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the α and β-CGRP receptors. It is indicated for the prevention of migraine in adults.[1] While the mechanism by which eptinezumab exerts its clinical effect is unknown, it is characterized by inhibition of nociceptive signaling, CGRP-mediated neurogenic inflammation and vasodilation.[2]

It is estimated that the prevalence of self-reported migraine or severe headache in the United States (US) among adults is 15.3% (95% confidence interval [CI] 14.75-15.85).[3] The cumulative lifetime incidence of migraine was estimated to be 43% in women and 18% in men in a self-reported survey of 120,000 US households.[4] In the US, it is estimated that there are 36 million people with migraine.[5] Based on 2013 Medical Expenditure Panel Survey (MEPS) data, the US prevalence of chronic migraine (CM), defined as headache occurring ≥15 days/month for 3 months with migraine features on ≥8 days/month, is estimated at 1.8% of the population or 4.2 million adults.[6,7]

1.1.2 Clinical Data

The efficacy and safety of eptinezumab was evaluated as a preventive treatment of migraine in two phase III, randomized, double-blind, placebo-controlled six-month studies: PROMISE-1 which enrolled patients with episodic migraine (EM), and PROMISE-2 which enrolled patients with CM.[8,9]

In PROMISE-1, 888 adults with frequent EM (baseline average of approximately 8.6 mean migraine days/month) were randomized and treated with eptinezumab 30 mg, 100 mg, or 300 mg or placebo intravenously (IV) every three months for two doses. The primary study endpoint was mean change from baseline in monthly migraine days (MMDs) over weeks 1-12 following the first infusion. Results for eptinezumab 100 mg (-3.9) and 300 mg (-4.3) demonstrated a statistically significant reduction in mean MMDs from baseline (p=0.1082 and p=0.0001, respectively) vs. placebo (-3.2).[8] In PROMISE-2, 1,072 adults with CM were randomized and treated with eptinezumab 100 or 300 mg or placebo IV every three months for two doses. The primary study endpoint was mean change from baseline in MMDs over weeks 1-12 following the first infusion. Results for eptinezumab 100 mg and 300 mg demonstrated a statistically significant reduction in mean MMDs from baseline (-7.7 and -8.2 respectively) vs. placebo (-5.6) over weeks 1-12 (p<0.0001 both doses).[9] Eptinezumab was found to reduce the prevalence of episodic and chronic migraine in weeks 1 - 24 of treatment (two infusions) in PROMISE-1 and PROMISE-2.[10]

1.2 Rationale for the Study

There are three other preventive migraine medications in the same class as eptinezumab [i.e., anti-CGRP monoclonal antibodies (mAbs)] and they include: erenumab, fremanezumab and galcanezumab. All three of these medications are approved for the prevention of migraine.[11,12,13] A key point of difference is that the other three anti-CGRP mAbs are subcutaneous injectables. Another important therapy option for migraine prevention is onabotulinumtoxinA (Botox). However, Botox is approved for the prevention of migraine in patients with CM only.[14] Botox is an intramuscular injection and is often considered at the same point in the treatment algorithm as anti-CGRP mAbs for patients who require more advanced care for migraine relief.[15]

While there is strong scientific evidence of the efficacy of eptinezumab versus placebo in randomized controlled trials, there is limited understanding of how eptinezumab compares to other anti-CGRP mAbs or Botox on migraine prevention in real-world settings. Therefore, we propose an exploratory, six-month, prospective, randomized, cohort study to evaluate the "Early Value of Eptinezumab in the Community (EVEC)." This exploratory study will provide important learnings to help direct future studies to examine how eptinezumab compares to other advanced preventive medications in a real-world community setting.

2 Objectives

This exploratory study has multiple objectives within the overall aim to examine how eptinezumab compares to other advanced preventive medications in a real-world community setting. These objectives include exploring the comparative effectiveness on patient reported outcomes (PROs) including and healthcare resource utilization (HRU). In addition, we will assess participant preferences for shared decision making, participant satisfaction with their treatment and confidence in managing their own health. Specifically, the objectives of EVEC include:

1. **Patient-identified most bothersome symptom (PI-MBS):** This will be measured on a daily basis using the PI-MBS. Participant will select the symptom that they find most impairs her or him at the time of reporting and rate the severity of that symptom. The difference between randomization groups evaluated at 4, 12 and 24 weeks following randomization.
2. **Good day/Bad Day scale:** The participant will report the number of "good days" and "bad days" they had in the previous week on a weekly basis using the Good Day/Bad Day scale. The difference between randomization groups evaluated at 4, 12, and 24 weeks.
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4. **Health resource utilization:** The participant will report their use of health services and medications on a daily basis using the smartphone app. The difference over time between the randomization groups will be evaluated at 4, 12, and 24 weeks.

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4. **Infusion Satisfaction Survey (ISS)**: Participants initiating therapy on eptinezumab will describe the satisfaction with care with the ISS at baseline and week 12

The impact of mediating factors including monthly migraine days, early prevention and perceived stress on these outcomes will be evaluated.

3 Study Design

3.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki.*[16]

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

Table 1: Criteria for Chronic Migraine Diagnosis per International Headache Society (IHS) International Classification of Headache Disorders 3rd edition (ICHD-3).[6]

1.1 Migraine without Aura	1.2 Migraine with 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	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*,[17] and applicable regulatory requirements.

Participants will be recruited from sites that are capable of administering all therapies within the study in an outpatient setting.

After giving consent, participants will be classified as living with either EM or CM per ICHD-3 guidelines (see Table 1) based upon their medical history. Within these strata, the participants living with EM will be randomized to eptinezumab or SC CGRP (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 anti-CGRP injectable of their choice (i.e., erenumab, fremanezumab or galcanezumab). Please see Figure 1 for further details on the randomization design.

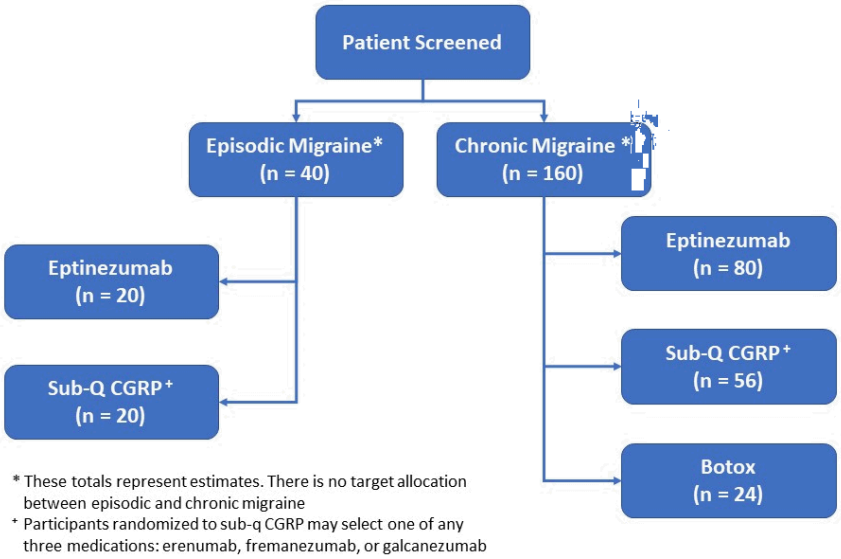

Figure 1: Randomization Design

Participants will be followed prospectively for 24 weeks; a follow-up phone call will 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 (as 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 HRU recorded in the eDiary, record HRU not reported in the eDiary, and record reasons for any changes in prescription or over-the-counter (OTC) medications. QOL data and HRU data will be collected from participants via the smartphone application (app) and from the site staff via the 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.

3.2 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.

3.2.1 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?" In particular, 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 principal 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.

3.3 Additional Study Rationale and Considerations

Study Population

Most payers in the US, as well as AHS treatment guidelines, require failure of two generic oral preventive medications before initiating treatment with an advanced preventive. Therefore, this is the target population for this study. While many payers require failure of at least one advanced preventive therapy before initiation of eptinezumab, this is due to economic, not clinical, considerations. Therefore, a purpose of EVEC is to assist payers in understanding the economic and clinical cost, if any, to patients and society of these decisions. In addition, we are limiting the sample to people experiencing at least 8 migraine days per month as these patients (i.e., high-frequency EM and CM patients) are those most likely to be referred for advanced preventive therapy.

Selection of doses

Dosing of all medications will be consistent with each product's FDA approved label. Treating physicians and their patients might use any dosage consistent with labelling and good clinical practice.

Primary objective

This is a pilot study, as such, there is no primary objective. All objectives are exploratory.

4 Ethics

4.1 Ethical Rationale

EVEC will provide patients, prescribers and payers important information regarding the comparative effectiveness of the studied treatments for migraine prevention to support decision making by these stakeholders. Information comparing the effectiveness of these treatments in a real-world setting is not currently available from any scientific source. Randomization to the various treatments included in the study is justified due to the equipoise that is created by this lack of information.

The participant will be fully informed about the study including the risks and benefit of his/her participation in the study.

The participant may withdraw from the study at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the participant is otherwise entitled.

In accordance with *Good Clinical Practice*,[17] qualified medical personnel at Lundbeck will be readily available to advise on study-related medical questions. Safety data will be reviewed regularly by Lundbeck's U.S. Pharmacovigilance department to ensure that prompt action is taken, if needed.

In accordance with *Good Clinical Practice*,[17] the investigator will be responsible for all study-related medical decisions.

4.2 Informed Consent

No study-related procedures, including any screening procedures, may be performed before the investigator has obtained written informed consent from the participant.

Changing (for example, discontinuing or down-tapering) a participant's concomitant medications prior to the Screening Visit to ensure that the participant meets the selection criteria is a study-related activity and must not occur before the Informed Consent Form has been signed.

It is the responsibility of the investigator or person designated by the investigator to obtain written informed consent from the participant. The informed consent process may be delegated, however, the requirements for the delegates must be documented prior to the start of the study. National laws must always be adhered to when allowing potential delegation. Any delegation must be documented in the site delegation log.

The investigator must identify vulnerable participants, that is, participants whose willingness to participate in this study might be unduly influenced by the expectation, regardless of whether it is justified, of benefits associated with participation, or of a retaliatory response

from senior members of a hierarchy in case of refusal to participate. Participants thus identified must be excluded from participation in the study.

Prior to obtaining written informed consent, the investigator or a designee must explain to the participants the aims and methods of the study and any reasonably expected benefits and foreseeable risks or inconveniences to the patients.

The participants must be informed:

- that their participation in the study is voluntary and that they are free to withdraw from\ the study at any time without justifying their decision
- of their right to request a copy of their personal data from the study via the investigator
- of the possibility of withdrawing consent (see section 8.9) of their right to receive information about the study results from the investigator on the patients' own initiative; the results will be available approximately 1 year after the end of the study

The participants must be informed that persons authorized by Lundbeck and authorized personnel from certain authorities (domestic, foreign, data protection agencies, or institutional review boards [IRBs]) may view their medical records. The participants must also be informed that de-personalized copies of parts of their medical records may be requested by authorized personnel from certain authorities (domestic, foreign, data protection agencies, or IRBs) for verification of study procedures and/or data. The confidentiality of the patients will in all cases be respected. The participants must be given ample time and opportunity to enquire about details of the study prior to deciding whether to participate in the study.

It is the responsibility of the investigator to ensure that all questions about the study are answered to the satisfaction of the participants. Prior to allowing a participant to participate in the study, an Informed Consent Form must be signed and dated by the participant and signed and dated by the investigator or a designee on the same day. The participants must be given a copy of the signed *Informed Consent Form*.

4.3 Personal Data Protection

The data collected in this study will be processed in accordance with the specifications outlined in the Danish Data Protection Act and the European Union legislation[18] to ensure that requirements regarding personal data protection are met. If an external organization will process data on behalf of Lundbeck, a contractual procedure will be signed between Lundbeck or delegate and the external organization to ensure compliance with the above--mentioned legislation.

4.4 Institutional Review Board

This study will be conducted only after Lundbeck has received confirmation that the regulatory authorities have approved or confirmed notification of the study and that written approval of the protocol has been granted by the appropriate IRB.

The investigator must not allow any participants to participate in the study before receiving confirmation from Lundbeck or the CRO that the required approvals and/or notifications have been received. Permission for an investigator to start enrollment will be provided to the investigator in writing from Lundbeck or the CRO.

The IRB must be informed when specific types of protocol amendments have been made and written approval must be obtained before implementation of each amendment, if required by local law.

If applicable, interim reports on the study and reviews of its progress will be submitted to the IRB by the investigator at intervals stipulated in its guidelines.

5 Study Population

5.1 Number of Participants

Two hundred participants are planned for enrollment into the trial.

Adult participants with at least 8 or more migraine days per month, in two of the last three months prior to enrollment, who are being seen at participating sites and who meet the other inclusion and exclusion criteria will be invited to participate in the study.

The informed consent will include an explanation of the following:

1. Prior to randomization, participants will complete a decision exercise using a decision guide created to inform participants on treatment options for migraine prevention. Then participants will complete the SDM-Q-9 to indicate what they think would be their preferred migraine prevention treatment (see Appendix IV), followed by completion of the SURE Test (see Appendix VI).
2. The consent form will inform the patient that the treatment preference indicated after the review of the decision guide will not impact the treatment to which they are randomized. Additionally, the consent form will clearly indicate that should the patient not agree to initiate treatment with the medication to which they were randomized, their participation in the study will be discontinued.
3. Regardless of the treatment the participant is randomized to, the cost of the study medication (i.e., eptinezumab, Botox, erenumab, fremanezumab or galcanezumab) and administration will be covered by Lundbeck for the six-month duration of the trial.

5.2 Participant Recruitment

Participants will be competitively recruited from approximately 10 sites in the US that offer all therapeutic options in the study.

The investigators will be notified immediately when the recruitment period comes to an end.

5.3 Selection Criteria

Participant selection is based on the inclusion and exclusion criteria listed below.

Participants who meet each of the inclusion criteria and none of the exclusion criteria at the Screening Visit and prior to first medication dose at Baseline (Visit 2) are eligible to participate in this study.

Inclusion Criteria

1. The participant is able to read and understand the Informed Consent Form.
2. The participant has signed the Informed Consent Form.
3. The participant is aged ≥ 18 years of age.
4. Have a diagnosis of migraine per IHS ICHD-3 guidelines at least 12 months prior to screening.
5. Have a history of ≥ 8 migraine days/month in two of the previous three months as confirmed by the treating physician through medical records.
6. Have a history of failure of at least 2 previous oral migraine preventive treatments as defined in the AHS Consensus Statement (see Appendix II).[15]
7. Be able to understand the clinical description of treatment options and have the capability to participate fully in making their treatment preferences known.
8. Be willing to accept randomization to any of the possible study medications if allocated to that treatment arm.
9. Have no restriction in venous access that would restrict the ability to receive infusion treatment.
10. Be willing and capable of completing daily reports and other participant reported outcome measures using a smartphone-based application.
11. Have their own smartphone or tablet and agree to allow the study application to be downloaded to it.
12. Agree to not post any personal medical data or information related to the study on any website or social media site (e.g., Facebook, Twitter) during the study.
13. Be able to read, understand and complete all required forms and questionnaires in English.

Exclusion Criteria

1. The participant has previously been enrolled in this study.
2. The participant is a member of the study personnel or of their immediate families or is a subordinate (or immediate family member of a subordinate), to any of the study personnel.
3. The participant has a history of severe drug allergy or hypersensitivity, or known hypersensitivity or intolerance to either eptinezumab, erenumab, fremanezumab, galcanezumab or their excipients.
4. The participant has previous history of use of any of the study drugs (i.e. eptinezumab, Botox, erenumab, fremanezumab or galcanezumab). Participants who have used oral

CGRP inhibitors atogepant or rimegepant for prevention are also excluded. Note that only previous Botox use for treatment of migraine is exclusionary. Prior use of Botox for cosmetic purposes is allowed. Participants with a history of acute use of rimegepant or ubrogepant (but not for prevention) are permitted to enroll.

5. The participant has a diagnosis of CM and has hypersensitivity to botulinum toxin preparation or to any of the components in the formulation.
6. The participant has used opioids or butalbital-containing products greater than 4 days per month in the last month.
7. The participant is pregnant, <6 months post-partum, or breastfeeding.
8. The participant has a disease or takes medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with the conduct or interpretation of the study.
9. The participant is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.

5.4 Participants with Medication Overuse Headache

Participants with a dual diagnosis of CM along with medication overuse headache (MOH) attributable to regular acute medication overuse (e.g. triptans, ergotamine, or combination analgesics greater than 10 days per month) are eligible for enrollment in the study. Participants with CM and MOH who use opioids or butalbital-containing products greater than 4 days per month will be excluded. The participant's clinician will determine if participants meet the criteria for MOH. The ICHD-3 criteria[19] (listed below) and MOH checklist (see Appendix XVII) will be provided to the clinical sites for them to make their assessments. The participant's MOH status will be noted in the CRF.

ICHD-3 criteria for MOH:

- Headache occurring on ≥15 days/month in a participant with a pre-existing headache disorder
- Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
- Not better accounted for by another ICHD-3 diagnosis.

5.5 Withdrawal Criteria

Information on participants who withdraw from the study will be collected in the withdrawal section of the CRF.

A participant must be withdrawn from the study if:

- the participant withdraws their consent (defined as a participant who explicitly takes back their consent); section 8.9 states how the patient's data will be handled
- the participant is lost to follow-up (defined as a participant who fails to comply with scheduled study visits or contact, who has not actively withdrawn from the study, and

for whom no alternative contact information is available [this implies that at least two documented attempts have been made to contact the patient])

- the investigator considers it, for safety and/or study compliance reasons, in the best interests of the participant that they be withdrawn from treatment
- All participants will be permitted to withdraw at their choice or upon advice of their treating physician. Information collected from the participant prior to withdrawal will remain in the study data set.

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.

Products purchased with study-specific vouchers cannot be used for an off-label indication. Participants must meet the criteria for CM at baseline in order to be randomized to onabotulinumtoxinA (Botox®). Participants who do not comply with this requirement will be withdrawn from the study.

Participants who become pregnant will be withdrawn from the study and counselled to enroll in the Lundbeck pregnancy registry. The Lundbeck pregnancy registry is a prospective, observational study in the United States that will be initiated prior to the end of this trial.

Participants who withdraw will not be replaced.

6 Investigational Medicinal Products

6.1 Treatment Regimen

Participants will be randomized to their initial migraine prevention medication. Participants must receive the first dose of their allocated medication at the Baseline Visit (Visit 2). However, during the remainder of the study observation period, treatment choices will be based upon the treating clinician's judgement and the participant's preference (See Section 6.3.1 below for more details). No additional direction will be given by the CRO or the study sponsor. However, any participant wishing or needing to switch to an alternate medication outside of the study-specific guidelines for doing so, as described in Section 6.3.1, will need to be withdrawn from the study. Participants switching to an advanced preventive medication other than their initially assigned treatment in accordance with Section 6.3.1 will be permitted to remain in the study. There will be no restrictions on the use of other migraine related medications during the study period for acute or preventive treatment if those medications are prescribed by the participant's treating physician. However, products purchased with study-specific vouchers cannot be used for an off-label indication. Participants must meet the criteria for CM at baseline in order to be randomized to onabotulinumtoxinA (Botox®). Any changes in migraine preventive medications, prescribed or OTC, will be reported in the smartphone application by the participant. The reason for any treatment change will be

investigated by the study coordinator and recorded in the CRF. Any adverse events identified as the cause of a medication switch (e.g. lack of efficacy) will be reported according to Section 10.3.

6.2 IMPs, Formulations, and Strengths

IMPs for this trial will not be supplied directly by Lundbeck. Medications for this study will be obtained using pharmacy voucher cards. These cards will allow for study-specific advanced preventive medications to be obtained from the local pharmacy without cost; the voucher cards will not be used for any other medications including acute migraine treatments. Study-specific voucher cards will be used to cover the cost of any study-specific advanced preventive medications, provided it is used per the FDA approved label.

After randomization is complete, study site personnel will need to obtain the first dose of medication to be administered to the participant during the Baseline Visit (Visit 2).

Participants who will be using subcutaneous anti-CGRP injectables will be instructed on how to use the voucher card at the retail pharmacy of their choice to cover the cost of their anti-CGRP medication throughout the study. For participants assigned to Botox or eptinezumab, study staff will need to obtain these medications using the voucher cards prior to Visit 5 to ensure the medication is available for administration during the visit.

The IMPs to be used in this study are:

Eptinezumab – Participants allocated to the eptinezumab arm will begin treatment using eptinezumab which is available as a 100 mg/mL or 300 mg/mL solution, as per the product label. The first dose will be given at baseline during visit 2 and the second dose will be given during visit 5 at week 12 (see Panel 4).

OnabotulinumtoxinA – Participants allocated to Botox will be given the first dose at baseline during visit 2 and the second dose will be given during visit 5 at week 12 (see Panel 4). Botox will be given as per the product label for the treatment of migraine.

Erenumab – Participants will be trained to self-administer the first dose at baseline during visit 2, and then will self-administer doses 2-6 monthly as per the product label. Participants will be given a voucher card to obtain follow-up doses of this medication for the next 5 months. Erenumab will be given as per the product label for either the 70 mg or 140 mg doses. Note that this protocol defines the term, “monthly” as every 28 days.

Fremanezumab – Participants will be trained to self-administer the first dose at baseline during visit 2. Following the baseline dose, the participant will either administer 225 mg monthly for months 2 – 6 or administer 675 mg 3 months after the baseline dose (quarterly). Participants will be given a voucher card to obtain follow-up doses of this medication either for the next 5 months or for 1 additional refill 3 months post-baseline. Fremanezumab will be given as per the product label. Note that this protocol defines the term, “monthly” as every 28 days, and “quarterly,” as every 84 days.

Galcanezumab – Participants will be trained to self-administer the first dose at baseline during visit 2. At the advisement of the provider, participants may receive a 240 mg loaded dose at baseline followed by monthly doses of 120 mg for months 2 - 6. Participants will be given a voucher card to obtain follow-up doses of this medication for the next 5 months. Galcanezumab will be given as per the product label. Note that this protocol defines the term, "monthly" as every 28 days.

6.3 Method of Assigning Participants to Treatment

Each participant will be assigned a unique study ID by the EDC system, and that number will be used to identify that patient throughout the study. Although assignment of treatments to patients will be randomized, all treatments will be open-label; there will be no blinding to treatment received. The randomization scheme for assigning participants to one of the treatment arms is illustrated in Figure 1.

6.3.1 Change in Treatment

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 anti-CGRP injectable (i.e., erenumab, fremanezumab or galcanezumab), they may not do so until week 12 (visit 5), after the treatment window for their initial treatment has ended. 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 anti-CGRP 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 anti-CGRP 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.

6.4 IMP Accountability

Treatment type, along with the date(s) on which treatments are administered, will be recorded in the eCRF.

The investigator and the pharmacist (if applicable) must agree to only dispense study-specific IMP to participants enrolled in the study. The investigator or the pharmacist (if applicable) must maintain an adequate record of the receipt and distribution of the study-specific IMPs that they obtain for study participants (see Section 6.2). This record must be available for inspection at any time.

7 Concomitant Medication

Concomitant medication is any medication other than the IMPs that are taken during the study from Screening up until the participant completes the study at Visit 8. This includes all prescription and over-the-counter 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 enrollment in the study, the disorder must be recorded as an adverse event.

8 Study Visit Plan

8.1 Overview

An overview of the procedures and assessments to be conducted during the study and their timing is presented in Panel 1, Panel 2, Panel 3, and Panel 4. Details are in section 9.

After completing or withdrawing from the study, the patient must be treated in accordance with usual clinical practice.

Panel 1: eDiary Collected Assessments at Visit 1

Assessments
• SDM-Q-9 • SURE Test • PAM-10

Panel 2: eDiary Collected Assessments at Visit 2

Assessments
• EQ-5D-5L[(a)] • PSS[(a)] • MIDAS[(a)] • HIT-6[(a)] • PI-MBS[(a)] • Daily Headache Status Report (see Panel 3 for details)

(a) Collected prior to initial treatment given at Visit 2

Panel 3: Post-Baseline eDiary Collected Assessments

Assessments	Reporting Schedule				
	Daily	Weekly[a]	Monthly[b]	Quarterly[c]	Early Termination
Daily Headache Status Report: - Did they have a headache in the previous 24 hours? Y/N	X				X
If answer is "Yes" to "Daily Headache Status" then participants will be prompted to report their **Daily Headache Symptoms**: - What symptoms did they experience with the headache? - How do they rate the severity of the symptoms? - What was the most "bothersome" of the symptoms (i.e. PI-MBS)?	X				X
If answer is "Yes" to "Daily Headache Status" then participants will be prompted to report their **Acute Headache Medication Usage**: - What medication(s) did they take (if any) to relieve the headache? - How do they rate the effectiveness of the medication(s) taken?	X				X
If answer is "Yes" to "Daily Headache Status" then participants will be asked if they considered this headache to be a migraine.	X				X
If answer is "No" to "Daily Headache Status" then participants will be prompted to respond to the following: - Do they have any residual symptoms lingering between headaches? - Have they experienced any "warning" symptoms prior to a headache? - What degree of impact did each of these symptoms have?	X				X

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

Panel 4: Assessments Administered via Site staff

Study procedures	Screening Visit	Baseline Visit	Monthly Follow-Up	Monthly Follow-Up	Monthly Follow-Up	End of Treatment / Early Termination	Safety Follow-Up
		Day 0	Days 28 & 56 (+/- 3 days)	Day 84 (+/- 3 days)	Days 112 & 140(+/- 3 days)	Day 168 (+ 7 days)	56 days (+/- 5 days) after End of Treatment / Early Termination
	Visit 1	Visit 2	Visits 3-4 [f]	Visit 5[g]	Visits 6-7 [f]	Visit 8 [f]	Visit 9
Written informed consent	✓						
Review inclusion and exclusion criteria	✓	✓					
Demography	✓						
Medical history inclusive of migraine, psychiatric, cardiac and family medical history	✓						
Vital signs	✓						
Concomitant medications and use of tobacco products	✓	✓	✓	✓	✓	✓	
Adverse events (continuous monitoring)[a]	✓	✓	✓	✓	✓	✓	✓
Adverse drug reactions (continuous monitoring)		✓	✓	✓	✓	✓	
Administration of Decision Guide	✓						

Study procedures	Screening Visit	Baseline Visit	Monthly Follow-Up	Monthly Follow-Up	Monthly Follow-Up	End of Treatment / Early Termination	Safety Follow-Up
		Day 0	Days 28 & 56 (+/- 3 days)	Day 84 (+/- 3 days)	Days 112 & 140(+/- 3 days)	Day 168 (+ 7 days)	56 days (+/- 5 days) after End of Treatment / Early Termination
	Visit 1	Visit 2	Visits 3-4 [f]	Visit 5[g]	Visits 6-7 [f]	Visit 8 [f]	Visit 9
Randomization to treatment arm	✓[d]						
Participant training on eDiary	✓						
Participant training on CGRP administration [b]		✓					
Administration of Treatment		✓[e]		✓[h]			
Infusion Satisfaction Survey [c]		✓		✓			
Provide instructions to obtain additional doses of CGRP [a]		✓					
Review eDiary use		✓	✓	✓	✓		
Healthcare Resource Utilization		✓	✓	✓	✓	✓	
eDiary close out						✓	

(a) AE monitoring begins upon signing ICF
(b) Only for participants in CGRP arm
(c) Only for participants receiving eptinezumab treatment; completed using paper questionnaire
(d) will need to be performed by site after participant qualifies in order for site to be prepared for appropriate treatment at Visit 2
(e) eptinezumab infusion, Botox or CGRP
(f) Conducted via telephone or videoconference
(g) Conducted on site only for participants receiving Eptinezumab infusion or Botox; conducted via telephone or videoconference for those in CGRP group
(h) Eptinezumab infusion or Botox, those receiving subcutaneous anti-CGRP medications are also encouraged to attend in person (see section 8.6 below).

8.2 Screening Visit (Visit 1)

Screening assessments are to be conducted within 21 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 Investigator, or qualified designee, will conduct the following procedures at this visit and record the data in the eCRF:

- Conduct of Informed Consent procedures
- Assignment of participant identification number (automatically assigned by EDC system)
- Review of inclusion and exclusion criteria
- Demography
- Medical history
- Includes migraine history, psychiatric history, cardiac history and family migraine history
- Vital signs
- Concomitant medications and use of tobacco products
- Review of AEs
- Download smartphone app to participant's phone or tablet
- Participant training on use of eDiary
- Administration of Decision Guide

Participants who provide consent and are confirmed by site study staff to be eligible will be provided with the following PROs at the time of screening for completion via their eDiary:

- SDM-Q-9
- SURE test
- PAM-10

In addition, participants will complete the Daily Headache Status Report beginning with the screening visit.

Re-screening of patients who screen fail will be allowed.

8.3 Process for Randomization to Treatment Arms

Participants will be randomized to their respective treatment arms after determining eligibility to participate at the Screening Visit and prior to Baseline (Visit 2). Randomization will be completed in the EDC system. Participants with episodic migraine will be randomized to eptinezumab or SC CGRP (i.e. erenumab, fremanezumab or galcanezumab) in a 1:1 manner. Those experiencing chronic migraine 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 anti-CGRP injectable of their choice (i.e. erenumab, fremanezumab or galcanezumab). Please see Figure 1 for further details on the randomization design.

8.4 Baseline Visit (Visit 2)

This visit is to occur within 21 days of Visit 1. Prior to the participant arriving for the Baseline Visit, the treatment arm for the participant will need to be determined, and the first dose for administration will need to be obtained.

At the time of the Screening visit, the participant, with assistance from the site, will record the expected date of the Baseline visit within the app. This date can be modified, as needed, to accommodate rescheduled appointments within the allowable 21-day window from Screening to Baseline. On the day of Baseline, the app will notify the participant to complete their Baseline PROs. Prior to treating the participant, the site will confirm the completion of the Baseline PROs.

On the day of the visit, the participant will complete the following assessments in their eDiary prior to initiation of treatment (see Panel 2):

- EQ-5D-5L
- PSS
- MIDAS
- HIT-6
- PI-MBS

The participant will also complete the Daily Headache Status Report in their eDiary on this date. This may occur before or after the visit, depending on the time of the visit.

The Investigator, or qualified designee, will conduct the following procedures at this visit and record the data in the eCRF:

- Review of inclusion and exclusion criteria (prior to treatment)
- Review of AEs (prior to treatment)
- Review of concomitant medications and tobacco use (prior to treatment)
- Review of eDiary use
- Review Healthcare Resource Utilization
- Participant training on self-injections of subcutaneous anti-CGRP mAbs (for participants assigned to this treatment arm)
- Administration of first treatment
- Infusion Satisfaction Survey (post-treatment; for participants receiving eptinezumab only)
- Review of ADRs (starting after treatment administration)
- Provide instructions for how to obtain additional doses of subcutaneous anti-CGRP injectables to participant for future use (for participants assigned to this treatment arm)

- Review participant instructions until next visit
- Schedule next visit

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 anti-CGRP mAb. For participants in the subcutaneous anti-CGRP arm, the first dose should be self-administered by the participant under the supervision of the site staff.

8.5 Visits 3 & 4 (Days 28 & 56; +/- 3 days)

These visits will be conducted via telephone or videoconference. Both visits have a window of +/- 3 days.

The Investigator, or qualified designee, will conduct the following procedures at this visit and record the data in the eCRF:

- Review of AEs and ADRs
- Review of concomitant medications and tobacco use
- Review of eDiary use
- Review Healthcare Resource Utilization
- Review participant instructions for next visit
- Schedule next visit

8.6 Visit 5 (Day 84; +/- 3 days)

This visit will only be conducted on site for patients who need to receive their second treatment of eptinezumab or Botox. To maintain equivalence with the those receiving eptinezuamab and Botox it is preferable that this visit occur in person for those receiving the subcutaneous anti-CGRP as well, however it is acceptable to conduct this visit via telephone or videoconference. This visit has a window of +/-3 days.

The Investigator, or qualified designee, will conduct the following procedures at this visit and record the data in the eCRF:

- Review of AEs and ADRs
- Review of concomitant medications and tobacco use
- Administration of treatment (second eptinezumab treatment OR second Botox treatment)
- Infusion Satisfaction Survey (post-treatment; for participants receiving eptinezumab only)
- Review Healthcare Resource Utilization
- Review of eDiary use
- Review participant instructions until next visit
- Schedule next visit

8.7 Visits 6 & 7 (Days 112 & 140; +/- 3 days)

These visits will be conducted via telephone or videoconference. Both visits have a window of +/- 3 days.

The Investigator, or qualified designee, will conduct the following procedures at this visit and record the data in the eCRF:

- Review of AEs and ADRs
- Review of concomitant medications and tobacco use
- Review Healthcare Resource Utilization
- Review of eDiary use
- Review participant instructions for next visit
- Schedule next visit

8.8 End of Treatment (Visit 8; Day 186 +7 days) / Early Termination

This visit will be conducted via telephone or videoconference. The End of Treatment visit has a window of + 7 days.

The Investigator, or qualified designee, will conduct the following procedures at this visit and record the data in the eCRF:

- Review of AEs and ADRs
- Review of concomitant medications and tobacco use
- Review Healthcare Resource Utilization
- Close out of eDiary
- Schedule next visit

8.9 Withdrawal Visit

Participants who withdraw from the study prior to Visit 8 will be asked to complete an Early Termination Visit, if at all possible. The visit must be scheduled as soon as possible after withdrawal. All information collected at an Early Termination Visit s to be recorded in the Visit 8 forms of the eCRF.

In addition, all assessments normally scheduled to be completed by the participants at Visit 8 in the eDiary (Panel 3) will be completed on the day of the Early Termination Visit. In order for the PROs to be provided to the participant via the smartphone application on the day of the Early Termination Visit, site study staff will need to complete the End of Treatment form within the EDC system and select the reason for early termination. The completion of this form will notify the CRO to send the Early Termination PROs to the participant and discontinue any future notifications for PRO completion.

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 (section 10.5).

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 will 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.

8.10 Safety Follow-up Visit

A safety follow-up will be conducted to capture AEs that occur during the Safety Follow-up Period as well as to follow up on the outcome of adverse events ongoing at the end of the Treatment Period (at Visit 8 / Early Termination). This visit will be conducted via telephone or videoconference. The Investigator, or qualified designee, will contact the participant 8 weeks (56 days, +/- 5 days) after their final visit (Visit 8 or Early Termination Visit) to record any new AEs and to follow-up on any AEs that were ongoing at the end of their previous visit. This visit is required for all participants who received at least one dose of any treatment; this visit is not required for participants who screen fail.

For adverse events that were ongoing at the end of the Treatment Period and that resolved during the Safety Follow-up Period, the stop date must be recorded. For non-serious adverse events still ongoing at the safety follow-up, the *Ongoing Adverse Event* checkbox on the *Adverse Event Form* must be ticked. SAEs must be followed until the event has recovered, stabilized, or recovered with sequelae.

8.11 End-of-Study Definition

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.

9 Assessments

9.1 Screening and Baseline Procedures and Assessments

Demographics and Baseline Characteristics
The following participant characteristics will be collected by the investigator at the time of screening and entered into the eCRF:

Socio-demographic variables

- Year of birth
- Sex
- Marital status
- Race/ethnicity
- Zip code
- Highest educational level attained
- Current employment status

Clinical variables

- Number of migraine days in each of the past three months (note that this must be confirmed with the treating physician prior to enrollment)
- 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

9.1.1 Diagnostic Assessments

IHS ICHD-3 guidelines sections 1.1, 1.2 and 1.3 for Migraine or Chronic Migraine are the diagnostic criteria to be used when assessing participant eligibility (see Table 1). Fulfilment of criteria for EM or CM according to the inclusion criteria in this protocol will be confirmed by the investigator from the participant's medical record.

A migraine day for both chronic and episodic migraine is defined as any day with a headache that meets the chronic migraine definition as outlined in the IHS guidelines (section 1.3.1.1) for controlled trials of preventive treatment of chronic migraine in adults. This is defined as a day with a headache that lasts at least 4 hours; meets ICHD-3 criteria C and D for migraine without aura (1.1), B and C for migraine with aura (1.2), or ICHD-3 criteria for probable migraine (1.5); or a day with a headache of a minimum 30-minute duration that is successfully treated with a triptan, ergotamine, or other migraine-specific acute medication.

9.1.2 eDiary

The participants will be instructed to complete an eDiary daily from the Screening Visit until the End of Treatment/Early Termination Visit. The eDiary will be an application that participants can use on their smartphone or tablet. The eDiary consists of applications and reports which will be used to derive the migraine and headache endpoints, and health related quality of life endpoints. At the Screening Visit, the participant must be assisted with the provisioning and training of the eDiary. During the End of Treatment/Early Termination Visit, eDiary close out will be performed.

At the Screening Visit, the site staff will assist the participant in downloading the eDiary application to their smartphone or tablet. Each participant will receive comprehensive training from site staff on the use of the eDiary. Site staff will also instruct participants on the requirement for timely and daily completion of the eDiary. The assessments to be completed by the participants using the eDiary are detailed in Panel 1, Panel 2 and Panel 3

9.1.3 Efficacy and Clinical Outcomes Assessments

All participant reported outcomes will be collected online using the eDiary unless specifically stated otherwise below.

The following participants-reported outcomes will be measured:

- **Daily headache status** – to be reported as part of the participant's daily report in the eDiary. This is how participant's migraine days and data for the PI-MBS is also captured. The participant will receive a push notification from the eDiary on their smartphone or tablet asking them to answer a series of questions (see Panel 3 for details).
- **Patient-Identified Most Bothersome Symptom (PI-MBS)** – The PI-MBS is a modified version of the Most Bothersome Symptom (MBS) tool that is commonly used in acute migraine prevention studies. In the traditional MBS, patients are asked to identify which symptom of their migraines is most bothersome to them from a list of: nausea/vomiting, photophobia or phonophobia. The PI-MBS is a modified version of this tool and does not restrict patients to select their most bothersome symptom from the aforementioned three categories. Instead, in the PI-MBS, patients are prompted to describe in their own words which symptom of their migraine is most bothersome to them. The PI-MBS data will be captured daily via the smartphone app when participants are prompted to report if they had a headache (see Appendix III).

- **Decision guide** – the research team at Lundbeck partnered with Northwestern University to create a decision guide that provides patients information on the treatment options being utilized in this study. Decision guides help people choose between two or more healthcare options based on what is most important to them. The participant will review the decision guide, as provided by the site staff, when receiving study information at the time of screening (Visit 1). After the participant has sufficiently reviewed the material the site staff will ask the participant what their choice for treatment is based on reading the decision guide. Once the decision has been documented, the participant will electronically complete the SDM-Q-9, followed by the SURE test, to determine if there is any decision conflict or regret with the participant's decision. The informed consent will ensure participants are aware that they may be randomized to a treatment arm that is not in accordance with their treatment decision (see Appendix V).
- **9-item Shared Decision-Making Questionnaire (SDM-Q-9)** - The SDM-Q-9 measures the extent to which patients are involved in the process of decision-making from the perspective of the patient. The questionnaire contains nine items, each describing one step of the SDM process.[20] 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); (see Appendix IV).
- **The SURE test** – the SURE test is a brief screening questionnaire the patient uses to assess their readiness and capacity to decide or to determine whether they are comfortable with their decision (see Appendix VI).
- **The Patient Activation Measure (PAM-10)** – The Patient Activation Measure evaluates the knowledge, skills, and confidence a patient has in managing his or her health conditions.[21] 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.[22] (see Appendix VII).
- **EuroQoL-5Dimension-5Level – The EQ-5D-5L** is a utility elicitation instrument that asks participants five questions to capture their quality of life over the previous day. Each question captures a "dimension" of life (self-care, mobility, anxiety/depression, pain/discomfort, usual activities). For each dimension, the participant is asked to respond on one of five levels of problems that they might have with the activities covered by the dimension ranging from "no problems" to "extreme problems/cannot do (see Appendix VIII).
- **Good Day/Bad Day Scale** – 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 (see Appendix IX).
- **Perceived Stress Scale (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. (see Appendix X).

- **Migraine Disability Assessment (MIDAS)** – The MIDAS Questionnaire was developed to assess headache-related disability. 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[23] (see Appendix XI).
- **Infusion Satisfaction Survey** – All participants receiving eptinezumab (regardless of initial treatment assignment) will complete a brief survey describing their satisfaction with the infusion experience after each infusion while on site using a paper questionnaire (see Appendix XII).
- **Treatment Satisfaction Questionnaire for Medication (TSQM)** – All participants will complete the TSQM at the end of the study (Visit 8 or Early Termination Visit) to measure their satisfaction with their medication (see Appendix XIII).
- **Headache Impact Test (HIT-6)** – The HIT-6 was designed to provide a global measure of adverse headache impact. This 6-item scale measures the adverse impact of headache on social functioning, role functioning, vitality, cognitive functioning and psychological distress, as well as the severity of headache pain[24] (see Appendix XIV).

9.2 Healthcare Resource Utilization

All participants will be counselled at the time of enrollment to report any interaction with the healthcare system using the smartphone app (see Appendix XV). Participants will receive push notifications from the smartphone application on a periodic basis (3 times per week) to remind them of this requirement. Interactions to be reported include:

- Physician office visits
- Outpatient service use (i.e., lab visits, imaging, rehabilitation, etc.)
- Outpatient surgery
- Urgent care visits
- Emergency room visits
- Inpatient services
- Changes in prescription drug use (other than for migraine care; new medication or medication change)

As part of the monthly study visits the study coordinator will review the participant's reported utilization using the Healthcare Resource Utilization Follow-Up Questionnaire (see Appendix XVI). They will confirm with the participant each entry made into the smartphone application and, in doing so, will obtain additional detail regarding each interaction.

The coordinator should ask if there were any additional healthcare interactions that were not reported. If so, they should note those in the CRF and, for each, ask the questions provided in the Healthcare Resource Utilization Follow-Up Questionnaire (see Appendix XVI).

If any AEs or SAEs are noted as a result of this review by the site staff, those should be documented appropriately in the patient chart and the eCRF.

Validation of the reported healthcare use will be conducted by acquiring the insurance records of participants who agree to the option of allowing their records to be used for this purpose.

9.3 Safety Assessments

See Chapter 10 for further information on adverse events.

9.3.1 Vital Signs

The investigator may appoint a designee to measure vital signs, provided this is permitted according to local regulations and provided the investigator has trained the designee how to measure vital signs. The investigator must take responsibility for reviewing the findings. Pulse rate and blood pressure will be measured in a manner consistent with the site's standard operating procedures.

Any out-of-range vital sign considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*.

9.4 Treatment Compliance

Treatment compliance will be assessed by recording the date of each treatment administration in the eCRF. This will consist of on-site administration of treatment with eptimezumab or Botox as administered at Visit 2 and 5, and initial treatment with erenumab, fremanezumab or galcanezumab at Visit 2. For subsequent injections of erenumab, fremanezumab or galcanezumab, the site staff will verify the date administered during the monthly study visits.

10 Adverse Events

10.1 Definitions

10.1.1 Adverse Event Definitions[25]

Adverse event – is any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any un-favorable and unintended sign (including clinically significant out-of-range values from relevant tests, such as clinical safety laboratory tests, vital signs, ECGs), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it is considered related to the medicinal product.

It is Lundbeck policy to collect and record all adverse events, including pre-treatment adverse events, that is, those that start after the patient has signed the *Informed Consent Form* and prior to the first dose of IMP.

Serious adverse event – is any adverse event that:

- results in death
- is life-threatening (this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent any of the SAEs defined above)
Examples of medically important events are intensive treatment for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Planned hospitalizations or surgical interventions for a condition that existed before the patient signed the *Informed Consent Form* and that did not change in intensity are not adverse events. Emergency room visits that do not result in admission to the hospital are not necessarily SAEs; however, they must be evaluated to determine whether they meet any of the SAE definitions (for example, life-threatening or other serious [medically important] event).

Non-serious adverse event – is any adverse event that does not meet the definition of an SAE. If there is any doubt as to whether an adverse event meets the definition of an SAE, a conservative viewpoint must be taken, and the adverse event must be reported as an SAE.

Suspected unexpected serious adverse reaction – is any adverse event that is assessed as serious, unexpected (its nature or intensity is not consistent with the current version of the USPI/labelling for any of the IMPs), and related to a medicinal product by either the investigator or Lundbeck.

Overdose – is a dose taken by a patient that exceeds the dose prescribed to that patient. Any overdose (and associated symptoms) must, at a minimum, be recorded as a non-serious adverse event.

10.1.2 Adverse Event Assessment Definitions

Assessment of Intensity

The investigator must assess the *intensity* of the adverse event using the following definitions, and record it on the *Adverse Event Form* in the eCRF:

- Mild – the adverse event causes minimal discomfort and does not interfere in a significant manner with the patient's normal activities.

- Moderate – the adverse event is sufficiently uncomfortable to produce some impairment of the patient's normal activities.
- Severe – the adverse event is incapacitating, preventing the patient from participating in the patient's normal activities.

Assessment of Causal Relationship

The investigator must assess the *causal relationship* between the adverse event and the IMP using the following definitions, and record it on the *Adverse Event Form and the Serious Adverse Event Form (if applicable),* in the eCRF:

- Probable – the adverse event has a strong temporal relationship to the IMP or recurs on rechallenge, and another etiology is unlikely or significantly less likely.
- Possible – the adverse event has a suggestive temporal relationship to the IMP, and an alternative etiology is equally or less likely.
- Not related – the adverse event has no temporal relationship to the IMP or is due to underlying/concurrent disorder or effect of another drug (that is, there is no causal relationship between the IMP and the adverse event).

An adverse event is considered causally related to the use of the IMP when the causality assessment is *probable* or *possible*.

For pre-treatment adverse events, a causality assessment is not relevant.

Assessment of Outcome

The investigator must assess the *outcome* of the adverse event using the following definitions, and record it on the *Adverse Event Form* in the eCRF:

- Recovered – the patient has recovered completely, and no symptoms remain.
- Recovering – the patient's condition is improving, but symptoms still remain.
- Recovered with sequelae – the patient has recovered, but some symptoms remain (for example, the patient had a stroke and is functioning normally, but has some motor impairment).
- *Not recovered* – the patient's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
- *Death*

10.2 Pregnancy

Although not necessarily considered an adverse event, a pregnancy in a patient in the study must be recorded on an *Adverse Event Form* in the eCRF, even if no adverse event associated with the pregnancy has occurred. Pregnancies must be reported to Lundbeck using the same expedited reporting timelines as those for SAEs.

An uncomplicated pregnancy should not be reported as an SAE; hospitalization for a normal birth should not be reported as an SAE. If, however, the pregnancy is associated with an SAE, the appropriate serious criterion must be indicated on the *Adverse Event Form*. Examples of pregnancies to be reported as SAEs (medically important) are spontaneous abortions, stillbirths, and malformations.

Participants who become pregnant will be withdrawn from the study and counselled to enroll in the Lundbeck pregnancy registry. The Lundbeck pregnancy registry is a prospective, observational study in the United States that will be initiated prior to the end of this trial. If a participant does not wish to participate in the Lundbeck pregnancy registry, then the investigator must follow up on the *outcome* of the pregnancy and report it on a *Pregnancy Form* (paper). The follow-up must include information on the neonate at least up until the age of 1 month.

10.3 Recording Adverse Events

Adverse events (including pre-treatment adverse events) and adverse drug reactions must be recorded on an *Adverse Event Form*. The investigator must provide information on the adverse event / drug reaction, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates; intensity; causal relationship to the IMP; action taken; and outcome. If the adverse event is not related to the IMP, an alternative etiology must be recorded, if available. If the adverse event is an overdose, the nature of the overdose must be stated (for example, medication error, accidental overdose, or intentional overdose). If the intensity changes during the course of the adverse event, this must be recorded on the *Adverse Event Form*.

If the adverse event is *serious*, this must be indicated on the *Adverse Event Form*. Furthermore, the investigator must report the SAE to Lundbeck immediately (within 24 hours) after becoming aware of it (see section 10.4).

If individual adverse events are later linked to a specific diagnosis, the diagnosis should be reported and linked to the previously reported adverse events.

10.4 Reporting Serious Adverse Events

The investigator must report SAEs to Lundbeck immediately (within 24 hours) after becoming aware of them by completing the *Adverse Event Form* in the eCRF.

The initial entry of the SAE in the *Adverse Event Form* must contain as much information as possible and, if more information about the patient's condition becomes available, the *Adverse Event Form* must be updated with the additional information.

If the investigator cannot report the SAE in the eCRF within 24 hours of becoming aware of the event, then he or she must complete and sign the *Serious Adverse Event Fallback Form* and send it to Lundbeck Global Patient Safety, US at:

Fax: +1 (847) 282-1003
email: gpsus_query@lundbeck.com

Lundbeck will assume responsibility for reporting SAEs to the authorities in accordance with local requirements.

It is the investigator's responsibility to be familiar with local requirements regarding reporting SAEs to the IRB and to act accordingly.

10.5 Treatment and Follow-up of Adverse Events

Patients with adverse events must be treated in accordance with usual clinical practice at the discretion of the investigator.

The investigator must follow up on non-serious adverse events until resolution or the Safety Follow-up Visit, whichever comes first. At the Safety Follow-up Visit, information on new SAEs, if any, and stop dates for previously reported adverse events must be recorded.

The investigator must follow up on all SAEs until the patient has recovered, stabilized, or recovered with sequelae, and report to Lundbeck all relevant new information using the same procedures and timelines as those for the initial *Serious Adverse Event Form*.

SAEs that are spontaneously reported by a patient to the investigator within 30 days after the Safety Follow- up Visit must be reported to Lundbeck via the e-mail address noted in Section 10.4. In this case, an e-mail describing the reported SAE will be sufficient; Lundbeck Global Patient Safety US will follow-up should additional information be required.

These SAEs will be recorded in the Lundbeck safety database.

11 Data Handling and Record Keeping

11.1 Data Collection

11.1.1 Electronic Case Report Forms

eCRFs will be used to collect the data related to the study as collected by the Investigators (or designees) at study visits (see Panel 4).

The eCRFs use third party software to capture data via an online system on a device. When the investigator enters data in the eCRF (ideally during the visit or as soon as possible [<3 days] thereafter), the data will be securely transmitted to a central database over a secured web server, and all entries and modifications to the data will be logged in an audit trail.

Access to the system will only be granted after appropriate and documented training. Written instructions for using the system will be provided along with the training.

Electronic signatures will be used where signatures are required on pages and/or visits. Automated data entry checks will be implemented where appropriate; other data listings may be reviewed and evaluated for accuracy by the sponsor and/or representatives from the CRO. All entries, corrections, and changes must be made by the investigator or a delegate.

11.1.2 Electronic Diary (eDiary)

An eDiary, which is an app that will be downloaded to each participant's smart phone or tablet, will be used to collect information from the participants throughout the course of the study, from Visit 1 through Visit 8 (see Panel 1, Panel 2 and Panel 3).

The eDiary uses third party software to capture data via an online system on a mobile device. When the participant enters data in the eDiary, the data will be transmitted via a protected SSL to a central database where it will be securely stored, and all data entries will be logged in an audit trail. No entries will be able to be modified, once entered. Participants will be provided instructions on how to use the eDiary at Visit 1 by the site staff. Access to the system (for site staff, CRO staff and Lundbeck staff) will only be granted after appropriate and documented training.

11.1.3 Patient Data

11.1.3.1 Recording of Patient Data

All participant data collected by a participating site will be documented in the participant's medical record or a study-specific record (paper or electronic format) and will contain information to support all data entered into the EDC.

11.1.3.2 Clinical Outcome Assessments

Clinical outcomes will be recorded by participating sites into the EDC system as per Panel 4

11.1.3.3 Serious Adverse Event Fallback Forms

Serious Adverse Event Fallback Forms must be used when the eCRF cannot be accessed.

11.1.4 External Data

All electronic data will be transferred using a secure method accepted by Lundbeck.

The following electronic data will be transferred by the CRO / third-party vendor and kept in a secure designated storage area outside the eCRF:

- eDiary data

11.2 Retention of Study Documents at the Site

11.2.1 eCRF data

If a site closes before the study has been completed, the investigator will continue to have read-only access to the eCRF until the study has been completed. The change to read-only status will take place once all data for the site has been reviewed and the forms have been locked. After the study has been completed, all user access to the eCRF will be revoked. Renewed access to the eCRF will be given if corrections or updates to the database are required.

At the end of the study, the site will be provided with all data related to the site (including eCRF data, queries, and the audit trail) using a secure electronic medium; the secure storage of these data at the site is the responsibility of the investigator. When confirmation of receipt of the data has been received from all sites, all user access to the eCRF will be revoked. If, for some reason, the data are not readable for the full retention period (25 years or in accordance with national requirements, whichever is longer), the investigator may request that the data be re-sent by the sponsor.

11.2.2 Other Study Documents

The investigator must keep the investigator's set of documents in the investigator TMF / Essential Documents Binder for at least 25 years after the *Clinical Study Report* has been approved or in accordance with national requirements, whichever is longer. Lundbeck will remind the investigator in writing of this obligation when the *Clinical Study Report Synopsis* is distributed to the site.

If off-site storage is used, a study-specific binder will remain at the site after the other study-specific documents have been shipped for off-site storage. This binder is considered part of the investigator TMF and must be kept in a secure place by the site for the required period of time. The binder must contain, at a minimum, the following documents: a copy of the *Investigator TMF Index*, a certified copy of the *Patient Identification Code List*, and a *Retrieval Form*.

When the required storage period has expired, the documents may be destroyed in accordance with regulations.

12 Monitoring Procedures

During the study, the CRO will review the study data on an ongoing basis to identify incorrect, inconsistent, and missing data. Any discrepancies or clarifications will be identified and directed to the sites using the query tool within the EDC system. Sites will be required to respond to all generated queries sufficiently before the query can be closed.

13 Audits and Inspections

Authorized personnel from Medical, Regulatory and Clinical Quality Assurance, H. Lundbeck A/S, and quality assurance personnel from business partners may audit the study at any time to assess compliance with the protocol and the principles of *Good Clinical Practice* and all other relevant regulations.

The investigator must be aware that representatives from regulatory authorities may also wish to inspect source data, such as medical records. The investigator must notify Lundbeck, without delay, of an announced inspection by a regulatory authority.

During audits and inspections, the investigator must permit direct access to all the source documents, including medical records and other documents pertinent to the study.

During audits and inspections, the auditors and inspectors may request relevant parts of medical records. No personal identification apart from the screening numbers will appear on these copies.

Patient data will not be disclosed to unauthorized third parties, and patient confidentiality will be respected at all times.

14 Protocol Compliance

Lundbeck has a “no-waiver” policy, which means that permission will not be given to deviate from the protocol.

If a deviation occurs, the investigator or designee must inform the CRO and they must review, discuss, and document the implications of the deviation.

15 Study Termination

Lundbeck or a pertinent regulatory authority may terminate the study or part of the study at any time. The reasons for such action may include, but are not limited to, safety concerns.

If the study is terminated or suspended, the investigator must promptly inform the patients and ensure appropriate therapy and follow-up. Furthermore, the investigator and/or sponsor must promptly inform the IRB and provide a detailed written explanation. The pertinent regulatory authorities must be informed in accordance with national regulations.

If the risk/benefit evaluation changes after the study is terminated, the new evaluation must be provided to the IRB if it will have an impact on the planned follow- up of the patients who participated in the study. If so, the actions needed to protect the patients must be described.

16 Statistical Methodology

16.1 Responsibilities

Biostatistics, Lundbeck LLC, will perform the statistical analyses for this study.

16.2 Analysis Population

The eligible population will comprise all participants who give their informed consent and met the selection criteria. All participants completing at least one daily report after receiving their initial treatment at the Baseline Visit will be considered in the analysis sample. All data collected from participants who withdraw from the study will be collected up until the date of the withdrawal.

The safety population will consist of all participants who receive at least one infusion of eptinezumab.

16.3 Safety Analyses

16.3.1 Analysis of Adverse Events

Adverse event and adverse drug reaction data will be tabulated and reported. No additional analyses are planned.

16.3.2 Sample Size and Power

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. However, for illustrative purposes we provide the power analysis here. Based upon the PROMISE trials and Phase IIIa studies of other medications to be evaluated in EVEC we expect to see a 2-day difference in the average monthly migraine days (MMD) at 13 weeks and a standard deviation of 6.0 around this measure. Based on this we expect to have 83% power to assess this difference with a sample size of 200 participants, assuming no significant loss to follow-up.

16.4 Statistical Analysis Plan

A *Statistical Analysis Plan* describing the handling of data issues and the planned statistical analyses in more detail will be prepared by Lundbeck LLC, before the study is completed.

17 Clinical Study Report and Publications

17.1 Data Ownership

The data collected in this study are the property of Lundbeck.

17.2 Clinical Study Report

Upon completion of the study, a *Clinical Study Report* will be prepared by Regulatory Medical Writing, Lundbeck LLC.

17.3 Summary of Clinical Study Results

Upon completion of the study and when the study results are available, the patient has the right to be informed by the investigator about the overall study results.

17.4 Publications

The results of this study will be submitted for publication.

Lundbeck will submit results information to ClinicalTrials.gov for this study.

The primary publication based on this study must be published before any secondary publications. Authors of the primary publication must fulfil the criteria defined by the ICMJE.[26]

18 Indemnity and Insurance

In the event of study-related injuries or deaths, insurance for the patients and indemnity of the investigators and those of their employees, servants, or agents whose participation in this study has been documented are provided. Insurance and liability will be in accordance with applicable laws and *Good Clinical Practice*.

19 Finance

19.1 Site Agreements

The financial agreements with each site are addressed in one or more documents. Both parties must sign the agreements before each site is initiated.

19.2 Financial Disclosure

All the investigators, including sub-investigators, participating in the study must complete a *Financial Disclosure Form*

Appendix I
Clinical Study Protocol
Authentication and Authorization

Clinical Study Protocol
Authentication and Authorization

Study title: Early Value of Eptinezumab in the Community (EVEC)

Study No.: 19766N

Edition No.: 2.0

Date of edition: 02 June 2022

This document has been signed electronically. The signatories are listed below.

Authentication

I hereby confirm that I am of the opinion that the ethical and scientific basis of this study is sound.

Study Lead: PPD

Global Patient Safety responsible: PPD

Authorization

I hereby confirm that I am of the opinion that the ethical and scientific basis of this study is sound.

Head of HEOR and Value Evidence: PPD

Appendix II

The American Headache Society Position Statement on Integrating New Migraine Treatments into Clinical Practice

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AHS Consensus Statement

The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice

American Headache Society

Objective.—To provide healthcare professionals with updated guidance in the use of novel preventive and acute treatments for migraine in adults.

Background.—The principles of preventive and acute pharmacotherapy for patients with migraine have been outlined previously, but the emergence of new technologies and treatments, as well as new formulations of previously established treatments, has created a need for an updated guidance on the preventive and acute treatment of migraine.

Methods.—This statement is based on a review of existing guidelines and principles for preventive and acute treatment of migraine, as well as the results of recent clinical trials of drugs and devices for these indications. Input was sought from health insurance providers, employers, pharmacy benefit service companies, device manufacturers, pharmaceutical and biotechnology companies, patients, and patient advocates. Expert clinicians and researchers in the field of headache medicine from across North America and the European Union provided input and feedback.

Results.—The principles of pharmacologic preventive treatment of migraine with oral treatments have been as follows: use evidence-based treatments when possible and appropriate; start with a low dose and titrate slowly; reach a therapeutic dose if possible; allow for an adequate treatment trial duration; establish expectations of therapeutic response and adverse events; and maximize adherence. Newer injectable treatments may work faster and may not need titration. The principles of acute treatment include: use evidence-based treatments when possible and appropriate; treat early after the onset of a migraine attack; choose a nonoral route of administration for selected patients; account for tolerability and safety issues; consider self-administered rescue treatments; and avoid overuse of acute medications. Neuromodulation and biobehavioral therapy may be appropriate for preventive and acute treatment, depending on the needs of individual patients. Neuromodulation may be useful for patients who prefer nondrug therapies or who respond poorly, cannot tolerate, or have contraindications to pharmacotherapy.

Conclusions.—This statement updates prior recommendations and outlines the indications for initiating, continuing, combining, and switching preventive and acute treatments of migraine.

Key words: migraine, treatment, acute, preventive, principles

Abbreviations: AE adverse event, CBT cognitive behavioral therapy, CGRP calcitonin gene-related peptide, DHE dihydroergotamine, FIS Functional Impairment Scale, HIT Headache Impact Test, HRQoL health-related quality of life, ICHD International Classification of Headache Disorders, IM intramuscular, IV intravenous, mAbs monoclonal antibodies, MFIQ Migraine Functional Impact Questionnaire, MHD monthly headache day, MIDAS Migraine Disability Assessment, Migraine-ACT Migraine Assessment of Current Therapy, MMD monthly migraine day, MPFID Migraine Physical Function Impact Diary, MSQ Migraine-Specific Quality of Life, mTOQ Migraine Treatment Optimization Questionnaire, NSAID nonsteroidal anti-inflammatory drug, PGIC Patient Global Impression of Change, PPMQ-R Patient Perception of Migraine Questionnaire-Revised, SC subcutaneous, WPAI Work Productivity and Activity Impairment

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From the American Headache Society.

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INTRODUCTION

Migraine is a chronic neurologic disease characterized by attacks of throbbing, often unilateral headache that are exacerbated by physical activity and associated with photophobia, phonophobia, nausea, vomiting,[1] and, in many patients, cutaneous allodynia.[2-6] About one third of patients have migraine with an aura that precedes or occurs during some attacks, while approximately three quarters of patients experience a premonitory phase prior to the onset of headache.[7] Diagnoses of migraine can be refined based on the frequency of monthly migraine days (MMDs) and monthly headache days (MHDs); patients with fewer than 15 MMDs or MHDs have episodic migraine, and those with at least 15 MHDs, of which at least 8 are MMDs, have chronic migraine (Table 1).[1]

Migraine is very common, and the burden of illness is often substantial. The 1-year period prevalence in women and men is 18 and 6%, respectively, and prevalence peaks between the ages of 25 and 55.[8-10] Attacks can significantly impair functional ability at work or school, at home, and in social situations.[11-13] Migraine ranks as the second most disabling neurologic condition globally in terms of years lost to disability.[14,15] Migraine is associated with a considerable financial burden, with annual total costs estimated at $27 billion in the United States.[16,17]

The pain and associated symptoms of migraine, as well as its life consequences, can be addressed with acute treatments, preventive treatments, or both.[18,19] However, because the severity, frequency, and characteristics of migraine vary among persons and, often, within individuals over time,[20] and symptom profiles or biomarkers that predict efficacy and side effects for individuals have not yet been identified,[21,22] optimizing treatment for particular patients remains challenging. At present, treatment plans are individualized based on patient preference; status with respect to pregnancy, lactation, or plans to conceive; the frequency and severity of attacks; the presence, type, and severity of associated symptoms; attack-related disability; prior treatment response; the presence of comorbid and coexistent illness; contraindications (eg, cardiovascular disease); factors such as body habitus and physiological measures (eg, blood pressure, heart rate); and the use of concomitant medications. A process of trial and error is often necessary before treatment can be optimized.

Table 1.—ICHD-3 Criteria for Episodic and Chronic Migraine[1]

Episodic migraine
A. At least 5 attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)
C. Headache has at least 2 of the following 4 characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least 1 of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. Not better accounted for by another diagnosis
Chronic migraine
A. Migraine-like or tension-type-like headache on ≥15 days/month for >3 months that fulfill criteria B and C
B. Occurring in a patient who has had at least 5 attacks fulfilling criteria B-D for migraine without aura and/or criteria B and C for migraine with aura
C. On ≥8 days/month for >3 months, fulfilling any of the following:
1. Criteria C and D migraine without aura
2. Criteria B and C for 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 diagnosis

ICHD, International Classification of Headache Disorders.

The development and emergence of novel medications, device technologies, novel formulations of established drug therapies, and biologics has led to much needed advances in the acute and preventive treatment of migraine. The appropriate and cost-effective integration of these new treatments is of utmost importance to prescribing healthcare providers and their patients. The American Headache Society, in keeping with its mission of improving the lives of people with headache, and in response to requests from multiple stakeholders, sought to establish clinical parameters for the initiation and continuation of novel acute and preventive treatments. Input was therefore elicited from multiple stakeholders, including health insurance providers, employers, pharmacy benefit service companies, device manufacturers, pharmaceutical and biotechnology companies, patients, patient advocates, and experts in headache medicine from North American and Europe.

This statement on the principles of migraine medical care is designed to provide healthcare professionals with guidance in the use of preventive and acute treatments. It contains information about:

- Preventive and acute treatment goals
- Indications for preventive treatment
- Identification of patients who need prevention
- Identification of patients who need a novel acute or preventive treatment
- Successful treatment plans

Much of this information has been previously described[21,23-27] and is based on the pioneering work of Silberstein and the US Headache Consortium. Since then, studies of new neuromodulation technologies and medical therapies require updated expert guidance on the use of preventive treatment for patients with migraine. In addition, neuromodulation, pharmacotherapies, biologics, new formulations of previously established acute, migraine-specific treatments, and biobehavioral therapies have recently been evaluated. This statement updates prior recommendations. The hope is that providers will find this document helpful in selecting the appropriate patient for selected acute and preventive treatments to improve outcomes among their migraine patients with unmet needs.

PREVENTIVE TREATMENT

The goals of migraine prevention are to:[21-23]

- Reduce attack frequency, severity, duration, and disability
- Improve responsiveness to and avoid escalation in use of acute treatment
- Improve function and reduce disability
- Reduce reliance on poorly tolerated, ineffective, or unwanted acute treatments
- Reduce overall cost associated with migraine treatment
- Enable patients to manage their own disease to enhance a sense of personal control
- Improve health-related quality of life (HRQoL)
- Reduce headache-related distress and psychological symptoms

Preventive treatments are an important part of the overall approach for a proportion of people with migraine, and multiple evidence-based guidelines are available.[19,22,24-27] None of the currently available oral preventive treatments were designed specifically for migraine, and many oral preventive treatments have limited to moderate efficacy, moderate to high rates of adverse events (AEs), contraindications, or interactions that limit use. These factors explain in part why few patients with migraine use preventive treatment (3–13%), even though it is believed that nearly 40% of those with episodic migraine, and almost all of those with chronic migraine, in the general population would benefit.[8,28]

Indications for Preventive Treatment.—The recommendations for when to initiate preventive treatment are unchanged. Patients with migraine should be considered for preventive treatment in any of the following situations:[21-23]

- Attacks significantly interfere with patients' daily routines despite acute treatment
- Frequent attacks (≥4 MHDs)
- Contraindication to, failure, or overuse of acute treatments, with overuse defined as:
  - 10 or more days per month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused

Table 2.—Identifying Patients for Preventive Treatment[8] – Modified Criteria

Prevention should be…	Headache days/month	Degree of disability required[†]
Offered	6 or more	None
	4 or more	Some
	3 or more	Severe
Considered	4 or 5	None
	3	Some
	2	Moderate

[†]As measured by scores on the Migraine Disability Assessment scale.[29]

  - 15 or more days per month for nonopioid analgesics, acetaminophen, and nonsteroidal antiinflammatory drugs (NSAIDs [including aspirin])
- AEs with acute treatments
- Patient preference

Prevention should also be considered in the management of certain uncommon migraine subtypes, including hemiplegic migraine, migraine with brainstem aura, migraine with prolonged aura, and those who have previously experienced a migrainous infarction, even if there is low attack frequency.[21-23]

Patient Identification.—Patients are most often selected for preventive treatment based on attack frequency and degree of disability. Consensus guidelines identify groups of patients where preventive treatment should be either "offered" or "considered" based on these parameters (Table 2).[8] Another element of identification involves reviewing the history of medication use for acute treatment and treatment response. Those with migraine with poorly controlled attacks are at risk of acute medication overuse, medication overuse headache (Table 3) and progression to chronic migraine, and it is possible that overuse of medications for the acute treatment of headache may reduce the effectiveness of some preventive treatments.[22,30] Before a preventive treatment plan is developed, measures to ensure appropriate use (eg, drug type, route and timing of administration, frequency) of acute treatments coupled with education and lifestyle modifications should be initiated.[1]

Developing Treatment Plans for Traditional Oral Preventive Therapies.—Preventive treatment selection is based on evidence of efficacy, provider experience, tolerability, patient preference, headache subtype, and comorbidities, taking into account women of childbearing potential, especially those who are currently pregnant, breastfeeding or attempting to conceive. There are several basic principles to guide the initiation, titration, and, if necessary, cessation of preventive treatment.[21,23,31]

Use Evidence-Based Preventive Treatments.—The use of evidence-based treatments (Table 4) is important to the success of migraine prevention. Based on the level of evidence for efficacy and the American Academy of Neurology (AAN) scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (divalproex sodium, valproate sodium, topiramate); beta-blockers (metoprolol, propranolol, timolol); and frovatriptan (for short-term preventive treatment of menstrual migraine). An important exception to the use of valproate sodium and

Table 3.—ICHD-3 Criteria for Medication Overuse Headache

A) Headache occurring on ≥15 days/month in a patient with a preexisting headache disorder

B) Regular overuse for >3 months of 1 or more drugs that can be taken for acute and/or symptomatic treatment of headache, with medication overuse defined as:

1. 10 or more days/month for ergot derivatives, triptans, opioids, combination analgesics[†], and a combination of drugs from different classes that are not individually overused
2. 15 or more days/month for nonopioid analgesics, acetaminophen, and NSAIDs (including aspirin)

C) Not better accounted for by another diagnosis

ICHD, International Classification of Headache Disorders; NSAID, nonsteroidal antiinflammatory drug.
[†]Drugs of 2 or more classes, each with analgesic effect (eg, acetaminophen+codeine) or acting as adjuvants (eg, caffeine).

Table 4.—Treatments With Evidence of Efficacy in Migraine Prevention (Adapted from Silberstein et al[19])

Established efficacy[†]	Probably effective[‡]	Possibly effective[§]
Antiepileptic drugs[‖]	Antidepressants	ACE inhibitors: Lisinopril
Divalproex sodium[‖]	Amitriptyline	Alpha-agonists
Valproate sodium[‖]	Venlafaxine	Clonidine
Topiramate[‖]	Beta-blockers	Guanfacine
Beta-blockers	Atenolol	Antiepileptic drugs: Carbamazepine
Metoprolol	Nadolol	Beta-blockers
Propranolol		Nebivolol
Timolol		Pindolol
Triptans: Frovatriptan[¶]		Antihistamines: Cyproheptadine
OnabotulinumtoxinA[32]		Angiotensin receptor blockers: Candesartan

ACE, angiotensin-converting enzyme.
[†]More than 2 Class I trials based on AAN Scheme for Classification of Evidence.[33]
[‡]One Class I or 2 Class II studies based on AAN Scheme for Classification of Evidence.[33]
[§]One Class II study based on AAN Scheme for Classification of Evidence.[33]
[‖]Not for use in women of childbearing potential who are not using an appropriate method of birth control.[34,35]
[¶]Short-term prevention of menstrual migraine.
[‡‡]For prevention of chronic migraine.

topiramate is that, due to risk of birth defects, it must not be prescribed to women of childbearing potential who are not using a reliable method of birth control.[34,35] The following treatments available by prescription are probably effective and should be considered for migraine prevention: antidepressants (amitriptyline, venlafaxine); beta-blockers (atenolol, nadolol); and angiotensin receptor blockers (candesartan).[19,33] Although evidence can narrow the range of therapeutic options, it does not replace clinical judgment. Preventive treatment plans must be designed to meet the needs of individual patients, and they may involve combining older and newer treatments as well as complex or nontraditional approaches.[19] In addition, evidence-based medicine is dynamic, and current practices may reflect the incorporation of more recent clinical trial results before they reach the creation or revision of existing treatment guidelines.

Start Low and Titrate.—Start oral treatments at a low dose and titrate slowly until the target response develops, the maximum or target dose is reached, or tolerability issues emerge.[21,23] When there is a partial but suboptimal response or dose-limiting AEs, combining preventive drugs from different drug classes may be useful.

Reach a Therapeutic Dose.—With oral treatments, set an initial target dose (eg, 100 or 200 mg topiramate) and advise patients to stop the titration if the maximal dose is reached, when efficacy is optimal, or when AEs become intolerable.

Give an Adequate Trial.—Give oral preventive treatments an adequate trial of at least 8 weeks at a target or usual effective dose to optimize the possibility of a therapeutic response. Before lack of effectiveness can be determined in patients with chronic migraine, prevention plans should be followed for a minimum of 8 weeks at a target therapeutic dose for oral treatments. If there is no response to treatment after 8 weeks at a target or usual effective dose switching preventive treatments is recommended. Patients with a partial response should be counseled that cumulative benefits may occur over 6 to 12 months of continued use.

Establish Realistic Expectations.—When patients are introduced to migraine prevention, they may expect that attacks will cease soon after starting treatment but most established therapies have treatment latencies. The patient should be involved in the process to help establish individual treatment expectations. Thus, it is crucial that patients understand that any of the following can define success in migraine prevention:

- 50% reduction in the frequency of days with headache or migraine
- Significant decrease in attack duration as defined by patient
- Significant decrease in attack severity as defined by patient
- Improved response to acute treatment
- Reduction in migraine-related disability and improvements in functioning in important areas of life
- Improvements in health related quality of life and reduction in psychological distress due to migraine

In some patients, a less than 50% reduction in monthly headache days (MHDs) produces benefits while in others, especially those with daily or continuous headache, a significant reduction in the overall severity of headache may lead to improvements in function and HRQoL and a reduction in headache-related disability.[36] Patients should also understand the most common AEs and their typical frequency and severity, as well as the potential for rare but serious AEs. The success of preventive therapy depends on establishing realistic patient expectations for the given treatment(s).[23]

Optimize Drug Selection.—The selection of preventive treatment should be based on evidence for efficacy; provider experience; tolerability; patient preference; headache subtype; comorbid and coexistent illnesses; concomitant medications; physiological factors (eg, heart rate, blood pressure); body habitus; and pregnancy or the potential for pregnancy among women. Comorbid and coexistent conditions are very important; drug selection may involve choosing treatments known to have efficacy for a comorbid condition or by avoiding drugs that may exacerbate comorbid or coexisting illness or interact with coadministered medications. A single drug for multiple conditions should be avoided if there is a risk of undertreatment of any single condition,[37] as optimal treatment may require the use of a separate class of medication.[23] Try to avoid preventive treatments (especially valproate sodium and topiramate[34,35]) in pregnant or lactating women and those who are trying to conceive, and discuss the potential for AEs on a pregnancy and a developing fetus in women of childbearing age. Since migraine may improve or remit over time, it is important to reevaluate therapeutic response and, if possible, taper or discontinue treatment if patients no longer meet the criteria for offering preventive treatment. However, caution must be exercised in patients who have established, longstanding chronic migraine or in those who have failed multiple prior attempts with preventive treatments. Once control is established, like the control of any chronic disease, the decision to discontinue or taper treatment should be a shared decision between patient and clinician, as it is possible that premature discontinuation can lead to exacerbation and control may not be easily recaptured even after restarting a treatment that was once effective.

Maximize Adherence.—The long-term adherence to oral preventive treatment is poor, mainly due to suboptimal efficacy and poor tolerability.[28] A study of adherence to 14 oral migraine preventive medications used to treat patients with chronic migraine (N = 8688) found adherence rates between 26 to 29% at 6 months and 17 to 20% at 12 months.[38] Patient education about dose adjustments, treatment expectations, and AEs may improve adherence. Patient preference is important in treatment decisions and shared decision making leads to improved outcomes. Potential treatment-emergent AEs need to be considered.

Developing Treatment Plans for Injectable Preventive Therapies.—As of this writing, there are 4 injectable preventive therapies for migraine marketed in the United States: onabotulinumtoxinA and 3 monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) (fremanezumab, galcanezumab) or the CGRP receptor (erenumab).[39-43] OnabotulinumtoxinA is approved for chronic migraine, and erenumab, fremanezumab, and galcanezumab are approved for episodic and chronic migraine. While the principles of preventive therapy for oral preventives generally apply to injectable preventives, there are several notable points of contrast. First, there is no need for gradual dose escalation. The optimal dose of onabotulinumtoxinA is 155 units, and it is given as the initial dose. Erenumab is available in 2 doses (70 mg and 140 mg), either of which can be used as a starting dose. Fremanezumab is supplied in 2 doses, 225 mg and 675 mg, to support monthly and quarterly dose regimens, respectively,[44] and galcanezumab is provided in a 120 mg dose intended for monthly use following an

initial loading dose of 240 mg.[45] The lack of need for slow dose escalation, the rapid onset of therapeutic benefits, and the favorable tolerability profiles are advantages that injectable therapies have in common. In the section on emerging therapies, we will discuss the use of these approved injectable therapies and the likely role of emerging treatments, including CGRP-targeted therapies.

Measuring Response to Preventive Treatment.—Determining the efficacy and tolerability of preventive treatment is a patient-driven decision that may not exactly mirror the endpoints used in clinical trials. In general, a significant reduction (eg, 50%) in MHDs is a useful benchmark in both clinical trials and practice.[46] However, efficacy is variable between patients, and a successful therapeutic outcome depends not only on a reduction in MHD frequency, but also on the persistence and severity of pain and associated symptoms, level of disability, and functional capacity. Therefore, patient-centric and validated outcome measures that evaluate the effect of treatment on functional capacity, disability, and quality of life are important for determining whether meaningful change has occurred and, often, guiding clinical decision-making with respect to changes in dose, adding additional preventive treatment, or switching to an alternative treatment. Examples of these measures are included in Appendix A.

EMERGING PREVENTIVE OPTIONS

While erenumab targets the CGRP receptor, 3 other mAbs (fremanezumab, galcanezumab, eptinezumab) target the CGRP ligand. These biologic agents have demonstrated efficacy, safety, and tolerability for the preventive treatment of episodic and chronic migraine in phase 2 and phase 3 randomized, placebo-controlled trials,[43,44,47-55] and they represent the first mechanism-based and disease-specific class of preventive treatment that was designed, developed, and made available for migraine since methysergide was Food and Drug Administration approved in 1962.[56] At the time of this writing, erenumab, fremanezumab, and galcanezumab are available for use in migraine prevention, and filing is expected for eptinezumab in 2019.[57] These agents can be administered every 4 weeks (fremanezumab, galcanezumab) by subcutaneous (SC) injection or every 12 weeks by SC (fremanezumab) or intravenous (IV) (eptinezumab) infusion. None of these agents requires dose titration. All may achieve rapid treatment effects over days to weeks, and are effective in patients who have failed prior preventive treatment, as well as in those on concurrent oral preventive treatments. The lack of hepatic metabolism or renal clearance avoids interactions with concomitant drugs and these biologics may be added to or used in conjunction with other oral or injectable preventive treatments for migraine. In addition, tolerability profiles are similar to placebo, with injection site reactions being the most common.[43,44,47-55] Conclusions about long-term safety will require real-world clinical experience from use in large, heterogeneous patient populations.

These biologics will almost certainly be a higher cost to health insurance plans and patients than currently available oral generic preventive drugs. Therefore, to achieve cost-effective care while ensuring access to those most appropriate for these treatments, it is important that the indications for initiating treatment with anti-CGRP mAbs are widely understood and followed closely (Table 5). Clinical judgment may result in an emerging treatment being added to 1 or more established treatments. If initiating treatment with an anti-CGRP mAb in a patient already on a preventive treatment, since the risk of drug-mAb interactions is minimal or nonexistent, it is appropriate to add the mAb to the existing regimen and make no other changes until the effectiveness of the mAb is determined. Outcomes as outlined below should be assessed and shared decision-making between patient and provider should guide decisions on the appropriate use of polytherapy or monotherapy.

CGRP small-molecule receptor antagonists are also being studied as preventive treatments for migraine, though published data are not yet available.

Measuring Response to Emerging Preventive Options.—Measuring the response to anti-CGRP mAbs will be patient- and healthcare professional-dependent and will be guided by the same outcome metrics described previously for preventive treatments, with emphasis on migraine/headache days, migraine-related disability, impact, and functional impairment. Measuring outcomes for patients on mAbs and making a decision regarding continuation requires 3 months of outcome data for

Table 5.—Indications for Initiating Treatment With Monoclonal Antibodies to Calcitonin Gene-Related Peptide or Its Receptor

Use is approved when ALL of the following are met:
A. Prescribed by a licensed medical provider[†]
B. Patient is at least 18 years of age
C. Diagnosis of ICHD-3 migraine with or without aura[‡] (4–7 monthly headache days) and both of the following:
a. Inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the following:
1. Topiramate
2. Divalproex sodium/valproate sodium[§]
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
4. Tricyclic antidepressant: amitriptyline, nortriptyline
5. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
6. Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline
b. At least moderate disability (MIDAS>11, HIT-6>50)
D. Diagnosis of ICHD-3 migraine with or without aura[‡] (8–14 monthly headache days) and inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the following:
a. Topiramate
b. Divalproex sodium/valproate sodium[§]
c. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
d. Tricyclic antidepressant: amitriptyline, nortriptyline
e. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
f. Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline
E. Diagnosis of ICHD-3 chronic migraine[‡] and EITHER a or b:
a. Inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the following:
1. Topiramate
2. Divalproex sodium/valproate sodium[§]
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
4. Tricyclic antidepressant: amitriptyline, nortriptyline
5. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
6. Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline
b. Inability to tolerate or inadequate response to a minimum of 2 quarterly injection (6 months) of onabotulinumtoxinA

AAN-AHS, American Academy of Neurology-American Headache Society; HIT, Headache Impact Test; ICHD, International Classification of Headache Disorders; MHDs, monthly headache days; MIDAS, Migraine Disability Assessment.
[†]Doctor of medicine, doctor of osteopathy, advanced practice provider (DDS [Doctor of Dental Surgery] or DMD [Doctor of Medicine in Dentistry or Doctor of Dental Medicine]).
[‡]Patient can only meet criteria for C, D, or E.
[§]Not for use in women of childbearing potential who lack an appropriate method of birth control.[34,35]

patients receiving monthly injections or 6 months of follow-up for a treatment designed for quarterly injection or infusion.

Based on emerging evidence, a significant proportion of patients who do not achieve at least a 50% reduction in MHDs in the 4 weeks after the first SC dose may achieve a response in the 4 weeks after a second dose. Similarly, a smaller yet significant proportion of patients will respond in 4 to 8 weeks after a third consecutive SC dose. Therefore, it is recommended that the benefits of anti-CGRP mAbs be assessed after 3 months of treatment for those administered monthly and 6 months after the start of quarterly treatments. After 3 or 6 months of treatment, clinicians and patients should reassess the benefits of mAbs and continue treatment only if treatment benefits can be documented (Table 6). Evidence of treatment benefits may be provided by at least 1 of the following:

1. A reduction in mean monthly headache days of 50% or more relative to the pretreatment

Table 6.—Criteria for Continuation of Monoclonal Antibodies to Calcitonin Gene-Related Peptide or Its Receptor or Neuromodulation Therapy[†]

Reauthorization after initial use[‡] is approved when EITHER of the following criteria are met:
1. Reduction in mean monthly headache days of ≥50% relative to the pretreatment baseline (Diary documentation or healthcare provider attestation)
2. A clinically meaningful improvement in ANY of the following validated migraine-specific patient-reported outcome measures:
a. MIDAS
i. Reduction of ≥5 points when baseline score is 11–20
ii. Reduction of ≥30% when baseline scores >20
b. MPFID
i. Reduction of ≥5 points
c. HIT-6
i. Reduction of ≥5 points

HIT, Headache Impact Test; MHD, monthly headache day; MIDAS, Migraine Disability Assessment; MPFID, Migraine Physical Function Impact Diary.
Reauthorization duration: Indefinite; guided by patient response and healthcare provider attestation.
[†]Exceptions to these criteria may be made under circumstances when deemed medically indicated by the prescribing licensed healthcare provider.
[‡]Initial authorization: 3 months for treatments administered monthly; for treatments delivered quarterly (every 3 months), 2 cycles of treatment (6 months).

baseline (Diary documentation is recommended but not required).

2. A clinically meaningful improvement in a validated migraine-specific patient-reported outcome measure, including but not limited to:
   - A reduction of at least 5 points or more in Migraine Disability Assessment (MIDAS) score for those whose baseline score was between 11 and 20
   - A 30% reduction in MIDAS score for those with baseline scores above 20
   - Reduction of 5 or more points on the Migraine Physical Function Impact Diary (MPFID)
   - Reduction in scores on the 6-item Headache Impact Test (HIT-6) of at least 5 points[58]
   - Other documented benefits reported by clinician and patient

ACUTE TREATMENT

The following are goals of acute migraine treatment:[22]

- Rapid and consistent freedom from pain and associated symptoms without recurrence
- Restored ability to function
- Minimal need for repeat dosing or rescue medications
- Optimal self-care and reduced subsequent use of resources (eg, emergency room visits, diagnostic imaging, healthcare provider and ambulatory infusion center visits)
- Minimal or no AEs

Effective acute treatment can reduce the pain, associated symptoms, and disability associated with attacks. Suboptimal acute treatment leads to an increase in migraine-related disability and disease progression.[59]

Indications for Acute Treatment.—All patients with migraine should be offered a trial of acute treatment. The following principles may help to improve outcomes in patients with migraine.[22]

Developing Treatment Plans.—*Use Evidence-Based Treatments.*—Use NSAIDs (including aspirin), nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations (eg, aspirin + acetaminophen + caffeine) for mild-to-moderate attacks and migraine-specific agents (triptans, dihydroergotamine [DHE]) for moderate or severe attacks and mild-to-moderate attacks that respond poorly to NSAIDs or caffeinated combinations. Treat at the first sign of pain to improve the probability of achieving freedom from pain and reduce attack-related disability. Acute treatments considered effective or

probably effective based on a 2015 American Headache Society expert review of evidence from controlled trials[18] are presented in Table 7.

Choose a Nonoral Route of Administration for Severe Nausea or Vomiting.—Use a nonoral formulation in patients whose attacks are associated with severe nausea or vomiting or who have trouble swallowing orally administered medications. This includes sumatriptan 3, 4, or 6 mg SC and intranasal and inhaled powder formulations and ketorolac in intranasal and intramuscular (IM) formulations.[60-64] Dihydroergotamine SC and intranasal spray are alternatives. Consider IV DHE and an antiemetic for especially refractory headaches. In addition, antiemetics, such as prochlorperazine suppositories (for both headache and nausea), may be useful. Nonoral routes of administration should also be considered in patients who do not respond well to traditional oral treatments or experience significant nausea or vomiting early during attacks.

Account for Tolerability and Safety Issues.—The tolerability and safety of certain acute treatments may preclude usage in sensitive patients and those with certain coexistent or comorbid illnesses. For instance, NSAIDs can cause serious gastrointestinal and cardiovascular side effects; triptans and ergotamine derivatives should be avoided or used with caution in patients with coronary artery disease, peripheral vascular disease, uncontrolled hypertension, and other vascular risk factors and disorders. Failure to account for tolerability and safety issues in prescribing may cause patients to limit, delay, or forego acute treatment altogether.[65]

Consider Self-Administered Rescue.—When first-line acute treatment does not bring relief, patients may require rescue medication. Depending on the initial treatment, options for outpatient rescue include SC sumatriptan, DHE injection or intranasal spray, or corticosteroids (eg, dexamethasone, IM ketorolac); inpatient options may include parenteral formulations of triptans, DHE, antiemetics, NSAIDs (eg, ketorolac), anticonvulsants (eg, valproate sodium and topiramate [not in women of childbearing potential who are not using an appropriate method of birth control[34,35]]), corticosteroids, and magnesium sulfate. Consider recommending a self-administered rescue treatment for patients with severe attacks and those who have a history of nonresponse or variable response to acute treatment.

Avoid Medication Overuse.—Migraine patients who need to use acute treatments on a regular basis should be instructed to limit treatment to an average of 2 headache days per week, and patients observed to be exceeding this limit should be offered preventive treatment.[18] Patients who have medication overuse despite the use of preventive treatment may require an escalation in dose, a change in preventive therapy, or the addition of another preventive treatment including but not limited to established drugs, biologics, neuromodulation, and biobehavioral approaches.

Measuring Response to Acute Treatment.—Response to acute treatment of migraine can be

Table 7.—Assessment of Acute Treatments for Migraine[18]

Established efficacy[†]	Probably effective
Triptans	Ergotamine and other forms of DHE
Ergotamine derivatives	NSAIDs: ketoprofen, IV and IM ketorolac, flurbiprofen
NSAIDs: aspirin, diclofenac, ibuprofen, naproxen	IV magnesium[†]
Opioids: butorphanol[§]	Isometheptene-containing compounds
Combination medications	Combinations: codeine/acetaminophen, tramadol/acetaminophen[‡]
	Antiemetics: prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide

DHE, dihydroergotamine; IV, intravenous; IM, intramuscular; NSAID, nonsteroidal antiinflammatory drug.
[†]Consider single-pulse transcranial magnetic stimulation, noninvasive vagus nerve stimulation, or electrical trigeminal nerve stimulation in patients who prefer nondrug treatments or in whom drug treatment is ineffective, intolerable, or contraindicated.
[‡]In migraine with aura.
[§]Use is not recommended.

assessed in many ways, but the efficacy endpoints typically used in clinical trials may not fully reflect the outcomes valued by patients[66-68] or the need for ease of use in clinical practice. Failure to understand patient preferences may reduce adherence, discourage patients from continuing treatment, and limit the ability to match treatment with patient needs. As with preventive treatment, patient-oriented, validated outcome measures of acute treatment success can help to verify that patients have experienced a meaningful response and identify the need for adjustments to a therapeutic regimen. For acute treatment, examples of these measures are listed in Appendix B.

EMERGING ACUTE TREATMENTS

Emerging agents with novel mechanisms of action that have demonstrated efficacy for the acute treatment of migraine include the small molecule CGRP receptor antagonists, ubrogepant[69-72] and rimegepant,[73-76] and lasmiditan,[77] a selective serotonin (5-HT_{1F}) receptor agonist. Unlike triptans and ergotamine derivatives, these novel treatment options do not result in constriction of blood vessels and may have a special role in patients with cardiovascular contraindications to triptans. These novel agents will almost certainly be more costly to health insurance plans and patients than currently available oral triptans for which generic options are available. Therefore, to achieve cost-effective care while ensuring access to those most appropriate for these treatments, it is important that the indications for initiating treatment with novel acute oral medications, including ubrogepant, rimegepant, and lasmiditan, are widely understood and followed closely.

Patients who have contraindications to the use of triptans or who have failed to respond to or tolerate at least 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire (eg, Migraine Treatment Optimization Questionnaire [mTOQ], Migraine Assessment of Current Therapy [Migraine-ACT], Patient Perception of Migraine Questionnaire-Revised [PPMQ-R], Functional Impairment Scale [FIS], Patient Global Impression of Change [PGIC]) or healthcare provider attestation, are eligible for ubrogepant, rimegepant, lasmiditan, or a neuromodulation device. Coverage should be provided until at least 2 attacks are treated to determine efficacy and tolerability. Continuation of coverage should be based on the frequency of migraine attacks in an average month and response to a validated acute treatment patient-reported outcome questionnaire or clinical assessment of improvement by the healthcare provider.

NEUROMODULATION AND BIOBEHAVIORAL THERAPIES

Neuromodulation.—Several noninvasive devices have been developed for the treatment of patients with migraine. These treatments modulate pain mechanisms involved in headache by stimulating the nervous system centrally or peripherally with an electric current or a magnetic field.[78] Based on results demonstrating efficacy and safety in clinical trials, the United States Food and Drug Administration has cleared:[79,80]

- Single-pulse transcranial magnetic stimulation for the acute and preventive treatment of migraine
- Electrical trigeminal nerve stimulation for the acute and preventive treatment of migraine
- Noninvasive vagus nerve stimulation for the acute treatment of migraine

Patients who prefer nondrug therapies and those who have failed to respond to, have contraindications to, or poor tolerability with pharmacotherapy may be candidates for neuromodulation.

Biobehavioral Therapies.—As with all chronic medical conditions, education and lifestyle modification is important in the management of migraine. Minimizing exposure and managing unavoidable trigger factors, appropriate and individualized nutrition advice, exercise, and adequate hydration should be implemented and personalized for each patient.

There is a large and growing body of published evidence examining the use of behavioral therapies for migraine (and other forms of headache) including meta-analytic studies and evidence-based reviews. Biobehavioral therapy, including cognitive behavioral therapy (CBT) and biofeedback, and relaxation therapies have been shown to be effective in the acute and preventive treatment of migraine and have Grade A evidence for their use preventively.[81-85] The US Headache

Consortium advised that nonpharmacologic treatments might be particularly well suited for patients who:[22]

- Prefer nonpharmacologic interventions
- Have inadequate response, poor tolerance, or medical contraindications to specific pharmacologic treatments
- Are pregnant, lactating, or planning to become pregnant
- Have a history of acute medication overuse as defined in the section on *Indications for Preventive Treatment*
- Exhibit significant stress or deficient stress-coping skills

They identified the following goals for behavioral interventions as preventive treatment for headache:

- Reduced frequency and severity of headache
- Reduced headache-related disability
- Reduced reliance on poorly tolerated or unwanted pharmacotherapies
- Enhanced personal control of migraine
- Reduced headache-related distress and psychological symptoms

Biobehavioral therapies may be used alone or in conjunction with pharmacologic and interventional treatments. Evidence suggests that combining biobehavioral interventions with pharmacotherapy provides greater benefits than either modality alone.[82,83,86]

CONCLUSIONS

Patients with migraine featuring severe, disabling, or frequent attacks, as well as those who cannot tolerate or are nonresponsive to acute treatment, are candidates for preventive treatment. The decision to initiate preventive treatment should be based on the frequency of individual attacks, average number of days with migraine or moderate or severe headache, and degree of disability. The choice of treatment should be based on evidence of efficacy, provider experience, tolerability, patient preference, headache subtype, comorbid and coexistent disease, concomitant medications, and the potential for childbearing. The principles of preventive treatment with oral treatments include initiating treatment with evidence-based treatments at a low dose, titrating until clinical benefits are achieved, giving each treatment a trial of 2 to 3 months, avoiding overuse of acute treatments. Measuring the overall efficacy and tolerability of preventive treatment is a patient-driven decision made in partnership and after consultation with their healthcare provider. Validated patient-centric outcome measures that evaluate the effect of treatment on functional capacity, disability, and quality of life are important for guiding clinical treatment decisions to continue, add, combine, or switch preventive treatments.

Many evidence-based acute treatments are available, including triptans, ergotamine derivatives, NSAIDs (including aspirin), nonopioid analgesics, and analgesic combinations. As with preventive pharmacologic treatment, to individualize the choice of medication(s), evidence of efficacy, potential medication side effects, patient-specific contraindications, and drug interactions should be considered. Noninvasive vagus nerve stimulation is approved for the acute treatment of migraine pain, and single-pulse transcranial magnetic stimulation, supraorbital nerve stimulation are nonpharmacologic options that may be effective for the acute and preventive treatment of migraine, especially in those for whom pharmacologic treatment is contraindicated, poorly tolerated, ineffective, or not preferred. Empirically validated behavioral treatments with Grade A evidence for the prevention of migraine, including CBT, biofeedback, and relaxation therapies, should be considered in the management of migraine. These modalities may also be used alone or in addition to pharmacologic treatment, particularly in those with a partial therapeutic response and are excellent options for pregnant/lactating women as well as people with contraindications to certain treatments. In addition, all people with migraine will benefit from education and migraine-related lifestyle guidance.

It is the intent of the American Headache Society that this position statement will be reviewed annually and updated, if appropriate, based on the emergence of new evidence.

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APPENDIX A

Validated Instruments that May Be Used to Measure Meaningful Change after a Therapeutic Intervention for Migraine Prevention

Disease-specific instruments are more likely to be sensitive to change and reflect the impact of a particular treatment on migraine-related disability.

- Patient Global Impression of Change scale (PGIC)[87]
- Migraine Functional Impact Questionnaire (MFIQ), a 26-item self-administered instrument for the assessment of the impact of migraine on physical functioning, usual activities, social functioning, and emotional functioning over the past 7 days[88]
- Migraine-Specific Quality of Life questionnaire (MSQ v2.1)[89]
- Migraine Physical Function Impact Diary (MPFID), a 13-item self-administered instrument that assesses the impact of migraine on everyday activities and physical impairment in the past 24 hours[90]
- Headache Impact Test (HIT-6)[58]
- Migraine Disability Assessment (MIDAS)[29]
- Work Productivity and Activity Impairment (WPAI), a general instrument adapted for migraine that evaluates migraine-related disability and costs[91,92]
- Generic measures of health-related quality of life (HRQoL) reflect the overall effect of an illness and the impact of treatment on a subject's perception of their ability to live a useful and fulfilling life[93,94]

APPENDIX B

Validated Instruments That May Be Used to Measure Meaningful Change After a Therapeutic Intervention for Acute Treatment of Migraine

These assessment tools have been shown to be reliable, accurate, and easy to use, and their regular application in clinical practice has the potential to improve efficacy outcomes and patient satisfaction with treatment.

- Migraine Treatment Optimization Questionnaire (mTOQ), a validated, self-administered questionnaire that assesses efficacy based on 4 aspects of response to acute treatment[95]
- Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire, a 4-item assessment tool that evaluates how a recently prescribed acute treatment is working and identifies patients who might benefit from a change in acute treatment[96]
- Patient Perception of Migraine Questionnaire (PPMQ-R), a reliable and valid measure of patient satisfaction with acute migraine treatment in patients with frequent migraine attacks[97]
- Functional Impairment Scale (FIS), a 4-item assessment of function that has demonstrated sensitivity in clinical trials[98,99]

As with preventive treatment, the prescribing licensed healthcare provider's judgment on the best treatment option for a selected patient is sufficient to initiate a new treatment.

Appendix III

Patient-Identified Most Bothersome Symptom (PI-MBS)

PATIENT-IDENTIFIED MOST BOTHERSOME SYMPTOM (PI-MBS)	
Which of the following has been the single most bothersome symptom you have with your headaches before you take any medication?	☐ Head pain that worsened with any movement, or routine physical activity
	☐ Throbbing head pain
	☐ Nausea
	☐ Vomiting
	☐ Sensitivity to sound
	☐ Sensitivity to light
	☐ Difficulty concentrating or thinking clearly
	☐ Visual aura
	☐ Other aura
	☐ Other
If "Other", show the following:	
Please specify:	_____

Internal Reference: PATIENT-IDENTIFIED MOST BOTHERSOME SYMPTOM (PI-MBS)				
Table	**Variable**	**Label**	**Code List**	**Instruction**
PI	PIMBSQ1	Which of the following has been the single most bothersome symptom you have with your headaches before you take any medication?	HEAD PAIN – Head pain that worsened with any movement, or routine physical activity THROBBING – Throbbing head pain NAUSEA – Nausea VOMITING – Vomiting PHONOPHOBIA – Sensitivity to sound PHOTOPHOBIA – Sensitivity to light DIFFICULTY CONCENTRATING – Difficulty concentrating or thinking clearly VISUAL AURA – Visual aura OTHER AURA – Other aura OTHER - Other	
PI	MBSOTSPY	Please specify		Free text

Appendix IV

The 9-Item Shared Decision Making Questionnaire (SDM-Q-9)

The 9-item Shared Decision Making Questionnaire (SDM-Q-9)

[Example] Please indicate which health complaint/problem/illness the consultation was about:

[Example] Please indicate which decision was made:

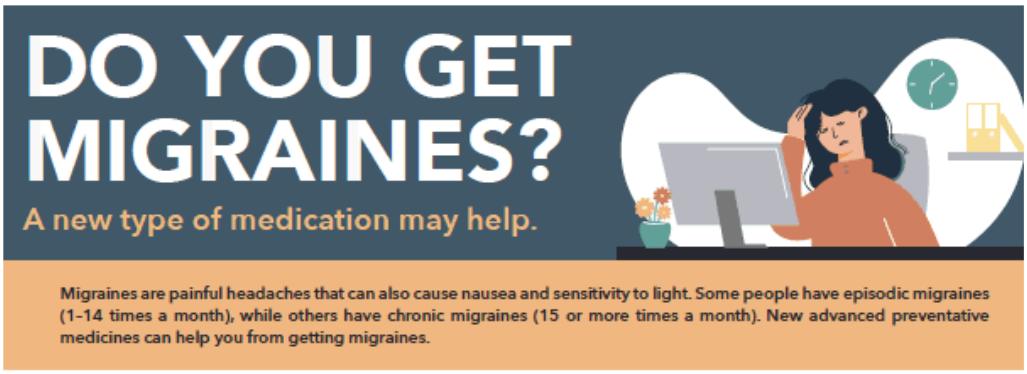
Nine statements related to the decision-making in your consultation are listed below. For each statement please indicate how much you agree or disagree.

	completely disagree	strongly disagree	somewhat disagree	somewhat agree	strongly agree	completely agree
1. My doctor made clear that a decision needs to be made.	❑	❑	❑	❑	❑	❑
2. My doctor wanted to know exactly how I want to be involved in making the decision.	❑	❑	❑	❑	❑	❑
3. My doctor told me that there are different options for treating my medical condition.	❑	❑	❑	❑	❑	❑
4. My doctor precisely explained the advantages and disadvantages of the treatment options.	❑	❑	❑	❑	❑	❑
5. My doctor helped me understand all the information.	❑	❑	❑	❑	❑	❑
6. My doctor asked me which treatment option I prefer.	❑	❑	❑	❑	❑	❑
7. My doctor and I thoroughly weighed the different treatment options.	❑	❑	❑	❑	❑	❑
8. My doctor and I selected a treatment option together.	❑	❑	❑	❑	❑	❑
9. My doctor and I reached an agreement on how to proceed.	❑	❑	❑	❑	❑	❑

Martin Härter & Isabelle Scholl, University Medical Center Hamburg-Eppendorf, Germany

Appendix V

Decision Guide



Migraines are painful headaches that can also cause nausea and sensitivity to light. Some people have episodic migraines (1–14 times a month), while others have chronic migraines (15 or more times a month). New advanced preventative medicines can help you from getting migraines.

How do you know which migraine treatment might be right for you?

	Aimovig (Erenumab)	Ajovy (Fremanezumab)	Emgality (Galcanezumab)	Vyepti (Eptinezumab)	BOTOX® (OnabotulinumtoxinA)
What does it treat?	episodic/chronic migraine	episodic/chronic migraine	episodic/chronic migraine	episodic/chronic migraine	chronic migraine
How is it administered?	you give yourself an injection (abdomen, thigh or upper arm)	you give yourself an injection or your provider gives it to you (abdomen, thigh or upper arm)	you give yourself an injection* (abdomen, thigh or upper arm)	a health care provider gives you an IV (30 minute procedure)	a health care provider gives you multiple injections (around the head and neck) (15 minute procedure)
How often?	once a month	once every 1 to 3 months	once a month	once every 3 months	once every 3 months
How do I store it?	refrigerated (Can be kept in original carton at room temp. (68-77°F) for up to 7 days after refrigeration.)	refrigerated (Can be kept in original carton at room temp. (68-77°F) for up to 24 hours after refrigeration.)	refrigerated (Can be kept in original carton at room temperature (86°F) for up to 7 days after refrigeration.)	N/A	N/A
What are the most common side effects?†	injection site reactions constipation **	injection site reactions	injection site reactions	allergic reactions stuffy nose and scratchy throat	injection site reactions allergic reactions (includes itching, rash, red itchy welts, wheezing, asthma symptoms, dizziness or feeling faint) dry mouth, tiredness headache, neck pain, eye problems, drooping eyebrows ***

*Migraine: 1st dose = 2 injections | subsequent doses = 1 injection
**Individuals should not take Aimovig if they are allergic to rubber or latex (needle shield is made of natural rubber latex)
***Individuals should not use Botox if they: have a disease that affects the muscles and nerves, have or have had a breathing problem such as asthma or emphysema, have or have had swallowing problems, have or have had bleeding problem, have plans to have surgery, have had surgery on their face, have weakness in the forehead muscles, have drooping eyelids, have any changes in the way their face normally looks.
† Side effects and risks were all taken from the drug-specific FDA-approved patient information forms

Migraine Treatments *continued from reverse*

	Aimovig (Erenumab)	Ajovy (Fremanezumab)	Emgality (Galcanezumab)	Vyepti (Eptinezumab)	BOTOX® (OnabotulinumtoxinA)
Call your healthcare provider if:	**allergic reactions** (including rash or swelling of the face, mouth, tongue or throat; trouble breathing) *May occur within hours to days after treatment.* **constipation with serious complications** **high blood pressure or worsening high blood pressure**	**allergic reactions** (including itching, rash and hives; swelling of the face, mouth, tongue or throat; and trouble breathing) *May occur within hours up to 1 month after treatment.*	**allergic reactions** (including itching, rash, and hives; swelling of the face, mouth, tongue or throat; and trouble breathing) *May occur within days after treatment.*	**allergic reactions** (including rash, hives, and redness in the face; swelling of the face, mouth, tongue or throat; and trouble breathing)	**trouble breathing or swallowing** *May occur hours to weeks after treatment.* **spread of toxins can happen days to weeks after treatment and lead to botulism*** (botulism symptoms include: loss of strength and muscle weakness all over the body, double vision, blurred vision and drooping eyelids, hoarseness or change or loss of voice, trouble saying words clearly, loss of bladder control)
How well does it treat chronic migraines?‡	7 7 fewer migraine days /month	5 5 fewer migraine days/month	5 5 fewer migraine days/month	8 8 fewer migraine days/month	8 to 9 8 to 9 fewer migraine days/month
How well does it treat episodic migraines?‡	3 to 4 3 to 4 fewer migraine days /month	3 to 4 3 to 4 fewer migraine days /month	4 to 5 4 to 5 fewer migraine days/month	4 4 fewer migraine days/month	not enough data to support FDA approval for this indication
Find out more:	www.aimovig.com	www.ajovyhcp.com	www.emgality.com	www.vyeptihcp.com	www.botoxchronicmigraine.com

Appendix VI

The SURE Test

SURE Test version for clinical practice

Yes equals 1 point
No equals 0 point

If the total score is less than 4, it indicates the probability that a patient experiences clinically significant decisional conflict.

		Yes [1]	No [0]
Sure of myself	Do you feel SURE about the best choice for you?		
Understand information	Do you know the benefits and risks of each option?		
Risk-benefit ratio	Are you clear about which benefits and risks matter most to you?		
Encouragement	Do you have enough support and advice to make a choice?		

Appendix VII

The Patient Activation Measure (PAM-10)

Name	
ID	
Date	

Below are statements people sometimes make when they talk about their health. Please indicate how much you agree or disagree with each statement as it applies to you personally.

Circle the answer that is most true for you today. If the statement does not apply, select N/A.

1.	When all is said and done, I am the person who is responsible for taking care of my health.	Strongly Disagree	Disagree	Agree	Strongly Agree	N/A
2.	Taking an active role in my own health care is the most important thing that affects my health.	Strongly Disagree	Disagree	Agree	Strongly Agree	N/A
3.	I know what each of my prescribed medications do.	Strongly Disagree	Disagree	Agree	Strongly Agree	N/A
4.	I am confident that I can tell whether I need to go to the doctor or whether I can take care of a health problem myself.	Strongly Disagree	Disagree	Agree	Strongly Agree	N/A
5.	I am confident that I can tell a doctor concerns I have even when he or she does not ask.	Strongly Disagree	Disagree	Agree	Strongly Agree	N/A
6.	I am confident that I can follow through on medical treatments I may need to do at home.	Strongly Disagree	Disagree	Agree	Strongly Agree	N/A
7.	I have been able to maintain (keep up with) lifestyle changes, like eating right or exercising.	Strongly Disagree	Disagree	Agree	Strongly Agree	N/A
8.	I know how to prevent problems with my health.	Strongly Disagree	Disagree	Agree	Strongly Agree	N/A
9.	I am confident I can figure out solutions when new problems arise with my health.	Strongly Disagree	Disagree	Agree	Strongly Agree	N/A
10.	I am confident that I can maintain lifestyle changes, like eating right and exercising, even during times of stress.	Strongly Disagree	Disagree	Agree	Strongly Agree	N/A

Appendix VIII

EuroQoL-5Dimension-5Level (EQ-5D-5L)

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

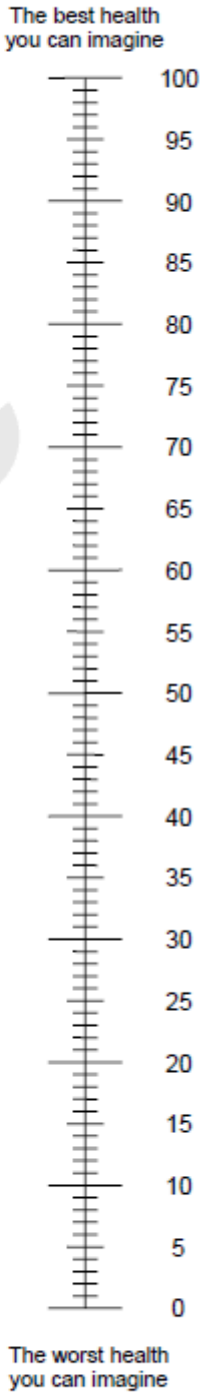
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Appendix IX

Good Day / Bad Day Scale

Good Day / Bad Day Scale

Over the past week, please indicate the total number of *good days* and *bad days* you have had.

The total for both days must add up to 7.

Good days: _____

Bad Days: _____

Appendix X

Perceived Stress Scale (PSS)

Perceived Stress Scale

A more precise measure of personal stress can be determined by using a variety of instruments that have been designed to help measure individual stress levels. The first of these is called the Perceived Stress Scale.

The Perceived Stress Scale (PSS) is a classic stress assessment instrument. The tool, while originally developed in 1983, remains a popular choice for helping us understand how different situations affect our feelings and our perceived stress. The questions in this scale ask about your feelings and thoughts during the last month. In each case, you will be asked to indicate how often you felt or thought a certain way. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer fairly quickly. That is, don't try to count up the number of times you felt a particular way; rather indicate the alternative that seems like a reasonable estimate.

For each question choose from the following alternatives:
0 - never 1 - almost never 2 - sometimes 3 - fairly often 4 - very often

_____ 1. In the last month, how often have you been upset because of something that happened unexpectedly?

_____ 2. In the last month, how often have you felt that you were unable to control the important things in your life?

_____ 3. In the last month, how often have you felt nervous and stressed?

_____ 4. In the last month, how often have you felt confident about your ability to handle your personal problems?

_____ 5. In the last month, how often have you felt that things were going your way?

_____ 6. In the last month, how often have you found that you could not cope with all the things that you had to do?

_____ 7. In the last month, how often have you been able to control irritations in your life?

_____ 8. In the last month, how often have you felt that you were on top of things?

_____ 9. In the last month, how often have you been angered because of things that happened that were outside of your control?

_____ 10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

Figuring Your PSS Score

You can determine your PSS score by following these directions:

- First, reverse your scores for questions 4, 5, 7, and 8. On these 4 questions, change the scores like this:

  0 = 4, 1 = 3, 2 = 2, 3 = 1, 4 = 0.

- Now add up your scores for each item to get a total. My total score is _____.

- Individual scores on the PSS can range from 0 to 40 with higher scores indicating higher perceived stress.
  - Scores ranging from 0-13 would be considered low stress.
  - Scores ranging from 14-26 would be considered moderate stress.
  - Scores ranging from 27-40 would be considered high perceived stress.

The Perceived Stress Scale is interesting and important because your perception of what is happening in your life is most important. Consider the idea that two individuals could have the exact same events and experiences in their lives for the past month. Depending on their perception, total score could put one of those individuals in the low stress category and the total score could put the second person in the high stress category.

Disclaimer: The scores on the following self-assessment do not reflect any particular diagnosis or course of treatment. They are meant as a tool to help assess your level of stress. If you have any further concerns about your current well being, you may contact EAP and talk confidentially to one of our specialists.

State of New Hampshire
Employee Assistance Program

Appendix XI

Migraine Disability Assessment (MIDAS)

The Migraine Disability Assessment Test

The **MIDAS** (Migraine Disability Assessment) questionnaire was put together to help you measure the impact your headaches have on your life. The information on this questionnaire is also helpful for your primary care provider to determine the level of pain and disability caused by your headaches and to find the best treatment for you.

INSTRUCTIONS

Please answer the following questions about ALL of the headaches you have had over the last 3 months. Select your answer in the box next to each question. Select zero if you did not have the activity in the last 3 months. Please take the completed form to your healthcare professional.

_____ 1. On how many days in the last 3 months did you miss work or school because of your headaches?

_____ 2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)

_____ 3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?

_____ 4. How many days in the last 3 months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)

_____ 5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

_____ Total (Questions 1-5)

What your Physician will need to know about your headache:

_____ A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.)

_____ B. On a scale of 0 - 10, on average how painful were these headaches? (where 0=no pain at all, and 10= pain as bad as it can be.)

Scoring: After you have filled out this questionnaire, add the total number of days from questions 1-5 (ignore A and B).

MIDAS Grade	Definition	MIDAS Score
I	Little or No Disability	0-5
II	Mild Disability	6-10
III	Moderate Disability	11-20
IV	Severe Disability	21+

If Your MIDAS Score is 6 or more, please discuss this with your doctor.

Appendix XII

Infusion Satisfaction Survey

INFUSION SATISFACTION SURVEY	
If "TXISS" = "YES", show the following:	
How many VYEPTI treatments has the patient received in total?	☐ 1 ☐ 2
Record the date of today's infusion treatment	_ _ / _ _ _ / _ _ _ _ DD MMM YYYY
Overall, I felt the infusion experience was positive	☐ Strongly disagree ☐ Disagree ☐ Not sure/no opinion ☐ Agree ☐ Strongly agree
Overall, I felt the infusion experience was convenient	☐ Strongly disagree ☐ Disagree ☐ Not sure/no opinion ☐ Agree ☐ Strongly agree
Receiving a treatment from my healthcare provider was reassuring	☐ Strongly disagree ☐ Disagree ☐ Not sure/no opinion ☐ Agree ☐ Strongly agree

I would prefer to receive my migraine medication another way other than infusion	☐ Strongly disagree ☐ Disagree ☐ Not sure/no opinion ☐ Agree ☐ Strongly agree
If "Agree" or "Strongly Agree" was selected, show the following:	
Please state how you would prefer to receive your migraine medication	_____
On a scale of zero to ten, how likely are you to recommend infusion treatment to a friend or family member? *A score of 0 means not at all likely, a score of 10 means extremely likely*	... ▼
What were the most important factors affecting your likelihood to recommend infusion?	_____
Have you previously received infusion treatment for a condition other than migraine?	☐ Yes ☐ No
If "YES" was selected, show the following:	
Was the treatment(s)	☐ Outpatient ☐ Inpatient ☐ Both

Internal Reference: INFUSION SATISFACTION SURVEY				
Table	**Variable**	**Label**	**Code List**	**Instruction**
IS	VYNUM	How many VYEPTI treatments has the patient received in total?	1 – 1 2 – 2	Confirm sequence
IS	VYTXDT	Record the date of today's infusion treatment		
IS	ISQ1	Overall, I felt the infusion experience was positive	STRONGLY DIAGREE – Strongly disagree DISAGREE – Disagree NOT SURE – Not sure/no opinion AGREE – Agree STRONGLY AGREE – Strongly agree	
IS	ISQ2	Overall, I felt the infusion experience was convenient	STRONGLY DIAGREE – Strongly disagree DISAGREE – Disagree NOT SURE – Not sure/no opinion AGREE – Agree STRONGLY AGREE – Strongly agree	
IS	ISQ3	Receiving a treatment from my healthcare provider was reassuring	STRONGLY DIAGREE – Strongly disagree DISAGREE – Disagree NOT SURE – Not sure/no opinion AGREE – Agree STRONGLY AGREE – Strongly agree	
IS	ISQ4	I would prefer to receive my migraine medication another way other than infusion	STRONGLY DIAGREE – Strongly disagree DISAGREE – Disagree	

			NOT SURE – Not sure/no opinion AGREE – Agree STRONGLY AGREE – Strongly agree	
IS	ISQ5	Please state how you would prefer to receive your migraine medication		Free text
IS	ISQ6	On a scale of zero to ten, how likely are you to recommend infusion treatment to a friend or family member?	0 – 0 1 – 1 2 – 2 3 – 3 4 – 4 5 – 5 6 – 6 7 – 7 8 – 8 9 – 9 10 – 10	
IS	ISQ7	What were the most important factors affecting your likelihood to recommend infusion?		Free text
IS	ISQ8	Have you previously received infusion treatment for a condition other than migraine?	Y – Yes N – No	
IS	ISQ9	Was the treatment(s)	OUTPATIENT – Outpatient INPATIENT – Inpatient BOTH – Both	

Appendix XIII

Treatment Satisfaction Questionnaire for Medication (TSQM)

TSQM *(Version 1.4)*

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it.* For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

4. As a result of taking this medication, do you experience any side effects at all?

☐$_1$ Yes
☐$_0$ No (if No, then please skip to Question 9)

[Clinical Trial Version] 1

5. How bothersome are the side effects of the medication you take to treat your condition?

☐1 Extremely Bothersome
☐2 Very Bothersome
☐3 Somewhat Bothersome
☐4 A Little Bothersome
☐5 Not at All Bothersome

6. To what extent do the side effects interfere with your physical health and ability to function (i.e., strength, energy levels, etc.)?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

7. To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

8. To what degree have medication side effects affected your overall satisfaction with the medication?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

9. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

10. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

11. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

12. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

13. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

Appendix XIV

Headache Impact Test (HIT-6)

HIT-6™ Headache Impact Test

HIT is a tool used to measure the impact headaches have on your ability to function on the job, at school, at home and in social situations. Your score shows you the effect that headaches have on normal daily life and your ability to function. HIT was developed by an international team of headache experts from neurology and primary care medicine in collaboration with the psychometricians who developed the SF-36® health assessment tool. This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

When you have headaches, how often is the pain severe?

never rarely sometimes very often always

How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

never rarely sometimes very often always

When you have a headache, how often do you wish you could lie down?

never rarely sometimes very often always

In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

never rarely sometimes very often always

In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

never rarely sometimes very often always

In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

never rarely sometimes very often always

☐ +	☐ +	☐ +	☐ +	☐
COLUMN 1 6 points each	COLUMN 2 8 points each	COLUMN 3 10 points each	COLUMN 4 11 points each	COLUMN 5 13 points each

To score, add points for answers in each column.

If your HIT-6 is 50 or higher:

You should share your results with your doctor. Headaches that stop you from enjoying the important things in life, like family, work, school or social activities could be migraine.

☐
TOTAL SCORE

Appendix XV

Healthcare Resource Utilization

HEALTHCARE RESOURCE UTILIZATION	
Have you used any health services since your last report?	☐ Yes ☐ No
If "Yes", show the following:	
Date of HRU interaction	__ / ___ / ____ DD MMM YYYY
Which type of health care resource was used?	☐ Physician office visit ☐ Outpatient service use ☐ Outpatient surgery ☐ Urgent care visit ☐ Emergency room visit ☐ Hospitalization ☐ Changes in prescription drug use or a new prescription for a medication
Do you have another healthcare resource not previously reported to record?	☐ Yes ☐ No

Internal Reference: HEALTHCARE RESOURCE UTILIZATION				
Table	**Variable**	**Label**	**Code List**	**Instruction**
HR	HRUYN	Have you used any health services since your last report?	Y – Yes N – No	
HR	HRUDATE	Date of HRU interaction		
HR	HRUTYPE	Which type of health care resource was used?	PHYSICIAN OFFICE VISIT – Physician office visit OUTPATIENT SERVICE USE – Outpatient service use OUTPATIENT SURGERY – Outpatient surgery URGENT CARE VISITS – Urgent care visits EMERGENCY ROOM VISITS – Emergency room visits INPATIENT SERVICES – Hospitalization CHANGES IN PRESCRIPTION DRUG USE – Changes in prescription drug use or a new prescription for a medication	
HR	HRUADD	Do you have another healthcare resource not previously reported to record?	Y – Yes N – No	

Appendix XVI

Healthcare Resource Utilization Follow-Up Questionnaire

Healthcare Resource Utilization Follow-Up Questionnaire	
Are there any HRUs to report?	☐ Yes ☐ No
Visit Date	_ _ / _ _ _ / _ _ _ _ DD MMM YYYY
Which type of health care resource was utilized?	☐ Physician office visit ☐ Outpatient service use ☐ Outpatient surgery ☐ Urgent care visit ☐ Emergency room visit ☐ Inpatient services ☐ Changes in prescription drug use
Date of HRU interaction	_ _ / _ _ _ / _ _ _ _ DD MMM YYYY
If "Physician office visit" is selected for "HRTYPE", show the following:	
What type of physician did the patient visit?	
If "PHYSTYPE" is "Other", show the following:	
Please specify the type of physician	_____
Was the purpose of this visit for a routine physical examination?	☐ Yes ☐ No
Was this a maternity visit?	☐ Yes ☐ No ☐ N/A
If "ROUTINE" = "No" and "MATRNITY" = "No" or "NA", show the following	
What was the reason for the visit?	_____

Was this a….	☐ First visit ☐ Follow-up visit for this issue
Did the visit require a referral from another physician?	☐ Yes ☐ No
If "Outpatient service use" is selected for "HRTYPE", show the following:	
For which reason was the outpatient service use	☐ A laboratory test ☐ Physical or occupational therapy ☐ Imaging test ☐ Other
If "OUTREAS" = "Imaging", show the following:	
Please specify the type of imaging	
If "OUTIMAGE" is "Other", show the following:	
Please specify the other type of imaging	_____
If "OUTREAS" = "Other", show the following:	
Please specify the other reason for the outpatient service	_____
If "Outpatient surgery" is selected for "HRTYPE", show the following:	
Please specify the type of surgery	_____
If "Urgent Care Visit" is selected for "HRTYPE", show the following:	
Please specify the condition that prompted the urgent care visit	_____
If "Emergency Room Visit" is selected for "HRTYPE", show the following:	
Please specify the reason for the ER visit	_____
Please specify any imaging procedures that were conducted during the ER visit	
If "ERIMAGE" is "Other", show the following:	
Please specify the other type of imaging	_____
If "Inpatient Services" is selected for "HRTYPE", show the following:	

Please specify the reason for admission	_____
Please specify the length of stay, in days (if less than 24 hours, enter, "1"):	_ _
Is there another HRU to record?	☐ Yes ☐ No

Internal Reference: HEALTHCARE RESOURCE UTILIZATION FOLLOW-UP QUESTIONNAIRE				
Table	**Variable**	**Label**	**Code List**	**Instruction**
HR	HRUYN	Are there any HRUs to report?	Y – Yes N – No	Only show on the first page of this log module
HR	HRVISDAT	Visit Date		
HR	HRTYPE	Which type of health care resource was utilized?	PHYSICIAN OFFICE VISIT – Physician office visit OUTPATIENT SERVICE USE – Outpatient service use OUTPATIENT SURGERY – Outpatient surgery URGENT CARE VISITS – Urgent care visits EMERGENCY ROOM VISITS – Emergency room visits INPATIENT SERVICES – Inpatient services CHANGES IN PRESCRIPTION DRUG USE – Changes in prescription drug use	Informational validation for "CHANGES IN PRESCRIPTION DRUG USE" to inform user to record new/changed medication on the CM eCRF Informational validation for any option **other than** "CHANGES IN PRESCRIPTION DRUG USE" to review the HRU for possible AEs and record on AE eCRF, if applicable
HR	HRUDATE	Date of HRU interaction		
HR	PHYSTYPE	What type of physician did the patient visit?	ALLERGIST – Allergist CARDIO – Cardiologist DERM – Dermatologist ENDO – Endocrinologist GASTRO – Gastroenterologist GP – Family/General/Primary INTERNAL MEDICINE – Internal Medicine NEURO – Neurologist OBGYN – Obstetrician/Gynecologist ONCOLOGIST – Oncologist	

			OPHTHAL – Ophthalmologist PSYCHIATRIST – Psychiatrist SURGEON – Surgeon OTH – Other	
HR	TYPEOTH	Please specify the type of physician		Free text
HR	ROUTINE	Was the purpose of this visit for a routine physical examination?	Y – Yes N – No	
HR	MATRNITY	Was this a maternity visit?	Y – Yes N – No	If "Yes", informational text advising site to record AE
HR	REASON	What was the reason for the visit?		Free text
HR	VISTYPE	Was this a….	FIRST VISIT – first visit FOLLOW-UP VISIT – follow-up visit for this issue	
HR	REFERRAL	Did this visit require a referral from another physician?	Y – Yes N - No	
HR	OUTREAS	For which reason was the outpatient service use	LABORATORY TEST – A laboratory test PHYSICIAL OR OCCUPATIONAL THERAPY – Physical or occupational therapy IMAGING – Imaging test OTHER – Other	
HR	OUTIMAGE	Please specify the type of imaging	CT – CT scan MRI – MRI PET – PET US – Ultrasound XRAY – X-ray OTH – Other	
HR	IMAGEOTH	Please specify the other type of imaging		Free text

HR	HROTHSPY	Please specify the other reason for the outpatient service		Free text
HR	SURGTYPE	Please specify the type of surgery		Free text
HR	UCREAS	Please specify the condition that prompted the urgent care visit		Free text
HR	ERREAS	Please specify the reason for the ER visit		Free text
HR	ERIMAGE	Please specify any imaging procedures that were conducted during the ER visit	CT – CT scan MRI – MRI PET – PET US – Ultrasound XRAY – X-ray OTH – Other	
HR	ERIMGOTH	Please specify the other type of imaging		Free text
HR	ADMISSON	Please specify the reason for admission		Free text Informational validation advising site to record the event on the AE eCRF
HR	ADMLENGH	Please specify the length of stay, in days (if less than 24 hours, enter, "1"):		Query if value is outside of the range of 1 – 31; do not allow a value of "0"; leading "0" for values 1 – 9
HR	HRUADD	Is there another HRU to record?	Y – Yes N – No	

Appendix XVII

Medication - Overuse Headache Criteria (MOH)

From International Headache Society ICHD-3 Classification

(8.2 Medication-overuse headache (MOH) - ICHD-3 Accessed April 12, 2022)

8.2 Medication-overuse headache (MOH)

Previously used terms:

Drug-induced headache; medication-misuse headache; rebound headache.

Coded elsewhere:

Patients with a pre-existing primary headache who, in association with medication overuse, develop a new type of headache or a significant worsening of their pre-existing headache that, in either case, meets the criteria for 8.2 *Medication-overuse headache* (or one of its subtypes) should be given both this diagnosis and the diagnosis of the pre-existing headache. Patients who meet criteria for both 1.3 *Chronic migraine* and 8.2 *Medication-overuse headache* should be given both diagnoses.

Description:

Headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days/month, depending on the medication) for more than 3 months. It usually, but not invariably, resolves after the overuse is stopped.

Diagnostic criteria:

A. Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder
B. Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache[1;2;3]
C. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. Patients should be coded for one or more subtypes of 8.2 *Medication-overuse headache* according to the specific medication(s) overused and the criteria for each below. For example, a patient who fulfils the criteria for 8.2.2 *Triptan-overuse headache* and the criteria for one of the subforms of 8.2.3 *Non-opioid analgesic-overuse headache* should receive both these codes. The exception occurs when patients overuse combination-analgesic medications, who are coded 8.2.5 *Combination-analgesic-overuse headache* and not according to each constituent of the combination-analgesic medication.
2. Patients who use multiple drugs for acute or symptomatic treatment of headache may do so in a manner that constitutes overuse even though no individual drug or class of drug is overused; such patients should be coded 8.2.6 *Medication-overuse headache attributed to multiple drug classes not individually overused*.
3. Patients who are clearly overusing multiple drugs for acute or symptomatic treatment of headache but cannot give an adequate account of their names and/or quantities are coded 8.2.7 *Medication-overuse headache attributed to unspecified or unverified overuse of*

multiple drug classes until better information is available. In almost all cases, this necessitates diary follow-up.

Comments:

8.2 *Medication-overuse headache* is an interaction between a therapeutic agent used excessively and a susceptible patient. Among those with a previous primary headache diagnosis, most have 1. *Migraine* or 2. *Tension-type headache* (or both); only a small minority have other primary headache disorders such as 3.3 *Chronic cluster headache* or 4.10 *New daily persistent headache*.

The diagnosis of 8.2 *Medication-overuse headache* is extremely important clinically. Epidemiological evidence from many countries indicates that more than half of people with headache on 15 or more days/month have 8.2 *Medication-overuse headache*. Clinical evidence shows that the majority of patients with this disorder improve after discontinuation of the overused medication, as does their responsiveness to preventative treatment. Simple advice on the causes and consequences of 8.2 *Medication-overuse headache* is an essential part of its management and can be provided with success in primary care. An explanatory brochure is often all that is necessary to prevent or discontinue medication overuse. Prevention is especially important in patients prone to frequent headache.

The behaviour of some patients with 8.2 *Medication-overuse headache* is similar to that seen with other drug addictions, and the Severity of Dependence Scale (SDS) score is a significant predictor of medication overuse among headache patients.

In the criteria below for the various subtypes, the specified numbers of days of medication use considered to constitute overuse are based on expert opinion rather than on formal evidence.

It is recognized that cross-sectional population-based studies estimating the prevalence of 8.2 *Medication-overuse headache* can record the coexistence in participants of headache on ≥15 days/month and overuse of drugs for acute and/or symptomatic treatment of headache but are rarely able to collect information on earlier headache, on duration of the current headache or medication overuse, and/or that might support a presumption of causation. In consequence, either or both of criteria A and B may not be entirely fulfilled. Provided that criteria are not fulfilled for another ICHD-3 diagnosis, such cases should be reported as *probable medication-overuse headache* (pMOH), although ICHD-3 does not provide a coding for this

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