Synopsis – Trial 19766N

Trial 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

Investigators

7 principal investigators at 7 sites in 1 country

Trial Sites

7 sites in the United States

Publication

None

Trial Period

First participant first visit – 04 March 2022 (the date when the first *Informed Consent Form* was signed)

Trial terminated – 06 February 2023

Last participant last visit – 14 April 2023 (the date of the last protocol-specified contact with any participant)

Objectives and Endpoints

This exploratory study had multiple objectives within the overall aim to examine how eptinezumab compares to other advanced preventive medications in a real-world community setting. These objectives included exploring the comparative effectiveness on PRO including PI-MBS, good days and bad days, QOL, and HRU. We planned to evaluate the impact of mediating factors including monthly migraine days, early prevention, and perceived stress on these outcomes. Finally, we planned to assess participant preferences for shared decision-making, patient satisfaction with their treatment, and confidence in managing their own health.

Specifically, the objectives of EVEC included:

1. **PI-MBS:** This was planned to be measured on a daily basis using the PI-MBS. Participant would select the symptom that they find most impairs them at the time of

reporting and rate the severity of that symptom. The difference between randomization groups was planned to be evaluated at 4, 12, and 24 weeks following randomization.

2. **Good day/bad day scale:** The participant would 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 was planned to be evaluated at 4, 12, and 24 weeks following randomization.
3. **EQ-5D-5L:** The participant would complete the EQ-5D questionnaire on a weekly basis to indicate their preference for their current health state. The difference between randomization groups was planned to be evaluated at 4, 12, and 24 weeks following randomization.
4. **HRU:** The participant would report their use of health services and medications on a daily basis using the smartphone app. The difference over time between the randomization groups was planned to be evaluated at 4, 12, and 24 weeks following randomization.
5. **HIT-6:** The participant would report the impact of headache on their quality of life using the 6-item HIT-6 scale. This would be done each month. The difference in change over time between randomization groups was planned to be evaluated at 4, 12, and 24 weeks following randomization.
6. **MIDAS:** The participant's perception of their degree of disability would be evaluated by the MIDAS scale. This would be measured quarterly. The difference in change over time between randomization groups was planned to be evaluated at 4, 12, and 24 weeks following randomization.
7. **TSQM:** The participants' reported satisfaction with treatment would be evaluated at the study closeout visit (i.e., visit #9). This was planned to 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 was planned to be compared between the randomization groups from baseline to Week 24.

Additional Outcomes (not between group comparisons)

1. **SDM-Q-9:** The participant would report their satisfaction with shared decision-making using SDM-Q-9 following education on treatment options. This was planned to be evaluated at Screening and Week 24.
2. **SURE Scale:** The participant would report their readiness to decide or determine their comfort with their treatment decision using the SURE scale. This was planned to be evaluated at Screening.
3. **PAM-10:** The participant would report their knowledge, skills, and confidence to manage their health condition via the PAM-10. This was planned to be evaluated at Screening and Weeks 12 and 24.
4. **ISS:** Participants initiating therapy on eptinezumab would describe the satisfaction with care with the ISS at baseline and Week 12.

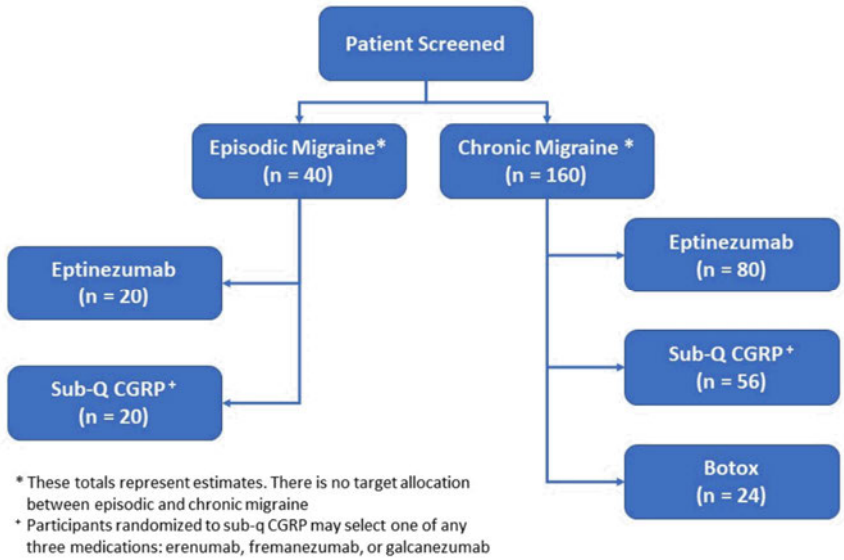
Exploratory Objective	Endpoints
• To examine how eptinezumab compares to other advanced preventive medications in a real-world community setting.	This was a pilot study; as such, there was no primary objective. All objectives were exploratory. • Exploratory endpoints: – PI-MBS – Good day/bad day scale – EQ-5D-5L – HRU – HIT-6 – MIDAS – TSQM – Medication switching – SDM-Q-9 – SURE scale – PAM-10 – ISS
HIT-6 = 6-item Headache Impact Test; HRU = health resource utilization; ISS = Infusion Satisfaction Survey; MIDAS = Migraine Disability Assessment; PAM-10 = 10-item Patient Activation Measure; PI-MBS = Patient-identified most bothersome symptom; SDM-Q-9 = 9-item Shared Decision-Making Questionnaire; SURE = Sure of myself, Understand information, Risk-benefit ratio, Encouragement; TSQM = Treatment Satisfaction Questionnaire for Medication.	

Trial Methodology

EVEC was 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.

This study was designed in accordance with the *Declaration of Helsinki*[1] and in compliance with *Good Clinical Practice*[2] and applicable regulatory requirements. This was 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 had a history of >8 migraine days in 2 of the past 3 months prior to enrollment and have documented failure to at least 2 previous oral preventive treatments per the AHS Consensus Statement. Participants were recruited from sites that were capable of administering all therapies within the study in an outpatient setting. After giving consent, participants were classified as having either EM or CM per ICHD-3 guidelines based on their medical history. Within these strata, the participants with EM were randomized to eptinezumab or SC CGRP (i.e., erenumab, fremanezumab, or galcanezumab) in a 1:1 manner. Those with CM were randomized to eptinezumab, SC CGRP, or onabotulinumtoxinA in a 3:2:1 manner. Participants randomized to the SC CGRP injectable arm were 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



The following methodology describes what was planned. Participants would be followed prospectively for 24 weeks, and a follow-up phone call would be made to each participant 8 weeks after study completion at the End of Treatment/Early Termination Visit. At Screening, all participants would be trained to use an eDiary (as a smartphone app) that would 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 would also prompt participants 3 times each week to report any interactions with the healthcare system (e.g., office visits, emergency room visits/urgent care visits, hospitalizations, prescription medication). The site staff would 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 medications. QOL data and HRU data would be collected from participants via the smartphone app and from the site staff via the electronic data capture. QOL assessments include the EQ-5D-5L, HIT-6, good day/bad day scale, and MIDAS. Participants would 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 would be measured using the SDM-Q-9 (at Screening and Week 24). Participant confidence in the treatment selection they made would be measured via the SURE test (at the Screening Visit only). Participants' knowledge, skill, and confidence in managing their own health would be assessed at Screening, Week 12 and Week 24 via the PAM-10 instrument. Participants' satisfaction with their treatment experience would be assessed at Week 24 via the TSQM. The SDM-Q-9, SURE test, PAM, and TSQM would be completed electronically.

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

Due to the challenges of recruiting patients who are naïve to previous use of advanced preventive medication, which reflected the fact that many anti-CGRP-eligible patients already received an anti-CGRP, the study was terminated early as it represented limited scientific value. All subjects ongoing at the time of the study termination notice were required to conduct an early termination visit within 2 weeks of their site being notified of study termination. After the early termination visit was completed, sites were required to conduct a safety follow-up visit within 56 days (±5 days) of the early termination visit. No further data were collected on subjects who were in Screening at the time of the study termination notification. All subjects in Screening and enrolled in the study at the time of the termination notification were given the option to continue the study treatment they were randomized to; however, no additional data were collected on the subjects after the early termination visit and safety follow-up visit.

Number of Participants Planned

200 participants were planned for enrollment.

Diagnosis and Main Selection Criteria

Adult participants with at least 8 or more migraine days per month, in 2 of the last 3 months prior to enrollment, who were being seen at participating sites, who:

- were ≥18 years of age.
- had a diagnosis of migraine per ICHD-3 guidelines at least 12 months prior to Screening.
- had a history of ≥8 migraine days/month in 2 of the previous 3 months as confirmed by the treating physician through medical records.
- had a history of failure of at least 2 previous oral migraine preventive treatments as defined in the AHS Consensus Statement.
- were able to able to understand the clinical description of treatment options and have the capability to participate fully in making their treatment preferences known.
- had no restriction in venous access that would restrict the ability to receive infusion treatment.
- were willing and capable of completing daily reports and other PRO measures using a smartphone-based app.
- had their own smartphone or tablet and agree to allow the study app to be downloaded to it.
- had no previous use of any of the study drugs. Participants who had used oral CGRP inhibitors atogepant or rimegepant for prevention were also excluded.

IMPs, Doses and Modes of Administration, Batch Numbers

Note: In this study, all IMPs were commercially available drugs.

IMPs used in this study included (Table 1):

- Eptinezumab – 100 mg/mL or 300 mg/mL solution, as per the product label at baseline and at week 12; IV.

- OnabotulinumtoxinA – dosing as per product label for the treatment of migraine at baseline and at week 12; SC.
- Erenumab – 70 mg or 140 mg every 28 days, as per the product label; SC.
- Fremanezumab – 225 mg every 28 days or 675 mg every 84 days, as per the product label; SC.
- Galcanezumab – 240 mg loading dose as applicable followed by doses of 120 mg every 28 days, as per the product label; SC.

Medications for this study were obtained using pharmacy voucher cards, which were provided by Lundbeck. These cards allow for study-specific advanced preventive medications to be obtained from the local pharmacy without cost; the voucher cards were not used for any other medications including acute migraine treatments. Study-specific voucher cards were used to cover the cost of any study-specific advanced preventive medications, provided they are used per the label approved by the Food and Drug Administration. Batch numbers were not available.

Table 1. Duration of treatment

IMP	Dose	Duration	Frequency
Eptinezumab	100 mg/mL or 300 mg/mL	12 weeks	Quarterly
OnabotulinumtoxinA	Per product label	12 weeks	Quarterly
Erenumab	70 mg or 140 mg	6 months	Monthly
Fremanezumab	225 mg	6 months	Monthly
Fremanezumab	675 mg	3 months	Quarterly
Galcanezumab	240 mg loading dose	Once	Once
Galcanezumab	120 mg	5 months	Monthly

IMP = investigational medicinal product.

Participants were allowed to switch to an alternative preventive treatment after they received their initial treatment with the medication to which they were randomized. For participants who received eptinezumab or onabotulinumtoxinA as their initial treatment and elected to switch to an SC anti-CGRP injectable (i.e., erenumab, fremanezumab or galcanezumab), they could not do so until Week 12 (Visit 5), after the treatment window for their initial treatment had ended. Participants who received eptinezumab or onabotulinumtoxinA at Week 12 (Visit 5) were not permitted to switch their treatment for the remaining duration of the study. Participants initially treated with an SC anti-CGRP injectable could only switch to eptinezumab, or onabotulinumtoxinA at Week 12 (Visit 5) due to the design of the study. However, these participants could switch to another SC anti-CGRP injectable medication at any time, once the treatment window for their previous injection had ended. No changes in treatment were permitted after Visit 7 and all changes in treatment were to be documented in the electronic case report form.

Statistical Methodology

The following describes the statistical methodology planned in the protocol. Due to trial termination, only descriptive statistics of the enrolled patients were completed. See protocol for additional details of the planned efficacy analyses.

The following analysis sets were planned for use to analyze and present the data:

- RAND – The eligible population was planned to be composed of all participants who gave 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 would be considered in the analysis sample. All data collected from participants who withdrew from the study would be collected up until the date of the withdrawal.
- SAF – The safety population was planned to consist of all participants who received treatment.

Safety analysis plan: Adverse event and adverse drug reaction data would be tabulated and reported. No additional analyses were planned.

Sample size and power: EVEC was 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, based on the PROMISE trials and phase IIIa studies of other medications evaluated in EVEC, we expected to see a 2-day difference in the average monthly migraine days at 13 weeks and a standard deviation of 6.0 around this measure. Based on this, we expected to have 83% power to assess this difference with a sample size of 200 participants, assuming no significant loss to follow-up.

A Statistical Analysis Plan describing the handling of data issues and the planned statistical analyses in more detail was prepared by Lundbeck. Due to study termination, statistics only consisted of descriptive statistics for the patient population, stratified by treatment groups.

Participant Disposition and Analysis Sets

- A total of 39 individuals were screened. Seven patients failed Screening.
- A total of 32 individuals were eligible for enrollment and randomized (RAND).

Inclusion criteria 6 was “Have a history of failure of at least 2 previous oral migraine preventive treatments as defined in the AHS Consensus Statement.[3]” Of the 32 eligible patients, a total of 11 unique patients had one or more registered previous oral preventive treatment failure not listed in the AHS Consensus Statement. These included butalbital, cyclobenzaprine HCL, eletriptan, ergotamine, gabapentin, sumatriptan, verapamil, and zolmitriptan.

- 31 participants were treated (SAF); 1 patient who was randomized to eptinezumab withdrew consent prior to their first dose. Four patients switched treatment.
- 26 participants were enrolled in the study at the end of data entry on 14 April 2023. These participants were withdrawn from the study at termination. Six participants withdrew from the study prior to study termination.

Table 2. Randomization and withdrawals by Treatment

	Total	Erenumab	Fremanezumab	OnabotulinumtoxinA	Galcanezumab	Eptinezumab
Participants randomized, n (%)	32	3 (9.4)	2 (6.2)	2 (6.2)	8 (25.0)	17 (53.1)
Participants randomized (RAND):						
Participants completed	0	0	0	0	0	0
Participants withdrawn	32	3	1	1	8	17
Primary reason for withdrawal:						
Study terminated	26	2	2	2	5	15
Withdrew consent	2	0	0	0	1	1
Lost to follow-up	4	1	0	0	2	1
Analysis sets:						
RAND	32	3 (9.4)	2 (6.2)	2 (6.2)	8 (25.0)	17 (53.1)
SAF	31	3 (9.7)	2 (6.5)	2 (6.5)	8 (26.7)	16 (51.6)
Note: 1 patient withdrew consent prior to receiving treatment (randomized to eptinezumab); this patient did not request their data be removed from the study.						

Table 3. Treatment switching

Site	Subject	Screening date	Baseline date	Drug randomized to	Treatment switched to	Date of treatment switch
[redacted]				Galcanezumab	Fremanezumab 225 mg	[redacted]
				Eptinezumab	Fremanezumab 675 mg	
				Eptinezumab	Fremanezumab 225 mg	
				Eptinezumab	Fremanezumab 675 mg	

Demographics and Baseline Characteristics of the Trial Population

As the study was terminated early, results for the 32 enrolled patients were reported using the Screening Visit as the reference time point, and not the Baseline Visit, as not all patients had a Baseline Visit date.

The mean (SD) age of the 32 enrolled patients was 41.2 (12.1) years. Most patients were female (n=28; 87.5%), married (n=13; 40.6%), not Hispanic or Latino (n=23; 71.9%), White (n=21; 65.6%), and were employed full time (n=20; 62.5%). All patients reported a zip code. More patients were classified as EM (n=18; 56.2%) than CM (n=14; 43.8%). Mean (SD) number of migraine days in the first, second, and third month prior to Screening were 11.6 (4.9), 12.2 (4.5), and 11.8 (5.3), respectively. Mean (SD) age at onset of first migraine was 24.2 (11.5) years of age. Family medical history of migraine was reported in most patients (n=19; 61.3%) including in mother (n=11; 57.9%), father (n=2; 10.5%), brother (n=4; 21.1%), or sister (n=8; 42.1%).

The 3 most common first oral preventive treatments patients had previously failed included topiramate (n=12; 37.5%), gabapentin (n=4; 12.5%), and amitriptyline (n=3; 9.4%). The 3 most common second oral preventive treatment patients had previously failed included topiramate (n=9; 28.1%), duloxetine (n=5; 15.6%), and gabapentin (n=3; 9.4%). Migraine-related medications used in >10% of patients included topiramate (n=23; 71.9%), gabapentin (n=8; 25.0%), ibuprofen (n=8; 25.0%), duloxetine (n=6; 18.8%), amitriptyline (n=5; 15.6%), paracetamol (n=5; 15.6%), propranolol (n=5; 15.6%), acetylsalicylic acid, caffeine, paracetamol (n=4; 12.5%), metoprolol (n=4; 12.5%), and sumatriptan (n=4; 12.5%). Medications in use at the Screening Visit in >10% of patients included ibuprofen (n=7; 21.9%), paracetamol (n=5; 15.6%), vitamins (not otherwise specified) (n=4; 12.5%), and sertraline (n=4; 12.5%). Habitual cigarette smoking or vaping was reported as current in 2 patients each (6.2%), former in 7 (21.9%) and 2 (6.2%), and never in 23 (71.9%) and 29 (90.6%) patients, respectively. No patients reported habitual smokeless tobacco use.

In addition to the inclusion criteria of migraine, medical and psychiatric conditions occurring in >10% of patients included anxiety (n=11; 34.4%); asthma, depression (each n=6; 18.8%); cesarean delivery, drug hypersensitivity, gastroesophageal reflux disease, hypertension, seasonal allergy, headache (each n=5; 15.6%); cholelithiasis, nausea, obesity, endometriosis, insomnia, irritable bowel syndrome, and attention deficit hyperactivity disorder (each n=4; 12.5%). Cardiac history included cardiac murmur, sinus tachycardia, irregular heart rate, and ventricular extrasystoles each in 1 patient (3.1%). Cardiovascular history included hypertension (n=5; 15.6%), cardiac murmur, cerebrovascular accident, sinus tachycardia, irregular heart rate, and ventricular extrasystoles (each n=1; 3.1%).

Efficacy Results

The study was terminated early, and no efficacy analysis was conducted.

Safety Results

SAF consisted of all patients that received treatment (n=31). The AE incidence is summarized below for the entire trial. There were no deaths and no SAEs in the study. There were 22 non-serious AEs in total.

In the eptinezumab group, 4 of 16 participants experienced one or more non-serious AEs. There were no AEs reported by more than one participant in the eptinezumab group.

Table 4. Individuals with one or more AEs

Individuals with one or more AEs				
Erenumab (n=3)	Fremanezumab (n=2)	OnabotulinumtoxinA (n=2)	Galcanezumab (n=8)	Eptinezumab (n=16)
0	0	0	6	4

Four individuals switched treatment (1 patient from galcanezumab to fremanezumab; 3 patients from eptinezumab to fremanezumab). No AE occurred after any treatment switch. In summary, no safety issues were identified from patients taking eptinezumab or the comparator drugs. No significant safety issues were observed.

Table 5.Adverse Events by randomization group

Preferred term, n	Erenumab (n=3)	Fremanezumab (n=2)	OnabotulinumtoxinA (n=2)	Galcanezumab (n=8)	Eptinezumab (n=16)
Attention deficit hyperactivity disorder	0	0	0	1	0
Bronchitis	0	0	0	0	1
COVID-19	0	0	0	1	0
Ear infection	0	0	0	0	1
Facial pain	0	0	0	0	1
Gastric ulcer	0	0	0	0	1
Gastroenteritis viral	0	0	0	0	1
Influenza	0	0	0	0	1
Migraine	0	0	0	1	0
Neck pain	0	0	0	0	1
Oropharyngeal pain	0	0	0	0	1
Pelvic floor dysfunction	0	0	0	0	1
Pruritus	0	0	0	0	1
Sinusitis	0	0	0	2	0
Swelling face	0	0	0	0	1
Upper respiratory tract infection	0	0	0	1	1
Urinary tract infection	0	0	0	1	1
Vulvovaginal candidiasis	0	0	0	0	1
Vulvovaginal mycotic infection	0	0	0	0	1
Total number of events	**0**	**0**	**0**	**7**	**15**

Overall Summary

EVEC was an exploratory study to examine how eptinezumab compared to other advanced preventive medications in patients with EM or CM in a real-world community setting. A total of 32 patients were enrolled and randomized. Due to the challenges of recruiting patients who are naïve to previous use of advanced preventive medication and the reduction in scientific value of the study based on the projected timeline to complete enrollment, the study was terminated early. No efficacy analyses were completed; no significant safety issues were observed.

Report Date

14 December 2023

This trial was conducted in compliance with *Good Clinical Practice*.