CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

ERENUMAB (AIMOVIG)

(Novartis Pharmaceuticals Canada Inc.)

Indication: For prevention of migraine in patients who have had at least four migraine days monthly

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Abbreviations

AE	adverse event
ASC-12	12-item Allodynia Symptom Checklist
ATP	active treatment phase
BDI-II	Beck Depression Inventory – II
CDR	CADTH Common Drug Review
CI	confidence interval
CGI-I	Clinical Global Impression – Improvement
CGRP	calcitonin gene-related peptide
CMWPC	clinically meaningful within-patient change
CrI	credible interval
DBTP	double-blind treatment phase
EAS	efficiency analysis set
EF	emotional function
EQ-5D	EuroQol 5-Dimensions
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
ERE	erenumab
FAS	full analysis set
HIT-6	six-item Headache Impact Test
HRQoL	health-related quality of life
ICER	Institute for Clinical and Economic Review
ICHD-3	International Classification of Headache Disorders, third edition
ITC	indirect treatment comparison
ITT	intention-to-treat
LS	least squares
MCID	minimal clinically important difference
MD	mean difference
MIDAS	Migraine Disability Assessment Scale
MHD	monthly headache day
MMD	monthly migraine day
MPFID	migraine physical function impact diary
MSQ	Migraine-Specific Quality of Life Questionnaire
OLTP	open-label treatment phase
OR	odds ratio
PGIC	Patient Global Impression of Change

PGI-S	Patient Global Impression of Severity
PROMIS	Patient-Reported Outcomes Measurement Information System
RCT	randomized controlled trial
RFP	role function – preventive
RFR	role function – restrictive
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
WDAE	withdrawal due to adverse event

Drug	Erenumab (Aimovig)
Indication	For prevention of migraine in patients who have had at least four migraine days monthly
Reimbursement request	For prevention of migraine in adults with at least eight migraine days monthly and who have failed, are intolerant of, or have a contraindication to at least two migraine-prevention therapies
Dosage form(s)	Subcutaneous injection
NOC date	August 1, 2018 (70 mg/mL autoinjector), and April 11, 2019 (140 mg/mL autoinjector)
Sponsor	Novartis Pharmaceuticals Canada Inc.

Executive Summary

Introduction

Patients who suffer from migraine report migraine attacks that are characterized by severe headache (throbbing and diffuse pain) accompanied by other symptoms such as nausea and/or vomiting, dizziness, sensory hypersensitivity, and tingling or numbness in the extremities and/or face. Migraine can occur with or without aura, and the aura is characterized by a wide range of primarily neurological symptoms that can affect vision, speech, sensations, and muscle strength. Cognitive function can also be affected. In Canada, at least 2.6 million adult females and almost 1 million adult males suffer from migraine, although this may be an underestimate, as not everyone who suffers from migraine seeks medical help and therefore receives an official diagnosis.[1,2] Approximately three-quarters of patients experiencing migraine report impaired function, and one-third require bed rest during a migraine attack.[3]

There are two approaches to treating migraine; management of acute attacks and prophylaxis. The latter is typically only considered for those with more frequent migraines (more than four migraine days per month).[1] Many therapies used for migraine prophylaxis are used off-label, as they lack an official indication for this purpose from Health Canada. Topiramate is indicated in adults for the prophylaxis of migraine headache, and onabotulinum toxin A has a Health Canada indication for prophylaxis of chronic migraine (more than 15 headache days per month) and was previously reviewed by CADTH Common Drug Review (CDR). Aside from onabotulinum toxin A, the main categories of drugs used for migraine prophylaxis are antidepressants (tricyclics, serotonin-norepinephrine reuptake inhibitors), anticonvulsants (various), cardiovascular drugs (beta-blockers, calcium-channel blockers, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers), as well as pizotifen. There is a lack of understanding of how these drugs work in migraine prophylaxis. While they are generally safe and well-established drugs, they all have various tolerability issues for patients, and this is important, given that they are to be used on a chronic basis in migraine prophylaxis.

Erenumab is a monoclonal antibody that binds to and inhibits the calcitonin gene-related peptide (CGRP) receptor, which has been implicated in the pathophysiology of migraine, based on CGRP's vascular effects and the effects on transmission of pain signals in the central nervous system. It is administered by subcutaneous injection at a dosage of either 70 mg or 140 mg once monthly. It is indicated by Health Canada for the prevention of migraine in patients who have had at least four migraine days monthly. The sponsor

requests listing erenumab for prevention of migraine in adults with at least eight migraine days monthly and who have failed, are intolerant of, or have a contraindication to at least two migraine prevention therapies.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of erenumab for the prevention of migraine in adults who have at least four migraine days per month.

Results and Interpretation

Included Studies

Four international double-blind, randomized, and placebo-controlled trials funded by the sponsor were included in this review. STRIVE (N = 955, 1:1:1 ratio, erenumab 70 mg, erenumab 140 mg, and placebo), LIBERTY (N = 246, 1:1 ratio, erenumab 140 mg and placebo) and ARISE (N = 577 1:1 ratio, erenumab 70 mg and placebo) were conducted in patients with episodic migraine, defined as an average of between at least four and less than 15 migraine days per month, and less than 15 headache days per month, for the three months prior to screening. Study 295 studied patients with chronic migraine, defined as at least eight monthly migraine days (MMDs) and at least 15 monthly headache days (MHDs). In Study 295, patients received one of erenumab 70 mg (N = 191), erenumab 140 mg subcutaneously (N = 190), or matching placebo (N = 286). STRIVE had a 24-week double-blind treatment phase (DBTP) while the other studies involved 12-week double-blind phases. The primary outcome of STRIVE, ARISE, and Study 295 was the change from baseline in MMDs, while in LIBERTY the primary outcome was the proportion of patients who achieved a 50% reduction in MMDs. The proportion of patients with a 50% reduction in MMDs was a secondary outcome in other trials, as were the change from baseline in migraine physical function impact diary (MPFID) scores, Migraine-Specific Quality of Life Questionnaire (MSQ) results, MMDs requiring acute treatment, and cumulative monthly headache hours. The screening and diagnosis of migraine (with visual, sensory, speech and/or language, retinal, or brainstem aura or without aura) in the four studies were based on a prior history of various symptoms according to the third edition of the International Classification of Headache Disorders (ICHD-3).

Key critical appraisal issues include the relatively short-term follow-up (12 or 24 weeks of DBTP), given that this is a first-in-class drug with a novel mechanism of action. The lack of an active comparator is also a limitation, as is the fact that health-related quality of life (HRQoL) was only assessed as an exploratory outcome in the included trials. The sponsor did not perform an intention-to-treat (ITT) analysis as part of its primary analysis of continuous outcomes, and instead used imputation in sensitivity analyses, which were consistent with the results of the primary analysis.

Efficacy

In general, there were one to two days of reduction out of eight to nine MMDs compared to placebo during a three- to six-month treatment period among patients with episodic migraine. The reduction was more evident (2.5 days on average out of 18 MMDs at baseline) in patients with chronic migraine in Study 295. There was no substantial difference in the mean reduction of MMDs between erenumab 70 mg and 140 mg as shown in the four included studies. A validated minimum clinically important difference (MCID) for changes in migraine days was not identified, although some reports suggest a reduction of one day per month is clinically meaningful.[4] The clinical expert consulted by CDR for this

review suggested these reductions in migraine frequency may be clinically significant. The included studies also assessed the percentage of patients who experienced a 50% reduction in MMDs, and consistently more erenumab-treated patients compared with placebo patients reached this threshold. The results of subgroup analyses of reduction in migraine frequency generally appeared to remain statistically significant regardless of baseline MMDs, use of prophylaxis, number of failed prophylaxes, or whether patients exhibited medication overuse. There was an indication that in chronic migraine, patients who had previously been treated with onabotulinum toxin A did not respond as well as those who had not been similarly treated; however, this analysis was limited by a small sample size.

Erenumab also reduced the use of acute medication for episodic migraine by 0.6 to 1.5 days from a baseline of three to five days over three to six months and by 2 to 2.5 days from a baseline of nine days over three months in chronic migraine.

Change in cumulative monthly headache hours was a secondary outcome of Study 295. The cumulative number of headache hours was reduced in all groups in Study 295, and the difference in reduction was not statistically significant for erenumab 70 mg versus placebo, with a least squares (LS) mean difference (MD) of −9.54 hours (95% confidence interval [CI], −26.98 to 7.90; P = 0.28) but was statistically significant at the erenumab 140 mg dose versus placebo (LS MD = −19.31 hours; 95% CI, −36.71 to −1.92; P = 0.030).

In the STRIVE study, MPFID domain scores were reported as secondary outcomes. The mean monthly physical impairment domain score was reduced (improved) from baseline to months 4, 5, and 6 in all three groups, and this reduction was statistically significant versus placebo in both the erenumab 70 mg (LS MD = −1.86; 95% CI, −2.95 to −0.77; P < 0.001) and the erenumab 140 mg groups (LS MD = −2.43; 95% CI, −3.51 to −1.35; P < 0.001). The mean monthly impact on everyday activities score was reduced from baseline to months 4, 5, and 6 in all three groups, and this reduction was statistically significant versus placebo in the erenumab 70 mg (LS MD = −2.22; 95% CI; −3.28 to −1.16; P < 0.001) and the erenumab 140 mg groups (LS MD = −2.57; 95% CI, −3.62 to −1.51; P < 0.001). [redacted] Given that these MCIDs have not been independently validated and come with wide ranges, and that clinical significance was not met in ARISE, the clinical significance of these differences between erenumab and placebo is uncertain. Changes in these domains of the MPFID were also secondary outcomes in LIBERTY and ARISE, and the findings were similar to STRIVE, in that statistical significance was present but clinically significant differences between erenumab and placebo were found only in LIBERTY and not in ARISE. The MPFID was only assessed as part of a substudy of Study 295, for the purpose of validating the instrument.

Assessments of HRQoL in the included studies were made using the MSQ instrument, although only as an exploratory outcome. The improvements in MSQ were generally consistent in erenumab 70 mg and 140 mg during a three- to six-month treatment period, as were the magnitude of changes over placebo in STRIVE and ARISE.

Numerous other instruments for measuring response to treatment of migraine were assessed as exploratory outcomes across the various trials, including the six-item Headache Improvement Test (HIT-6), Migraine Disability Assessment Scale (MIDAS), 12-item Allodynia Symptoms Checklist (ASC-12), Patient-Reported Outcomes Measurement

Information System (PROMIS) Pain Interference Scale, and Beck Depression Inventory – II (BDI-II). As these were exploratory outcomes, statistical significance cannot be determined.

[redacted] A published network meta-analyses of chronic migraine found that erenumab was not favoured over topiramate or onabotulinum toxin A with respect to MMDs, use of acute medications, and all-cause discontinuation. In episodic migraine, erenumab was favoured only over topiramate, and not over propranolol or amitriptyline, for reducing MMDs. For reducing acute medication, only the higher dose of erenumab was favoured over the low dose of topiramate (50 mg). For all-cause discontinuations, both doses of erenumab were favoured over the higher dose of topiramate (200 mg) but not over any other comparator.

Harms

No deaths were reported in any of the included studies.

Adverse events (AEs) occurred in the STRIVE study in 57% and 56% of patients in erenumab groups and in 63% of those on placebo. In Study 295, AEs occurred in 44% and 47% of erenumab patients and in 39% of patients on placebo. In LIBERTY, AEs occurred in 55% of erenumab patients and 54% of those on placebo, while in ARISE they were reported in 48% of erenumab patients and 55% of those on placebo.

Serious adverse events (SAEs) were reported in 1% to 3% of patients and there were no clear and consistent differences between groups in any of the included studies. In STRIVE, 2.5% of erenumab 70 mg patients and 1.9% of erenumab 140 mg patients versus 2.2% of placebo patients had an SAE during the 24-week DBTP. In Study 295, SAEs occurred in 3.2% of erenumab 70 mg patients and 1.6% of erenumab 140 mg patients versus 2.5% of placebo patients during the 12-week DBTP. In LIBERTY, 1.7% of erenumab 140 mg versus 0.8% of placebo patients had an SAE, while in ARISE 1.1% of erenumab 70 mg and 1.7% of placebo patients had an SAE during the 12-week DBTP of these studies.

In STRIVE, 2.2% of patients in each of the erenumab groups withdrew due to an AE, versus 2.5% of patients in the placebo group. In Study 295 there were no withdrawals due to AEs among erenumab 70 mg patients, but 1.1% of patients in the 140 mg group and 0.7% of patients on placebo withdrew due to an AE. In LIBERTY there were no withdrawals due to AEs in the erenumab 140 mg group and 0.8% of patients in the placebo group withdrew due to an AE, while in ARISE 1.8% of patients in the erenumab 70 mg group and 0.3% of patients in the placebo group withdrew due to an AE.

Hypersensitivity reactions were a notable harm in this review, and these events were infrequent across the included studies. One case of hypersensitivity related to injection was reported in each of the erenumab and placebo groups in STRIVE, and one case was reported in the erenumab 70 mg group in ARISE. Other injection-related events, such as erythema, pain, and pruritus, were reported, with no clear and consistent differences between groups within studies. Vascular-related AEs were also a notable harm, based on the vascular effects of CGRP, but no clear or consistent differences were reported in hot flushes, hypertension, or hypotension between groups in any of the studies.

Potential Place in Therapy

The following is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

The clinical expert consulted by CDR noted that all of the currently available medications used for the prevention of migraine, with the exception of erenumab, were meant for use in other conditions (e.g., hypertension, depression, epilepsy), and only through their use in those conditions in people who had concomitant migraine has it been learned that they may be used for migraine prophylaxis. Patients with migraine as a group seem to be sensitive to medication AEs as they are often intolerant of the adverse effects of these medications — e.g., hypotension caused by beta-blockers, mental slowing caused by topiramate, or weight gain caused by amitriptyline. Because many are not able to take these medications at high enough doses for sufficiently long to achieve prophylactic benefit, they stop therapy prematurely. The clinical expert also noted that less than 30% of patients will respond to their first prophylactic treatment.[5,6] This means that patients often try multiple medications for three to nine months before being able to determine whether the drugs are effective. Consequently, and despite the availability of several drug options with different mechanisms of action, the need for drugs that can effectively prevent migraine with minimal adverse effects remains.

When assessing the effect of medications to prevent migraine, clinically meaningful outcomes include improvements in HRQoL, return to baseline functioning in a variety of domains (e.g., work, school, interpersonal, and recreational), reduced caregiver burden stemming from shorter migraine attacks, reduced frequency and severity of migraine attacks, and reduced overall number of headache days (typically captured with a patient's headache diary). Adverse effects are closely monitored; a medication with a minimal adverse effect profile would be expected to improve patient adherence to treatment and quality of life.

The clinical expert consulted by CDR indicated that most patients with more than four but fewer than 15 headache days per month would be prescribed an oral medication (e.g., an antihypertensive) as initial therapy. For patients with more than 15 headache days per month, the choices are typically between three agents: topiramate, onabotulinum toxin A, and erenumab. Erenumab is generally used as a second- or third-line treatment at present. However, because of its relatively specific mechanism of action and its seemingly few adverse effects, erenumab may be used earlier as a first-line therapy for some patients, including for those with more than four but fewer than 15 MMDs.

The clinical expert noted that it is not possible at present to identify patients who are most likely to respond to any of the available preventive therapies, including erenumab. Therapy discontinuation would be considered if:

- there was no effect after three months at the highest tolerated dose, or
- there was loss of effect for three consecutive months, or
- a patient has four or fewer headache days per month for at least nine months, and these headaches can be readily treated with an abortive therapy (i.e., triptan or a nonsteroidal anti-inflammatory drug).

How to discontinue erenumab is unclear; sudden discontinuation may increase the likelihood of rebound headaches, and an evidence-based protocol for slower discontinuation (e.g., increasing the dosing interval incrementally until discontinuation can be achieved) is not yet available.

Clinicians would likely assess response within three months of starting medication and at two three-month intervals thereafter. An annual or biannual assessment could be performed if the patient responds well and has minimal or no side effects.

The clinical expert indicated that it would be preferable for a patient receiving erenumab to be followed by a specialist in headache or neurology; however, this is likely impractical.

Conclusions

Results from the four included double-blind, randomized controlled trials (RCTs) suggest that both approved doses of erenumab reduce the frequency of monthly migraine and use of acute migraine medication versus placebo in patients with episodic migraine (defined as at least four to fewer than 15 MMDs) and chronic migraine (more than eight MMDs). These improvements in frequency of migraine were accompanied by functional improvement assessed by the MPFID in patients with episodic migraine; however the clinical significance of these improvements is uncertain. An important outcome for patients, HRQoL, was only assessed as an exploratory outcome, and therefore the statistical significance cannot be determined. No clear safety issues emerged from the included studies, and no clear and consistent tolerability issues were identified, although the studies were not powered to assess harms. Given the novel mechanism of erenumab, longer-term comparative studies are warranted. Indirect comparisons, both sponsor-submitted and published, did not suggest any advantage of erenumab compared to onabotulinum toxin A with respect to efficacy or persistence with therapy in patients with chronic migraine. A possible advantage of erenumab versus topiramate in reducing episodic migraine frequency was indicated.

Table 1: Summary of Results (STRIVE)

	STRIVE		
	ERE 70 mg (N = 317)	ERE 140 mg (N = 319)	Placebo (N = 319)
Migraine frequency			
Change from baseline to last 3 months in mean MMDs			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI)[a]	**70 mg:** −1.40 (−1.88 to −0.92); P < 0.001 **140 mg:** −1.85 (−2.33 to −1.37); P < 0.001		
Patients with 50% reduction in mean MMDs during the last 3 months, n (%)	135 (43.3)	159 (50.0)	84 (26.6)
Common odds ratio (95% CI)[b]	**70 mg:** 2.13 (1.52 to 2.98); P < 0.001 **140 mg:** 2.81 (2.01 to 3.94); P < 0.001		
Medication use			
Change from baseline in monthly acute migraine-specific medication treatment days, months 4, 5, and 6			
Mean (SD) baseline	3.24 (3.40)	3.42 (3.48)	3.43 (3.43)
Mean (SE) change from baseline at months 4, 5, and 6	−1.12 (0.13) N = 296	−1.64 (0.13) N = 302	−0.26 (0.14) N = 289
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSMs vs. placebo (95% CI)[a]	**70 mg:** −0.94 (−1.23 to −0.64); P < 0.001 **140 mg:** −1.42 (−1.71 to −1.12); P < 0.001		
Functional impact (MPFID)			
Change from baseline in mean monthly average physical impairment domain score, MPFID			
Mean (SD) baseline	12.56 (9.65)	11.98 (8.95)	12.24 (9.43)
Change (SE) from baseline, months 4, 5, and 6	−4.42 (0.48) N = 296	−4.83 (0.46) N = 302	−2.65 (0.48) N = 289
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSMs vs. placebo (95% CI)[a]	**70 mg:** −1.86 (−2.95 to −0.77); P < 0.001 **140 mg:** −2.43 (−3.51 to −1.35); P < 0.001		
Change from baseline in mean monthly average impact on everyday activities score, MPFID			
Mean (SD) baseline	14.04 (8.88)	13.00 (8.21)	13.65 (9.07)
Mean change (SE) from baseline at months 4, 5, and 6	−5.83 (0.45) N = 296	−5.83 (0.44) N = 302	−3.66 (0.49) N = 289
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM vs. placebo (95% CI)[a]	**70 mg:** −2.22 (−3.28 to −1.16); P < 0.001 **140 mg:** −2.57 (−3.62 to −1.51); P < 0.001		

	STRIVE		
	ERE 70 mg (N = 317)	ERE 140 mg (N = 319)	Placebo (N = 319)
Harms			
Patients with an AE, n (%)	180 (57.3)	177 (55.5)	201 (63.0)
Patients with an SAE, n (%)	8 (2.5)	6 (1.9)	7 (2.2)
AEs leading to withdrawal of drug, n (%)	7 (2.2)	7 (2.2)	8 (2.5)
Injection-site pain, n (%)	10 (3.2)	1 (0.3)	1 (0.3)
Injection-site erythema, n (%)	6 (1.9)	5 (1.6)	1 (0.3)
Injection-site hypersensitivity, n (%)	1 (0.3)	1 (0.3)	1 (0.3)
Vascular disorders	8 (2.5)	5 (1.6)	13 (4.1)

AE = adverse event; CI = confidence interval; ERE = erenumab; LSM = least squares mean; MMD = monthly migraine day; MPFID = migraine physical function impact diary; SAE = serious adverse event; SD = standard deviation; SE = standard error; vs. = versus.

[a] Adjusted analysis utilizes a generalized linear mixed-effects model that includes treatment, visit, treatment by visit interaction, stratification factors region and prior and/or current treatment with migraine prophylactic medication, and baseline value as covariates and assumes a first-order autoregressive covariance structure. P values for pairwise comparisons are nominal P values without multiplicity adjustment. Adjusted analysis results for the mean over months 4, 5, and 6 are obtained from the same generalized linear mixed-effects model using contrasts.

[b] Common odds ratios and P values are obtained from a Cochran-Mantel-Haenszel test, stratified by stratification factors region and prior and/or current treatment with migraine prophylactic medication. The same analysis is repeated for each visit. P values for pairwise comparisons are nominal P values obtained from the Cochran-Mantel-Haenszel test using data including placebo and corresponding erenumab-dose group only. The result of a Breslow-Day test for homogeneity of the odds ratio cross strata for responder derived from the mean over months 4, 5, and 6 is 0.84 for 70 mg and 0.82 for 140 mg.

Source: Clinical Study Report for STRIVE.[7]

Table 2: Summary of Results (Study 295)

	Study 295		
	ERE 70 mg N = 191	ERE 140 mg N = 190	Placebo N = 286
Migraine frequency			
Change from baseline in MMDs			
Mean (SE) baseline MMDs	17.94 (0.32)	17.78 (0.34)	18.24 (0.28)
Mean (SE) change from baseline at week 12	−6.63 (0.45) N = 178	−6.53 (0.50) N = 182	−4.24 (0.38) N = 267
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI)[a]	**70 mg**: −2.46 (−3.52 to −1.39); P < 0.001 **140 mg**: −2.45 (−3.51 to −1.38); P < 0.001		
Patients with 50% reduction in mean MMDs from baseline during the last 3 months n (%)	75 (39.9)	77 (41.2)	66 (23.5)
Adjusted odds ratio (95% CI)	**70 mg**: 2.18 (1.46 to 3.27); P < 0.001 **140 mg**: 2.34 (1.56 to 3.51); P < 0.001		
Medication use			
Change from baseline in monthly acute migraine-specific medication baseline to week 12			
Mean (SE) baseline	8.77 (0.53)	9.68 (0.51)	9.42 (0.45)
Mean (SE) change from baseline to week 12	−3.25 (0.37) N = 178	−4.26 (0.38) N = 182	−1.62 (0.26) N = 267
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSMs (95% CI)[a]	**70 mg: −**1.86 (−2.60 to −1.13); P < 0.001 **140 mg**: −2.55 (−3.28 to −1.82); P < 0.001		

	Study 295		
	ERE 70 mg N = 191	ERE 140 mg N = 190	Placebo N = 286
Change from baseline in cumulative monthly headache hours			
Mean (SD) baseline monthly headache hours	223.61 (9.23)	215.06 (9.03)	235.28 (7.52)
Mean (SD) change from baseline at week 12	−66.58 (7.30) N = 178	−72.36 (8.74) N = 182	−59.26 (6.07) N = 267
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI)[a]	**70 mg:** −9.54 (−26.98 to 7.90); P = 0.28 **140 mg:** −19.31 (−36.71 to −1.92); P = 0.030		
Harms			
Patients with an AE, n (%)	83 (43.7)	88 (46.8)	110 (39.0)
Patients with an SAE, n (%)	6 (3.2)	2 (1.1)	7 (2.5)
AEs leading to withdrawal of drug, n (%)	0 (0.0)	2 (1.1)	2 (0.7)
Injection-site pain	7 (3.7)	7 (3.7)	3 (1.1)
Injection-site erythema	1 (0.5)	6 (3.2)	0

AE = adverse event; CI = confidence interval; ERE = erenumab; LSM = least squares mean; SAE = serious adverse event; SD = standard deviation; SE = standard error.

[a] Adjusted analysis utilizes a generalized linear mixed-effect model, which includes treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assumes a first-order autoregressive covariance structure. P values for pairwise comparisons are nominal P values without multiplicity adjustment.

[b] The adjusted odds ratios and P values are obtained from a Cochran-Mantel-Haenszel test after the missing data are imputed as nonresponse, stratified by stratification factors region and medication overuse. The same analysis is repeated for each visit. P values for pairwise comparisons are nominal P values obtained from the Cochran-Mantel-Haenszel test using data including placebo and corresponding erenumab-dose group only.

[c] Adjusted analysis utilizes an analysis of covariance model that includes treatment, stratification factors region and medication overuse, and baseline value as covariates and the same analysis is repeated for each visit. P values for pairwise comparisons are nominal P values without multiplicity adjustment.

Source: Clinical Study Report for Study 295.[8]

Table 3: Summary of Results (LIBERTY and ARISE)

	LIBERTY		ARISE	
	ERE 140 mg N = 119	Placebo N = 124	ERE 70 mg N = 286	Placebo N = 286
Migraine frequency				
Patients with at least a 50% reduction from baseline in MMDs, **week 12 n (%) (primary outcome in LIBERTY)**	**36 (30.3)**	**17 (13.7)**	112 (39.7)	85 (29.5)
Odds ratio (95% CI)	2.73 (1.43 to 5.19); P = 0.002[a]		1.59 (1.12 to 2.27); P = 0.010[a]	
Change from baseline in MMDs (primary outcome in ARISE)				
Mean (SD) baseline	9.3 (2.58)	9.3 (2.71)	8.13 (2.57)	8.38 (2.58)
Week 12, mean (SE) change from baseline	−1.76 (0.44) N = 118	−0.15 (0.41) N = 120	−2.89 (0.23) N = 268	−1.96 (0.25) N = 270
LSM estimate (95% CI)	NR	NR	−2.88 (−3.30 to −2.47)	−1.84 (−2.25 to −1.43)
Mean difference between groups (95% CI)	−1.61 (−2.70 to −0.52); P = 0.004[b]		−1.04 (−1.61 to −0.47); P < 0.001[c]	
≥ 75% response rate at week 12	14 (11.8)	5 (4.0)	54 (19.1)	34 (11.8)
Odds ratio (95% CI)[a]	3.16 (1.11 to 9.01); P = 0.025		1.79 (1.12 to 2.87); P = 0.015	
100% response rate at week 12	7 of 119 (5.9)	0 of 124 (0.0)	18 (6.4)	7 (2.4)
Odds ratio (95% CI)[a]	NA		2.76 (1.13 to 6.75) P = 0.021	
Migraine medication use				
Change from baseline in monthly acute migraine-specific medication				
Mean (SD) baseline	4.8 (2.95)	4.4 (2.84)	3.75 (3.65)	3.43 (3.59)
Mean (SD) change from baseline at week 12	−1.26 (0.24) N = 118	0.48 (0.29) N = 120	−1.30 (0.17) N = 268	−0.59 (0.15) N = 270
LSM change (95% CI), baseline to week 12	NR	NR	−1.21 (−1.48 to −0.94)	−0.62 (−0.89 to −0.35)
Mean difference between groups (95% CI)	−1.73 (−2.46 to −1.01); P < 0.001[b]		−0.59 (−0.96 to −0.21); P = 0.002[c]	
Functional impairment				
Change in physical impairment and everyday activities, MPFID				
Mean (SD) baseline, physical impairment	12.57 (9.64)	12.03 (8.99)	10.73 (8.92)	11.38 (9.08)
MPFID, physical impairment domain LSM (SE) change from baseline to week 12	−1.85 (0.84) N = 118	1.61 (0.80) N = 120	−3.18 (0.41)	−1.88 (0.40)
Mean difference between groups (95% CI)	−3.46 (−5.70 to −1.23); P = 0.003[b]		−1.30 (−2.40 to −0.19); P = 0.021[c]	
MPFID, everyday activities domain mean (SD) baseline	13.99 (8.89)	13.05 (8.25)	12.99 (8.66)	13.59 (8.90)
MPFID, everyday activities domain LSM (SE) change from baseline to week 12	−3.36 (0.83) N = 118	0.55 (0.81) N = 120	−4.51 (0.45)	−3.13 (0.45)
Mean difference between groups (95% CI)	−3.91 (−6.12 to −1.70); P < 0.001[b]		−1.38 (−2.60 to −0.15); P = 0.028[c]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	LIBERTY		ARISE	
	ERE 140 mg N = 119	Placebo N = 124	ERE 70 mg N = 286	Placebo N = 286
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
Adverse events				
Patients with an AE, n (%)	65 (54.6)	67 (54.0)	136 (48.1)	158 (54.7)
Patients with an SAE, n (%)	2 (1.7)	1 (0.8)	3 (1.1)	5 (1.7)
AE leading to drug discontinuation, n (%)	0	1 (0.8)	5 (1.8)	1 (0.3)
Hypersensitivity (SAE)	-	-	1 (0.3)	0
Injection-site erythema	3 (2.5)	4 (3.2)	-	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; CI = confidence interval; ERE = erenumab; LSM = least squares mean; MMD = monthly migraine day; MPFID = migraine physical function impact diary; SAE = serious adverse event; SD = standard deviation; SE = standard error.

[a] Cochran-Mantel-Haenszel test adjusting for stratification factor (four to seven vs. eight to 14 migraine days at baseline in LIBERTY and region and prior and/or current therapies in ARISE).

[b] Linear mixed-effects model includes treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit.

[c] Adjusted analysis utilizes a generalized linear mixed-effects model that includes treatment, visit, treatment by visit interaction, stratification factors region and prior and/or current treatment with migraine prophylactic medication, and baseline value as covariates and assumes a first-order autoregressive covariance structure. P values are nominal P values without multiplicity adjustment.

[d] The common odds ratios and P values are obtained from a Cochran-Mantel-Haenszel test, stratified by stratification factors region and prior and/or current treatment with migraine prophylactic medication. The same analysis is repeated for each visit. P values are nominal P values obtained from the Cochran-Mantel-Haenszel test. The result of a Breslow-Day test for homogeneity of odds ratios across strata at week 12 (month 3) is 0.89.

Source: Clinical Study Report for LIBERTY[9] and ARISE.[10]

Introduction

Disease Prevalence and Incidence

Migraine is a complex neurological disorder, the precise cause of which is not completely understood. Patients who suffer from migraine report migraine attacks characterized by severe headache (throbbing, diffuse pain) and accompanied by other symptoms such as nausea and/or vomiting, dizziness, sensory hypersensitivity, and tingling or numbness in the extremities and/or face. Migraines can occur with or without aura, and the aura is characterized by a wide range of primarily neurological symptoms that can affect vision, speech, sensations, and muscle strength. Cognitive function can also be affected. All of these symptoms associated with migraine can impair quality of life, and patients also report that their quality of life is affected even when they do not have a migraine, as they fear the next attack. Patients report numerous social and financial impacts of migraine, including social relationships, which are affected by exhaustion and frequent migraine attacks. Based on a study published in 2011, at least 2.6 million adult females and almost 1 million adult males in Canada suffer from migraine,[1,2] although this may be an underestimate, as not everyone who suffers from migraine seeks medical help and therefore does not receive an official diagnosis. Approximately three-quarters of patients experiencing migraine report impaired function, and one-third require bed rest during a migraine attack.[3]

Standards of Therapy

There are two approaches to treating migraine: management of acute attacks and prophylaxis. The latter is typically considered only for those with more frequent migraines (at least four MMDs). Topiramate is an oral anticonvulsant that is indicated in adults for the prophylaxis of migraine headache, and is considered a first-line option for migraine prophylaxis according to the clinical expert consulted by CDR. Onabotulinum toxin A has a Health Canada indication for chronic migraine prophylaxis and was previously reviewed by CDR. It is administered by 31 subcutaneous injections in various muscles of the head and neck, and thus is an invasive and technically challenging procedure. Pizotifen is an orally administered serotonin and tryptamine antagonist that also has an approved indication for migraine prophylaxis. Many other therapies used for migraine prophylaxis are used off-label, as they lack an official indication for this purpose from Health Canada. Broadly speaking, the main categories are antidepressants (tricyclics, serotonin-norepinephrine reuptake inhibitors), anticonvulsants (various), and cardiovascular drugs (beta-blockers, calcium-channel blockers, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers). There is a lack of understanding of how the mechanisms of these drugs are useful in migraine prophylaxis. While they are generally safe, well-established drugs, they all pose various tolerability issues for patients, and this is important, given that they are to be used on a chronic basis in migraine prophylaxis.

In clinical practice, patients on migraine prophylaxis frequently discontinue or switch treatments due to lack of efficacy or tolerability.[5,6]

Drug

Erenumab is a monoclonal antibody that binds to and inhibits the CGRP receptor, and CGRP likely contributes to the pathophysiology of migraine through its vascular effects and ability to transmit pain signals in the central nervous system. It is administered by

subcutaneous injection at a dose of either 70 mg or 140 mg once monthly. It is indicated by Health Canada for the prevention of migraine in patients who have had at least four MMDs.

Table 4: Key Characteristics of Botox, Tricyclic Antidepressants, Beta-Blockers, Anticonvulsants, SNRIs, Calcium-Channel Blockers, ACE Inhibitors, ARBs, and Pizotifen

	Erenumab	Onabotulinum toxin A	Beta-blockers	Anticonvulsants
Drugs most commonly used in migraine			Propranolol Timolol Nadolol Metoprolol	Topiramate Gabapentin Valproic acid
Mechanism of action	Binds to CGRP	Inhibits presynaptic release of CGRP, and other neurotransmitters	Beta1-receptor antagonists	Multiple mechanisms of action
Indication[a]	For prevention of migraine in patients who have at least four migraine days monthly	For prophylaxis of headaches in adults with chronic migraine (≥ 15 days/month with headache lasting ≥ 4 hours/day	Migraine prophylaxis: propranolol, timolol Others: None for migraine Various cardiovascular indications	Topiramate: migraine prophylaxis Topiramate/others: epilepsy
Route of administration	Subcutaneous injection	Intramuscular Injection	Oral	Oral
Recommended dose	70 mg or 140 mg once monthly	5 units to 31 different sites, across 7 different head-and-neck muscle areas	Varies by drug	Varies by drug
Serious side effects and safety issues	Hypersensitivity reactions	Spread of toxin beyond injection site (e.g., breathing difficulties)	Rebound syndrome Bronchospasm	Valproic acid: Hepatotoxicity
Other				
	TCAs and SNRIs	**CCBs**	**ACE inhibitors and ARBs**	**Pizotifen**
Drugs most commonly used in migraine	Amitriptyline Nortriptyline Venlafaxine	Flunarizine Verapamil	Lisinopril Candesartan	-
Mechanism of action	Inhibits reuptake of serotonin, norepinephrine	Blocks L-type calcium channels	Inhibits effects of angiotensin 2	Blocks 5HT-2 receptors, histamine (H1) receptors

	TCAs and SNRIs	CCBs	ACE inhibitors and ARBs	Pizotifen
Indication[a]	None for migraine Depression Anxiety	Flunarizine: Migraine prophylaxis Others: None for migraine Various cardiovascular indications	None for migraine Hypertension Heart failure	Prevention of migraine: recommended for those with ≥ 3 attacks monthly and fail to respond to symptomatic treatment and have reduced QoL
Route of administration	Oral	Oral	Oral	Oral
Recommended dose	Varies between drug	Varies between drug	Varies between drug	1 mg/day to 6 mg/day, up to 3 mg in a single dose
Serious side effects and safety issues	Hypertension Serotonin syndrome Conditions that may be exacerbated by anticholinergic effects (TCA mainly)	Heart block	Angioedema	Conditions that may be exacerbated by anticholinergic effects

5HT-2 = serotonin-2; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CCB = calcium-channel blocker; CGRP = calcitonin gene-related peptide; QoL = quality of life; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

[a] Health Canada indication.

Source: Product monographs from e-CPS.[11]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of erenumab for the prevention of migraine in adults who have at least four migraine days per month.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those meeting the selection criteria in Table 5.

Table 5: Inclusion Criteria for the Systematic Review

Patient population	Adult patients with migraine who have had at least 4 migraine days per month **Subgroups of interest:** • Patients who have failed (i.e., due to lack of efficacy, intolerance, or clinical contraindication) prior oral prophylactic medications • Number of migraine days per month at baseline • Patients who exhibit signs of medication overuse headache versus those who do not
Intervention	Erenumab 70 mg or 140 mg by subcutaneous injection, once monthly
Comparators	Pharmacologic interventions: • Tricyclic antidepressants • Beta-blockers • Anticonvulsants • Calcium-channel blockers • Serotonin-norepinephrine reuptake inhibitors • Onabotulinum toxin A • Pizotifen • Angiotensin-receptor blockers (e.g., candesartan) • Angiotensin-converting enzyme inhibitors Placebo
Outcomes	**Key outcomes:** • HRQoL using validated scales • Headache symptoms (e.g., HIT-6 score) • Other patient-reported outcomes (e.g., MIDAS) • Headache/migraine frequency (number of headache and/or migraine days or episodes) • Acute headache pain medication intake • Duration of effect and re-treatment intervals • Health care resource utilization (e.g., emergency visits) • Loss of work days **Harms outcomes:** AEs, SAEs, WDAEs, AEs of special interest (e.g., anaphylaxis and/or hypersensitivity reactions, antibody formation, vascular events)
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; HIT-6 = six-item Headache Impact Test; HRQoL = health-related quality of life; MIDAS = Migraine Disability Assessment Scale; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

A literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the Peer Review of Electronic Search Strategies (PRESS) checklist (https://www.cadth.ca/resources/finding-evidence/press).[12]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. The main search concept was Aimovig (erenumab). Clinical trial registries searched included the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on May 31, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on October 16, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[13] Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Results

Findings from the Literature

Four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 6, Table 7, and Table 8. A list of excluded studies is presented in Table 19.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

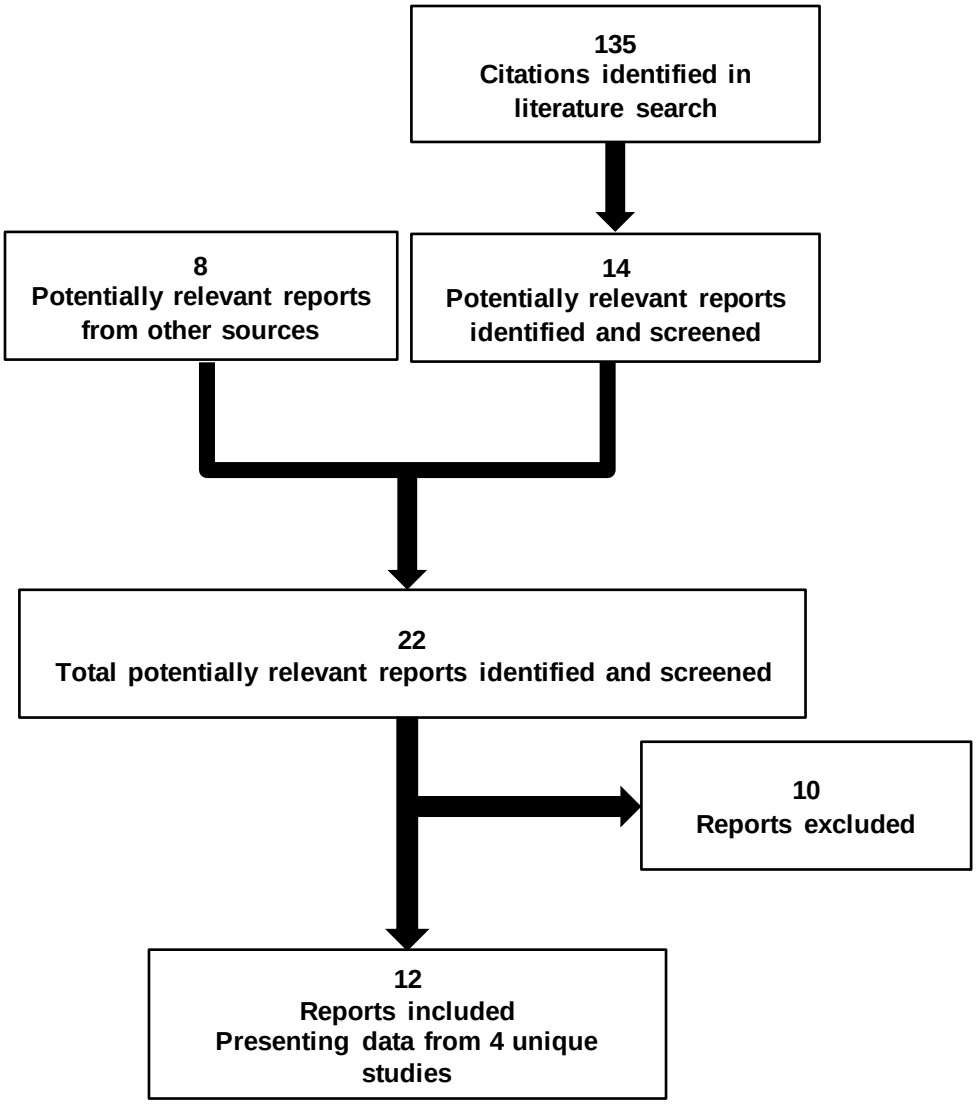


Table 6: Details of Included Studies (STRIVE)

		STRIVE
Designs and Populations	**Study design**	Double-blind, randomized controlled trial, placebo-controlled, multi-centre, parallel-group
	Study period	July 17, 2015, to September 5, 2016
	Locations	121 centres: Canada, US, Europe
	Randomized (N)	N = 955
	Inclusion criteria	• Adults ≥ 18 to ≤ 65 years of age • History of migraine (with or without aura) for ≥ 12 months prior to screening by ICHD-3 (Headache Classification Committee of the International Headache Society, 2013) based on medical records and/or patient self-report • Migraine frequency: ≥ 4 and < 15 migraine days per month on average across the 3 months prior to screening • Headache (i.e., migraine and non-migraine headache) frequency: < 15 headache days per month on average across the 3 months prior to screening • Migraine frequency: ≥ 4 and < 15 migraine days during the baseline phase based on eDiary calculations • Headache frequency: < 15 headache days during the baseline phase based on eDiary calculations

	Exclusion criteria	• Older than 50 years of age at migraine onset
		• History of cluster headache or hemiplegic migraine headache
		• Unable to differentiate migraine from other headaches
		• No therapeutic response with > 2 of the following 7 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial:
		  ○ Category 1: divalproex sodium, sodium valproate
		  ○ Category 2: topiramate
		  ○ Category 3: beta-blockers
		  ○ Category 4: tricyclic antidepressants
		  ○ Category 5: serotonin-norepinephrine reuptake inhibitors
		  ○ Category 6: flunarizine, verapamil
		  ○ Category 7: lisinopril, candesartan
		• No therapeutic response is defined as no reduction in headache frequency, duration, or severity after administration of the medication for at least 6 weeks at the generally accepted therapeutic dose(s) based on the investigator's assessment. The following scenarios do not constitute lack of therapeutic response:
		  ○ Lack of sustained response to a medication
		  ○ Failure to tolerate a therapeutic dose
		• Received onabotulinum toxin A in the head and/or neck region within 4 months prior to the start of the baseline phase or during the baseline phase
		• Concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase; if only 1 prophylactic medication is used, the dose must be stable within 2 months prior to the start of the baseline phase and throughout the study
		• Taken the following for any indication in any month during the 2 months prior to the start of the baseline phase:
		  ○ Ergotamines or triptans on ≥ 10 days per month
		  ○ Simple analgesics (nonsteroidal anti-inflammatory drugs or acetaminophen) on ≥ 15 days per month
		  ○ Opioid or butalbital-containing analgesics on ≥ 4 days per month
		  ○ Active chronic pain syndromes (such as fibromyalgia and chronic pelvic pain)
		• History of major psychiatric disorder (such as schizophrenia and bipolar disorder), or current evidence of depression based on a BDI-II total score > 19 at screening; patients with anxiety disorder and/or major depressive disorder are permitted in the study if they are considered by the investigator to be stable (with a BDI-II score ≤ 19) and are taking no more than 1 medication

		STRIVE
		for each disorder patients must have been on ;a stable dose within the 3 months prior to the start of the baseline phase • History of seizure disorder or other significant neurological conditions other than mig raine; a single childhood febrile seizure is not exclusionary • Malignancy within the 5 years prior to screening, except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ • HIV infection by history of hepatic disease by history or total bilirubin ≥ 2.0 × ULN or alanine transaminase or aspartate aminotransferase ≥ 3.0 × ULN, as assessed by the central laboratory at initial screening • Myocardial infarction, stroke, TIA, unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening
DRUGS	**Intervention**	Erenumab 70 mg or 140 mg subcutaneous once monthly
	Comparator(s)	Placebo
DURATION	**Phase**	
	Screening	Screening up to 3 weeks then 4 week baseline phase
	Double-blind	24 weeks (followed by 28-week active treatment phase)
	Follow-up	12 weeks
OUTCOMES	**Primary end point**	Change from baseline in mean monthly migraine days
	Other end points	**Secondary** *Efficacy* • Patients with at least 50% reduction from baseline in mean monthly migraine days • Change from baseline in mean monthly acute migraine-specific medication treatment days • Change from baseline in mean physical impairment domain score as measured by the MPFID • Change from baseline in mean impact on everyday activities domain score as measured by the MPFID *Safety* AEs, clinical laboratory values and vital signs, erenumab antibodies **Exploratory** • Change from baseline in mean HIT-6 scores over the last 3 months (months 4, 5, and 6) of the DBTP • Change from baseline in monthly migraine days at assessment time points • Change from baseline in mean monthly migraine attacks over the last 3 months of the DBTP • Change from baseline in monthly migraine attacks at assessment time points • Change from baseline in mean monthly headache (migraine and non-migraine headache) days over the last 3 months of the DBTP • Change from baseline in monthly headache (migraine and non-migraine headache) days at assessment time points • ≥ 50% reduction from baseline in MMDs at assessment time points • ≥ 75% reduction from baseline in mean MMDs over the last 3 months of the DBTP • ≥ 75% reduction from baseline in MMDs at assessment time points • 100% reduction from baseline in mean MMDs over the last 3 months of the DBTP • 100% reduction from baseline in MMDs at assessment time points • Change from baseline in mean monthly acute headache-medication treatment days over the last 3 months of the DBTP • Change from baseline in monthly acute headache-medication treatment days at assessment time points • Change from baseline in monthly acute migraine-specific medication treatment days at assessment time points

		STRIVE
		• Change from baseline in mean monthly hours of migraine headache over the last 3 months of the DBTP • Change from baseline in monthly hours of migraine headache at assessment time points • Change from baseline in mean monthly average severity of migraine pain over the last 3 months of the DBTP • Change from baseline in monthly average severity of migraine pain at assessment time points • Change from baseline in migraine-related disability and productivity as measured by the modified MIDAS over the last 3 months of the DBTP • Change from baseline in migraine-specific quality of life, as measured by the MSQ, version 2.1, over the last 3 months of the DBTP • Achievement of at least a 5-point reduction from baseline on mean monthly average physical impairment domain scores over the last 3 months of the DBTP as measured by the MPFID • Achievement of at least a 5-point reduction from baseline on mean monthly average impact on everyday activities domain scores over the last 3 months of the DBTP as measured by the MPFID • Change from baseline in mean monthly days with impairment as measured by the MPFID over the last 3 months of the DBTP • Change from baseline in mean monthly days with physical impairment as measured by the MPFID over the last 3 months of the DBTP • Change from baseline in mean monthly days with impact on everyday activities as measured by the MPFID over the last 3 months of the DBTP • Change from baseline in the overall impact on everyday activities score as measured by the MPFID stand-alone item over the last 3 months of the DBTP
NOTES	**Publications**	Goadsby (2017)[14]

AE = adverse event; BDI-II = Beck Depression Inventory – II; DBTP = double-blind treatment phase; HIT-6 = six-item Headache Impact Test; ICHD-3 = International Classification of Headache Disorders, third edition; MIDAS = Migraine Disability Assessment Scale; MMD = monthly migraine day; MPFID = migraine physical function impact diary; MSQ = Migraine-Specific Quality of Life Questionnaire; TIA = transient ischemic attack; ULN = upper limit of normal.

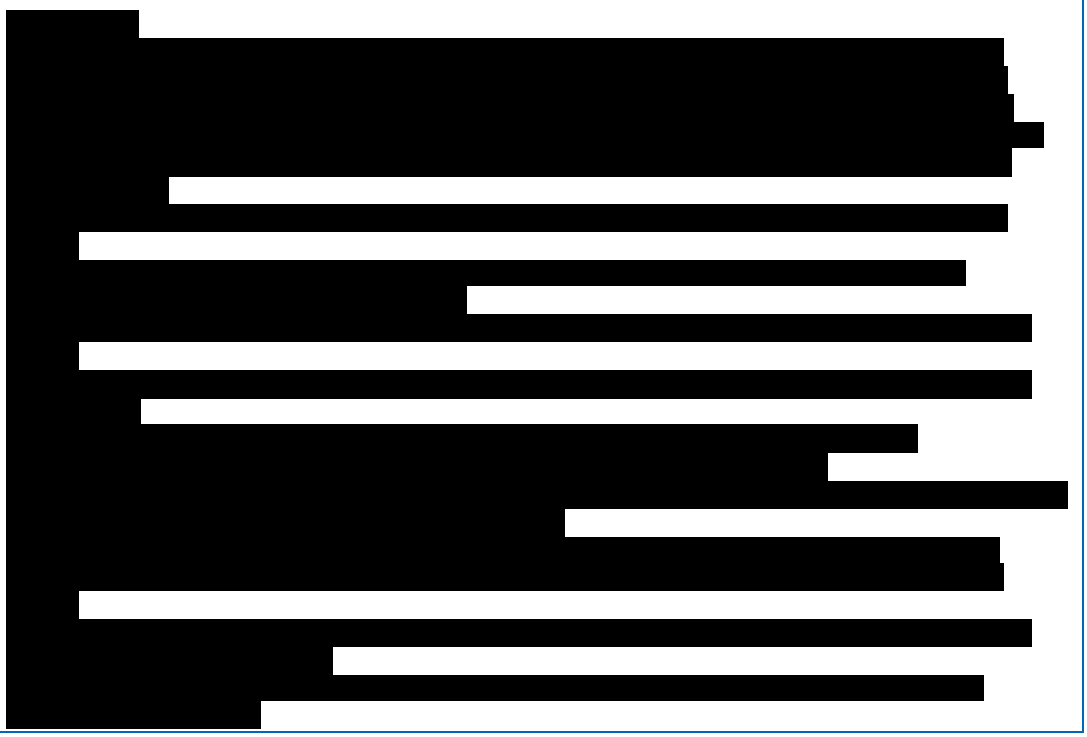
Note: Four additional reports were included (FDA clinical and statistical reviews,[15,16] Health Canada reviewer's report,[17] and sponsor's submission[18]).

Source: Clinical Study Report for STRIVE.[7]

Table 7: Details of Included Studies (Study 295)

		Study 295
Designs and Populations	**Study design**	Double-blind randomized controlled trial, placebo-controlled, multi-centre, parallel-group (phase II)
	Study period	March 5, 2014, to April 28, 2016
	Locations	69 sites: Canada, US, Europe
	Randomized (N)	N = 667
	Inclusion criteria	• Adults ≥ 18 to ≤ 65 years of age • History of ≥ 5 attacks of migraine without aura and/or migraine with visual, sensory, speech and/or language, retinal or brainstem aura according to the IHS Classification ICHD-3 • History of ≥ 15 headache days per month of which ≥ 8 headache days were assessed by the patient as migraine days per month in each of the 3 months prior to screening • ≥ 15 headache days of which ≥ 8 days meet criteria as migraine days during the baseline phase based on eDiary calculations • ≥ 4 distinct headache episodes, each lasting ≥ 4 hours or, if shorter, associated with use of a triptan or ergot derivative on the same calendar day during the baseline phase, based on eDiary calculations

	Exclusion criteria	• Older than 50 years of age at migraine onset
		• History of cluster headache or hemiplegic migraine headache
		• Chronic migraine with continuous pain, in which the patient does not experience any pain-free periods (of any duration) during the 1 month prior to screening
		• Unable to differentiate migraine from other headaches
		• Taken an opioid and/or opioid-containing analgesic for any indication on greater than 12 days during the 3 months prior to screening
		• Taken a butalbital-containing analgesic for any indication on greater than 6 days during the 3 months prior to screening
		• No therapeutic response in prophylaxis of migraine after an adequate therapeutic trial to > 3 of the following medication categories. These medication categories include:
		  ○ Category 1: divalproex sodium, sodium valproate
		  ○ Category 2: topiramate
		  ○ Category 3: beta-blockers
		  ○ Category 4: tricyclic antidepressants
		  ○ Category 5: flunarizine or verapamil
		  ○ Category 6: venlafaxine, desvenlafaxine, duloxetine, or milnacipran
		  ○ Category 7: onabotulinum toxin A
		  ○ Category 8: lisinopril or candesartan
		• Changing the dose of a concomitant medication that is not prescribed for migraine prophylaxis but that may have migraine prophylactic effects within 1 month prior to screening
		• Received onabotulinum toxin A in the head and/or neck region within 4 months prior to screening
		
		Excluded medical conditions:
		• Currently diagnosed with fibromyalgia, and/or chronic pelvic pain
		• History of major psychiatric disorder (such as schizophrenia or other psychotic disorders, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder), or current evidence of depression based on a BDI-II total score > 24 at screening. Patients with generalized anxiety disorder and/or major depressive disorder are permitted in the study if they are on no more than 1 medication for each disorder. Patients may not have experienced an anti-anxiety or antidepressant medication adjustment in the 3 months prior to screening and must demonstrate clinical stability. Patients who require the daily use of antipsychotic medications (drugs for which the primary indication is for treatment of schizophrenia, e.g., haloperidol or aripiprazole) or as-needed use of antipsychotic medications for any major psychiatric disorder are excluded. Use of low doses of antipsychotic medications as symptomatic treatment for nausea or insomnia (for example, 50 mg or less of quetiapine for insomnia) is acceptable
		• History of seizure disorder or other significant neurological conditions other than migraine; childhood febrile seizures are not exclusionary)

		Study 295
		• Use of any anticoagulant within 6 months prior to screening (antiplatelet agents are allowed) • Malignancy, except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ within the last 5 years Poorly controlled hypertension in the judgment of the investigator, or systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg as measured at the screening or week −4 study visits • Myocardial infarction, stroke, TIA, unstable angina, coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening
DRUGS	**Intervention**	Erenumab 70 mg or 140 mg subcutaneous once monthly
	Comparator(s)	Placebo
DURATION	**Phase**	
	Screening	Screening up to 3 weeks then 4-week baseline phase
	Double-blind	12 weeks
	Follow-up	12 weeks
OUTCOMES	**Primary end point**	Change in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase
	Other end points	**Efficacy** • ≥ 50% reduction from baseline in monthly migraine days in the last 4 weeks of the 12-week double-blind treatment phase • Change from baseline in monthly acute migraine-specific medication treatment days in the last 4 weeks of the 12-week double-blind treatment phase • Change from baseline in cumulative monthly headache hours in the last 4 weeks of the 12-week double-blind treatment phase **Safety** AEs, clinical laboratory values, vital signs, and anti-erenumab antibodies 

		Study 295
		[redacted]
Notes	**Publications**	Tepper (2017)[19]

AE = adverse event; BDI-II = Beck Depression Inventory – II; BP = blood pressure; ICHD-3 = International Classification of Headache Disorders, third edition; IHS = International Headache Society; MHD = monthly headache day; MIDAS = Migraine Disability Assessment Scale; MPFID = migraine physical function impact diary; MSQ = Migraine-Specific Quality of Life Questionnaire; PGIC = Patient Global Impression of Change; PROMIS = Patient-Reported Outcomes Measurement Information System; TIA = transient ischemic attack.

Note: Four additional reports were included (FDA clinical and statistical reviews,[15,16] Health Canada reviewer's report,[17] and sponsor's submission[18]).

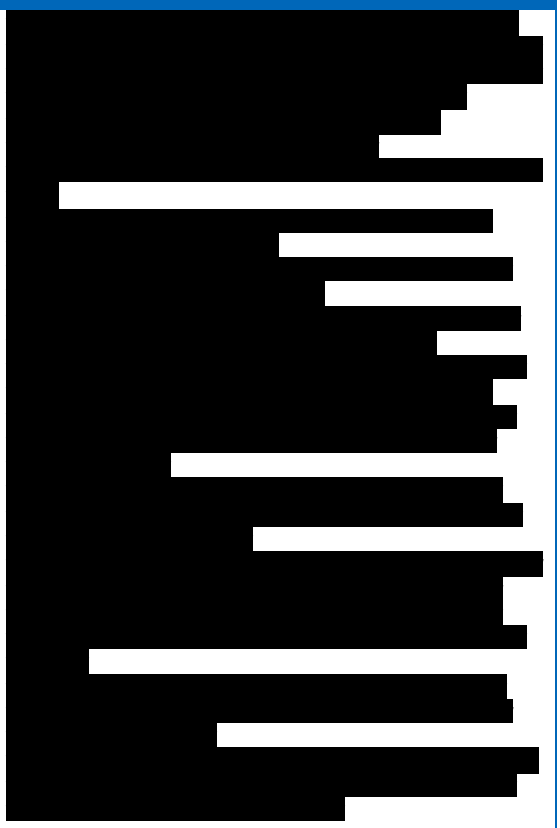
Source: Clinical Study Report for Study 295.[8]

Table 8: Details of Included Studies (LIBERTY and ARISE)

		LIBERTY	ARISE
Designs and Populations	**Study design**	Double-blind, randomized controlled trial, placebo-controlled, parallel-group	Double-blind, multi-centre, placebo-controlled, parallel-group
	Study period	March 20, 2017, to October 27, 2017	July 20, 2015, to July 11, 2016
	Locations	59 centres: Australia, Europe	69 centres: US, Europe
	Randomized (N)	N = 246	N = 577
	Inclusion criteria	• Adults 18 to 65 years of age • Migraine (with or without aura) for ≥ 12 months prior to screening according to ICHD-3 • 4 to 14 days per month (in at least 2 separate attacks) of migraine • Symptoms (based on ICHD-3 criteria) on average across the 3 months prior to screening based on retrospective reporting • < 15 days per month of headache symptoms (i.e., migraine and non-migraine) • Failed 2 to 4 prior migraine prophylaxis treatments out of the following: propranolol/ metoprolol, topiramate, flunarizine, valproate/divalproex, amitriptyline, venlafaxine, lisinopril, candesartan • Locally approved products (e.g., oxetorone or pizotifen) • Failed one and then failed or was not suitable for a second of the following: propranolol or metoprolol, topiramate, or flunarizine • Failed or was not suitable to receive valproate or divalproex	• Adults 18 to 65 years of age • History of migraine with or without aura for ≥ 12 months prior to screening according to ICHD-3 • Experienced ≥ 4 and < 15 migraine days per month with < 15 headache days per month, on average across the 3 months prior to screening • Migraine frequency: ≥ 4 and < 15 migraine days during the baseline phase based on eDiary calculations • Headache frequency: < 15 headache days during the baseline phase based on eDiary calculations

		LIBERTY	ARISE
		• Migraine frequency of 4 to 14 migraine days during the baseline epoch, confirmed by the eDiary	
	Exclusion criteria	• Older than 50 years of age at migraine onset • Unable to differentiate migraine from other headaches • History of cluster headache or hemiplegic migraine headache • Failed > 4 prior migraine prophylaxis treatments out of the following: propranolol or metoprolol, topiramate, flunarizine, valproate or divalproex, amitriptyline, venlafaxine, lisinopril, candesartan, locally approved products (e.g., oxetorone or pizotifen) • Used a prophylactic migraine medication within 5 half-lives, or a device or procedure within one month prior to the start of the baseline phase or during the baseline phase • Prior onabotulinum toxin A treatment in the head/neck region (including other licensed indications) within 4 months prior to the start of the baseline epoch or during the baseline epoch • Used the following for any indication in the 1 month prior to the start of the baseline phase or during the baseline phase: ○ ergotamines or triptans ≥ 10 days/month, or ○ simple analgesics (NSAIDs), acetaminophen ≥ 15 days/month, or ○ opioid- or butalbital-containing analgesics ≥ 4 days/month • Active chronic pain syndromes (e.g., fibromyalgia or chronic pelvic pain) • History or current evidence of major psychiatric disorder that might have interfered with the ability to properly report clinical outcomes • Current evidence of depression based on a BDI-II total score of > 19 at screening. Patients with anxiety disorder and/or major depressive disorder were permitted in the study if they were considered by the investigator to be stable and were taking no more than one medication per disorder. Patients must have been on a stable dose within the 3 months prior to the start of the baseline phase • History of seizure disorder or other significant neurological conditions other than migraine • Scored “yes” on item 4 or item 5 of the suicidal ideation section of the Columbia Suicide Severity Rating Scale if this ideation	• Older than 50 years of age at migraine onset • Unable to differentiate migraine from other headaches • History of cluster headache or hemiplegic migraine headache No therapeutic response with > 2 of the following 7 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial: • divalproex sodium, sodium valproate • topiramate • beta-blockers • tricyclic antidepressants • SNRIs • flunarizine, verapamil • lisinopril, candesartan No therapeutic response is defined as no reduction in headache frequency, duration, or severity after administration of the medication for at least 6 weeks at the generally accepted therapeutic dose(s) based on the investigator’s assessment. The following scenarios do not constitute lack of therapeutic response: • Lack of sustained response to a medication • Failure to tolerate a therapeutic dose • Used a prohibited medication, device, or procedure within 2 months prior to the start of the baseline phase or during the baseline phase • Received onabotulinum toxin A in the head and/or neck region within 4 months prior to the start of the baseline phase or during the baseline phase • Concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase; if only 1 prophylactic medication is used, the dose must be stable within 2 months prior to the start of the baseline phase and throughout the study • Taken the following for any indication in any month during the 2 months prior to the start of the baseline phase: ○ ergotamines or triptans on ≥ 10 days per month, or ○ simple analgesics (NSAIDs or acetaminophen) on ≥ 15 days per month, or ○ opioid- or butalbital-containing analgesics on ≥ 4 days per month

		LIBERTY	ARISE
		occurred within the past 6 months, or the patient responded "yes" to any item of the suicidal behaviour section, except for the "Non-Suicidal Self-Injurious Behavior" (item also included in the suicidal behavior section) if this behaviour occurred in the past 2 years • Myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery or other revascularization procedures within 12 months prior to screening • History or current diagnosis of ECG abnormalities that indicated significant risk of safety for patients who participated in the study • Hepatic disease by history or total bilirubin ≥ 2× ULN or alanine aminotransferase or aspartate aminotransferase ≥ 3× ULN as assessed by central laboratory at initial screening	• Myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening • Patient has any clinically significant vital sign, laboratory, or ECG abnormality during screening that, in the opinion of the investigator, could pose a risk to patient safety or interfere with the study evaluation
DRUGS	**Intervention**	Erenumab 140 mg subcutaneously once monthly	Erenumab 70 mg subcutaneously once monthly
	Comparator(s)	Placebo	Placebo
DURATION	**Phase**		
	Screening	6 weeks	7 weeks
	Double-blind	12 weeks (156 weeks OL extension)	12 weeks (28 week OL extension)
	Follow-up	12 weeks	8 weeks
OUTCOMES	**Primary end point**	Patients who achieved ≥ 50% reduction from baseline in MMDs in the last month of the DBTE	Change from baseline in MMDs in the last month of the DBTP
	Other end points	• Change from baseline in MMDs in the last month (month 3) of the DBTE • Change from baseline to month 3 of the MPFID "impact on everyday activities" domain score • Change from baseline to month 3 of the MPFID "physical impairment" domain score • Change from baseline in acute monthly migraine-specific treatment days in the last month (month 3) of the DBTE • Patients who achieved ≥ 75% reduction from baseline in MMD in the last month of the DBTE • Patients who achieved a 100% reduction from baseline in MMD in the last month of the DBTE **Exploratory** • EQ-5D-5L • WPAI-Headache • HIT-6	• ≥ 50% reduction from baseline in MMDs over last month of DBTP • Change from baseline in monthly acute migraine-specific medication treatment days in the last month of the DBTP • Achievement of ≥ 5-point reduction from baseline in average impact on everyday activities domain scores over the last month of the DBTP as measured by the MPFID • Achievement of ≥ 5-point reduction from baseline in average physical impairment domain scores over the last month of the DBTP as measured by the MPFID [redacted]

		LIBERTY	ARISE
		• BDI-II • DNA collection • Anti-erenumab antibody collection • Blood biomarker collection **Harms** • AEs, serious AEs • Pregnancies • Laboratory values and vital signs • Anti-erenumab antibodies	 **Harms** • AEs • Clinical laboratory values and vital signs • Antibodies to erenumab
NOTES	**Publications**	Reuter (2018)[20]	Dodick (2018)[21]

AE = adverse event; BDI-II = Beck Depression Inventory – II; DBTE = double-blind treatment epoch; DBTP = double-blind treatment phase; ECG = electrocardiogram; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; HIT-6 = six-item Headache Impact Test; ICHD-3 = International Classification of Headache Disorders, third edition; MMD = monthly migraine day; MPFID = migraine physical function impact diary; NSAID = nonsteroidal anti-inflammatory drug; OL = open label; ULN = upper limit of normal; SNRI = serotonin-norepinephrine reuptake inhibitor; WPAI = Work Productivity and Activity Impairment.

Note: Four additional reports were included (FDA clinical and statistical reviews,[15,16] Health Canada reviewer's report,[17] and sponsor's submission[18]).

Source: Clinical Study Report for LIBERTY[9] and ARISE.[10]

Included Studies

Description of Studies

Four multinational, manufacturer-sponsored, double-blind, randomized, placebo-controlled trials were included in this review. STRIVE (N = 955; 1:1:1 ratio; erenumab 70 mg, erenumab 140 mg, and placebo), LIBERTY (N = 246; 1:1 ratio; erenumab 140 mg and placebo) and ARISE (N = 577; 1:1 ratio; erenumab 70 mg and placebo) were conducted in patients with episodic migraine (i.e., < 15 days per month of headache symptoms), and

Study 295 enrolled patients with chronic migraine (i.e., ≥ 15 days per month of headache symptoms). The screening and diagnosis of migraine (with visual, sensory, speech and/or language, retinal or brainstem aura or without aura) in the four studies were based on a prior history of various symptoms according to ICHD-3. All four studies had highly restricted inclusion and exclusion criteria for patient enrolment. For example, patients were excluded if there was no therapeutic response with greater than two or three prophylaxis treatments (STRIVE, Study 295 and ARISE), or failed more than four treatments (LIBERTY). Only STRIVE and Study 295 included Canadian sites and patients.

In Study 295, a phase II trial, patients were randomized at a 1:1:2 ratio to erenumab 70 mg (N = 191), erenumab 140 mg (N = 190), or placebo (N = 286). STRIVE had a 24-week DBTP while the other three studies were 12-week double-blind phases and all included 12 weeks of follow-up.

The primary outcome of STRIVE, ARISE, and Study 295 was the change from baseline in MMDs, while in LIBERTY the primary outcome was the proportion of patients who achieved a 50% reduction in MMDs. The proportion of patients with a 50% reduction in MMDs was a secondary outcome in the other three trials, as were the change from baseline in MPFID scores, in MMDs requiring acute treatment, and in cumulative monthly headache hours. In Study 295, after a screening period of up to three weeks, patients entered a four-week baseline period, in which baseline characteristics were documented. All studies had a baseline and/or screening phase ranging from six to seven weeks. The DBTP in STRIVE was followed by a 28-week active treatment period (ATP), during which all patients received erenumab, re-randomized to either the 70 mg or 140 mg dose. Twelve weeks of follow-up were conducted after all treatment phases for safety.

Randomization was carried out using an interactive voice/web response system. In Study 295 and STRIVE, randomization was stratified by region and medication overuse (yes/no) at baseline. In ARISE, randomization was stratified by region (North America versus other) and treatment status with respect to migraine prophylaxis (current treatment, prior treatment only, or no treatment), while in LIBERTY randomization was stratified by migraine frequency at baseline (four to seven versus eight to 14 MMDs).

Subgroups explored in Study 295 included age (less than the median versus equal to or greater than median), sex, race (white or other), region (North America or other), medication overuse (yes or no), selected acute medications for on-study use, prior prophylaxis, failed prophylaxis, and "other subgroup variables as deemed appropriate." In STRIVE and ARISE, subgroups included region, prior and/or current prophylaxis, body mass index (less than the median versus equal to or greater than the median), baseline MMDs (less than eight or eight or more), and treatment failure of prior prophylaxis (failed or not failed). In LIBERTY, subgroups were analyzed by age (less than the median versus equal to or greater than the median), sex, MMD (four to seven MMD or eight to 14 MMD), and treatment failure of prior prophylaxis based on a post hoc analysis (at least two or more than two).

Populations

Inclusion and Exclusion Criteria

All studies enrolled adults (18 to 65 years of age) with a history of migraine for at least one year, according to the ICHD-3 classification system (Table 6, Table 7, and Table 8). In STRIVE, LIBERTY, and ARISE, patients had to have at least four and fewer than 15 MMDs

and headache more than 15 days monthly in the three months prior to screening. In Study 295, patients were to have at least eight migraine days per month and at least 15 headache days. LIBERTY additionally stipulated that patients had to have failed two to four migraine prophylaxis drugs out of a given list.

All studies excluded patients older than 50 years at first onset of migraine. STRIVE and ARISE excluded patients who had failed more than two migraine prophylaxis medications from a list of seven different categories of medications, and Study 295 excluded patients who had failed more than three prior prophylaxis medications from a similar list, both of which appeared to include all relevant comparators. All studies excluded patients with a history (within 12 months) of cardiovascular or cerebrovascular disease.

Baseline Characteristics

In all studies, patients were in their early 40s and the majority (> 80%) were female and Caucasian (> 90%) (Table 9 and Table 10). More than 80% of patients were described as having migraine without aura, with the exception of LIBERTY, in which approximately 65% had migraine without aura. Patients had migraine for approximately 20 to 25 years on average across studies. Migraines were most frequent in Study 295 (approximately 18 MMDs), which involved chronic migraine, while there were an average of approximately eight or nine MMDs in the other studies. Patients in Study 295 also had more days in which they used migraine medication (approximately nine days per month) compared to the other studies (three to four days per month with medication). The majority of patients in Study 295 (> 70%) had tried migraine prophylaxis medication, while these numbers were smaller in STRIVE (44%) and ARISE (50%). In STRIVE, approximately 40% of patients had failed at least one prior prophylaxis drug, while 17% had failed two prior prophylaxis drugs, and in Study 295 two-thirds failed at least one prior prophylaxis and close to half had failed two or more. In LIBERTY, almost all patients (99%) had failed at least two prophylaxis drugs, and these data were not reported in ARISE.

Aside from some small demographic differences, baseline characteristics were generally similar between groups within studies.

Table 9: Summary of Baseline Characteristics (STRIVE and Study 295)

	STRIVE			Study 295		
	ERE 70 mg (N = 317)	ERE 140 mg (N = 319)	Placebo (N = 319)	ERE 70 mg (N = 191)	ERE 140 mg (N = 190)	Placebo (N = 286)
Demographics						
Mean (SD) age, years	41.1 (11.3)	40.4 (11.1)	41.3 (11.2)	41.4 (11.3)	42.9 (11.1)	42.1 (11.3)
Female, n (%)	268 (84.5)	272 (85.3)	274 (85.9)	166 (86.9)	160 (84.2)	226 (79.0)
Race, n (%)						
• White	281 (88.6)	293 (91.8)	277 (86.8)	176 (92.1)	184 (96.8)	268 (93.7)
• Black or African-American	24 (7.6)	18 (5.6)	24 (7.5)	10 (5.2)	6 (3.2)	11 (3.8)
• Asian	5 (1.6)	4 (1.3)	8 (2.5)	4 (2.1)	0 (0.0)	4 (1.4)
• American Indian or Alaska Native	0 (0.0)	1 (0.3)	2 (0.6)	0	0	0
• Multiple	1 (0.3)	0 (0.0)	2 (0.6)	0	0	0
• Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.3)	0 (0.0)	0	0	0

	STRIVE			Study 295		
	ERE 70 mg (N = 317)	ERE 140 mg (N = 319)	Placebo (N = 319)	ERE 70 mg (N = 191)	ERE 140 mg (N = 190)	Placebo (N = 286)
• Other	6 (1.9)	2 (0.6)	6 (1.9)	1 (0.5)	0 (0.0)	3 (1.0)
Disease characteristics						
Targeted neurological disease diagnosis, n (%)						
• Migraine with aura	[redacted]	[redacted]	[redacted]	81 (42.4)	71 (37.4)	124 (43.4)
• Migraine without aura	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monthly migraine days at baseline, mean (SD)	8.29 (2.47)	8.34 (2.48)	8.23 (2.51)	17.85 (4.39)	17.78 (4.72)	18.22 (4.73)
Monthly headache days at baseline, mean (SD)	9.07 (2.61)	9.28 (2.54)	9.26 (2.58)	20.49 (3.82)	20.73 (3.83)	21.12 (3.93)
Monthly acute migraine-specific medication use in days at baseline, mean (SD)	3.21 (3.39)	3.41 (3.48)	3.41 (3.43)	8.76 (7.16)	9.66 (7.02)	9.46 (7.58)
Monthly MPFID impact on everyday activities scores at baseline, mean (SD)	13.99 (8.89)	13.05 (8.25)	13.66 (9.07)	NR	NR	NR
Monthly MPFID physical impairment scores at baseline mean (SD)	12.57 (9.64)	12.03 (8.99)	12.24 (9.43)	NR	NR	NR
Medication use						
Acute headache medications used in baseline phase, n (%)						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Migraine-specific	179 (56.5)	192 (60.2)	191 (59.9)	143 (74.9)	149 (78.4)	225 (78.7)
• Non–migraine specific	243 (76.7)	256 (80.3)	244 (76.5)	167 (87.4)	161 (84.7)	246 (86.0)
Prior treatment with migraine prophylactic medication, n (%)						
Previously never failed prophylactic treatment	[redacted]	[redacted]	[redacted]	64 (33.5)	64 (33.7)	86 (30.1)
Failed ≥ 1 prior prophylactic medication class	127 (40.1)	116 (36.4)	127 (39.8)	127 (66.5)	126 (66.3)	200 (69.9)
Failed ≥ 2 prior prophylactic medication classes	49 (15.5)	58 (18.2)	54 (16.9)	93 (48.7)	92 (48.4)	142 (49.7)

	STRIVE			Study 295		
	ERE 70 mg (N = 317)	ERE 140 mg (N = 319)	Placebo (N = 319)	ERE 70 mg (N = 191)	ERE 140 mg (N = 190)	Placebo (N = 286)
Treatment with migraine prophylaxis, n (%)						
• Naive	175 (55.2)	187 (58.6)	178 (55.8)	[redacted]	[redacted]	[redacted]
• Prior use only	133 (42.0)	124 (38.9)	131 (41.1)	[redacted]	[redacted]	[redacted]
• Current use	9 (2.8)	8 (2.5)	10 (3.1)	NR	NR	NR
Number of patients reporting any prior prophylactic medication, n	139	128	138			
Ever used prophylactic medication topiramate, n (%)	NR	NR	NR	89 (46.6)	97 (51.1)	150 (52.4)
Ever used onabotulinum toxin A, n (%)	NR	NR	NR	50 (26.2)	43 (22.6)	65 (22.7)
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERE = erenumab; MPFID = migraine physical function impact diary; SD = standard deviation; SNRI = serotonin-norepinephrine reuptake inhibitor.

Source: Clinical Study Report for STRIVE[7] and Study 295.[8]

Table 10: Summary of Baseline Characteristics (LIBERTY and ARISE)

	LIBERTY		ARISE	
	ERE 140 mg N = 121	Placebo N = 125	ERE 70 mg N = 286	PLACEBO N = 291
Demographics				
Age, mean (SD) years	44.6 (10.50)	44.2 (10.55)	42.3 (11.4)	42.2 (11.5)
Female, n (%)	97 (80.2)	103 (82.4)	245 (85.7)	247 (84.9)
Race, n (%)				
• White	112 (92.6)	115 (92.0)	259 (90.6)	259 (89.0)
• Black or African-American	0	0	[redacted]	[redacted]
• Asian	0	1 (0.8)	[redacted]	[redacted]
• Native Hawaiian or other Pacific Islander	0	0	[redacted]	[redacted]
• Multiple	0	0	[redacted]	[redacted]
• Unknown	0	1 (0.8)	[redacted]	[redacted]
• Other	[redacted]	[redacted]	[redacted]	[redacted]
Disease characteristics				
Aura status during baseline, n (%)				
• Migraine with aura	42 (34.7)	45 (36.0)	146 (51.0)	144 (49.5)
• Migraine without aura	79 (65.3)	80 (64.0)	[redacted]	[redacted]
Disease duration of migraine with or without aura, mean (SD), years	26.6 (12.12)	23.7 (10.91)	21.70 (12.62)	20.03 (12.08)
MMDs at baseline, mean (SD)	9.3 (2.58)	9.3 (2.71)	8.14 (2.65)	8.38 (2.60)
MMDs by strata, n (%)				
• Strata 1: 4 to 7 migraine days per month	36 (29.8)	38 (30.4)	NR	NR
• Strata 2: 8 to 14 migraine days per month	85 (70.2)	87 (69.6)	NR	NR
MHDs at baseline mean (SD)	10.1 (2.81)	10.1 (2.68)	9.08 (2.68)	9.30 (2.72)
Monthly migraine attacks mean (SD)	5.4 (1.23)	5.1 (1.41)	NR	NR
Monthly days of acute migraine-specific medication, mean (SD)	4.8 (2.95)	4.4 (2.84)	3.70 (3.64)	3.42 (3.59)
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Moderate depression (20 to 28)	[redacted]	[redacted]	NR	NR
Medication use				
Acute headache medication, n (%)				
• None	6 (5.0)	2 (1.6)	6 (2.1)	8 (2.7)
• Any acute medication	115 (95.0)	123 (98.4)	280 (97.9)	283 (97.3)
○ Migraine-specific	102 (84.3)	109 (87.2)	178 (62.2)	174 (59.8)
○ Only non-migraine specific	13 (10.7)	14 (11.2)	NR	NR
○ Non-migraine specific	NR	NR	224 (78.3)	236 (81.1)
Prior migraine prophylactic medication failed, n (%)				
< 2	1 (0.8)	1 (0.8)	NR	NR
2	43 (35.5)	52 (41.6)	NR	NR

	LIBERTY		ARISE	
	ERE 140 mg N = 121	Placebo N = 125	ERE 70 mg N = 286	PLACEBO N = 291
3	44 (36.4)	49 (39.2)	NR	NR
4	33 (27.3)	23 (18.4)	NR	NR
> 4	0	0	NR	NR
Treatment with migraine prophylactic medication, n (%)				
• Naive	NR	NR	[redacted]	[redacted]
• Prior use only	NR	NR	123 (43.0)	125 (43.0)
• Current use	NR	NR	[redacted]	[redacted]
Failed prior migraine prophylactic medication, n (%)				
• Amitriptyline	49 (40.5)	63 (50.4)	NR	NR
• Candesartan	26 (21.5)	26 (20.8)	NR	NR
• Flunarizine	32 (26.4)	38 (30.4)	NR	NR
• Metoprolol	46 (38.0)	48 (38.4)	NR	NR
• Propranolol	60 (49.6)	51 (40.8)	NR	NR
• Topiramate	105 (86.8)	104 (83.2)	NR	NR
• Valproate	43 (35.5)	25 (20.0)	NR	NR
• Venlafaxine hydrochloride	6 (5.0)	7 (5.6)	NR	NR
• Lisinopril	2 (1.7)	0	NR	NR
• Other locally approved prophylactic meds	9 (7.4)	13 (10.4)	NR	NR
Prior prophylactic medications, n (%)				
• Divalproex/valproate	NR	NR	17 (12.7)	12 (9.1)
• Topiramate	NR	NR	86 (64.2)	75 (56.8)
• Beta-blockers	NR	NR	52 (38.8)	61 (46.2)
• Tricyclic antidepressants	NR	NR	25 (18.7)	32 (24.2)
• Serotonin-norepinephrine reuptake inhibitors	NR	NR	9 (6.7)	7 (5.3)
• Flunarizine/verapamil/lomerizine	NR	NR	13 (9.7)	19 (14.4)
• Lisinopril/candesartan	NR	NR	16 (11.9)	11 (8.3)
• Other	NR	NR	43 (32.1)	44 (33.3)
Treatment failure n (%)	NR	NR	117 (87.3)	115 (87.1)
• Lack of efficacy	NR	NR	94 (70.1)	83 (62.9)
○ With therapeutic dose	NR	NR	82 (61.2)	76 (57.6)
○ Without therapeutic dose	NR	NR	23 (17.2)	15 (11.4)
• Adverse reaction	NR	NR	56 (41.8)	64 (48.5)
Discontinue due to reason other than treatment failure, n (%)	NR	NR	37 (27.6)	48 (36.4)
• Prophylactic medication no longer clinically necessary	NR	NR	17 (12.7)	14 (10.6)
• Other	NR	NR	24 (17.9)	37 (28.0)

ERE = erenumab; MHD = migraine headache day; MMD = monthly migraine day; SD = standard deviation.

Source: Clinical Study Report for LIBERTY[9] and ARISE.[10]

Interventions

Erenumab was administered via subcutaneous injection, at a dosage of either 70 mg or 140 mg once monthly, depending on the study. Patients assigned to the 140 mg dose received two consecutive injections of 70 mg. Injections were administered by an investigator or study personnel into the upper arm, upper thigh, or abdomen, and patients were observed for 30 minutes post-injection.

In Study 295 patients were allowed a maximum of one migraine prophylaxis drug, which they had to have been taking at a stable dose for at least two months prior to the start of the baseline period. This was a late protocol amendment and no patients were reported as using additional migraine prophylaxis during the study. A lengthy list of migraine prophylaxis medications that were allowed did not include onabotulinum toxin A:

- divalproex sodium, sodium valproate, topiramate, carbamazepine, or gabapentin
- all beta-blockers
- all tricyclic antidepressants
- flunarizine, lomerizine, or verapamil
- venlafaxine, desvenlafaxine, duloxetine, or milnacipran
- butterbur, feverfew, magnesium, or riboflavin
- lisinopril or candesartan
- clonidine, guanfacine, cyproheptadine, methysergide, or pizotifen.

In ARISE and STRIVE, a maximum of one medication from a similar list of medications was allowed. A small percentage of patients in each trial (6% in ARISE and 3% in STRIVE) used these other prophylaxis drugs during the study and there were no clear differences in use between groups (Table 9 and Table 10). LIBERTY did not appear to allow patients to use another migraine prophylaxis drug during the trial.

Patients continued on best supportive care, meaning that they could receive therapies for acute attacks or non-pharmacologic interventions such as biofeedback. These were recorded in patient electronic diaries. Patients were to agree with the investigator at baseline on what the appropriate abortive medications would be, then remain on those medications as much as possible.

Outcomes

Appendix 5 provides detailed descriptions of the outcome measures.

The primary outcome of all studies was the frequency of MMDs; in LIBERTY this was reported as the percentage of patients with a 50% reduction in MMDs at week 12 and in the other studies it was reported as the change from baseline in MMDs to the end of the DBTP. Patients used electronic diaries to record onset and severity of migraine and headache in general, as well as medication use. Monthly use of acute migraine medication was a secondary outcome in many of the included studies. The MCID for reduction in MMDs is unclear.

The MPFID was a secondary outcome in all of the included studies except Study 295, in which it was exploratory and part of an optional substudy. It was performed at baseline and daily throughout the studies by the patient. The MPFID tool was developed by the sponsor, and consists of 13 questions encompassing two domains: seven questions on impacts on

everyday activities and five questions on physical impairment, along with a single item related to global assessment of function.[8] This is a self-administered instrument, in which patients are asked how they were feeling over the past 24 hours. It is scored on a five-point scale, with higher scores indicating a more negative impact on function.[8] Domain scores are transformed to a 100-point scale, and the daily MPFID is averaged over a 28-day period. The MCID for within-group changes was 3, with the between-group MCID ranging from −1.60 to −2.54 for the physical impairment domain and from −0.87 to −2.62 for the everyday activities domain.

The MSQ is a disease-specific instrument that assesses the impact of migraine on a patient's HRQoL. An exploratory outcome in STRIVE, Study 295, and LIBERTY, it was performed at monthly study visits. Version 2.1 of the MSQ was used by the studies in this review. The MSQ assesses HRQoL across three domains: role function – restrictive (RFR), using seven items assessing how migraine limits one's daily social and work-related activities; role function – preventive (RFP), using four items assessing how migraine prevents these activities, and emotional function (EF), using three items assessing the emotions associated with migraine. Participants respond to the 14 items based on a four-week recall period and using a six-point Likert scale that ranges from none of the time, a little bit of the time, and some of the time to a good bit of the time, most of the time, and all of the time; responses are assigned scores of 1 to 6, respectively.[22] Raw dimension scores are computed as a sum of item responses and are rescaled to a 0-to-100 scale, producing an overall score for each domain. A higher score indicates better HRQoL. The resulting MCIDs varied depending on whether migraine was episodic or chronic, and varied by domain. For the RFR domain, the group-level MCID was 3.2 in episodic migraine and 10.9 in chronic migraine; for the RPR domain, MCIDs were 4.6 and 8.3 for episodic and chronic migraine, respectively; and for the EF domain they were 7.5 and 12.2, respectively. [23,24]

The HIT-6 score was assessed as an exploratory outcome in all included studies, and the instrument was used at monthly study visits. The HIT-6 is a short version of a web-based, multi-question health assessment that quantifies the impact of headache on a patient's life [25] using computerized adaptive testing technology to select and ask only survey questions relevant to the respondent. The full version comprises 84 possible questions that cover topics such as functional health and well-being. Optional questions may be used to obtain information on pain, medications, and treatment satisfaction.[25] The HIT-6 was developed for practical reasons[26] from a pool of 89 questions (54 from HIT and 35 suggested by clinicians).[26] The HIT-6 measures pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress.[27] Each of the six items is answered on a five-point Likert scale, with answers of never, rarely, sometimes, very often, or always assigned scores of 6, 8, 10, 11, or 13 points, respectively. Total HIT-6 scores range from 36 to 78; a higher score indicates a greater impact of the disease on the daily life of the respondent.[27,28] The scores may be also interpreted using four groupings: a score of no more than 49 points indicates little or no impact, a score of 50 to 55 reflects some impact, a score of 56 to 59 indicates substantial impact, and a score of 60 or greater reflects severe impact.[27] For patients with episodic migraine, the within-group MCID was −2.5 and the between-group MCID was −1.5, and for chronic daily headaches it was −2.3.[28,29]

The MIDAS score is an exploratory outcome assessed at monthly study visits. It evaluates headache-related disability through five questions regarding the number of days lost in three domains: schoolwork or work for pay; housework or chores; and family, social, or leisure activities.[30] The last two questions capture additional days with significant limitations to activity (≥ 50% reduced productivity) in the employment domains and household work

domains.[31] The questions, which are answered based on a three-month recall interval, are selected to ensure the questions accurately capture self-reported information while providing enough time to capture the long-term experience with headaches.[31] An overall score for the questionnaire is calculated by summing the lost days recorded in the five questions. Two additional questions that are not included in the scoring ask about the frequency of headaches and intensity of headache pain. These are used mainly to provide clinicians with additional information for management of treatment decisions. The overall score translates to a four-point grading scale: grade I = scores ranging from 0 to 5; grade II = 6 to 10; grade III = 11 to 20; and grade IV = 21 or greater. No MCID was identified for this instrument.

The Work Productivity and Activity Impairment (WPAI) instrument is an exploratory outcome that was assessed weekly in LIBERTY via an electronic diary. It is a self-administered questionnaire that measures impairments in work and activities during the past seven days due to general health or a specific health problem.[9] The instrument poses six questions and results in four scores: absenteeism (work time missed), presenteeism (impairment at work or reduced on-the-job effectiveness), work productivity loss (overall work impairment or absenteeism plus presenteeism), and activity impairment. The questionnaire elicits information on the number of days or hours missed from work, days or hours worked, days during which the performing of work was challenging, and the extent to which the patient was limited at work (work impairment). No migraine-specific MCID was found for this instrument.

The EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) questionnaire was an exploratory outcome in LIBERTY and was performed via an electronic diary at monthly visits. It consists of a descriptive system and a Visual Analogue Scale (VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension requires a response based on five levels, with a level 1 response indicating "no problems," level 2 "slight problems," level 3 "moderate problems," level 4 "severe problems," and level 5 "extreme problems" or "unable to perform," which is the worst response in the dimension.[32] Respondents are asked to choose the level that reflects their health state for each of the five dimensions. The numerical values assigned to levels 1 to 5 for each dimension reflect rank-order categories of function. In terms of measurement properties, these are ordinal data; they do not have interval properties and therefore should not be summed or averaged to produce, for example, an individual dimension "score." Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm that takes the local patient and population preferences into account. The index score is therefore a country-specific value and a major feature of the EQ-5D-5L instrument.[33] The range of index scores will differ according to the scoring algorithm used; however, in all EQ-5D-5L scoring algorithms, 0 represents the health state "dead" and 1.0 reflects "perfect health." Negative scores are also possible for health states that society (not the individual patient) considers to be "worse than dead."

The BDI-II is an updated version of the original, well-validated inventory, a widely used measure of symptoms related to depression.[34] The BDI-II is a self-reported questionnaire based on a two-week recall that assesses the severity of depression through 21 items, each based on a four-point scale that ranges from 0 to 3, with higher scores corresponding to greater severity of depressive symptoms.[9] The scores for each of the items are summed to generate an overall BDI-II score that is categorized by four severity grades: minimal depression (score of 0 to 13), mild depression (14 to 19), moderate depression (20 to 28),

and severe depression (29 to 63).[9] No migraine-specific MCID was found for this instrument.

The PROMIS Pain Interference Scale Short Form 6b was administered weekly as an exploratory outcome in Study 295. The short form is a six-item, patient-reported instrument that measures the level of pain interference on aspects of day-to-day life, based on a seven-day recall period.[8] More specifically, it measures the level of pain interference on enjoyment of life, ability to concentrate, day-to-day activities, enjoyment of recreational activities, doing activities away from home, and socializing with others. Each of the six items are answered on a five-point scale composed of the following responses and corresponding scores: "not at all" = 1; "a little bit" = 2; "somewhat" = 3; "quite a bit" = 4; and "very much" = 5. A total raw score is the sum of the values for each item, and ranges from a total score of 6 to 30, with a higher score corresponding to a higher level of pain interference. The total raw score is rescaled to a standardized t score with a mean of 50 and a standard deviation (SD) of 10, which is then reported as the final score.[8] No migraine-specific MCID was found for this instrument.

The ASC-12 is an exploratory outcome that was assessed at baseline and weeks 4 and 12 in Study 295. The ASC-12 is used to measure the frequency of symptoms related to allodynia (pain).[8,35] The checklist poses the question "How often do you experience increased pain or an unpleasant sensation on your skin during your most severe type of headache when you engage in each of the following?" and provides the following situations: combing hair; pulling hair back (e.g., in a ponytail); shaving one's face; wearing eyeglasses, contact lenses, earrings, a necklace, or tight clothing; taking a shower (when the water hits one's face); resting one's face or head on a pillow; exposure to heat (e.g., cooking, washing face with hot water); and exposure to cold (e.g., using an ice pack, washing face with cold water).[8] Possible answers to each situation include: "does not apply to me," "never," "rarely," "less than half the time," and "half the time or more." Each response reflecting one of the first three options receives a score of 0, "less than half the time" receives a score of 1, and "half the time or more" receives a score of 2. A total score is then derived from a sum of the scores for each of the 12 questions. A total score of 0 to 2 corresponds to no allodynia, 3 to 5 to mild allodynia, 6 to 8 to moderate allodynia, and 9 or more to severe allodynia. No migraine-specific MCID was found for this instrument.

The Clinical Global Impression – Improvement (CGI-I) and Patient Global Impression of Change (PGIC) scales were assessed as exploratory outcomes in Study 295 at weeks 4 and 12. CGI-I is a global assessment of the change in clinical status from treatment initiation conducted by a clinician (such as a physician, nurse practitioner, or physician's assistant) throughout the study.[8] In Study 295, clinicians were asked to assess patients according to the following question: "Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment. Compared to his condition at admission to the project, how much has he changed?" The clinician then answers on a scale from 0 to 7, ranging from "not assessed" or "very much improved" (score of 0 or 1, respectively) to "no change" (4) to "very much worse" (7). The PGIC is similar to the CGI-I; however, it is a global assessment of the change in clinical status completed by the patient.[8] In Study 295, this involved respondents that were asked to answer the following question: "Since beginning treatment at this clinic, how would you describe the change (if any) in activity limitations, symptoms, emotions, and overall QoL, related to you painful condition?" Unlike the CGI-I, patients answered this question two ways: using the seven-point scale ranging from "no change (or conditions get worse)" to "a great deal better, and a considerable improvement that has made all the difference" and a VAS, ranging from "much better" (or a

score of 0) to “much worse” (or a score of 10). No migraine-specific MCIDs were found for these instruments.

Statistical Analysis

A mixed-effect model repeated measure analysis was applied to continuous primary and secondary outcomes in the included studies. The model included treatment group, baseline value, stratification factors, scheduled visits, and the interaction of treatment groups with scheduled visit, without any imputation of missing data. For dichotomous outcomes (such as percent of patients with 50% reduction in headaches), a stratified Cochran-Mantel-Haenszel test was used. Missing data were imputed as nonresponse. In LIBERTY, the test was stratified by MMDs (four to seven or eight to 14), and the 50% responder outcome was the primary outcome in this study.

Power calculations were performed in all studies. In Study 295, calculations were based on a mean difference in MMDs between groups of −1.9 and an SD of 6.1, and these estimates were derived from three RCTs involving Botox and topiramate. The planned sample sizes for Study 295 (N = 186 for erenumab and N = 279 for placebo) provide 85% power using a two-sample t-test with a two-sided significance level of 0.04 (erenumab 70 mg versus placebo) and 0.01 (erenumab 140 mg versus placebo). The sample sizes assumed a 10% dropout rate. In STRIVE, a treatment effect (mean ± SD) of −1.12 ± 3.78 for the erenumab 70 mg group and −1.30 ± 3.78 for the erenumab 140 mg group was assumed to calculate a sample size of 284 patients per group, providing 90% power using a two-sided t-test with significance levels of 0.04 (erenumab 70 mg) and 0.01 (erenumab 140 mg). These estimates of treatment effects over placebo were based on the phase II Study 178. The investigators went on to state that this sample would provide 97% power to detect a difference of 0.96 between erenumab and placebo for MMDs and 95% power to detect a difference of 15.5% for the secondary outcome (50% responder). LIBERTY assumed a difference of 20% between erenumab 140 mg and placebo for the 50% responder outcome, which was the primary outcome of this study. This estimate, which would provide 90% power at a two-sided alpha of 0.05, arrived at a sample of N = 110 per group. ARISE used the same assumptions as STRIVE to arrive at its power calculations.

Multiplicity was accounted for by use of a hierarchical gate-keeping procedure and the Hochberg method. In Study 296, for the primary outcome, the threshold for statistical significance was set at P = 0.04 for the erenumab 70 mg group and at P = 0.01 for the erenumab 140 mg group. As long as one of the two doses was found to be statistically significant, testing could proceed on the secondary outcomes, using those same thresholds for statistical significance. In ARISE, where only the erenumab 70 mg dose was investigated, a gate-keeping procedure was used. If the primary outcome was found to be statistically significant at a threshold of P < 0.05, then the first two secondary outcomes were to be tested using a significance level on P < 0.04. If these were statistically significant, then the last two secondary outcomes would be tested at a significance level of P < 0.05. However if these first two secondary outcomes were not statistically significant, an alpha of P < 0.01 was to be used as a threshold for statistical significance for the last two secondary outcomes.

Across the studies, the primary analysis of continuous outcomes (such as change from baseline in MMDs) did not impute missing data, although sensitivity analyses employed the last observation carried forward and inverse probability weighted methods and multiple imputation with assumption of data missing at random and not missing at random . For dichotomous outcomes, missing data were imputed as nonresponders.

Analysis Populations

A full analysis set (FAS), which included all subjects randomized in the study, was used to tabulate demographic and baseline characteristics, patient disposition, and important protocol deviations. In LIBERTY this was the randomized analysis set. The efficacy analysis set (EAS) included all patients who received at least one dose of the investigational product and had at least one change from baseline measurement in MMDs or one diary entry during the DBTP. In LIBERTY this was the FAS. The EAS was used for analyses of efficacy end points and patient-reported outcomes. The safety analysis set included all randomized subjects who received at least one dose of the investigational product and was used for safety outcome.

The per-protocol set was a subset of the EAS that included patients who received the weeks 12, 16, and 20 investigational product in STRIVE and week 8 product in the other studies and did not have important protocol deviations, missing monthly migraine day measurements at any week 16, 20, or 24 visits, missing administrations of the investigational product, or a partial dose at any week 12, 16, or 20 visits (based on blinded information), or who received a box containing a product different from their assigned treatment at any visit among weeks 12, 16, and 20 (based on unblinded information). The per-protocol set was used for sensitivity analyses on primary and secondary efficacy end points. For the final analysis at week 12 in Study 295 and ARISE, patients who received the week 8 investigational product and did not have important protocol deviations or good clinical practices violations, and those who did not have an observed MMD value at week 12 were excluded.

Patient Disposition

Withdrawals in Study 295 amounted to 7% of placebo patients and 4% of each erenumab group (Table 11 and Table 12). In STRIVE, withdrawals amounted to 12% of those on placebo and 10% of the erenumab 70 mg and 9% of the erenumab 140 mg groups. Withdrawals were similar between erenumab and placebo groups in LIBERTY (3% versus 2%) and ARISE (5% versus 6%).

Table 11: Patient Disposition (STRIVE and Study 295)

Characteristics	STRIVE			Study 295		
	ERE 70 mg N = 317	ERE 140 mg N = 319	Placebo N = 319	ERE 70 mg N = 191	ERE 140 mg N = 190	Placebo N = 286
Screened	1,492			953		
Randomized	317	319	319	191	190	286
Patients who never received treatment	[redacted]	[redacted]	[redacted]	1 (0.5)	2 (1.1)	4 (1.4)
Patients who received treatment	314 (99.1)	319 (100.0)	319 (100.0)	190 (99.5)	188 (98.9)	282 (98.6)
Patients who discontinued DBTP	**33 (10.4)**	**27 (8.5)**	**37 (11.6)**	**7 (3.7)**	**8 (4.2)**	**21 (7.3)**
• Decision by sponsor	1 (0.3)	1 (0.3)	1 (0.3)	4 (2.1)	2 (1.1)	5 (1.7)
• Patient request	28 (8.8)	21 (6.6)	27 (8.5)	NR	NR	NR
• Lost to follow-up	4 (1.3)	5 (1.6)	9 (2.8)	2 (1.0)	2 (1.1)	7 (2.4)
• Withdrawn consent	NR	NR	NR	1 (0.5)	4 (2.1)	9 (3.1)
Efficacy analysis set inclusion	312 (98.4)	318 (99.7)	316 (99.1)	188 (98.4)	187 (98.4)	281 (98.3)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	STRIVE			Study 295		
	ERE 70 mg N = 317	ERE 140 mg N = 319	Placebo N = 319	ERE 70 mg N = 191	ERE 140 mg N = 190	Placebo N = 286
[redacted]						

DBTP = double-blind treatment phase; ERE = erenumab; GCP = good clinical practice; MMD = monthly migraine day; NR = not reported.

Source: Clinical Study Report for STRIVE and Study 295.[8]

Table 12: Patient Disposition (LIBERTY and ARISE)

Characteristics	LIBERTY		ARISE	
	ERE 140 mg N = 121	PLACEBO N = 125	ERE 70 mg N = 286	PLACEBO N = 291
Screened	333		887	
Discontinued prior to completing baseline period	96 (28.8)		NR	
• Screen failure	88 (26.4)		NR	
• Withdrawal by patient	8 (2.4)		NR	
Randomized	121	125	286	291
Patients who completed DBTP	118 (97.5)	122 (97.6)	271 (94.8)	275 (94.5)
Patients who discontinued DBTP	**3 (2.5)**	**3 (2.4)**	**15 (5.2)**	**16 (5.5)**
• Protocol deviation	2 (1.7)	1 (0.8)	0	0
• Pregnancy	0	1 (0.8)	0	0
• Patient/guardian decision	1 (0.8)	1 (0.8)	[redacted]	[redacted]
• Decision by sponsor	0	0	[redacted]	[redacted]
• Lost to follow-up	0	0	2 (0.7)	3 (1.0)
Patients entering OLE	118 (97.5)	122 (97.6)	NR	NR
Patients who completed open-label treatment phase	NR	NR	51 (17.8)	50 (17.2)
Patients continuing open-label treatment phase	NR	NR	203 (71.0)	202 (69.4)
Patients who discontinued open-label treatment phase	NR	NR	14 (4.9)	18 (6.2)

Characteristics	LIBERTY		ARISE	
	ERE 140 mg N = 121	PLACEBO N = 125	ERE 70 mg N = 286	PLACEBO N = 291
• Protocol-specified criteria	NR	NR	4 (1.4)	6 (2.1)
• Decision by sponsor	NR	NR	1 (0.3)	0
• Patient request	NR	NR	7 (2.4)	10 (3.4)
• Lost to follow-up	NR	NR	2 (0.7)	2 (0.7)
Randomized analysis set	121 (100)	125 (100)	NR	NR
Full analysis set	119 (98.3)	124 (99.2)	NR	NR
Safety analysis set	119 (98.3)	124 (99.2)	NR	NR
Efficacy analysis set inclusion	NR	NR	282 (98.6)	288 (99.0)
Safety analysis set inclusion	NR	NR	283 (99.0)	289 (99.3)
Open-label treatment phase set	NR	NR	268 (93.7)	270 (92.8)
Per-protocol analysis set inclusion	NR	NR	262 (91.6)	260 (89.3)

DBTP = double-blind treatment phase; ERE = erenumab; OLE = open-label extension; NR = not reported.

Source: Clinical Study Report for LIBERTY[9] and ARISE.[10]

Exposure to Study Treatments

Table 13: Exposure

Characteristics	STRIVE			Study 295		
	ERE 70 mg N = 317	ERE 140 mg N = 319	Placebo N = 319	ERE 70 mg N = 191	ERE 140 mg N = 190	Placebo N = 286
Mean (SD) exposure, days	[redacted]	[redacted]	[redacted]	82.8 (10.01)	83.8 (6.84)	82.5 (10.78)
	LIBERTY		ARISE			
	ERE 140 mg N = 119	Placebo N = 124	ERE 70 mg N = 286	PLACEBO N = 286		
Mean (SD) exposure, weeks (LIBERTY), days (ARISE)	[redacted]	[redacted]	[redacted]	[redacted]		

ATP = active treatment phase; EOS = end of study; ERE = erenumab; DBTP = double-blind treatment phase; SD = standard deviation.

Note: In STRIVE, duration of exposure to DBTP investigational product (IP) is calculated as (minimum [last DBTP dose date + 27, first ATP dose date – 1, EOS date] – first double-blind dose date + 1) for subjects who receive active ATP IP dose, and (minimum [last DBTP IP dose date + 27, EOS date] – first DBTP IP dose date + 1) for subjects who did not receive any ATP IP dose.[7] In other studies, duration of exposure to DBTP IP is calculated as minimum (last DBTP IP dose date + 28, EOS date – first DBTP IP dose date).[8-10]

Critical Appraisal

Internal Validity

All studies were double-blinded and a matching placebo injection was used to facilitate blinding and allocation concealment. Patients' withdrawal due to AEs was not substantially different between treatment arms. There were no signals of treatment-emergent AEs that could have led to unblinding considerable enough to affect the assessments of drug effect. No substantial loss to follow-up due to either AEs or other reasons was reported. The treatment compliance as monthly injection appeared to be complete and comparable between treatment groups in all the studies.

Overall, the quality of the conduct of the four trials for a three- to six-month duration was reasonably appropriate as judged by the number of patients with missing data, premature withdrawals of study, and treatment. In particular, missing data for dichotomous outcomes (e.g., headache) were imputed as nonresponders. This is a conservative method of imputation for dichotomous outcome measures that tend to bias results toward the null, although it may be less conservative in non-ITT–based analyses and differential withdrawals in the comparator group. The proportion of patients withdrawing was approximately 10% or less across studies, with differences of no more than 3% between groups within any study. This method of imputation is less likely to have biased results in favour of erenumab than if withdrawals were higher or there was a larger difference between groups in withdrawals.

The primary analyses for continuous outcomes did not attempt to impute missing data, and this excluded data for between approximately 5% and 10% of the population, depending on the study. The number of patients with missing data appears to approximate the number of early withdrawals; presumably the patients with missing data are those who withdrew prematurely from the study. The sponsor did apply various imputation methods in sensitivity analyses of these outcomes, and the results were consistent with that of the primary analysis. Nevertheless, an ITT analysis is preferred as a primary analysis as it is more conservative and accounts for all randomized patients.

The outcome measures of headache, including patient-reported outcomes, such as MSQ, HIT-6, and MPFID using diaries, questionnaires and other instruments were assessed for their validity, test-retest reliability and responsiveness to change (Appendix 5). Those outcomes are subjective in nature and may have been prone to recall bias, although such bias may not have differed between the treatment groups. For example, the construct validity on migraine-specific quality-of-life measures using HIT-6 was moderate, or in some cases low (e.g., between HIT-6 and the role physical and social functioning scales [$r = -0.36$ and $r = -0.38$, respectively] and the bodily pain and mental health scales [$r = -0.25$ and $r = -0.27$, respectively]; see Appendix 5), as long as the validity of the outcome measures were assessed using the correlation coefficients from those studies in the literature. The use of MPFIDs generally showed sound validity and reliability. The assessment of those quality-of-life and patient-important outcomes need to take these factors into consideration, not just statistically significant differences between treatment arms.

External Validity

All four of the included studies set up a list of stringent enrolment criteria resulting in a selected patient population that may be more likely to demonstrate a more favourable benefit-risk profile than how the drug could be used in a “real world” setting. For example, only a minority of patients in STRIVE (approximately 17%) or approximately half of patients in Study 295 had failed two or more commonly used prophylactic migraine therapies (indicating difficult to treat), or had a history of major psychiatric disorders, the use of more than one medication to control anxiety, or various cardiovascular diseases, such as myocardial infarction, stroke, or hypertension. The sponsor-requested criteria for reimbursement is adults with at least eight MMDs and who have failed, are intolerant of, or have a contraindication to at least two migraine prevention therapies.

Although the risk of migraine tends to decrease as patients reach the age of 50 to 65 years, the fact that CGRP has vascular effects suggests that it may also have cardiovascular effects, and this may potentially exacerbate existing cardiovascular disease. The study

patients in the four trials tended to suffer from fewer complications associated with other severe chronic diseases that require multiple drugs for treatment. This presents a potential generalizability issue, as we are not able to determine whether erenumab is safe to use, for example, in patients with cardiovascular disease, or whether there would be a similar benefit-risk profile in patients on multiple psychotropic drugs.

All the included studies were placebo-controlled, which is a limitation when trying to assess the comparative efficacy and harms of erenumab compared to other drugs used as migraine prophylactics. Although many migraine prophylactics lack official indications for this disorder, drugs such as onabotulinum toxin A and topiramate do have indications for migraine prophylaxis. Head-to-head comparisons of these would be useful. The sponsor did provide an indirect comparison of erenumab versus onabotulinum toxin A in patients with chronic migraine. The results are summarized and appraised in Appendix 8.

The included studies were all of relatively short duration for assessing the long-term safety and efficacy of erenumab, a first-in-class drug with a novel mechanism of action. The longest exposure to the drug in a DBTP was 24 weeks in STRIVE, and the other studies ran for only 12 weeks. Although there were extensions and ATPs with up to 64 weeks of exposure to erenumab, these lacked a placebo comparator and had other methodological shortcomings, most notably a change in dosing while the study was ongoing.

The clinical expert consulted by CADTH for this review concluded that the baseline demographics and disease characteristics were generally reflective of the population that would be expected to receive this drug in Canada. The expert noted that the mean age was slightly older than would be expected; however, this small difference is unlikely to have an impact on the generalizability of the findings. Health Canada noted that the percent of female patients enrolled in the studies may be slightly higher than would be expected of migraine patients in Canada.[17] Although women make up the majority of migraine sufferers in Canada, the percentages are not quite as high as seen in the included studies. The clinical expert also noted that STRIVE patients could not have had "no therapeutic response" to any more than two prior prophylactic medications, for example, and this may have been unnecessarily restrictive, given how difficult this population can be to treat.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Table .

Migraine Frequency

Frequency of migraines was the primary outcome of each of the included studies, expressed either as a mean change from baseline in MMDs, or the percentage of patients with a 50% reduction in MMDs.

In STRIVE, there was a decrease in MMDs in months 4, 5, and 6 compared to baseline (eight MMDs on average) in each of the groups, and the difference between groups was statistically significant for both the erenumab 70 mg dose (LS MD between groups of −1.40 days; 95% CI, −1.88 to −0.92; P < 0.001) and the erenumab 140 mg group (LS MD between groups of −1.85 days; 95% CI, −2.33 to −1.37; P < 0.001). In Study 295, the mean change from baseline (18 MMDs on average) to week 12 was larger with erenumab 70 mg (−2.46 days; 95% CI, −3.52 to −1.39; P < 0.001) and with erenumab 140 mg (−2.45 days; 95% CI, −3.51 to −1.38; P < 0.001) versus placebo. In ARISE, there was a larger reduction in MMDs from baseline (eight on average) with erenumab 70 mg versus placebo at week

12 (LS MD = −1.04 days; 95% CI, −1.61 to −0.47; P < 0.001). The change from baseline in MMDs was a secondary outcome in LIBERTY, which reported a larger decrease from baseline (nine MMDs on average) at week 12 with erenumab 140 mg versus placebo (LS MD = −1.61 days; 95% CI, −2.70 to −0.52; P = 0.004). In general, there was a reduction of one to two days out of eight to nine MMDs compared to placebo during a 12- to 24-week treatment period among those patients with episodic migraine. The reduction was more evident (2.5 days on average out of 18 MMDs at baseline) in patients with chronic migraine, as shown in Study 295. There was no substantial difference in the mean reduction of MMDs between erenumab 70 and 140 mg, as shown in the included studies.

In STRIVE, over a 24-week DBTP, the percentage of patients with a 50% reduction in mean MMDs was larger with erenumab 70 mg (43%; odds ratio [OR] = 2.13; 95% CI, 1.52 to 2.98; P < 0.001) and with erenumab 140 mg (50%; OR = 2.81; 95% CI, 2.01 to 3.94; P < 0.001) compared with placebo (27%). In Study 295, the percentage of patients with a 50% reduction in mean MMDs was higher with erenumab 70 mg (40%; OR = 2.18; 95% CI, 1.46 to 3.27; P < 0.001) and with erenumab 140 mg (41%; OR = 2.34; 95% CI, 1.56 to 3.51; P < 0.001) versus placebo (24%) at month 3. In ARISE, the percentage of patients who had a 50% reduction in MMDs was higher with the erenumab 70 mg group than with placebo (40% versus 30%; OR = 1.59; 95% CI, 1.12 to 2.27; P = 0.010). The percentage of patients with a 50% reduction in MMDs was the primary outcome of LIBERTY, which reported a larger percentage of patients treated with erenumab 140 mg versus placebo (30% versus 14%; OR = 2.73; 95% CI, 1.43 to 5.19; P = 0.002).

Change in cumulative monthly headache hours was a secondary outcome of Study 295. The cumulative number of headache hours was reduced in all groups in Study 295, and the difference in reduction was not statistically significant for the erenumab 70 mg versus placebo (LS MD = −9.54; 95% CI, −26.98 to 7.90; P = 0.28) but was statistically significant at the erenumab 140 mg dose versus placebo (LS MD = −19.31; 95% CI, −36.71 to −1.92; P = 0.030).

Subgroups

In STRIVE, statistically significant improvements were maintained for the change from baseline to month 6 regardless of whether patients had current or prior migraine prophylaxis, whether they had fewer than eight MMDs, and whether they had failed prior prophylaxis. It is not clear whether prior prophylaxis included onabotulinum toxin A.

In Study 295, responses appeared to be statistically significant between erenumab and placebo for subgroups of patients with previous headache-medication overuse and those who did not have prior overuse, those who had used one or more or two or more prior prophylactic medications, those who had used prior prophylactic topiramate, those who had never used topiramate, patients with fewer than the median baseline MMDs, and those who had a baseline MMDs equal to the median or greater. For the subgroup of patients who had prior use of onabotulinum toxin A, there did not appear to be a statistically significant improvement at either erenumab dose versus placebo, while those who had never used onabotulinum toxin A had statistically significant responses.

However, in ARISE, subgroups based on use of prior migraine prophylactics (ever versus never used), baseline MMDs (fewer than eight versus at least eight), or whether they failed prior prophylaxis (yes or no) all appeared to have statistically significant treatment effects versus placebo. It is not clear whether prior prophylaxis included onabotulinum toxin A.

In LIBERTY, in the subgroup analysis based on number of prior failed migraine prophylaxis, the only subgroup not to report statistical significance versus placebo was composed of those who had failed four prior drugs. Those with four to seven MMDs did not have a statistically significant treatment effect versus placebo. These findings may have been limited by the small sample size. It is unclear whether prior prophylactics included onabotulinum toxin A.

Migraine Medication Use

Acute migraine medication use was approximately three days per month at baseline and was reduced in all STRIVE groups from baseline to months 4, 5, and 6. There was a larger reduction in the erenumab 70 mg group (LS MD = −0.94 days; 95% CI, −1.23 to −0.64; P < 0.001) and erenumab 140 mg (LS MD = −1.42 days; 95% CI, −1.71 to −1.12; P < 0.001) versus placebo.

In Study 295, the monthly average days on acute migraine medication use was nine to 10, and there was a larger mean change from baseline to week 12 in days with acute medication use for erenumab versus placebo in both erenumab 70 mg (LS MD = −1.86 days; 95% CI, −2.60 to −1.13; P < 0.001) and erenumab 140 mg (LS MD = −2.55 days; 95% CI, −3.28 to −1.82; P < 0.001).

A reduction was reported in monthly medication use versus placebo in LIBERTY with erenumab 140 mg (LS MD = −1.73 days; 95% CI, −2.46 to −1.01; P < 0.001) and in ARISE with erenumab 70 mg (LS MD = −0.59 days; 95% CI, −0.96 to −0.21; P = 0.002). As in STRIVE, the monthly average days on acute migraine medication use in these two studies was three to five at baseline.

A similar reduction of an average of one or two days out of three to five days prior to erenumab 140 mg treatment was apparent in those patients with episodic migraine over a three- to six-month treatment in STRIVE and LIBERTY, whereas the reduction was no more than one day for erenumab 70 mg in STRIVE and ARISE. The reduction in patients with chronic migraine was more evident, as demonstrated by Study 295, with an average of two to 2.5 days out of nine to 10 days per months over three months of treatment.

Patient-Reported Outcomes

Migraine Physical Function Impact Diary

In STRIVE, MPFID scores were reported as a secondary outcome. The mean monthly physical impairment domain score was reduced (improved) from baseline to months 4, 5 and 6 in all three groups, and this reduction was statistically significant versus placebo in both the erenumab 70 mg (LS MD = −1.86; 95% CI, −2.95 to −0.77; P < 0.001) and the erenumab 140 mg groups (LS MD = −2.43; 95% CI, −3.51 to −1.35; P < 0.001).

The mean monthly impact on everyday activities score was reduced from baseline to months 4, 5, and 6 in all three groups, and this reduction was statistically significant versus placebo in the erenumab 70 mg (LS MD = −2.22; 95% CI, −3.28 to −1.16; P < 0.001) and the erenumab 140 mg (LS MD = −2.57; 95% CI, −3.62 to −1.51; P < 0.001) groups.

Changes in these domains of the MPFID were also secondary outcomes in LIBERTY, in which a statistically significant reduction was observed in physical impairment domain scores from baseline to week 12 for erenumab 140 mg versus placebo (LS MD = −3.46; 95% CI, −5.70 to −1.23; P = 0.003) and in the everyday activities domain from baseline to

week 12 for erenumab 140 mg versus placebo (LS MD = −3.91; 95% CI, −6.12 to −1.70; P < 0.001).

In ARISE, the percentage of patients with a five-point improvement in domain scores was a secondary outcome, and at week 12 there was no statistically significant difference between erenumab 70 mg and placebo in the percentage of patients with improved everyday activity domain scores (OR = 1.22; 95% CI, 0.87 to 1.71; P = 0.26) or physical impairment domain scores (OR = 1.33; 95% CI, 0.92 to 1.90; P = 0.13). Change in domain scores was also reported as an exploratory outcome in ARISE. Physical domain and everyday activities scores were reduced in both erenumab and placebo groups, and the difference between groups was an LS MD of −1.30 (95% CI, −2.40 to −0.19; P = 0.021) for physical impairment and −1.38 (95% CI, −2.60 to −0.15; P = 0.028) for everyday activities.

The between-group MCID for the MPFID was between −1.60 and –2.54 for physical impairment and between −0.87 and −2.62 for everyday activities, based on data provided by the sponsor. The provided between-group MCID does not appear to have been independently validated, but the differences between erenumab and placebo are clinically significant in two of the three studies. MPFID was an exploratory outcome assessed only in a small group of patients as a substudy of Study 295, for the purpose of validating the instrument.

Headache Impact Test

The HIT-6 was an exploratory outcome in all four included studies. Scores were reduced (improved) from baseline to week 24 in all groups in STRIVE, with an LS MD of −2.1 (95% CI, −3.0 to −1.1) between erenumab 70 mg and placebo and −2.3 (95% CI, −3.2 to −1.3) between erenumab 140 mg and placebo. STRIVE also reported the percent of patients with a reduction in HIT-6 scores of five points or greater, and the ORs were 1.98 (95% CI, 1.44 to 2.73) for erenumab 70 mg versus placebo and 1.49 (95% CI, 1.09 to 2.04) for erenumab 140 mg versus placebo. Similarly, in Study 295, the scores were reduced in all groups, and the difference in reduction between groups for erenumab 70 mg and for erenumab 140 mg versus placebo was the same, with an LS MD of −2.5 (95% CI, −3.7 to −1.2). The HIT-6 scores were also reduced in all groups in LIBERTY (LS MD between erenumab 140 mg and placebo of −2.95; 95% CI, −4.49 to −1.41) and ARISE (LS MD between erenumab 70 mg and placebo of −2.3; 95% CI, −3.3 to −1.3). These findings on HIT-6 met the pre-reported MCID. The MCID was −1.5 for patients with episodic migraine and −2.3 for chronic daily headaches. However, given that these were exploratory outcomes, the clinical significance of these findings is uncertain.

LIBERTY also reported the percentage of patients achieving certain milestones on the HIT-6 (moderately, substantially, and severely impacted by their headache). The ORs comparing erenumab 140 mg to placebo were: moderate impact, 0.68 (95% CI, 0.30 to 1.53; P = 0.348); substantial impact, 0.43 (95% CI, 0.25 to 0.77; P = 0.004); and severe impact, 0.42 (95% CI, 0.25 to 0.71; P = 0.001).

Allodynia Symptom Checklist

Scores for the ASC-12 decreased from baseline to week 12 in in all groups in Study 295. In the erenumab 70 mg group versus placebo, the LS MD was −0.39 (95% CI, −0.83 to 0.06; P = 0.087) and in the erenumab 140 mg group it was −0.42 (95% CI, −0.86 to 0.03; P = 0.065). No migraine-specific MCID was found for this outcome.

Patient-Reported Outcomes Measurement Information System

Change from baseline in PROMIS scores was an exploratory outcome of Study 295. All groups had reduced scores from baseline to week 12, and the difference between erenumab 70 mg and placebo was −1.99 (95% CI, −3.12 to −0.86; P < 0.001) and for erenumab 140 mg versus placebo it was −2.62 (95% CI, −3.77 to −1.47; P < 0.001). No migraine-specific MCID was found for this outcome.

Beck Depression Inventory – II

The change from baseline in BDI-II scores was an exploratory outcome of LIBERTY. The difference between erenumab 140 mg and placebo was −0.44 (95% CI, −1.31 to 0.43; P = 0.318). No migraine-specific MCID was found for this outcome.

Health-Related Quality of Life

The MSQ was assessed as an exploratory outcome in all four included studies. The RFR, RFP, and EF scores of the questionnaire increased (improved) from baseline to month 6 in all groups in STRIVE. For the RFR, the LS MD between erenumab 70 mg and placebo was 5.12 (95% CI, 2.81 to 7.42) and for erenumab 140 mg versus placebo the LS MD was 6.47 (95% CI, 4.17 to 8.77). For the RFP score, erenumab 70 mg versus placebo the LS MD was 4.21 (95% CI, 2.15 to 6.28) and for erenumab 140 mg versus placebo it was 5.43 (95% CI, 3.37 to 7.49). For the EF score for erenumab 70 mg versus placebo, the LS MD was 5.21 (95% CI, 2.83 to 7.58) and for erenumab 140 mg versus placebo it was 6.73 (95% CI, 4.36 to 9.10).

For the change from baseline to week 12 in Study 295 for RFR, the LS MD between erenumab 70 mg and placebo was 5.95 (95% CI, 2.28 to 9.62) and for erenumab 140 mg versus placebo it was 7.35 (95% CI, 3.67 to 11.03); in ARISE between erenumab 70 mg and placebo it was 5.48 (95% CI, 2.81 to 8.16). In Study 295 the change from baseline to week 12 for the RFP for erenumab 70 mg versus placebo was an LS MD of 4.13 (95% CI, 0.87 to 7.39) and erenumab 140 mg versus placebo had an LS MD of 4.94 (95% CI, 1.67 to 8.20), while in ARISE between erenumab 70 mg and placebo the LS MD was 3.57 (95% CI, 1.11 to 6.04). In Study 295, the change from baseline to week 12 for the EF score for erenumab 70 mg versus placebo was an LS MD of 8.32 (95% CI, 4.27 to 12.36) and for erenumab 140 mg versus placebo the LS MD was 8.90 (95% CI, 4.85 to 12.96), while in ARISE between erenumab 70 mg and placebo the LS MD was 4.48 (95% CI, 1.60 to 7.35). The MSQ was not assessed in LIBERTY.

Overall, the improvements in MSQ were generally consistent in erenumab 70 and 140 mg during a three- to six-month treatment period, as were the magnitude of changes over placebo in STRIVE and ARISE.

As demonstrated in previous studies, MCIDs in the MSQ varied by domain and depending on whether migraine was episodic or chronic. For the RFR domain, the group-level MCID was 3.2 for episodic migraine and 10.9 for chronic migraine; for the RFP domain, MCIDs were 4.6 and 8.3 for episodic and chronic migraines, respectively, and for the EF domain the MCIDs were 7.5 and 12.2, respectively. Despite erenumab 70 mg or 140 mg showing a clinically significant improvement in RFP domains in episodic migraine, the benefit on patient's qualify of life generally could not be recognized as clinically significant in the other two domains, regardless of episodic or chronic migraine.

Scores on the EQ-5D-5L VAS and index were exploratory outcomes of LIBERTY. The LS MD for the VAS between erenumab 140 mg and placebo was 0.97 (95% CI, −3.75 to 5.70), while for index scores, the LS MD for erenumab 140 mg versus placebo was 0.01 (95% CI, −0.03 to 0.04).

Loss of Work Days

The WPAI instrument was used to assess the percent of work time missed due to migraine, and the LS MD between erenumab 140 mg and placebo in LIBERTY was −4.11 (95% CI, −9.02 to 0.80; P = 0.100). This was the only study that assessed this outcome.

Table 14: Key Efficacy Outcomes (STRIVE)

	STRIVE		
	ERE 70 mg (N = 317)	ERE 140 mg (N = 319)	Placebo (N = 319)
Migraine frequency			
Change from baseline to last 3 months in mean MMDs during DBTP			
Mean (SD) baseline	8.31 (2.45)	8.33 (2.48)	8.25 (2.51)
Mean (SE) change from baseline in mean over months 4, 5, and 6	−3.36 (0.21) N = 296	−3.83(0.18) N = 302	−1.95 (0.22) N = 289
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI)[a]	**70 mg:** −1.40 (−1.88 to −0.92); P < 0.001 **140 mg:** −1.85 (−2.33 to −1.37); P < 0.001		
Patients with 50% reduction in mean MMDs during the last 3 months, n (%)	135 (43.3)	159 (50.0)	84 (26.6)
Common odds ratio (95% CI)[b]	**70 mg:** 2.13 (1.52, 2.98); P < 0.001 **140 mg:** 2.81 (2.01, 3.94); P < 0.001		
Migraine attacks per month			
Mean (SD) baseline	5.24 (1.48)	5.16 (1.42)	5.12 (1.49)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
Medication use			
Change from baseline in monthly acute migraine-specific medication treatment days months 4, 5, and 6			
Mean (SD) baseline	3.24 (3.40)	3.42 (3.48)	3.43 (3.43)
Mean (SE) change from baseline at months 4, 5, and 6	−1.12 (0.13) N = 296	−1.64 (0.13) N = 302	−0.26 (0.14) N = 289
[redacted]	[redacted]	[redacted]	[redacted]

	STRIVE		
	ERE 70 mg (N = 317)	ERE 140 mg (N = 319)	Placebo (N = 319)
Difference in LSM vs. placebo (95% CI)[a]	**70 mg:** −0.94 (−1.23 to −0.64); P < 0.001 **140 mg:** −1.42 (−1.71 to −1.12); P < 0.001		
Functional impact			
Change from baseline in mean monthly average physical impairment domain score as measured by MPFID at months 4, 5, and 6 during DBTP			
Mean (SD) baseline	12.56 (9.65)	11.98 (8.95)	12.24 (9.43)
Mean change (SE) from baseline, months 4, 5, and 6	−4.42 (0.48) N = 296	−4.83 (0.46) N = 302	−2.65 (0.48) N = 289
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM vs. placebo (95% CI)[a]	**70 mg:** −1.86 (−2.95 to −0.77); P < 0.001 **140 mg:** −2.43 (−3.51 to −1.35); P < 0.001		
Change from baseline in mean monthly average impact on everyday activities score as measured by MPFID at months 4, 5, and 6 during the DBTP			
Mean (SD) baseline	14.04 (8.88)	13.00 (8.21)	13.65 (9.07)
Mean change (SE) from baseline at months 4, 5, and 6	−5.83 (0.45) N = 296	−5.83 (0.44) N = 302	−3.66 (0.49) N = 289
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM vs. placebo (95% CI)[a]	**70 mg:** −2.22 (−3.28 to −1.16); P < 0.001 **140 mg:** −2.57 (−3.62 to −1.51); P < 0.001		
≥ 75% reduction at months 4, 5, and 6, n (%)	65 (20.8)	70 (22.0)	25 (7.9)
[redacted]	[redacted]		
100% reduction at months 4, 5, and 6, n (%)	10 (3.2)	16 (5.0)	9 (2.8)
[redacted]	[redacted]		
≥ 5-point reduction from baseline in average physical impairment domain score (measured by MPFID) at months 4, 5, and 6	122 (39.1)	135 (42.5)	95 (30.1)
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		

	STRIVE		
	ERE 70 mg (N = 317)	ERE 140 mg (N = 319)	Placebo (N = 319)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Patient-reported outcomes (exploratory)	**N = 312**	**N = 318**	**N = 316**
HIT-6			
Change from baseline in HIT-6 total score (observed, GLIMMIX model)			
Mean (SD) baseline	60.3 (5.9)	59.2 (6.3)	59.8 (6.0)
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI) ERE vs. placebo[a]	**70 mg:** −2.1 (−3.0 to −1.1); P < 0.001 **140 mg:** −2.3 (−3.2 to −1.3); P < 0.001		
≥ 5-point reduction from baseline HIT-6, n (%)	176 (56.4)	158 (49.7)	126 (39.9)
Common odds ratio (95% CI) ERE vs. placebo[b,e]	**70 mg:** 1.98 (1.44, 2.73); P < 0.001 **140 mg:** 1.49 (1.09, 2.04); P = 0.013		
MIDAS			
Change from baseline in modified MIDAS total score (observed, GLIMMIX model)			
Mean (SD) baseline	14.5 (11.5)	12.9 (9.8)	14.9 (11.4)
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI) between ERE and placebo[a]	**70 mg:** −2.1 (−3.3 to −0.9); P < 0.001 **140 mg:** −2.8 (−4.0 to −1.7); P < 0.001		
MSQ			
Change from baseline in MSQ scores (observed, GLIMMIX model)			
MSQ-RFR score mean (SD) baseline	57.23 (17.39)	59.89 (18.42)	58.95 (19.11)
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI) between ERE and placebo[a]	**70 mg:** 5.12 (2.81 to 7.42) P < 0.001 **140 mg:** 6.47 (4.17 to 8.77) P < 0.001		
MSQ-RFP score mean (SD) baseline	70.87 (19.6)	72.58 (20.20)	71.17 (20.34)
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI) between ERE and placebo[a]	**70 mg:** 4.21 (2.15 to 6.28) P < 0.001 **140 mg:** 5.43 (3.37 to 7.49) P < 0.001		
MSQ-EF Score mean (SD) baseline	71.71 (23.64)	73.21 (22.91)	70.21 (24.75)

	STRIVE		
	ERE 70 mg (N = 317)	ERE 140 mg (N = 319)	Placebo (N = 319)
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI) between ERE and placebo[a]	**70 mg:** 5.21 (2.83 to 7.58) P < 0.001 **140 mg:** 6.73 (4.36 to 9.10) P < 0.001		

BDI-II = Beck Depression Inventory – II; CI = confidence interval; DBTP = double-blind treatment phase; EF = emotional function; ERE = erenumab; HIT-6 = six-item Headache Impact Test; LS = least squares; LSM = least squares mean; MD = mean difference; MIDAS = Migraine Disability Assessment Scale; MMD = monthly migraine day; MPFID = migraine physical function impact diary; MSQ = Migraine-Specific Quality of Life Questionnaire; RFP = role function – preventive; RFR = role function – restrictive; SD = standard deviation; SE = standard error; vs. = versus.

[a] Adjusted analysis utilizes a generalized linear mixed-effects model that includes treatment, visit, treatment by visit interaction, stratification factors region and prior and/or current treatment with migraine prophylactic medication, and baseline value as covariates and assumes a first-order autoregressive covariance structure. P values for pairwise comparisons are nominal P values without multiplicity adjustment. Adjusted analysis results for mean over months 4, 5, and 6 are obtained from the same generalized linear mixed-effects model using contrasts.

[b] The common ORs and P values are obtained from a Cochran-Mantel-Haenszel test, stratified by stratification factors region and prior and/or current treatment with migraine prophylactic medication. The same analysis is repeated for each visit. P values for pairwise comparisons are nominal P values obtained from the Cochran-Mantel-Haenszel test using data including placebo and corresponding erenumab-dose group only. The result of a Breslow-Day test for homogeneity of the OR cross strata for responder derived from the mean over months 4, 5, and 6 is 0.84 for 70 mg and 0.82 for 140 mg.

[c] The result of a Breslow-Day test for homogeneity of the OR cross strata for responder derived from the mean over months 4, 5, and 6 is 0.52 for 70 mg and 0.20 for 140 mg.

[d] The result of a Breslow-Day test for homogeneity of the OR cross strata for responder derived from the mean over months 4, 5, and 6 is 0.54 for 70 mg and 0.53 for 140 mg.

[e] The result of a Breslow-Day test for homogeneity of the OR cross strata for responder derived from the mean over months 4, 5, and 6 is 0.24 for 70 mg and 0.97 for 140 mg.

Source: Clinical Study Report for STRIVE.[7]

Table 15: Key Efficacy Outcomes (Study 295)

	Study 295		
	ERE 70 ng (N = 191)	ERE 140 mg (N = 190)	Placebo (N = 286)
Monthly migraine days			
Change from baseline in MMDs, observed, GLIMMIX model			
Mean (SE) baseline MMDs	17.94 (0.32)	17.78 (0.34)	18.24 (0.28)
Mean (SE) change from baseline at week 12	−6.63 (0.45) N = 178	−6.53 (0.50) N = 182	−4.24 (0.38) N = 267
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM vs. placebo (95% CI)[a]	**70 mg**: −2.46 (−3.52 to −1.39); P < 0.001 **140 mg**: −2.45 (−3.51 to −1.38); P < 0.001		
Patients with 50% reduction in mean MMDs from baseline during the last 3 months, n (%)	75 (39.9)	77 (41.2)	66 (23.5)
Adjusted odds ratio[b] (95% CI), ERE vs. placebo	**70 mg**: 2.18 (1.46 to 3.27); P < 0.001 **140 mg**: 2.34 (1.56 to 3.51); P < 0.001		
Migraine attacks			
Mean (SD) baseline	4.51 (1.67)	4.29 (1.61)	4.23 (1.74)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
Medication use			
Change from baseline in monthly acute migraine-specific medication baseline to week 12			
Mean (SE) baseline	8.77 (0.53)	9.68 (0.51)	9.42 (0.45)
Mean (SE) change from baseline to week 12	−3.25 (0.37) N = 178	−4.26 (0.38) N = 182	−1.62 (0.26) N = 267
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM vs. placebo (95% CI)[a]	**70 mg**: −1.86 (−2.60 to −1.13); P < 0.001 **140 mg**: −2.55 (−3.28 to −1.82); P < 0.001		
Monthly headache hours			
Mean (SD) baseline	223.61 (9.23)	215.06 (9.03)	235.28 (7.52)
Mean (SD) change from baseline at week 12	−66.58 (7.30) N = 178	−72.36 (8.74) N = 182	−59.26 (6.07) N = 267
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM vs. placebo (95% CI)[a]	**70 mg:** −9.54 (−26.98 to 7.90); P = 0.28 **140 mg:** −19.31 (−36.71 to −1.92); P = 0.030		
Patient-reported outcomes	**N = 188**	**N = 187**	**N = 281**
HIT-6			
HIT-6 total score mean (SE) baseline	63.4 (0.4)	62.7 (0.4)	63.3 (0.3)
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM vs. placebo (95% CI)[a]	**70 mg:** −2.5 (−3.7 to −1.2); P < 0.001 **140 mg:** −2.5 (−3.7 to −1.2); P < 0.001		

	Study 295		
	ERE 70 ng (N = 191)	ERE 140 mg (N = 190)	Placebo (N = 286)
MIDAS total score			
MIDAS total score mean (SE) baseline	65.8 (3.4)	60.9 (3.8)	68.0 (3.4)
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM vs. placebo (95% CI)[c]	**70 mg:** −11.86 (−19.34 to −4.39); P = 0.002 **140 mg:** −12.22 (−19.69 to −4.75); P = 0.001		
MSQ			
MSQ-RFR mean (SE) baseline	44.73 (1.33)	45.55 (1.40)	42.83 (1.05)
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSMs vs. placebo (95% CI) [a]	**70 mg:** 5.95 (2.28 to 9.62); P = 0.002 **140 mg:** 7.35 (3.67 to 11.03); P < 0.001		
MSQ-RFP mean (SE) baseline score	61.94 (1.58)	62.91 (1.54)	60.28 (1.19)
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM vs. placebo (95% CI) [a]	**70 mg:** 4.13 (0.87 to 7.39); P = 0.013 **140 mg:** 4.94 (1.67 to 8.20); P = 0.003		
MSQ-EF Mean (SE) baseline score	53.62 (1.84)	56.72 (1.95)	52.98 (1.54)
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM vs. placebo (95% CI) [a]	**70 mg:** 8.32 (4.27 to 12.36); P < 0.001 **140 mg:** 8.90 (4.85 to 12.96); P < 0.001		
ASC-12			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
PROMIS			
PROMIS mean (SE) baseline score	63.15 (0.34)	63.40 (0.37)	63.89 (0.25)
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI)[a]	**70 mg:** −1.99 (−3.12 to −0.86); P < 0.001 **140 mg:** −2.62 (−3.77 to −1.47); P < 0.001		

ASC-12 = 12-item Allodynia Symptom Checklist; CI = confidence interval; EF = emotional function; ERE = erenumab; HIT-6 = six-item Headache Impact Test; LSM = least squares mean; MIDAS = Migraine Disability Assessment Scale; MMD = monthly migraine day; MSQ = Migraine-Specific Quality of Life Questionnaire; PROMIS = Patient-Reported Outcomes Measurement Information System; RFP = role function – preventive; RFR = role function – restrictive; SD = standard deviation; SE = standard error; vs. = versus.

[a] Adjusted analysis utilizes a generalized linear mixed-effects model that includes treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assumes a first-order autoregressive covariance structure. P values for pairwise comparisons are nominal P values without multiplicity adjustment.

[b] The adjusted ORs and P values are obtained from a Cochran-Mantel-Haenszel test after the missing data are imputed as nonresponse, stratified by stratification factors region and medication overuse. The same analysis is repeated for each visit. P values for pairwise comparisons are nominal P values obtained from the Cochran-Mantel-Haenszel test using data including placebo and corresponding erenumab-dose group only.

[c] Adjusted analysis utilizes an analysis of covariance model that includes treatment, stratification factors region and medication overuse, and baseline value as covariates and the same analysis is repeated for each visit. P values for pairwise comparisons are nominal P values without multiplicity adjustment.

Source: Clinical Study Report for Study 295.[8]

Table 16: Key Efficacy Outcomes (LIBERTY, ARISE)

	LIBERTY		ARISE	
	ERE 140 mg (N = 119)	Placebo (N = 124)	ERE 70 mg (N = 286)	PLACEBO (N = 286)
Monthly migraine days				
Patients with at least a 50% reduction from baseline in MMDs by visit, n (%)				
Week 12 (primary outcome in LIBERTY)	**36 (30.3)**	**17 (13.7)**	112 (39.7)	85 (29.5)
Odds ratio (95% CI)	2.73 (1.43 to 5.19); P = 0.002[a]		1.59 (1.12 to 2.27); P = 0.010[d]	
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	3.28 [1.69, 6.38) P < 0.001[a]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	
Change from baseline in MMDs (primary outcome in ARISE)				
Mean (SD) baseline	9.3 (2.58)	9.3 (2.71)	8.13 (2.57)	8.38 (2.58)
Week 12, mean (SE) change from baseline	−1.76 (0.44)	−0.15 (0.41)	−2.89 (0.23) N = 268	−1.96 (0.25) N = 270
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM vs. placebo (95% CI)[b]	−1.61 (−2.70 to −0.52); P = 0.004		−1.04 (−1.61 to −0.47); P < 0.001[e]	
≥ 75% response rate at week 12	14 (11.8)	5 (4.0)	[redacted]	[redacted]
Odds ratio (95% CI)[a]	3.16 (1.11, 9.01); P = 0.025		[redacted]	
100% response rate at week 12	7 of 119 (5.9)	0 of 124 (0.0)	[redacted]	[redacted]
Odds ratio (95% CI)[a]	NA		[redacted]	
Migraine attacks				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	
Medication use				
Change from baseline in monthly acute migraine-specific medication				
Mean (SD) baseline	4.8 (2.95)	4.4 (2.84)	3.75 (3.65)	3.43 (3.59)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI), baseline to week 12	NR	NR	−1.21 (−1.48 to −0.94)	−0.62 (−0.89 to −0.35)
Difference in LSM vs. placebo (95% CI)	−1.73 (−2.46 to −1.01); P < 0.001[b]		−0.59 (−0.96 to −0.21); P = 0.002[e]	
Functional impact				
Change in physical impairment and everyday activities, MPFID				
Mean (SD) baseline, physical impairment	12.57 (9.64)	12.03 (8.99)	10.73 (8.92)	11.38 (9.08)
MPFID, physical impairment domain LSM (SE) change from week 12	−1.85 (0.84) N = 118	1.61 (0.80) N = 120	−3.18 (0.41)	−1.88 (0.40)
Mean difference between groups (95% CI)[b]	−3.46 (−5.70 to −1.23); P = 0.003		−1.30 (−2.40 to −0.19;) P = 0.021	
MPFID, everyday activities domain mean (SD) baseline	13.99 (8.89)	13.05 (8.25)	12.99 (8.66)	13.59 (8.90)

	LIBERTY		ARISE	
	ERE 140 mg (N = 119)	Placebo (N = 124)	ERE 70 mg (N = 286)	PLACEBO (N = 286)
MPFID, everyday activities domain LSM (SE) change from week 12	−3.36 (0.83) N = 118	0.55 (0.81) N = 120	−4.51 (0.45)	−3.13 (0.45)
Difference in LSM vs. placebo (95% CI)[b]	−3.91 (−6.12 to −1.70); P < 0.001		−1.38 (−2.60 to −0.15); P = 0.028	
5-point reduction from baseline in monthly average impact on everyday activity domain score, MPFID at week 12, n (%)	NR	NR	114 (40.4)	103 (35.8)
Common odds ratio vs. placebo (95% CI)	NR	NR	1.22 (0.87, 1.71); P = 0.26[d]	
5-point reduction from baseline in average physical impairment domain score, MPFID at week 12, n (%)	NR	NR	93 (33.0)	78 (27.1)
Common odds ratio vs. placebo (95% CI)		NR	1.33 (0.92 to 1.90); P = 0.13[d]	
HIT-6			**N = 282**	**N = 288**
Mean (SD) baseline	[redacted]	[redacted]	59.8 [redacted]	59.5 [redacted]
Mean (SD) change from baseline at week 12	−5.18 (6.59) N = 116	−2.23 (5.93) N = 124	NR	NR
Adjusted mean (SE) change from baseline to week 12	[redacted]	[redacted]	−4.9 (0.4)	−2.6 (0.4)
Difference between means (95% CI)[b]	−2.95 (−4.49 to −1.41); P < 0.001		−2.3 (−3.3 to −1.3); P < 0.001	
Patients with HIT-6 score ≥ 50 (moderate impact), week 12	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)[a]	[redacted]		[redacted]	[redacted]
Patients with HIT-6 score ≥ 56 (substantial impact), week 12	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)[a]	[redacted]		[redacted]	[redacted]
Patients with HIT-6 score ≥ 60 (severe impact), week 12	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)[a]	[redacted]		[redacted]	[redacted]
MIDAS				
Change from baseline in modified MIDAS[b] total score				
Mean (SD) baseline	NR	NR	14.1 [redacted]	13.6 [redacted]
LSM (SE) change from baseline to week 12	NR	NR	−5.5 (0.5)	−3.8 (0.5)
Difference in LSM vs. placebo (95% CI)[b]	NR	NR	−1.7 (−3.1 to −0.3); P = 0.021	
EQ-5D				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI) between means[b]	0.01 (−0.03 to 0.04); P = 0.630		NR	
MSQ				
MSQ-RFR score mean (SD) baseline	NR	NR	57.85 [redacted]	58.89 [redacted]

	LIBERTY		ARISE	
	ERE 140 mg (N = 119)	Placebo (N = 124)	ERE 70 mg (N = 286)	PLACEBO (N = 286)
LSM (SE) change from baseline to week 12	NR	NR	15.20 (0.98)	9.71 (0.98)
Difference in LSMs vs placebo (95% CI)[e]	NR	NR	5.48 (2.81, 8.16); P < 0.001	
MSQ-RFP score mean (SD) baseline	NR		70.50 [redacted]	72.44 [redacted]
LSM (SE) change from baseline to week 12	NR		12.01 (0.91)	8.44 (0.90)
Difference in LSM vs. placebo (95% CI) [e]	NR		3.57 (1.11, 6.04); P = 0.005	
MSQ-EF score mean (SD) baseline	NR		70.47 [redacted]	72.03 [redacted]
LSM (SE) change from baseline to week 12	NR		11.76 (1.06)	7.28 (1.05)
Difference in LSM vs. placebo (95% CI) [e]	NR		4.48 (1.60, 7.35); P = 0.002	
Beck Depression Inventory – II				
Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline to week 12	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE) change from baseline to week 12	[redacted]	[redacted]	[redacted]	[redacted]
Difference between means (95% CI)[c]	[redacted]		NR	NR
Work lost: WPAI				
Percent work time missed due to problem - Mean (SD) baseline	[redacted]	[redacted]	NR	NR
Mean (SD) change from baseline at week 12	−2.64 (11.88) N = 58	1.75 (19.33) N = 66	NR	NR
Adjusted mean (SE) change from baseline to week 12[b]	[redacted]	[redacted]	NR	NR
Difference between means (95% CI)	−4.11 (−9.02 to 0.80); P = 0.100		NR	

CI = confidence interval; EF = emotional function; EQ-5D= EuroQol 5-Dimensions; EQ-5D-5L= EuroQol 5-Dimensions 5-Levels; ERE = erenumab; HIT-6 = six-item Headache Impact Test; LSM = least squares mean; MIDAS = Migraine Disability Assessment Scale; MMD = monthly migraine day; MPFID = migraine physical function impact diary; MSQ = Migraine-Specific Quality of Life Questionnaire; NA = not applicable; NR = not reported; RFP = role function – preventive; RFR = role function – restrictive; SD = standard deviation; SE = standard error; VAS = Visual Analogue Scale; WPAI = Work Productivity and Activity Impairment; vs. = versus.

[a] Cochran-Mantel-Haenszel test adjusting for stratification factor (four to seven vs. eight to 14 migraine days at baseline) after missing data are imputed as nonresponse.

[b] A linear mixed-effects model includes treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit.

[c] Analysis of covariance model includes treatment group and stratification factor as fixed effects with baseline value as a covariate.

[d] The common ORs and P values are obtained from a Cochran-Mantel-Haenszel test, stratified by stratification factors region and prior and/or current treatment with migraine prophylactic medication. The same analysis is repeated for each visit. P values are nominal P values obtained from the Cochran-Mantel-Haenszel test. The result of a Breslow-Day test for homogeneity of ORs across strata at week 12 (month 3) is 0.89.

[e] Adjusted analysis utilizes a generalized linear mixed-effects model that includes treatment, visit, treatment by visit interaction, stratification factors region and prior and/or current treatment with migraine prophylactic medication, and baseline value as covariates and assumes a first-order autoregressive covariance structure. P values are nominal P values without multiplicity adjustment.

[f] The common ORs and P values are obtained from a Cochran-Mantel-Haenszel test, stratified by stratification factors region and prior and/or current treatment with migraine prophylactic medication. The same analysis is repeated for each visit. P values are nominal P values obtained from the Cochran-Mantel-Haenszel test. The result of a Breslow-Day test for homogeneity of ORs across strata at week 12 (month 3) is 0.89.

Source: Clinical Study Report for LIBERTY[9] and ARISE.[10]

Harms

Only those harms identified in the review protocol are reported below (Protocol section). See Table 17 and Table 18 for detailed harms data.

Adverse Events

Adverse events occurred in STRIVE in 57% and 56% of patients in erenumab groups and 63% with placebo. In Study 295, AEs occurred in 44% and 47% of patients in erenumab and in 39% of patients in placebo. In LIBERTY, AEs occurred in 55% of erenumab patients and 54% with placebo, and in ARISE they occurred in 48% of erenumab patients and 55% of those on placebo.

Serious Adverse Events

Serious adverse events were reported in 1% to 3% of patients and there were no clear and consistent differences between groups in any of the included studies. In STRIVE, 2.5% of erenumab 70 mg patients and 1.9% of erenumab 140 mg patients versus 2.2% of placebo patients had an SAE during the 24-week DBTP. The comparable figures for Study 295 were 3.2% of erenumab 70 mg patients and 1.6% of erenumab 140 mg patients versus 2.5% of those on placebo during the 12-week DBTP. In LIBERTY, 1.7% of erenumab 140 mg versus 0.8% of placebo patients had an SAE, while in ARISE 1.1% of erenumab 70 mg patients and 1.7% of placebo patients had an SAE during the 12-week double-blind treatment phases.

Withdrawal Due to Adverse Events

In STRIVE, 2.2% of patients in each of the erenumab groups withdrew due to an adverse event, versus 2.5% of patients in the placebo group. In Study 295 there were no withdrawals due to adverse events (WDAEs) among erenumab 70 mg patients, and 1.1% of patients in the 140 mg group and 0.7% of patients in placebo. In LIBERTY, there were no WDAEs in the erenumab 140 mg group and 0.8% of patients in placebo withdrew due to an AE, while in ARISE 1.8% of patients in the erenumab 70 mg group and 0.3% of patients in the placebo group withdrew due to an AE.

Mortality

There were no deaths in any of the included studies.

Notable Harms

Injection-site pain occurred in 3.2% of erenumab 70 mg patients and 0.3% of patients in the erenumab 140 mg and placebo groups in STRIVE, and in 4% of each of the erenumab groups and in 1% of placebo patients.

Table 17: Harms (STRIVE and Study 295)

	STRIVE			Study 295		
	ERE 70 mg (N = 314)	ERE 140 mg (N = 319)	Placebo (N = 319)	ERE 70 mg (N = 191)	ERE 140 mg (N = 190)	Placebo (N = 286)
Adverse events						
Patients with an AE, n (%)	180 (57.3)	177 (55.5)	201 (63.0)	83 (43.7)	88 (46.8)	110 (39.0)
AE in 5% of patients, any group						
Nasopharyngitis	31 (9.9)	35 (11.0)	32 (10.0)	6 (3.2)	3 (1.6)	16 (5.7)
Upper respiratory tract infection	21 (6.7)	15 (4.7)	18 (5.6)	-	-	-
Serious adverse events						
Patients with an SAE, n (%)	8 (2.5)	6 (1.9)	7 (2.2)	6 (3.2)	2 (1.1)	7 (2.5)
Occurring in > 1 patient						
• Cholelithiasis	[redacted]	[redacted]	[redacted]	No SAE in > 1 patient		
Deaths	0	0	0	0	0	0
Withdrawals due to adverse event						
AEs leading to withdrawal of investigational product, n (%)	7 (2.2)	7 (2.2)	8 (2.5)	0 (0.0)	2 (1.1)	2 (0.7)
Notable harms						
Injection-site pain	10 (3.2)	1 (0.3)	1 (0.3)	7 (3.7)	7 (3.7)	3 (1.1)
Injection-site erythema	6 (1.9)	5 (1.6)	1 (0.3)	1 (0.5)	6 (3.2)	0
[redacted]	[redacted]	[redacted]	[redacted]			
Hypersensitivity (SAE)	0	0	1 (0.3)			
Anti-erenumab antibodies						
• binding antibody–positive post-baseline	25 (8.0)	10 (3.2)	-	11 (5.8)	3 (1.6)	-
• neutralizing antibody–positive post-baseline	1 (0.3)	0	-	0	0	-
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]			
Vascular disorders	8 (2.5)	5 (1.6)	13 (4.1)	[redacted]	[redacted]	[redacted]
• hypertension	5 (1.6)	0	8 (2.5)	[redacted]	[redacted]	[redacted]
• hot flush	0	1 (0.3)	3 (0.9)	1 (0.5)	3 (1.6)	1 (0.4)

AE = adverse event; ERE = erenumab; SAE = serious adverse event.

Source: Clinical Study Report for STRIVE[7] and Study 295.[8]

Table 18: Harms (LIBERTY and ARISE)

	LIBERTY		ARISE	
	ERE 140 mg (N = 119)	Placebo (N = 124)	ERE 70 mg (N = 283)	PLACEBO (N = 289)
Adverse events				
Patients with an AE, n (%)	65 (54.6)	67 (54.0)	136 (48.1)	158 (54.7)
AE in 5% of patients in any group				
Injection-site pain	7 (5.9)	7 (5.6)	17 (6.0)	12 (4.2)
Nasopharyngitis	5 (4.2)	12 (9.7)	15 (5.3)	17 (5.9)
Upper respiratory tract infection	-	-	18 (6.4)	14 (4.8)
Serious adverse events				
Patients with an SAE, n (%)	2 (1.7)	1 (0.8)	3 (1.1)	5 (1.7)
Deaths	0	0	0	0
Withdrawals due to adverse event				
AE Leading to discontinuation of investigational product, n (%)	0	1 (0.8)	5 (1.8)	1 (0.3)
Notable harms, n (%)				
Hypersensitivity (SAE)	[redacted]	[redacted]	1 (0.3)	0
Injection-site erythema	3 (2.5)	4 (3.2)	-	-
Injection-site pruritus	[redacted]	[redacted]	-	-
Anti-erenumab antibodies	-	-	-	-
• binding antibody–positive post-baseline	0	-	12 (4.3)	-
• neutralizing antibody–positive post-baseline	0	-	1 (0.4)	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; ERE = erenumab; SAE = serious adverse event.

Source: Clinical Study Report for LIBERTY[9] and ARISE.[10]

Discussion

Summary of Available Evidence

Four double-blind RCTs were included in this review. Three of these studies included populations with episodic migraine, defined as at least four and fewer than 15 MMDs and fewer than 15 MHDs, and the other was in chronic migraine, defined as patients with at least eight MMDs and at least 15 MHDs. Three of the studies were 12 weeks in duration (Study 295, LIBERTY, and ARISE), while STRIVE involved 24 weeks of double-blind treatment. The primary outcome of all studies was based on migraine frequency, specifically MMDs, defined either as the change from baseline in MMDs to the end of the DBTP (STRIVE, Study 295, and ARISE), or the percentage of patients achieving a 50% reduction in MMDs (LIBERTY). Secondary outcomes, controlled for multiplicity, included other measures of MMDs, monthly use of acute migraine medication, and impact on function as measured by the MPFID along with a number of exploratory outcomes to assess quality of life.

Key critical appraisal issues included the relatively short-term follow-up (12 or 24 weeks of DBTP) for a first-in-class drug with a novel mechanism of action. The lack of an active comparator is also a limitation, as is the fact that HRQoL was only assessed as an exploratory outcome in the included trials. The sponsor did not perform an ITT analysis as part of its primary analysis of continuous outcomes, although sensitivity analyses did use imputation to account for missing data.

Interpretation of Results

Efficacy

Erenumab elicited statistically significant improvement in MMDs of generally one to two versus placebo; however, the lack of a validated MCID for this outcome makes it uncertain whether this reduction in MMDs would be perceptible by patients. The clinical expert consulted by CDR noted that this magnitude of reduction in MMDs may be clinically significant for certain patients, but it is not clear what factors would help predict which patients would find this reduction relevant. Moreover, the impact of erenumab on function and HRQoL is unclear. Functional improvement was primarily assessed using the MPFID, an instrument created and validated by the sponsor (see Appendix 5 for detailed review of outcomes included in the studies). Other patient-reported outcomes that are typically used to assess migraine therapies (MIDAS, HIT-6, and MSQ) were only assessed as exploratory outcomes. For the MSQ, a migraine-specific HRQoL instrument, the clinical significance of differences between erenumab and placebo was not consistently achieved across subscales, doses of erenumab, and type of migraines (episodic versus chronic). Patients made it clear to CDR that migraines have a significant impact on daily functioning, even affecting their social relationships and work productivity and absenteeism; however, the outcomes that assessed these parameters either failed to consistently demonstrate robust clinically significant improvement for erenumab over placebo or they were only assessed as exploratory outcomes. Therefore, although the clinical expert consulted by CDR for this review indicated the reduction in migraine frequency may be clinically significant to patients, there is no robust evidence that erenumab produces clinically significant improvement in function or in HRQoL.

A limitation of the included trials is the lack of an active comparator. Several drugs are used in migraine prophylaxis, mainly off-label, and according to the clinical expert consulted by CDR for this review, many present tolerability issues for patients. In their input to CDR, patients identified side effects as a major issue with their use of current therapies. Although erenumab appears to be a well-tolerated drug based on 12- or 24-week DBTPs in the included studies, its comparative harms and efficacy versus other, more well-established, and less-costly comparators is unknown, nor is it known how it compares to onabotulinum toxin A in the more restricted chronic migraine population. The sponsor submitted an indirect treatment comparison (ITC) that found no difference between erenumab and onabotulinum toxin A for the proportion of chronic migraine patients achieving a 50% reduction in MMDs, although there were several limitations of this analysis (see Appendix 8 for a detailed review).[36] In another network meta-analysis (NMA) in chronic migraine, erenumab was not favoured over onabotulinum toxin A nor topiramate in terms of MMDs, use of acute medications, and for all-cause discontinuation.[37] With respect to its efficacy in treating episodic migraine, when compared with topiramate, propranolol, or amitriptyline, erenumab 140 mg was favoured over topiramate (50 mg and 200 mg doses) and erenumab 70 mg was favoured over low-dose topiramate (50 mg) for MMDs.[37] However, in the percentage of patients achieving a 50% reduction in MMDs, erenumab was not favoured over any active comparators, and for all-cause discontinuation erenumab was only favoured over topiramate 200 mg.

The sponsor's listing request suggests that to be eligible for reimbursement of erenumab, patients should suffer from more frequent migraines (more than eight MMDs) than suggested by the indication (at least four MMDs) and have failed on at least two prior migraine therapies. Only Study 295 targeted this population of frequent migraine sufferers, a phenomenon commonly referred to as chronic migraine. According to the clinical expert consulted by CDR for this review, those with chronic migraine likely differ in migraine pathophysiology and may represent a more treatment-resistant population compared to those who suffer from episodic migraine. Although Study 295 had a shorter DBTP (12 weeks versus 24) compared to STRIVE, the treatment difference was numerically larger in Study 295 (a reduction of 2.5 MMDs from a baseline of 18) compared to STRIVE (a reduction of 1.4 to 1.9 MMD from a baseline of eight to nine). Although the baseline MMDs was higher, as expected, given the patient population in Study 295, this does at least suggest that erenumab is efficacious in those who suffer from chronic migraine as well as those with episodic migraine. With respect to migraine prophylaxis, experience with failed prophylaxis varied between trials, with the most experienced population being LIBERTY patients (99% had failed at least two prophylactic drugs) and the least experienced were STRIVE patients (approximately 17% had failed two prophylactic drugs). There was no clear indication from results in LIBERTY versus less-experienced populations in other trials or from subgroup analyses across all studies that, in general, failing prior prophylaxis attenuated the reduction in MMDs versus those who had no prior failures, nor was there an indication of a reduced response in those failing three or more versus two or more prior prophylactic drugs. In LIBERTY, it was only in patients who had failed four prior prophylaxis medications that a loss of statistically significant treatment effect was seen. As is the case in clinical practice, patients had prior experience with a wide variety of migraine prophylaxis drugs, including onabotulinum toxin A.

Of all the therapies approved for migraine prophylaxis, the one that most closely resembles erenumab with respect to mechanism of action is onabotulinum toxin A, which suppresses presynaptic release of a number of different neurotransmitters, including CGRP, and erenumab inhibits CGRP directly. Only limited subgroup data are available from the

included studies assessing responses in patients who previously received onabotulinum toxin A. In Study 295, although there was a relatively small sample, erenumab failed to demonstrate a statistically significant improvement in MMDs in the subgroup of patients who had received prior therapy with onabotulinum toxin A. Although this is a small sample, it does suggest that patients who previously tried onabotulinum toxin A may be less likely to respond to erenumab versus those who are naive to onabotulinum toxin A. Given the overlap in mechanisms, this is pharmacologically plausible and suggests that patients who have failed on onabotulinum toxin A may not be good candidates to try erenumab. More data are required to understand the sequencing of these drugs for migraine prophylaxis.

Three of the four included trials were of relatively short duration, 12 weeks, while STRIVE had a 24-week DBTP. There were extensions; Studies 255 and 178 (see Appendix 6 for a detailed review) featured treatment periods of up to 52 and 64 weeks, respectively. However, these studies no longer included a comparator, and were also limited by a dose change (an increase of erenumab 70 mg to erenumab 140 mg) and a lack of statistical analysis. Looking at the data for several of the key outcomes (MMDs, medication use, and monthly headache hours), it appears that the efficacy of erenumab was maintained through this longer follow-up. However, these data must be interpreted with caution due to the aforementioned limitations. The STRIVE study also featured an ongoing ATP. Although the focus of the review of the STRIVE ATP was on safety, the available efficacy results suggested a sustained effect of erenumab. Overall, although there is no clear evidence of a diminished response with erenumab over time, the evidence of long-term efficacy has several limitations. It is possible that efficacy responses could diminish over time with the development of neutralizing antibodies to erenumab, creating the need for continued follow-up and for longer-term double-blind RCTs.

Harms

No clear and consistent indications of any safety or tolerability issues were associated with the use of erenumab. Monoclonal antibodies are associated with hypersensitivity and injection-site reactions, but there was no clear indication this was an issue with erenumab. The clinical expert consulted by CDR for this review noted that the relative lack of safety and tolerability issues with erenumab when compared to other drugs for migraine prophylaxis may make it a popular option among patients. However, without a trial against an active comparator it is impossible to know whether erenumab will indeed be better tolerated than existing options for migraine prophylaxis. The long-term safety of this novel first-in-class drug has also not been established. Vascular effects are associated with CGRP, and the ability to block these effects is likely a major contributor to the efficacy of erenumab in migraine prophylaxis. While vascular disorders, a catch-all for any vascular-related side effects, were noted in the product monograph, there was little indication of these events in the double-blind phases of the included studies, and no clear signal of these events was observed in the extensions. The fact that patients with cardiovascular disease were excluded from the trials limits the conclusions that can be drawn about the safety of erenumab in this population, which may be more susceptible to any vascular effects of the drug. The relatively short DBTPs (maximum of 24 weeks) is also a limitation as vascular harms may need more time to develop, and the longer-term extensions, with weeks of data, lacked any control group, other than erenumab itself. This lack of longer-term comparative safety data is a limitation of this review.

Potential Place in Therapy

The following is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

The clinical expert consulted by CDR noted that all of the currently available medications used for the prevention of migraine, with the exception of erenumab, were meant for use in other conditions (e.g., hypertension, depression, epilepsy), and only through their use in those conditions in patients who had concomitant migraine has it been learned that such medications may be used for migraine prophylaxis. As a group, patients with migraine appear to be sensitive to, and intolerant of, the medications' adverse effects, including the hypotension caused by beta-blockers, the mental slowing caused by topiramate, and the weight gain caused by amitriptyline. Because many are not able to take these medications at sufficiently high doses for long enough to achieve prophylactic benefit, they stop therapy prematurely. As well, the clinical expert noted that less than 30% of patients will respond to their first prophylactic treatment.[5,6] As a result, patients often try multiple medications for three to nine months before being able to determine which options are effective. Consequently, and despite the availability of several drug options with different mechanisms of action, a need for drugs that are effective in preventing migraines with minimal adverse effects remains.

When assessing the effect of medications used for the prevention of migraine, clinically meaningful outcomes include improvements in HRQoL, return to baseline functioning in a variety of domains (e.g., work, school, interpersonal, and recreational), and reduced caregiver burden stemming from shorter migraine attacks, reduced frequency and severity of migraine attacks, and reduced overall number of headache days (typically captured with a patient's headache diary). Adverse effects are closely monitored; a medication with a minimal adverse effect profile would be expected to improve patient adherence to treatment and quality of life.

The clinical expert consulted by CDR indicated that most patients with more than four but fewer than 15 headache days per month would be prescribed an oral medication, such as an antihypertensive, as initial therapy. For patients with more than 15 MHDs, the choices are typically between three agents: topiramate, onabotulinum toxin A, and erenumab. Erenumab is generally used as a second- or third-line treatment at present. However, because of its more specific mechanism of action and what appears to be relatively few adverse effects, erenumab may be used earlier as a first-line therapy for some patients, including for those with more than four but fewer than 15 MHDs.

The clinical expert noted that it is not possible at present to identify patients who are most likely to respond to any of the available preventive therapies, including erenumab. Therapy discontinuation would be considered if:

- there was no effect after three months at the highest tolerated dose, or
- there was loss of effect for three consecutive months, or
- a patient has four or fewer headache days per month for at least nine months, and these headaches can be readily treated with an abortive therapy (i.e., triptan or nonsteroidal anti-inflammatory drugs).

How to discontinue erenumab is unclear; sudden discontinuation may increase the likelihood of rebound headaches, and an evidence-based protocol for slower discontinuation (e.g., increasing the dosing interval incrementally until discontinuation can be achieved) is not yet available.

Clinicians would likely assess response within three months of starting the medication and at two three-month intervals thereafter. After that, annual or biannual assessment could be performed if the patient has responded well and has minimal or no side effects.

The clinical expert indicated that it would be preferable for a patient receiving erenumab to be followed by a specialist in headache or neurology; however, this is likely impractical.

Conclusions

Results from four included double-blind RCTs suggest that both approved doses of erenumab reduce the frequency of monthly migraines and the use of acute migraine medication versus placebo in patients with episodic migraine (defined as at least four and fewer than 15 MMDs) and chronic migraine (more than eight MMDs). While these reductions in the frequency of migraine were accompanied by functional improvement assessed by the MPFID in patients with episodic migraine, the clinical significance of these improvements is uncertain. As an important outcome for patients, HRQoL was only assessed as an exploratory outcome, and statistical significance cannot be determined. No clear safety issues, and no clear and consistent tolerability issues, emerged from the included studies, although the studies were not powered to assess harms. Given the novel mechanism of erenumab, longer-term comparative studies are warranted. Indirect comparisons, both sponsor-submitted and published, did not suggest any advantage of erenumab compared to onabotulinum toxin A with respect to efficacy or persistence with therapy in patients with chronic migraine. However, a possible advantage of erenumab versus topiramate in reducing migraine frequency in episodic migraine was indicated.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group, Migraine Canada, provided input for this submission on behalf of its organization and Migraine Quebec. Migraine Canada is a national organization that supports, educates, and advocates for people living with migraines. The work of the organization is carried out through a volunteer board of directors composed of patients and health care professionals. Migraine Canada educates and raises awareness about migraines through electronic and print materials, a website, social media, workshops, and forums. Migraine Canada reported that it had received financial support over the past two years from Allergan Canada, Eli Lilly Canada, and Novartis Canada via the Canadian Headache Society. The patient input submission for this review was completed independently, and the assessment of survey results (described below) was completed by Migraine Canada alone. However, external assistance from a webmaster was used to post the survey online and collect and collate the raw results of a survey.

2. Condition-Related Information

Migraine Canada conducted an online survey designed and analyzed by the Volunteer Board of Migraine Canada. It was promoted on Facebook and Migraine Canada's Twitter account, and by email through migraine clinics in Canada. In addition, the survey was made available online through the following national and regional patient groups: Migraine Quebec (French, public website), Partage Migraine Quebec (French, private Facebook group), Chronic Migraine Awareness Canada (English, private Facebook group), and Help for Headaches (Ontario-based charity). The survey was open from June 4 to July 4, 2018, and received responses from 597 patients. Thirty-four percent of the respondents were between the age of 26 and 39, and 45% were between the age of 40 and 54, which is reflective of the migraine population. The group represented patients with low-frequency (one to six MHDs) episodic migraines (26%), high-frequency (seven to 14 MHDs) episodic migraines (32%) and chronic (≥ 15 MHDs) migraine attacks (42%), and 22% of the group was on short- or long-term disability. A follow-up survey specific to patients who had experience with Aimovig was conducted by Migraine Canada (open April 3 to May 12, 2019). This survey also included a French version that was published on Migraine Quebec's website (open April 18 to May 12, 2019). A total of 379 patients (174 from Migraine Canada, 205 from Migraine Quebec) participated. The majority were between 30 and 60 years old (83%) and female (92%), and 61% were living with chronic migraine.

Migraine is a neurological disease that can affect people of all ages, but it occurs most commonly in people between the ages of 25 and 55 and disproportionately affects women. It can be classified by frequency (episodic or chronic) and/or by the accompanying symptoms, such as the presence of an aura, vestibular, or hemiplegic effects. A patient experiences the disease in two main states, which are the active attack (ictal state) and in-between attacks (interictal state). An attack was characterized by the patient group as having a variety of symptoms, such as moderate-to-severe throbbing and diffuse pain, nausea, vomiting, dizziness, sensory hypersensitivity, and tingling or numbness in the extremities or face. As mentioned, there may be auras, which cause disturbances in vision, speech, sensations, and muscle strength. Cognition is also affected, with slowed thinking, lack of focus, and difficulty in reading and speaking. According to the patient group, attacks usually last between four and 72 hours. Even the in-between-attack phase, when symptoms

are not experienced, was characterized by a lowered quality of life. Patients fear the onset of the next attack and may limit activities to avoid triggers of migraines. Planning ahead may be difficult, as expressed by one caregiver: "There is a feeling of helplessness and lack of control where scheduling life is concerned. We are at the mercy of these attacks."

Migraine attacks have a significant impact on the lives of patients as well as the lives of their families. From the survey, 48% said the impact was minor, 40% reported that the impact was major, and 9% said that migraine was the main reason why they had no family or intimate relationships. Some of the more common themes regarding how migraine interferes with one's life were described, and include: requiring help with childcare while the parent experiences a migraine, financial repercussions due to sacrificing career decisions or the inability to work, missing out on social and family events, and a lack of understanding from the families of those living with what appears to be an "invisible" disease. They also described difficulty with intimacy and engaging in relationships due to exhaustion and/or frequent migraine attacks. The patient group described living with migraine as having a huge impact on work and the ability to work as well. In the survey, patients were asked to rate the impact of migraine on their life during the last three months. Twenty-five percent of respondents were disabled and unable to work, 26% worked part-time or missed three or more days of work per month, 25% missed one to two days per month, and 25% did not miss work but were still affected in their personal life. A few of these issues are highlighted by the following quotes from patients:

> "We hesitate to make plans and often have to cancel and stay home. My husband sometimes needs to come from work and finish the tasks I did not get to during the day. And take care of the kids. Sometimes he needs to miss work to watch the kids or find other childcare."
>
> "My wife and I do miss out on time together because she has to go to sleep. I've had to go to family functions without her and many times take the children to all activities and school because she just can't."
>
> "I am too physically and emotionally exhausted from being "on" for others at the end of the day to even speak with my husband. I help with my 2-year-old daughter but even that's a struggle. My husband and I rarely see each other or have any time alone. We are rarely intimate. It is a struggle. We are seeing a psychologist to help with this."

Lastly, the patient group stated that migraine can lead to anxiety and depression, as was reported by 80% of survey respondents. Patients described the impact that migraines have on their lives as causing stress, anxiety, depression, guilt, anger, and frustration. Forgoing social functions leads to loneliness, while attending them can be physically and emotionally exhausting. Further, patients feel that living with migraine is associated with stigmatization in all aspects of life, from their social network to employers and health care providers. There is no objective diagnostic test for migraine, and the lack of understanding and stigmatization only further contributes to feelings of guilt and shame.

3. Current Therapy-Related Information

Twenty-two percent and 5% of those who responded to Migraine Canada's initial survey and follow-up surveys, respectively, had tried one or two preventives, 22% and 26% had tried three or four preventives, and 45% and 69% had tried five or more. They noted that the survey did have a high proportion of patients who were referred to the survey by support groups and migraine clinics, and therefore have been diagnosed and treated for

migraine. Briefly, patients from the initial survey felt that currently available treatments were "completely insufficient." There is no cure and the treatment expectations are low, with a 50% reduction in frequency and intensity of migraine attacks being described as an outcome that "should be acceptable." Despite this, 74% of survey respondents have not found a treatment that provides at least a 50% improvement in symptoms. In addition, side effects were noted as a major problem and cause for discontinuation of treatment in both surveys. Of the survey respondents who had tried preventives, 67% to 68% reported experiencing a side effect that led to treatment discontinuation, 24% to 25% reported tolerable side effects, and 7% to 9% did not have side effects. The most common side effects reported by the initial survey included somnolence (76%), weight gain (54%), dizziness (58%), gastrointestinal upset (45%), mood difficulties (44%), and cognitive difficulties (53%).

Access to care for migraine is also an issue for patients. According to the patient group's summary of the initial survey, 27% of respondents took more than a year to see a neurologist or headache specialist, and satisfaction with care was low. Fifty-four percent of participants stated that they were dissatisfied or very dissatisfied with the care they received from their physicians (general practitioner or neurologist), and the majority described no improvement (33%) or mild improvement (49%).

4. Expectations About the Drug Being Reviewed

According to the patient group's initial survey, there are few headache specialists in Canada and many choose to practice at private outpatient clinics, limiting patient access to participation in clinical trials. Seven of the initial survey respondents were involved in one of the clinical trials for erenumab: five completed the study and two knew they had received erenumab. Neither of the patients reported side effects, and one stated that "It gave me my life back for 15 months, I didn't worry about having meds with me or if I was going to have to cancel plans. I lived." The follow-up surveys, which were specific to patients who had experience with Aimovig, indicated that 53% of patients reported an excellent or moderate response in terms of a decrease in headache days. Forty-three percent of patients reported that Aimovig clearly decreased the severity of migraine attacks, 32% reported "a little reduction," and 25% reported no reduction. Further, 70% of patients reported that Aimovig had reduced the usage of acute and/or abortive medications to varying degrees. The survey responses were highlighted by the following patient quote:

> "Migraines are not as intense and much easier to manage, without having to take as much other medications. Rarely do I have to cancel out on social and family events, which is always very upsetting and frustrating. At the age of 69, life is finally more tolerable. Thank you so much!"

With regards to safety and tolerability, the follow-up survey responses noted that the majority of survey respondents tolerated Aimovig well, with 44% reporting no side effects and 46% mild side effects. However, 6% reported severe side effects requiring medical advice. Commonly reported side effects included constipation and gastrointestinal issues, as well as injection-site rash or skin irritation. The majority of respondents from the initial and follow-up surveys (73% and 82%, respectively) preferred a monthly injection to a daily pill. When asked to describe what a good migraine preventive would be, many of the comments highlighted simply that patients would like a treatment that reduces the amount of pain (intensity) and frequency of attacks. They are looking for a treatment that improves their quality of life and lets them go about their days with minimal interference from migraine

attacks. There were also comments about the desire for a preventive that has reduced or minimal side effects.

5. Additional Information

Migraine Canada stated that there is no companion testing for migraine diagnosis or erenumab prescription. It also noted that its members are concerned about the stigmatization and lack of recognition of migraine, highlighting that patients are underdiagnosed and undertreated, referencing the World Health Organization's Atlas of Headache Disorders and Resources. Migraine was described as a severely neglected chronic illness in comparison to other diseases, such as diabetes, epilepsy or multiple sclerosis, that are associated with a significant amount of time lost due to disability.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–present) Embase (1974–present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 31, 2019
Alerts:	Weekly search updates until project completion
Study Types:	No filters were applied to limit retrieval by study type
Limits:	Publication date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word
.dq	Candidate Term Word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	l5l8VB78VT.rn,nm.
2	(aimovig* or erenumab* or AMG 334 or AMG334).ti,ab,kf,ot,hw,nm,rn.
3	or/1-2
4	3 use medall
5	*erenumab/
6	(aimovig* or erenumab* or AMG 334 or AMG334).ti,ab,kw,dq.
7	or/5-6
8	7 use oemezd
9	(conference review or conference abstract).pt.
10	8 not 9
11	4 or 10
12	remove duplicates from 11

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: Aimovig, erenumab, AMG 334, AMG334
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: Aimovig, erenumab, AMG 334, AMG334

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	May 2019
Keywords:	Aimovig, erenumab, AMG 334, AMG334, migraine
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- internet search.

Appendix 3: Excluded Studies

Table 19: Excluded Studies

Reference	Reason for exclusion
SUN, H., et al. Lancet Neurology 2016 15(4):382-90	Phase II nonpivotal study
SCHWEDT, T., et al. Journal of Headache and Pain 2018 19(1):92	Post hoc subgroup analysis
GOADSBY, P. J., et al. Journal of Neurology, Neurosurgery and Psychiatry 2017 88(5):e23-e24	Abstract
DODICK, D., et al. Journal of Neurology, Neurosurgery and Psychiatry 2017 88(5):e24	Abstract
ASHINA, M., et al. Neurology 2017 89(12):1237-1243	Inappropriate comparator
ASHINA, M., et al. Cephalalgia 2018 38(10):1611-1621	Subgroup
GOADSBY, P. J., et al. Cephalalgia 2019 39(7):817-826	Subgroup
TEPPER, S. J., et al. Neurology 2019 92(20):e2309-e2320	Subgroup
BUSE, D. C., et al. Cephalalgia 2018 38(10):1622-1631	Review
LIPTON, R. B., et al. Neurology 2019 92(19):e2250-e2260	Post hoc analysis

Appendix 4: Detailed Outcome Data

Table 20: Subgroup Analyses

	Subgroup analyses		
STRIVE **Change in MMDs by**	**ERE 70 mg** (N = 317)	**ERE 140 mg** (N = 319)	**Placebo** (N = 319)
Current or prior prophylaxis			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
Baseline MMDs			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
Treatment failure of prior prophylactic medication			
≥ 1 failed **Mean (SD) baseline**	8.71 (2.38) N = 127	8.48 (2.53) N = 116	8.70 (2.65) N = 126
[redacted]	[redacted]	[redacted]	[redacted]
LS MD between groups (95% CI)	70 mg: −2.02 (−2.81 to −1.23) 140 mg: −2.54 (−3.35 to −1.72)		
Non-failed **Mean (SD) baseline**	8.04 (2.46) N = 185	8.24 (2.45) N = 202	7.95 (2.37) N = 190

	Subgroup analyses		
[redacted]	[redacted]	[redacted]	[redacted]
LS MD between groups (95% CI)	70 mg: −0.94 (−1.54 to −0.34) 140 mg: −1.30 (−1.89 to −0.71)		
STUDY 295 Change in MMDs, responses by	**ERE 70 mg (N = 191)**	**ERE 140 mg (N = 190)**	**Placebo (N = 286)**
Medication overuse			
Yes Mean (SE) baseline	18.76 (0.52) N = 77	18.84 (0.51) N = 78	19.57 (0.42) N = 113
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM between groups (95% CI)	70 mg: −3.10 (−4.83 to −1.37) 140 mg: −3.10 (−4.81 to −1.39)		
No Mean (SE) baseline	17.37 (0.39) N = 111	17.03 (0.45) N = 109	17.35 (0.36) N = 168
[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM between groups (95% CI)	70 mg: −2.04 (−3.39 to −0.69) 140 mg: −2.02 (−3.38 to −0.67)		
Treatment failure of prior prophylactic medication			
Non-failed Mean (SE) baseline	17.08 (0.52) N = 64	17.05 (0.58) N = 62	17.46 (0.52) N = 84
[redacted]	−7.86 [redacted]	−6.14 [redacted]	−5.67 [redacted]
LS MD between groups (95% CI)	70 mg: −2.19 (−4.10 to −0.28) 140 mg: −0.47 (−2.39 to 1.46)		
Failed ≥ 1 drug Mean (SD) baseline	18.39 (0.40) N = 124	18.14 (0.42) N = 125	18.57 (0.33) N = 197
[redacted]	-5.98 [redacted]	-6.84 [redacted]	-3.51 [redacted]
LS MD between groups (95% CI)	70 mg: −2.47 (−3.76 to −1.18) 140 mg: −3.33 (−4.61 to −2.06)		
Failed ≥ 2 drugs Mean (SD) baseline	18.21 (0.46) N = 90	18.75 (0.46) N = 92	18.34 (0.37) N = 141
[redacted]	−5.38 [redacted]	-6.96 [redacted]	-2.68 [redacted]
LS MD between groups (95% CI)	70 mg: −2.71 (−4.20 to −1.21) 140 mg: −4.28 (−5.75 to −2.80)		
Prophylactic topiramate			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

	Subgroup analyses		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
Onabotulinum toxin A use	*N = 48*	*N = 43*	*N = 65*
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
Never used Mean (SE) baseline	17.74 (0.36) N = 140	17.87 (0.41) N = 144	18.12 (0.33) N = 216
LSM change from baseline to week 12 (95% CI)	−7.36 (−8.32 to −6.40)	−7.31 (−8.25 to −6.37)	−4.37 [redacted]
[redacted]	[redacted]		
Baseline MMDs			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
ARISE **Change from baseline to week 12 in MMDs by**	**ERE 70 mg** N = 286	**Placebo** N = 286	
Prophylactic medication			
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	

	Subgroup analyses		
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
Baseline MMDs			
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
Treatment failure of prior prophylactic medication			
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
LIBERTY **Migraine responders (50% reduction in MMDs) by**	**ERE 140 mg** (N = 119)	**Placebo** (N = 124)	
MMDs at baseline			
[redacted]			
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
[redacted]			
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
[redacted]			

	Subgroup analyses		
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	
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[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
[redacted]	[redacted]		

CI = confidence interval; ERE = erenumab; LSM = least squares mean; MMD = monthly migraine day; SD = standard deviation; SE = standard error.

Source: Clinical Study Report for STRIVE,[7] Study 295,[8] LIBERTY,[9] and ARISE.[10]

Appendix 5: Validity of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

Outcome measure	Study 295	STRIVE	ARISE	LIBERTY
MMDs	Primary	Primary	Primary	Primary
MPFID version 2.0	Exploratory	Secondary	Secondary	Secondary
MSQ version 2.1	Exploratory	Exploratory	Exploratory	NA
HIT-6	Exploratory	Exploratory	Exploratory	Exploratory
MIDAS	Exploratory	Exploratory	Exploratory	NA
WPAI-SHP	NA	NA	NA	Exploratory
EQ-5D-5L	NA	NA	NA	Exploratory
BDI-II	NA	NA	NA	Exploratory
PROMIS Pain Interference Scale Short Form 6b	Exploratory	NA	NA	NA
ASC-12	Exploratory	NA	NA	NA
CGI-I	Exploratory	NA	NA	NA
PGIC	Exploratory	NA	NA	NA

ASC-12 = 12-item Allodynia Symptom Checklist; BDI-II = Beck Depression Inventory – II; CGI-I = Clinician Global Impression – Improvement; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; HIT-6 = six-item Headache Impact Test; MIDAS = Migraine Disability Assessment Scale; MMD = monthly migraine day; MPFID = migraine physical function impact diary; MSQ = Migraine-Specific Quality of Life Questionnaire; NA = not applicable; PGIC = Patient Global Impression of Change; PROMIS = Patient-Reported Outcome Measures Information System; WPAI-SHP = Work Productivity and Activity Impairment Questionnaire – Specific Health Problem.

Findings

Table 21: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MCID
MMDs	Reduction in number of migraine days May be recorded by a patient diary	Not available	Patients with mixed headache conditions: 1-day increase in headache frequency associated with quality-of-life domains[a4]
MPFID (version 2.0)	13 items and 3 domains: • Impact on everyday activities • Physical impairment • Global assessment Each item rated on a 5-point scale	**Validity**[38] Construct validity (strong correlation with number of migraine days, number of headache days, number of bed days, PROMIS – physical function, HIT-6, and MSQ domains) **Reliability**[38] • Internal consistency demonstrated (impact on everyday activities: Cronbach's alpha = 0.97; physical impairment: alpha = 0.93) • Test-retest reliability was demonstrated (ICC > 0.70 for each domain) **Responsiveness** Not reported	Within-groups MCID (anchor-based) 3-point change from baseline for all 3 domains[38] Based on pooled dataset of patients from the ARISE trial for erenumab, and adults with EM who recently initiated or changed their migraine-preventive regimen[38] Between-groups MCID (anchor-based):[18] PI domain = −1.60 to −2.54 EA domain = −0.87 to −2.62
MSQ (version 2.1)	14 items and 3 domains: • MSQ-RFR • MSQ-RFP • MSQ-EF Each item rated on a 6-point Likert-type scale	**Validity** Patients with CM and EM: construct validity (strong correlation with HIT-6, moderate with MIDAS, and PHQ-4, weak with MHDs;[22] and discriminant validity by statistically significant differences between groups based on headache frequency, HIT-6, MIDAS, and PHQ-4[22] **Reliability** Patients with CM and EM: internal consistency demonstrated in the overall population (Cronbach's alpha = RFR 0.96, RPR 0.90, EF 0.87) and the CM and EM populations individually (Cronbach's alpha ≥ 0.86 for each of the MSQ domains)[22]	Patients with maximum of 15 headache days per month:[23] Group-level MCIDs (distribution-based) RFR = 3.2 RFP = 4.6 EFF = 7.5 Individual-level MCIDs (anchor-based) RFR = 4.9; 5.0 RFP = 5.0; 7.9 EF = 8.0; 10.6 Patients with CM:[24] within-group MCIDs (anchor-based) RFR = 10.9 (95% CI, 9.4 to 12.4) RFP = 8.3 (6.7 to 9.9) EF = 12.2 (10.2 to 14.3)

Outcome measure	Type	Conclusions about measurement properties	MCID
		Patients with CM: Cronbach's alpha ranges from 0.90 to 0.97 across the 3 domains[39] **Responsiveness** Patients with CM: large effect size for patients with ≥ 50% improvement and moderate effect size for patients with 30% to 50% improvement	
HIT-6	6 items: pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress Each item rated on a 5-point Likert-type scale	**Validity** Patients with CM and EM: moderate correlation with MIDAS scores (r = 0.56) and headache pain intensity (r = 0.46); and weak correlation (r = 0.29) with MHDs[40] **Reliability** Patients with CM and EM: internal consistency (Cronbach's alpha = 0.83 to 0.90) and test-retest reliability demonstrated (ICC = 0.77)[40] **Responsiveness** Patients with CM: Scores detected changes in disease status based on headache frequency and cumulative hours of headache	Patients with EM: within-group MCID = −2.5[29] between-group MCID = −1.5[29] Patients with chronic daily headaches: between-group MCID = −2.3[28]
MIDAS	7-item questionnaire that evaluates headache-related disability Based on a 3-month recall period	**Validity**[31,41] Concurrent validity among physician-confirmed patients with migraine, demonstrated through correlation with 90-day headache diary (Pearson's r = 0.50 to 0.77, Spearman's rho = 0.53 to 0.76) **Reliability** Internal consistency (Cronbach's alpha = 0.83)[42] Test-retest reliability (item-level,[31,42] r = 0.52 to 0.82, rho = 0.46 to 0.84; overall score,[31] r = 0.80 to 0.83, rho = 0.77 to 0.78). **Responsiveness** Not reported	Not identified
WPAI-SHP	6 items to measure impairments in work and activities	The general form has been validated, however no evidence found in patients with migraine	Not identified for migraine

Outcome measure	Type	Conclusions about measurement properties	MCID
EQ-5D-5L[32]	Generic instrument applied to many health conditions First part: Descriptive system to classify respondents into one of 243 health states: 5 dimensions with 5 possible levels Second part: 20 cm VAS with end points labelled 0 (worst imaginable health state) to 100 (best imaginable health state) Score generated with a multi-attribute utility function	No evidence found in patients with migraine	Not identified for migraine Non-specific MCID estimate = 0.056 (SD = 0.011)[43]
BDI-II[9]	21-item self-reported questionnaire Each item is answered on a 4-point scale Based on 2-week recall period	Evidence regarding the validity of the use of BDI-II in patients with migraines not identified	Not identified for migraine
PROMIS Pain Interference Scale Short Form 6b	6-item self-reported questionnaire Each item is answered on a 5-point scale Based on a 7-day recall period	Evidence regarding the validity of the use of PROMIS Pain Interference Scale Short Form 6b in patients with migraines not identified	Not identified for migraine
ASC-12	12-item self-reported checklist Patients provide 5 responses, which are assigned a score from 0 to 2 The sum of scores for the 12 items generate a total score	Evidence regarding the validity of the use of ASC-12 in patients with migraines not identified	Not identified for migraine
CGI-I	Global assessment of clinical change from initiation of treatment, performed by a clinician Answered on a scale from 0 to 7, with 7 representing worsening of symptoms	Evidence of validity not identified in patients with migraines	Not identified for migraine
PGIC	Self-reported global assessment of clinical change Answered on a scale from one (improvement of symptoms) to ten (worsening symptoms), and on a VAS	Evidence of validity not identified in patients with migraines	Not identified for migraine

ASC-12 = 12-item Allodynia Symptom Checklist; BDI-II = Beck Depression Inventory – II; CGI-I = Clinician Global Impression – Improvement; CM = chronic migraine; EA = everyday activities; EF = emotional function; EM = episodic migraine; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; HIT-6 = six-item Headache Impact Test; ICC = intra-class correlation coefficient; MCID = minimal clinically important difference; MIDAS = Migraine Disability Assessment Scale; MHD = monthly headache day; MMD = monthly migraine day; MPFID = migraine physical function impact diary; MSQ = Migraine-Specific Quality of Life Questionnaire; PGIC = Patient Global Impression of Change; PHQ-4 = Patient Health Questionnaire-4; PROMIS = Patient-Reported Outcome Measures Information System; RPR = role function – preventive; RFR = role function – restrictive; VAS = Visual Analogue Scale; WPAI-SHP = Work Productivity and Activity Impairment Questionnaire – Specific Health Problem.

[a] It is unclear how the quality-of-life domains were evaluated in this study and if the differences observed were clinically meaningful.

Migraine Days

Definitions of migraine days in the studies were in line with the criteria of migraine and probable migraine defined by the International Classification of Headache Disorders.[44] Values for MMDs were calculated using migraine-day data collected from patient-completed electronic diaries. Although migraine days are commonly used as a primary outcome in trials of interventions for migraine, no data were identified describing the validity and reliability of migraine days, nor were data identified regarding a validated MCID. Dodick et al. reported that a one-day reduction in headache frequency was clinically meaningful.[45] Dodick et al.[45] referenced a study by Silberstein et al.[4] that examined headache frequency and HRQoL. Silberstein et al. examined the characteristics of 703 patients 12 years of age or older who received onabotulinum toxin A using data from an open-label clinical study, conducted at 10 headache centres in the US. The majority of patients (65.6%) had chronic migraine (defined as the presence of at least 15 headache days per 28 days, of which at least half involved migraine or migrainous headache), although about 34% had other types of headache conditions, such as migraine not classified as chronic and tension-type headache. Headache frequency was measured with a patient-maintained daily headache record. Patients responded to the Headache Impact Questionnaire, the Headache Pain-Specific Quality of Life questionnaire, and the MIDAS questionnaire, and data were collected prospectively for up to one year, with 482 patients (68.6%) completing the entire one-year follow-up. The results state that: "A 1-day increase in HA [headache] frequency was associated with a greater likelihood of HA pain interfering with mood (4.0%, P < .001), recreational activities (4.0%, P = .004), or life enjoyment (4.0%, P = .001)." It is unclear which instruments the domains of mood, recreational activities, or life enjoyment were taken from. As well, it is unclear if the domains were selected a priori or if a relationship between headache frequency and the other domains of HRQoL of the three instruments was also tested, found not to be statistically significant, and not reported. Without knowing the scale on which these domains were based, it is difficult to determine if a 4% improvement was clinically meaningful. In addition, the time point and study sample size upon which these results are based are unclear. If it was at the one-year point, a large number of patients (N = 221) had dropped out by then and it is uncertain if data for these patients were imputed or omitted from the final results. No other studies were identified that specifically supplied an MCID for reduction in headache frequency in patients with chronic migraine. Rendas-Baum found that the MSQ differed significantly in patients with fewer then 10 headache days, 10 to 14 headache days, and at least 15 headache days per month.[39] The change in MSQ was greater among groups who experienced a greater decline in headache frequency. Rendas-Baum found that the HIT-6 score differed significantly across levels of headache frequency (i.e., fewer than 10 days, 10 to 14 days, and at least 15 days per month).[46] Patients who experienced at least 50% improvement in number of headache days had about a seven-point decrease in HIT-6 score, at least 30% to less than 50% improvement a decrease of 2.9 or 3.3 points, and less than 30% improvement a change of −0.7.

Migraine Physical Function Impact Diary

The developers of the MPFID created the instrument following a review of the literature that identified a lack of patient-reported outcome instruments that assessed the impact of migraine on physical functioning.[38,47] More specifically, they argued that existing instruments failed to collect information about the impact of migraine on "acts," such as difficulty moving the body, which in combination with "tasks" describe the impact of migraine on physical functioning.[38,47] The MPFID was therefore designed for use in clinical trials to

comprehensively assess the impact of migraine on a patient's physical functioning on a daily basis using an electronic diary in the erenumab trials.

The initial version of the MPFID (version 1.0) was a 17-item instrument. It recently underwent item analysis and reduction to create a 13-item version (2.0),[38] which was used in the erenumab trials. Version 2.0 of the MPFID is a 13-item self-reported questionnaire composed of two domains, the seven-item "impact on everyday activities," the five-item "physical impairment" domain, and a global question that assesses the overall impact on everyday activities.[7,38,48] Each item is answered based on a 24-hour recall period using a five-point scale (5 representing the greatest burden), with items pertaining to difficulty ranging from "without any difficulty" to "unable to do," and those pertaining to frequency ranging from "none of the time" to "all of the time."[7] The scores for each item of a domain are summed and converted to a scale from 0 to 100. A score for each domain and a third score for the global impact question are provided.[7]

A psychometric evaluation of the MPFID version 2.0 was conducted in a study by Kawata et al.[38] A total of 569 adults (18 to 64 years old) living with migraines were included in this observational study; 56.8% with episodic migraines (episodic migraine ≥ 4 and ≤ 14 MHDs in each of three months prior to screening) and 43.2% with chronic migraines (≥ 15 MHDs, of which at least eight were migraine days, in each of the three months prior to screening). The mean age was 39.9 years old and the majority were female (87.2%) and white (80.8%). Reliability was examined in the full study sample using test-retest reliability based on intra-class correlation coefficients (ICCs), and internal consistency based on Cronbach's alpha. Test-retest reliability was assessed among stable patients, defined by a PGIC response of "no change" (n = 224) and a change in the Patient Global Impression of Severity (PGI-S) score of no more than one point (n = 225), with measurements taken at baseline and week 4.[38] The MPFID demonstrated good test-retest reliability as the ICC was greater than 0.70 for each of the domains and the global assessment item (everyday activities domain: PGIC ICC = 0.74, PGI-S ICC = 0.81; physical impairment domain: PGIC ICC = 0.77, PGI-S ICC = 0.85; global impact: PGIC ICC = 0.70, PGI-S ICC = 0.78).[38,49] Using the full study sample (N = 569), internal consistency was demonstrated for both of the MPFID domains (impact on everyday activities: Cronbach's alpha = 0.97; physical impairment: alpha = 0.93).[38]

Convergent validity was assessed using Spearman's rank correlations between the baseline MPFID domain scores and other indicators of similar constructs, including number of migraine days, number of headache days, number of bed days, PROMIS physical function score, HIT-6, and the MSQ domains. A moderate (≥ |0.50|) correlation[50] was determined for all indicators, except "number of bed days," which exhibited a strong correlation (r = 0.71 and 0.73) with the global item and everyday activities domain, respectively. Construct validity was also demonstrated using the known-groups approach, which assessed whether the MPFID could differentiate between groups of varying degrees of disease severity. The following indicators were used to determine disease severity in terms of number of migraine days, level of migraine interference with daily activities, intensity of migraine pain, PROMIS physical function, HIT-6, and MSQ domains. Statistically significant (P < 0.01) differences between MPFID domain scores based on known groups were reported.[38]

An abstract submitted by the sponsor reported a clinically meaningful within-patient change (CMWPC) for the MPFID.[48] The data used to inform the development of a CMWPC were derived from the ARISE trial and an observational study relating to adults with episodic migraine. Anchor-based methods using ≥ 30% and ≥ 50% reduction in MMDs and ≥ 20%

and ≥ 50% reduction in the global MPFID score as a change from baseline were used to estimate the CMWPC, as well as distribution-based methods based on variability, which were considered supportive.[48] A change of at least three points in the MPFID everyday activities and physical impairment domains were reported as an estimate for the CMWP.

The sponsor also provided a between-groups MCID for the physical impairment and everyday activities domain scores of the MPFID. The MCID was determined by an anchor-based approach using a one-day difference in MMDs for the primary anchor and data from the topiramate migraine prevention development program. Two supportive anchors were used as well: the MSQ role function – restrictive domain score and the HIT-6 score. [redacted].[18] Additional information about the methodology was not provided and therefore a proper appraisal cannot be conducted. However, the sponsor noted that this MCID was acceptable by the FDA. Nonetheless, with a lack of strong evidence, this MCID remains uncertain.

In summary, the assessment of reliability and validity of the MPFID was well conducted, with appropriate measurements and reference groups used, but a formal analysis of responsiveness to change for the MPFID was not identified in the literature at this time. The abstract reporting on a CMWPC included a number of limitations that may be partly due to the brevity of the report. Nonetheless, the sample sizes and details regarding the results of the assessment of a CMWPC were not reported. The proposed minimally important difference should be considered and used with caution.

Migraine-Specific Quality of Life Questionnaire

The MSQ is a disease-specific instrument that assesses the impact of migraine on a patient's HRQoL. Version 1.0 of the MSQ was a 16-item instrument developed and validated by Jhingran et al.[51] Version 2.1 is a 14-item instrument developed by rewording several items for clarification and shortening the questionnaire for easier administration. MSQ version 2.1 was used by the studies in this review.

The MSQ assesses HRQoL across three domains: RFR includes seven items assessing how migraines limit one's daily social and work-related activities, RFP includes four items assessing how migraines prevent these activities, and EF includes three items assessing the emotions associated with migraine.[22] Participants respond to the 14 items based on a four-week recall period and using a six-point Likert-type scale that ranges from none of the time, a little bit of the time, some of the time, and a good bit of the time to most of the time and all of the time; scores of 1 to 6 are assigned, respectively. Raw dimension scores are computed as a sum of item responses and then rescaled to a 0-to-100-point scale, producing an overall score for each domain. A higher score indicates better HRQoL.[22]

A study by Bagley et al.[22] provided evidence of the validity and reliability of MSQ version 2.1 in patients with episodic and chronic migraine. The study was a web-based, cross-sectional survey conducted in 8,726 patients with episodic migraine (defined by < 15 MHDs) or chronic migraine (defined by ≥ 15 MHDs) from nine different countries. Of these, 499 patients (5.7%) had chronic migraine and their MSQ domain scores (SD) were RFR = 44.37 (22.07), RPR = 61.37 (26.10), and EF = 48.27 (28.12). Patients with episodic migraine (94.3%) had MSQ domain scores (SD) of 56.46 (24.13) for RFR, 71.68 (23.96) for RFP, and 67.20 (26.64) for EF. Reliability was assessed via internal consistency (measured with Cronbach's alpha) for the overall sample for RFR, RFP, and EF at 0.96, 0.90, and 0.87, respectively, and was acceptable based on a threshold of 0.70. Internal consistency

was also acceptable for both the episodic and chronic migraine samples as Cronbach's alpha was ≥ 0.86 for each of the MSQ domains. Construct validity was assessed using Pearson's correlation coefficients of the MSQ scores and other HRQoL instruments. Based on the overall patient population (chronic and episodic migraine), correlations were moderate to strong between the MSQ and HIT-6 (r = −0.60 to −0.71), weak to moderate for MSQ and Patient Health Questionnaire 4 (r = −0.31 to −0.42), weak for MSQ and MIDAS (r = −0.38 to −0.39) and for MSQ and HDPM (r = −0.17 to −0.24).[22,50] Overall this provided some support for convergent and discriminant validity of the MSQ. Similar results were also obtained for the chronic and episodic migraine groups alone.[22] Known-groups validity was also demonstrated using the same HRQoL measures, as a statistically significant difference was observed for the mean MSQ scores across migraine frequency groups.[22]

Rendas-Baum et al. provided further validation of MSQ version 2.1 in patients with chronic migraine undergoing prophylactic treatment.[39] Data were pooled from two clinical trials of onabotulinum toxin A, PREEMPT-1 and PREEMPT-2, and included 1,376 patients. For reliability, internal consistency at baseline was acceptable, with a Cronbach's alpha of 0.80 for all three scales and varying between 0.80 for EF and 0.93 for RFR. At 24 weeks, Cronbach's alpha remained acceptable and ranged from 0.90 to 0.97 across the three domains and the two studies. For construct validity, MSQ and HIT-6 scores were moderately to strongly correlated,[50] with Pearson values ranging from r = −0.59 (EF) to r = −0.75 (RFR) at baseline and r = −0.74 (EF and RFP) and r = −0.86 (RFR) at 24 weeks. For responsiveness, changes in MSQ scores indicated large and moderate effect sizes for patients who experienced at least 50% improvement and improvement between 30% and 50%, respectively.[39]

The MCID in the MSQ score was determined from a multi-centre, double-blind, placebo-controlled randomized trial of 328 patients with chronic migraine.[24] Chronic migraine was defined as the presence of at least 15 headache days over the last 28 days, of which at least half were migraines. Patients were randomized in a 1:1 ratio to receive topiramate at a maximum dose of 100 mg/day (n = 165) or placebo (n = 163) for 16 weeks. Mean age was 38.2 years (range 18 to 74 years) and 85% were female. The patients had suffered from chronic daily headaches for approximately nine years and reported 20 MHDs at baseline. Outcomes measured included MIDAS, MSQ, Subject's Global Impression of Change (SGIC), and PGIC. Both SGIC and PGIC, completed at the end of the study, used a seven-point scale with 1 = very much improved and 7 = very much worse.[24]

A MCID was established using an anchor-based approach, with SGIC as the anchor. The MCID was estimated as the change in MSQ domain score that corresponded to a unit improvement on the SGIC (i.e., the beta coefficient of the regression equation of MSQ domain with SGIC was the MCID). For change from baseline in MSQ-RFR versus SGIC, there was an improvement in RFR, with a regression-estimated MCID of 10.9. For change from baseline in MSQ-RFP versus SGIC, there was an improvement in RFP, with a regression-estimated MCID of 8.3. For change from baseline in MSQ-EF versus SGIC, there was improvement in EF, with a regression-estimated MCID of 12.2 (Table 22).[24]

Table 22: MCID for Each MSQ Domain – Within-Group Difference in Patients with Chronic Migraine

MSQ domain	Regression-estimated MCID (95% CI) within-group differences
Role function – restrictive	10.9 (9.4 to 12.4)
Role function – preventive	8.3 (6.7 to 9.9)
Emotional function	12.2 (10.2 to 14.3)

CI = confidence interval; MCID = minimal clinically important difference; MSQ = Migraine-Specific Quality of Life Questionnaire.

Source: Dodick et al.[24]

Cole et al. identified group-level and individual-level MCIDs for the RFR, RFP, and EF domains of the MSQ.[23] The analyses were performed on pooled data from two clinical trials of topiramate for migraine prophylaxis (N = 916) and the QualityMetric National Headache Survey (N = 1,016). The two trials were randomized, double-blind, and placebo-controlled from Canada and the US. Patients were 12 to 65 years of age, had a minimum six-month history of migraine, and experienced three to 12 migraines per month (but not more than 15 headache days a month during the 28-day baseline period). Patients were randomized to placebo or topiramate 50 mg, 100 mg, or 200 mg/day and continued on treatment for 18 weeks. The QualityMetric database included adults who resided in the contiguous 48 states of the US, were 18 to 65 years of age, could converse in English, and experienced a headache at least once in the past four weeks prior to the telephone interview. No intervention was administered to patients in the QualityMetric survey.

Group-level MCIDs were determined using a distribution-based technique, with Cohen's d effect sizes from the pooled topiramate trial data. Table 23 shows the group-level MCIDs for RFR, RFP, and EF domains of the MSQ.

Table 23: Group-Level MCIDs for the MSQ in Patients With a Maximum of 15 Headache Days per Month

MSQ Domain	Distribution-based: MCID
Role function – restrictive	3.2
Role function – preventive	4.6
Emotional function	7.5

MCID = minimal clinically important difference; MSQ = Migraine-Specific Quality of Life Questionnaire.

Source: Cole et al.[23]

Cole et al. also calculated individual-level MCIDs with anchor-based distribution and techniques.[23] In anchor-based techniques, the anchors were average monthly migraine rate (30%, 40%, or 50% reduction), migraine status (yes/no), MIDAS, more or fewer headaches compared with three months ago (yes/no), bothered by headaches more now compared with three months age (yes/no), and impact of migraine on life (i.e., everyday physical activities, feeling frustrated or irritable, limitations in daily activities, and overall quality of life). The individual-level MCIDs determined by Cole et al. from anchor-based techniques (Table 24) were generally smaller than those reported in Dodick et al. (Table 22). The MCIDs were 4.9 and 5.0 for RFR, 5.0 and 7.9 for RFP, and 8.0 and 10.6 for EF. Importantly, the MCIDs derived by Dodick et al. were based on patients with chronic migraine, whereas the datasets used by Cole et al. included patients with a maximum of 15 MHDs (i.e., most patients in the datasets used by Cole et al. would be below the threshold for classification of chronic migraine).

In one distribution-based technique, the MCIDs were calculated from one-half the SD of each MSQ domain, from the pooled topiramate trial dataset and the QualityMetric dataset separately. In a second distribution-based technique, the MCIDs were calculated from the standard error of the mean of the MSQ domains in the pooled clinical trial dataset. The MCIDs from distribution-based techniques ranged from 4.8 to 8.6 (RFR), 7.9 to 9.9 (RFP), and 10.6 to 12.4 (EF). The anchor-based MCIDs were similar to the distribution-based MCIDs using standard error of the mean, but were less than the distribution-based MCIDs using one-half SD (Table 24). The estimates based on anchor techniques are preferred to those of distribution techniques.

Table 24: Individual-Level MCIDs for MSQ in Patients with Episodic Migraine

MSQ domain	Anchor-based: MCID[a]	Distribution-based (half SD): MCID[b]	Distribution-based (SEM): MCID
Role function – restrictive	4.9; 5.0	8.3; 8.6	4.8
Role function – preventive	5.0; 7.9	9.9; 8.5	7.9
Emotional function	8.0; 10.6	12.4; 11.5	10.6

MCID = minimal clinically important difference; MSQ = Migraine-Specific Quality of Life Questionnaire; SD = standard deviation; SEM = standard error of mean.

[a] Estimates based on logistic and better-same-worse analysis.

[b] Estimates based on multiple databases (pooled topiramate trial and QualityMetric datasets).

Source: Cole et al.[23]

Headache Impact Test

The Headache Impact Test is a web-based, multi-question health assessment that quantifies the impact of headache on a patient's life.[25] It uses computerized adaptive testing technology to select and ask only survey questions that are relevant to the respondent. A total of 84 possible questions cover topics such as functional health and well-being. Optional questions may be used to obtain information on pain, medications, and treatment satisfaction.[25] The HIT-6 is a short-form version of the test developed for practical reasons.[26] Six items (questions) were selected from a pool of 89 questions (54 from the full test and 35 suggested by clinicians).[26] The HIT-6 measures pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress.[27] Each of the six items is answered on a five-point Likert scale based on the following responses: never, rarely, sometimes, very often, or always, which are assigned 6, 8, 10, 11, or 13 points respectively. Total HIT-6 scores range from 36 to 78; a higher score indicates a greater impact of the disease on the daily life of the respondent.[27,28] The scores may be interpreted using four groupings: a score less than or equal to 49 indicates little or no impact, a score of 50 to 55 reflects some impact, a score of 56 to 59 indicates substantial impact, and a score of 60 or higher reflects severe impact.[27]

HIT-6 was first tested by conducting an internet-based survey of 1,103 adults who had experienced a headache in the past four weeks that was not due to cold, flu, head injury, or a hangover.[26] A follow-up survey of 540 of the original adults was conducted 14 days after the first survey. For reliability, the instrument showed good internal consistency (Cronbach's alpha = 0.89 and 0.90 for the first and second survey, respectively) and test-retest reliability (ICC = 0.78, n = 540). With respect to construct validity, correlation between HIT-6 scores and the Short Form (8) Health Survey scales and summary scores were obtained. Weak correlations were observed between HIT-6 and the role physical and social functioning scales ($r = -0.36$ and $r = -0.38$, respectively) and with the bodily pain and mental health scales ($r = -0.25$ and $r = -0.27$, respectively).[26,50,52] HIT-6 scores correlated weakly with

physical summary score (r = −0.35) and mental summary score (r = −0.31). The authors of the study suggested that the weak correlation with other instruments may be due to the heterogeneity of the HIT-6 content. For responsiveness, the instrument was responsive to self-reported changes in headache impact. Scores improved with respondents who self-reported improved headache impact, whereas scores declined with respondents who self-reported worsening headache impact.[26]

A study by Kawata et al. was conducted in patients with chronic daily headaches (≥ 15 MHDs).[27] New patients at a headache clinic were asked to complete a set of questions on their first visit (N = 309). All patients were mailed a follow-up survey four months after their baseline assessment. The mean HIT-6 score was 65.6 (SD = 7.0), and 87% of patients reported having a score of 60 or more. For reliability, the instrument showed good internal consistency (Cronbach's alpha = 0.87). With respect to construct validity, correlation between HIT-6 scores and the Short Form (36) Health Survey domain scores were obtained. Moderate correlations were observed between HIT-6 scores and role physical (r = −0.52) and social functioning subscales (r = −0.57). Correlations were weak with the mental health (r = −0.22) and general health (r = −0.29) subscales of the Short Form (36) Health Survey.[27]

Further testing of HIT-6 was completed by Yang et al. in 2,049 patients with episodic or chronic migraine.[40] Adults who had participated in two studies (the National Survey of Headache Impact study and the HIT-6 validation study) were selected. Both studies had similar inclusion and exclusion criteria, and data were pooled. A total of 6.4% of respondents had chronic migraine with a HIT-6 score of 62.5 ± 7.8 (mean ± SD). Adults with episodic migraine represented 42.1% of the population (HIT-6 score of 60.2 ± 6.8), while the remainder (51.5%) had non-migraine headaches (HIT-6 score of 49.1 ± 8.7). For reliability, the instrument showed strong[52] internal consistency (Cronbach's alpha = 0.83 and 0.90 for the first and second interview, respectively, in the total sample) and test-retest reliability (ICC = 0.77 for HIT-6 validation study respondents). With respect to construct validity, correlation between HIT-6 scores and other scores (MIDAS, headache pain severity, and number of MHDs) were also obtained. A moderate correlation was observed between HIT-6 scores and total MIDAS scores (r = 0.56), demonstrating construct validity. Correlation was moderate (r = 0.46) and weak (r = 0.29) with headache pain intensity and MHDs, respectively. For discriminant validity, HIT-6 scores differed significantly between subgroups of chronic migraine (mean ± SD = 62.5 ± 7.8), episodic migraine (60.2 ± 7.8), and non-migraine headaches (49.1 ± 8.7) (P < 0.01). However, the sample size of the chronic migraine group was much smaller and may have affected these results. The authors also stated that patients with chronic migraine were more likely to report an increased impact severity level than patients with episodic migraine and non-migraine headaches, in that order.[40]

Rendas-Baum et al.[46] validated the HIT-6 scores in 1,384 patients with chronic migraine, pooled from PREEMPT-1 and PREEMPT-2. Validity, reliability, and responsiveness (i.e., ability to detect change) were evaluated. Convergent validity was assessed by correlation of HIT-6 with MSQ; if correlation coefficients were less than −0.40, then the HIT-6 was deemed as having convergent validity. Construct validity was examined by comparing mean scores across groups known to differ in number of headache days within a 28-day period (i.e., < 10, 10 to 14, and ≥ 15) and cumulative hours of headache within a 28-day period (i.e., < 140, 140 to < 280, 280 to < 420, and ≥ 420) at week 24. Test-retest reliability was assessed with the ICC in a stable subsample at weeks 8 and 12. Internal consistency was assessed with Cronbach's alpha, the average inter-item correlation, and the item-total

correlation at baseline and week 24. Ability to detect change was evaluated by the difference in HIT-6 scores among patients who were "much improved" (i.e., ≥ 50% decrease in headache frequency), "moderately improved" (i.e., ≥ 30% to < 50% decrease in headache frequency), or "not improved or worsening" (i.e., < 30% decrease in headache frequency or worsening). With respect to validity, the HIT-6 correlated moderately to strongly[50] with the MSQ (−0.86 to −0.59) and demonstrated convergent validity. For reliability, test-retest reliability was demonstrated with an ICC of 0.76 to 0.80. The HIT-6 also demonstrated internal consistency, with a Cronbach's alpha of 0.75 to 0.92, and average inter-item correlation and item-total correlation above the threshold of 0.40. For responsiveness, the HIT-6 scores were significantly higher for patients with greater improvement in headache frequency and cumulative hours of headache, showing that the instrument can detect changes in disease status.

The MCID for HIT-6 scores was determined by Coeytaux et al. from a study involving 71 patients who suffered from chronic daily headaches (≥ 15 MHDs).[28] Patients were randomly assigned to 10 acupuncture sessions administered over six weeks and usual medical care (n = 34) or to usual medical care alone (n = 37). Patients' mean age was 46 years (range 19 years to 83 years) and 80% were female. Patients suffered from a mean (SD) of 24.2 (5.8) headaches in the month prior to study enrolment. The mean pain severity was 6.4 (2.0) on an 11-point scale. There were no significant differences in baseline characteristics between the two groups.[28]

Before randomization, HIT-6 was administered at baseline and again at six weeks. At six weeks, the follow-up test included one additional question to determine the patients' perceived clinical change to define a meaningful or important clinical change: "Compared with six weeks ago, my headache condition is a) much better; b) somewhat better; c) about the same; d) somewhat worse; or e) much worse."[28] The MCID was established using an anchor-based approach that compared the HIT-6 scores of patients who reported clinical improvement to those of patients who reported no clinical change. Four different anchors were used: method 1 related HIT-6 change scores to levels of perceived improvement in clinical status; method 2 compared change in HIT-6 change scores associated with some perceived clinical change to scores associated with no change; method 3 compared HIT-6 follow-up scores between two levels of clinical improvement; and method 4 compared HIT-6 change scores associated with each level of change to scores associated with no perceived clinical change, using a linear regression model.[28]

Baseline HIT-6 scores were 64.9 (95 % CI, 62.7 to 67.1) in the acupuncture group and 64.1 (95% CI, 62.2 to 66.1) in the medical-care-only group. At six weeks, HIT-6 scores were 61.4 (95 % CI, 59.2 to 63.5) in the acupuncture group and 63.7 (95% CI, 62.0 to 65.5) in the medical-care-only group.[28] Similar MCID estimates were obtained using different anchors (Table 25). A between-group difference of HIT-6 change scores of 2.3 units suggests an improvement in a patient's headache condition that may be considered clinically important. Accuracy of recall may have been a limitation of the study given that patients had to recall their headache condition of six weeks before.

Table 25: MCIDs for HIT-6 Based on Four Methods

Method	Description	MCID, mean (95% CI)
Method 1	HIT-6 change: "somewhat better" minus "about the same"	−2.3 (−4.6 to −0.3)
Method 2	HIT-6 change: "somewhat better/worse" minus "about the same"	−2.7 (−4.4 to −1.0)
Method 3	Follow-up HIT-6: "somewhat better" minus "about the same"	−2.3 (−4.9 to −0.2)
Method 4	HIT-6 change: "somewhat better" compared with "about the same"	−2.3 (−4.3 to −0.3)

CI = confidence interval; HIT-6 = six-item Headache Impact Test; MCID = minimally clinically important difference.

Source: Coeytaux et al.[28]

Smelt et al. developed within-group and between-group MCIDs for the HIT-6 in patients with episodic migraine.[29] The dataset consisted of patients (N = 490) with migraine who participated in a randomized trial that compared a proactive approach by general practitioners with usual care in the Netherlands. The average age of patients was approximately 48 years, 86% were female, and patients experienced an average of approximately six MHDs. However, the diagnosis of migraine was not based on the International Headache Society criteria. Change scores on the HIT-6 from baseline to month 3 (N = 368) were compared with two anchor questions: (1) Compared to three months ago, how is your headache condition? a. much better, b. somewhat better, c. about the same, d. somewhat worse, e. much worse; and (2) Compared to three months ago, how often do headaches limit your usual daily activities? a. a lot less often now, b. somewhat less often now, c. about the same, d. somewhat more often now, e. a lot more often now. A within-group MCID was determined by a mean change approach, which defines the MCID as the mean change in HIT-6 score of the group of patients who reported being "somewhat better." The between-group MCID was determined by subtracting the mean change score in the group that reported to be "about the same" from the mean change score of the group that reported to be "somewhat better." An additional, receiver operating characteristic curve analysis was conducted to determine within-group MCID. The within-group MCID was estimated to be −2.5 points based on the mean change approach and −6.0 points based on the receiver operating characteristic curve approach. The between-group MCID was estimated to be −1.5 points.

Migraine Disability Assessment Scale

The MIDAS was created to facilitate physician-patient communication regarding a patient's experience with migraines.

The MIDAS questionnaire evaluates headache-related disability through five questions regarding the number of days lost in three domains: schoolwork or work for pay; housework or chores; and family, social, or leisure activities.[30] The last two questions capture additional days with significant limitations to activity (≥ 50% reduced productivity) in the employment domains and household work domains.[31] The questions are answered based on a three-month recall interval, which was selected to ensure the questions accurately capture self-reported information while also providing enough time to capture the long-term experience with headaches.[31] An overall score for the questionnaire is calculated by summing the lost days recorded in the five questions. Two questions, which are not included in the scoring, ask about the frequency of headaches and intensity of headache pain. These are mainly used to provide clinicians with additional information for management of treatment decisions. The overall score translates to a four-point grading scale: grade I = scores raging from 0 to 5; grade II = 6 to 10; grade III = 11 to 20; grade IV = 21 or greater. Grade I is

classified as minimal or infrequent disability, grade II = mild or infrequent disability, grade III = moderate disability, and grade 4 = severe disability.

The MIDAS questionnaire has been validated in terms of internal consistency and test-retest reliability in two studies by Stewart et al. Both studies collected data using telephone interviews and a clinically validated computer-assisted telephone interview to interview respondents about their headaches, with the results used to define cases of migraine in combination with International Headache Society criteria.[31,42] Individuals with a diagnosis of migraine headaches were invited to participate in the reliability studies. A total of 124 respondents with migraine and 100 non–migraine headache controls agreed to participate by completing the MIDAS questionnaire twice.[42] Response rates for the second questionnaire were 78% for the group of people with migraine and 80% for those without. Spearman and Pearson correlations were used to assess test-retest reliability between responses to the first and second questionnaires, and internal consistency for the overall score was evaluated using Cronbach's alpha. There was substantial agreement[53] based on Pearson's correlation, which ranged from 0.60 to 0.75 for each question, and Spearman's correlation, which ranged from 0.67 to 0.84, demonstrating test-retest reliability.[42] The overall MIDAS score also demonstrated internal consistency (Cronbach's alpha = 0.83).

Similar methods were used to evaluate reliability in the second study by Stewart et al.[31] This study received two completed questionnaires from 197 persons living with migraines (97 from the US and 100 from the UK), which were completed a median of 21.5 days apart. Each question of the MIDAS score was moderately to almost perfectly[53] correlated by Pearson's correlation coefficient (r = 0.52 to 0.82) and moderately to substantially correlated[53] by Spearman's correlation coefficient (rho = 0.46 to 0.71), demonstrating test-retest reliability.[31] Further, the overall MIDAS score also demonstrated test-retest reliability through a high correlation[53] (Pearson's r = 0.80 to 0.83 and Spearman's rho = 0.77 to 0.78).[31]

Concurrent validity of the MIDAS questionnaire was also assessed through a correlation between the MIDAS score and a 90-day headache diary, both of which were completed by 144 patients with physician-confirmed migraine diagnosis who were also trained to use the diary.[31,41] The individual items and overall MIDAS score demonstrated concurrent validity through a moderate-to-strong correlation[50] between the questionnaire and daily headache dairy (Pearson's r = 0.50 to 0.77, Spearman's rho = 0.53 to 0.76).[31,41]

Based on the studies summarized, the MIDAS questionnaire is considered reliable and valid for those experiencing headaches and migraines; however, the proportion of patients with chronic versus episodic migraine in these studies is unknown. Evidence regarding responsiveness or an MCID was not identified in this review.

Work Productivity and Activity Impairment Questionnaire – Specific Health Problem (WPAI-SHP)

The WPAI – Specific Health Problem (WPAI-SHP) is a self-administered questionnaire to measure impairments in work and activities during the past seven days due to general health or a specific health problem.[9] The instrument poses six questions and provides four scores: absenteeism (work time missed), presenteeism (impairment at work and/or reduced on-the-job effectiveness), work productivity loss (overall work impairment and/or absenteeism plus presenteeism), and activity impairment. The six questions are: Q1 = currently employed; Q2 = hours missed due to health problems; Q3 = hours missed other reasons; Q4 = hours actually worked; Q5 = degree health affected productivity while

working (using a 0-to-10 VAS); and Q6 = degree health affected productivity in regular unpaid activities (VAS).[54] The questionnaire elicits information on the number of days or hours missed from work, days or hours worked, days during which the performing of work was challenging, and the extent to which the patient was limited at work (work impairment). The work impairment domain is the sum of impairment in work productivity due to absenteeism (productivity loss due to a health-related absence from work, including personal time off, sick days off work, duration of short- or long-term disability, or worker's compensation days) and impairment due to decreased productivity while at work (reduced performance of productivity while at work due to health reasons, including time not being on a task and decreased work quality and quantity). The activity impairment domain refers to impairment in daily activities other than work. Four main outcomes can be generated from the WPAI-SHP and expressed in percentages by multiplying the following scores by 100: 1) percent work time missed due to health = Q2/(Q2 + Q4) for those who were currently employed; 2) percent impairment while working due to health = Q5/Q10 for those who were currently employed and actually worked in the past seven days; 3) percent overall work impairment due to health = Q2/(Q2 + Q4) + (1 - Q2)/(Q2 + Q4) × (Q5/Q10) for those who were currently employed; 4) percent activity impairment due to health = Q6/Q10 for all respondents. For those who missed work and did not actually work in the past seven days, the percent overall work impairment due to health will be equal to the percent work time missed due to health. The outcomes are reported as percentages in impairment, with higher numbers indicating greater impairment and less productivity. The WPAI-SHP is adapted to a specific disease or condition by replacing the word "problem" in the questions with the name of the disease or condition.[54] This outcome was included in the LIBERTY trials,[9] specifically for headaches. The general form of the survey was validated on a sample of 106 employed individuals who were affected by a symptom or health problem during the past seven days of recruitment.[54] However, no studies were found that validated the WPAI-SHP in patients with migraine.

An MCID for the WPAI-SHP in patients with migraine was not identified in the literature.

EuroQol 5-Dimensions 5-Levels

The EuroQol 5-Dimensions (EQ-5D) questionnaire is a generic self-reported quality-of-life instrument developed by the EuroQol Group that is applicable to a wide range of health conditions and treatments.[32] As a generic measure of HRQoL that can capture the net effect of treatment benefits and harms, the EQ-5D provides valuable information from a patient perspective. The original three-level version of the questionnaire was introduced in 1990 and was composed of five dimensions pertaining to HRQoL.[9,32] Respondents indicate their health status in terms of five HRQoL dimensions based on three levels of severity. To improve sensitivity and reduce ceiling effects, the three-level EQ-5D was updated in 2005 and expanded to five levels for respondents to answer each dimension with, creating the EQ-5D-5L, which was used in the LIBERTY study.[9,32]

The EQ-5D-5L consists of a descriptive system and a VAS. As mentioned, the descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses to each dimension can be made at five levels, where a level 1 response represents "no problems," level 2 "slight problems," level 3 "moderate problems," level 4 "severe problems," and level 5 "extreme problems" or "unable to perform," which is the worst response in the dimension.[32] Respondents are asked to choose the level that reflects their health state for each of the five dimensions. In total, there are 3,125 possible unique health states defined by the EQ-5D-5L, with 11111 and 55555

representing the best and worst health states, respectively, for each of the five domains. The numerical values assigned to levels 1 to 5 for each dimension reflect rank-order categories of function. In terms of measurement properties, these are ordinal data; they do not have interval properties and therefore should not be summed or averaged to produce, for example, an individual dimension "score." Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm that takes local patient and population preferences into account. Therefore, the index score is a country-specific value and a major feature of the EQ-5D instrument.[33] The range of index scores will differ according to the scoring algorithm used; however, in all scoring algorithms of the EQ-5D-5L, a score of 0 represents the health state "dead" and 1.0 reflects "perfect health." Negative scores are also possible for those health states that society (not the individual patient) considers to be "worse than dead."

The EuroQol VAS records the respondent's self-rated health on a vertical line with end points labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). The respondents are asked to mark an X on the line at the point that best represents their health on that day. The EQ-5D index and VAS scores can be summarized and analyzed as continuous data.[32,33] Hence, the EQ-5D produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121 or 21143
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the VAS.

The EQ-5D-5L has been validated in terms of feasibility, ceiling effects, discriminatory power, and convergent validity in a diverse patient population from six countries with chronic conditions.[32] However, evidence of validity in patients with migraines has not been identified. A Canadian-specific estimate of an MCID for the EQ-5D-5L was generated by simulating the effects of single-level transitions in each dimension.[43] The results yielded MCIDs with a summarized mean of 0.056 (SD = 0.011), and a summarized median of 0.056 (interquartile range, 0.049 to 0.063).[43]

Beck Depression Inventory – II

The BDI-II is an updated version of the original, well-validated inventory, which is a widely used measure of symptoms related to depression.[34] The BDI-II is a self-reported questionnaire based on a two-week recall that assesses the severity of depression through 21-items, each based on a four-point scale that ranges from 0 to 3, for which higher scores correspond to greater severity of depressive symptoms.[9] The scores for each of the items are summed to generate an overall BDI-II score that is categorized by four severity grades: minimal depression (score of 0 to 13), mild depression (14 to 19), moderate depression (20 to 28), and severe depression (29 to 63).[9]

An assessment of the psychometric properties of the BDI-II in patients with migraines was not identified, nor was a migraine-specific MCID.

PROMIS Pain Interference Scale

The PROMIS Pain Interference Scale Short Form 6b was used in Study 295. The Short Form (6b) is a six-item, patient-reported instrument that measures the level of pain interference on aspects of day-to-day life, based on a seven-day recall period.[8] More specifically, it measures the level of pain interference on enjoyment of life, ability to concentrate, day-to-day activities, enjoyment of recreational activities, doing activities away from home, and socializing with others. Each of the six items is answered on a five-point scale, using the following responses and corresponding scores: "not at all" = 1; "a little bit" = 2; "somewhat" = 3; "quite a bit" = 4; and "very much" = 5. The total raw score, which is calculated by summing the values for each item, ranges from 6 to 30, with a higher score corresponding to a higher level of pain interference. The total raw score is rescaled to a standardized t score with a mean of 50 and an SD of 10, which is then reported as the final score.[8]

An assessment of the psychometric properties of the PROMIS Pain Interference Scale Short Form 6b in patients with migraines was not identified, nor was a migraine-specific MCID.

Allodynia Symptom Checklist

The ASC-12 is another patient-reported outcome used in Study 295 included in this review. It is used to measure the frequency of symptoms related to allodynia, or pain due to a stimulus that does not normally provoke pain.[8,35]

The checklist poses the question "How often do you experience increased pain or an unpleasant sensation on your skin during your most severe type of headache when you engage in each of the following?", referring to the following situations: combing hair; pulling hair back (e.g., in a ponytail); shaving one's face; wearing eyeglasses, contact lenses, earrings, a necklace, or tight clothing; taking a shower (when the water hits one's face); resting one's face or head on a pillow; exposure to heat (e.g., cooking, washing face with hot water); and exposure to cold (e.g., using an ice pack, washing face with cold water).[8] Possible answers to each of the situations are "does not apply to me," "never," "rarely," "less than half the time," and "half the time or more." Each response reflecting one of the first three options receives a score of 0, "less than half the time" receives a score of 1, and "halt the time or more" receives a score of 2. A total score is derived from a sum of the scores for each of the 12 questions. A total score of 0 to 2 corresponds to no allodynia, 3 to 5 to mild allodynia, 6 to 8 to moderate allodynia, and 9 or higher to severe allodynia.

Migraine-specific evidence of validity and a corresponding MCID for the ASC-12 in patients with migraines was not identified.

Clinical Global Impression – Improvement and Patient Global Impression of Change Scales

The CGI-I scale is a global assessment of the change in clinical status from treatment initiation, conducted by a clinician (such as a physician, nurse practitioner, or physician's assistant) throughout the study.[8] In Study 295, clinicians were asked to assess patients using the following question: "Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment. Compared to his condition at admission to the project, how much has he changed?" The clinician then answers on a scale from 0 to 7, ranging from

"not assessed" or "very much improved" (score of 0 or 1, respectively) to "no change" (score of 4) to "very much worse" (score of 7).

The PGIC is similar to the CGI-I, but is completed by the patient.[8] In Study 295, this involved asking respondents to answer the following question: "Since beginning treatment at this clinic, how would you describe the change (if any) in activity limitations, symptoms, emotions, and overall QoL, related to your painful condition?" Unlike the CGI-I, patients answered this question two ways: using a seven-point scale ranging from "no change (or conditions get worse)" to "a great deal better, and a considerable improvement that has made all the difference;" and a VAS, ranging from "much better" (or a score of 0) to "much worse" (or a score of 10).

Both scales are among the most broadly used, rapid, and accessible measures for evaluating psychiatric outcomes in clinical trials. Despite widespread acceptance, psychometric validation of the scales has rarely been performed, particularly outside of specific disorders, such as schizophrenia, depression, and social anxiety. The scales have been criticized for lacking consistency, reliability, validity, scoring anchors, and responsiveness. It has been argued that global impression measures may not lend themselves well to the establishment of a clinically important change as they are too simple to measure treatment effects precisely, particularly as new drugs may only offer incremental benefits.[55-57] Evidence of validity or an MCID for patients with migraines was not identified for either of the global impression scales.

Appendix 6: Summary of Other Studies, Part I

Aim

To summarize details and findings of Study 255 and Study 178 related to the long-term safety, tolerability, and efficacy of erenumab (70 mg or 140 mg, subcutaneously once a month) in adults with migraines.

Findings

Study Design

Study 255 is a one-year open-label extension (OLE) of one of the pivotal trials for erenumab, Study 295. It was conducted in centres in North America and Europe. Study 295 included adult patients (age 18 to 65) with a history of chronic migraines, defined by having at least 15 headache days per month of which at least eight were considered migraine days. To be eligible for inclusion for the OLE, patients needed to complete the preceding double-blind trial without discontinuing the investigational product early. The development of clinically significant medical conditions, experiencing an SAE, or having poorly controlled hypertension (based on the opinion of the investigator) during the trial resulted in exclusion from the OLE.

Initially, all patients in Study 255 were to receive a monthly 70 mg dose of erenumab subcutaneously for the duration of the study (52 weeks); however, a protocol amendment was introduced to increase the dose to 140 mg. Patients remained on the 70 mg dose if they had their week-28 visit before the amendment was introduced; otherwise they were switched to the 140 mg dose at their next visit or were started on the 140 mg dose if they had enrolled after the protocol amendment was implemented. The primary end point for Study 255 was patient incidence of AEs. The secondary end points are listed in Table 26.

Study 178 is a phase II, randomized, double-blind, placebo-controlled study that was designed to evaluate the efficacy and safety of erenumab in adults with episodic migraines. The study consisted of screening and baseline phases (three and four weeks, respectively) followed by a 12-week DBTP and an open-label treatment phase (OLTP) of up to 256 weeks or five years and a 12-week follow-up period. Patients were randomized to one of four treatment groups during the DBTP: placebo, erenumab 7 mg, 21 mg, or 70 mg. Patients continuing to the OLTP received erenumab 70 mg (Figure 2). As with Study 255, a protocol amendment was introduced during the OLTP resulting in patients switching to a dose of 140 mg for the remainder of the study, which occurred at approximately 2.0 years into the OLTP.[58] For the purposes of this review of long-term safety and efficacy, the summary of Study 178 will focus on the OLTP. A secondary end point of AEs was included in Study 178; the primary end point did not apply to the OLTP. Additional secondary and exploratory end points are listed in Table 26.

Due to the dose-switching present in both studies, the data have been summarized using the dataset for all patients in Study 178, regardless of the dose received or the first dose received in the description of patient disposition and baseline characteristics for Study 255. Further, safety data for Study 255 were analyzed based on the dose received when the AE occurred, and is reported as such, as well the frequency of AEs among all patients. The efficacy results were reported by overall group (and not by dose received). Of note, the

FDA has stated that there is no apparent relationship between efficacy and erenumab concentration.[59]

[redacted] (Figure 2) [redacted].[60,61] Any data pertaining to safety were based on the most recent data available where possible, which includes a report based on data up until year 3,[58] as well as sponsor-provided data up until year 4.[62]

Figure 2: Overview of Study 178 Study Design

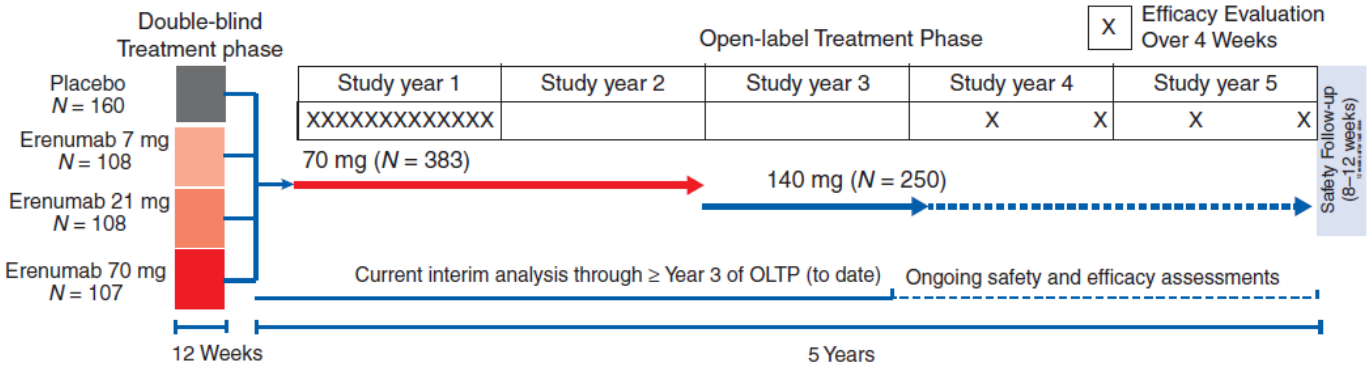

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Table 26: Study Characteristics

		Study 255	Study 178 (OLTP only)
Designs and Populations	**Study design**	Open-label, multi-centre, LTSE of phase III study (Study 295)	Open-label, multi-centre, LTSE of phase II study (Study 178)
	Study period	June 30, 2014, to May 26, 2017	October, 30, 2013, to January 28, 2016 (interim analyses, ongoing)
	Locations	North America and Europe	
	Enrolled (N)	609	383
	Inclusion criteria	Patient has provided informed consent prior to initiation of any study-specific activities or procedures Completed the 12-week study visit and did not end investigational product early during the double-blind trial period of the erenumab parent study (Study 295), and is appropriate for continued treatment **From Study 295:** Adults ≥ 18 to ≤ 65 years of age	Adults ≥ 18 years to ≤ 60 years of age with a history of migraine (with or without aura) for ≥ 12 months prior to screening according to the IHS Classification ICHD-2, based on medical records and/or self-report ≥ 4 and ≤ 14 MMDs in each of the 3 months prior to screening, and with < 15 headache days (migraine and non-migraine) per month (with ≥ 50% of headache days being migraine days) in each of the 3 months prior to screening were eligible for enrolment

		Study 255	Study 178 (OLTP only)
		History of ≥ 5 migraine attacks without aura and/or migraine with visual, sensory, speech and/or language, retinal or brainstem aura according to the IHS Classification ICHD-3 (Headache Classification Committee of the IHS, 2004) History of ≥ 15 headache days per month of which ≥ 8 headache days were assessed by the patient as MMDs in each of the 3 months prior to screening ≥ 15 headache days of which ≥ 8 headache days meet criteria as migraine days during the baseline phase based on the eDiary calculation ≥ 4 distinct headache episodes, each lasting ≥ 4 hours or, if shorter, associated with use of a triptan or ergot derivative on the same calendar day during the baseline phase, based on the eDiary calculations	
	Exclusion criteria	Development of any unstable or clinically significant medical, laboratory, or ECG abnormality following randomization into the parent study that, in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures or completion Experienced an SAE in Study 295 that was determined as potentially caused by the investigational product by the investigator [redacted] Systolic BP of 160 mm Hg and/or diastolic BP 100 mm Hg or greater at day 1 Use of excluded concomitant medications between week 8 and week 12 of Study 295 Pregnancy or breastfeeding	
DRUGS	**Intervention**	Patients enrolled prior to protocol amendment 2 and have had their week-28 visit: • Erenumab 70 mg monthly SC Patients enrolled after protocol amendment 2: • Erenumab 140 mg monthly SC Patients who enrolled prior to protocol amendment 2 and have not had their 28-week visit: • Erenumab 70 mg monthly SC with opportunity to increase to 140 mg monthly SC	Initially all patients received erenumab 70 mg monthly SC Protocol amendment: increased dosage of erenumab to 140 mg monthly SC (occurred at a median of 2.0 years of exposure in the OLTP)

		Study 255	Study 178 (OLTP only)
	Comparator(s)	NA	NA
Duration	**Phase**		
	Screening	Study 295	Up to 7 weeks
	Double-blind		12 weeks
	Open-label	52 weeks	Up to 256 weeks
	Follow-up	12 weeks	12 weeks after last dose
Outcomes	**Primary end point**	Patient incidence of AEs	Does not apply to OLTP
	Other end points[a]	**Secondary:** • Change from baseline in MMDs at assessment time points • Achievement of at least 50% reduction from baseline in MMDs at assessment time points • Change from baseline in acute migraine-specific medication treatment days at assessment time points • Change from baseline in cumulative monthly headache hours at assessment time points [redacted]	**Secondary:** *Safety* • AEs • Clinical laboratory values and vital signs • C-SSRS • Anti-erenumab antibodies [redacted]

		Study 255	Study 178 (OLTP only)
			[redacted]
Notes	**Publications**	None	Ashina (2019) Ashina (2017)

AE = adverse event; BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; HIT-6 = six-item Headache Impact Test; ICHD-2 = International Classification of Headache Disorders, second edition; ICHD-3 = International Classification of Headache Disorders, third edition; IHS = International Headache Society; LTSE = long-term safety extension; MIDAS = Migraine Disability Assessment Scale; MMD = monthly migraine day; MSQ v2.1 = Migraine-Specific Questionnaire version 2.1; NA = not applicable; OLTP = open-label treatment phase; PROMIS = Patient-Reported Outcomes Measurement Information System; SAE = serious adverse event; SC = subcutaneous.

[a] Bolded end points were included in this summary.

Source: Clinical Study Report for Study 255,[63] Clinical Study Report for Study 178,[60] Ashina (2019),[58] and Ashina (2017).[64]

Results

The patient disposition for Study 255 and the OLTP phase of Study 178 is summarized in Table 27. Totals of 609 (93.5% of randomized in Study 295) and 383 (79.3% of randomized to DBTP) patients were enrolled in Study 255 and Study 178, respectively. Of those who enrolled in Study 255, the investigational product was completed by 77.2% of patients, and 74.1% completed the product in Study 178. The most common reasons for discontinuation of erenumab were patient request (10.5% and 17.8% for Study 255 and Study 178, respectively), lack of efficacy (6.4% and 3.1%) and AEs (2.6% and 4.2%), as well as lost to follow-up (1.5% and 3.4%). Data regarding completion of the investigational product or study were not provided for Study 178 as it was ongoing at the time of reporting. The patient disposition of those who received the 140 mg dose of erenumab in Study 178 (n = 250) is summarized in Table 27.

Table 27: Patient Disposition (Full Analysis Set)

Characteristics	Study 255		Study 178 OLTP	
	ERE 70 mg (N = 549)	ERE 140 mg (N = 60)	ERE 70 mg (N = 383)	ERE 140 mg (n = 250)
Enrolled				
Investigational product				
Patients who received investigational product	549 (100.0)	60 (100.0)	383 (100.0)	250 (65.3)
Patients who completed investigational product	428 (78.0)	42 (70.0)	NR	NR
Patients who discontinued investigational product	121 (22.0)	18 (30.0)	132 (34.5)	14 (5.6)
Patient request	[redacted]	[redacted]	68 (17.8)	8 (3.2)
Adverse event	[redacted]	[redacted]	16 (4.2)	1 (0.4)
Decision by sponsor	[redacted]	[redacted]	1 (0.3)	1 (0.4)
Lost to follow-up	[redacted]	[redacted]	13 (3.4)	1 (0.4)
Lack of efficacy	[redacted]	[redacted]	12 (3.1)	0
Noncompliance	[redacted]	[redacted]	6 (1.6)	0
Protocol deviation	[redacted]	[redacted]	1 (0.3)	0
Pregnancy	[redacted]	[redacted]	5 (1.3)	0
Other	[redacted]	[redacted]	5 (1.3)	2 (0.8)
Study completion				
Patients who completed study	409 (74.5)	42 (70.0)	-	-
Patients who discontinued study	140 (25.5)	18 (30.0)	-	-
Decision by sponsor	[redacted]	[redacted]	-	-
Withdrawal of consent from study	[redacted]	[redacted]	-	-
Lost to follow-up	[redacted]	[redacted]	-	-
Death	[redacted]	[redacted]	-	-
Analysis sets			-	-
Full analysis set	549	60	383	-
Safety set	549	60	383	-

ERE = erenumab; OLTP = open-label treatment phase

Source: Clinical Study Report for Study 255[63] and Ashina (2019).[58]

The patients enrolled in Study 255 and Study 178 had a mean age of 42.8 (11.1) and 41.3 (10.9), respectively, and the majority were white (94.3% and 92.4%) and female (83.6% and 79.1%) (Table 28). At baseline, Study 178 patients reported a mean (SD) of 8.70 (2.68) MMDs, 9.76 (2.73) MHDs, and 4.25 (3.70) monthly migraine-specific medication days; these values were not reported for Study 255.

Prior prophylactic medication use was more common among patients in Study 255 than in Study 178 (74.5% versus 44.1%), as was prophylactic treatment failure (68.8% versus 36%), which includes discontinuation due to lack of efficacy and/or side effects.[58] The most commonly used prophylactic medications in both studies were topiramate, beta-blockers, and tricyclic antidepressants, and approximately half of patients (50.6%) in Study 255 had failed at least two prior prophylactic medication classes. The majority of treatment failures were due to lack of efficacy or an adverse reaction (Table 28).

Table 28: Baseline Characteristics (Full Analysis Sets)

	Study 255			Study 178 OLTP
	ERE 70 mg (N = 549)	ERE 140 mg (N = 60)	Total (N = 609)	Total (N = 383)
Age (years), mean (SD)	[redacted]	[redacted]	42.5 (11.3)	41.3 (10.9)
Female, n (%)	[redacted]	[redacted]	509 (83.6)	303 (79.1)
Race, n (%)				
White	[redacted]	[redacted]	574 (94.3)	354 (92.4)
Black or African-American	[redacted]	[redacted]	25 (4.1)	[redacted]
Asian	[redacted]	[redacted]	7 (1.1)	[redacted]
Multiple	[redacted]	[redacted]	-	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Targeted neurological disease diagnosis, n (%)				
Migraine with aura[a]	[redacted]	[redacted]	255 (41.9)	137 (35.8)
Migraine without aura[a]	[redacted]	[redacted]	529 (86.9)	[redacted]
Menstrual migraine	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]	-
Disease duration of migraine with or without aura (years), mean (SD)	[redacted]	[redacted]	[redacted]	20.93 (11.88)
Monthly migraine days at baseline, mean (SD)	[redacted]	[redacted]	[redacted]	8.70 (2.68)
Monthly headache days at baseline, mean (SD)	[redacted]	[redacted]	[redacted]	9.76 (2.73)
Monthly migraine-specific medication days, mean (SD)	[redacted]	[redacted]	[redacted]	4.25 (3.70)
Prior treatment with migraine prophylactic medication, n (%)				
Previously never failed prophylactic treatment	[redacted]	[redacted]	[redacted]	[redacted]
Failed ≥ 1 prior prophylactic medication class	[redacted]	[redacted]	[redacted]	138 (36)[e]
Failed ≥ 2 prior prophylactic medication classes	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients reporting any prior prophylactic medication (N1), n (%)	[redacted]	[redacted]	[redacted]	169 (44.1)
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Study 255			Study 178 OLTP
	ERE 70 mg (N = 549)	ERE 140 mg (N = 60)	Total (N = 609)	Total (N = 383)
[redacted]				
Patient-reported outcomes at baseline				
HIT-6, median (Q1 to Q3)	NR	NR	NR	61.0 (56.0 to 64.0)
MSQ, median (Q1 to Q3)				
MSQ-RFR	NR	NR	NR	60.0 (48.6 to 71.4)
MSQ-RFP	NR	NR	NR	75.0 (65.0 to 90.0)
MSQ-EF	NR	NR	NR	73.3 (60.0 to 86.7)
MIDAS, median (Q1 to Q3)				
Total score	NR	NR	NR	22.0 (11.0 to 38.0)
Absenteeism	NR	NR	NR	10.0 (5.0 to 19.0)
Presenteeism	NR	NR	NR	10.0 (5.0 to 19.0)

EF = emotional function; ERE = erenumab; HIT-6 = six-item Headache Impact Test; MIDAS = Migraine Disability Assessment Scale; MSQ = Migraine-Specific Questionnaire; NR = not reported; OLTP = open-label treatment phase; RFP = role functional – preventive; RFR = role functional – restrictive; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor.

[a] Individual patients could fall into either migraine category or both (with aura and without aura).

[b] % = n/N1 × 100

[c] Categories are not mutually exclusive and patients may contribute to more than one category.

[d] SSRIs include venlafaxine or desvenlafaxine, duloxetine, and milnacipran.

[e] Treatment failure includes discontinuation due to lack of efficacy and/or side effects.

Source: Clinical Study Report for Study 255,[63] November 2016 Interim Analysis,[61] Ashina (2019).[58]

A summary of the exposure to the investigational product is provided in Table 29. The mean (SD) number of days exposed to the investigational product during Study 255 was 316.1 (98.1). The number of patients exposed includes 549 who received erenumab 70 mg, and 259 who received erenumab 140 mg, 199 of whom received both doses.[63] As for Study 178, the mean (SD) days of exposure to erenumab (70 mg or 140 mg) was 529.7 (194.2) for the patients included in the data used for the efficacy outcomes, and a median (first quartile to third quartile) of 3.2 (1.3 to 3.4) years[58] for most patients included in the available data used for the safety outcomes, unless otherwise indicated.

Table 29: Exposure to Investigational Product (Safety Analysis Sets)

	Study 255			Study 178 OLTP	
	ERE 70 mg (N = 549)	ERE 140 mg (N = 259)	Total (N = 609)	Total (N = 383)	ERE 140 mg (n = 250)
Duration of exposure to investigational product					
Mean (SD), days	[redacted]	[redacted]	[redacted]	-	-
Median (minimum, maximum), days	[redacted]	[redacted]	[redacted]	-	-
EAS – mean (SD), days	-	-	-	[redacted]	-
EAS – median (minimum, maximum), days	-	-	-	[redacted]	-
SAS - Median (Q1 to Q3), years	-	-	-	3.2 (1.3 to 3.4)	1.2 (1.1 to 1.3)

EAS = efficacy analysis set; ERE = erenumab; OLTP = open-label treatment phase; Q1 = first quartile; Q3 = third quartile; SAS = safety analysis set.

Source: Clinical Study Report for Study 255,[63] November 2016 Interim Analysis,[61] Ashina (2019).[58]

Safety Results

A summary of the safety results after the 52-week Study 255, and up to approximately three years of the OLTP of Study 178 (unless otherwise indicated), are provided in Table 30. Briefly, 65.4% of patients in Study 255 and 87.5% of patients in Study 178 experienced an AE (treatment-emergent for Study 255; not indicated for Study 178) while receiving erenumab (70 mg and 140 mg). Although the AE incidence rate was high, most of the reported AEs occurred in fewer than 5% of patients in any group. The most frequently occurring AEs included viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, injection-site pain, fatigue, influenza, and back pain (Table 30). Notable harms were experienced by less than 1% of patients, except for vascular events, [redacted]

A total of [redacted] 39 (10.2%) SAEs was reported for Study 178, all of which were reported in less than 1% of patients. [redacted] and no deaths were reported in either study (Table 30).

Table 30: Adverse Events (Safety Analysis Sets, Study 255 – Treatment-Emergent, Study 178 – Not Specified)

	Study 255			Study 178 OLTP
	ERE 70 mg (N = 549)	ERE 140 mg (N = 259)	Total (N = 609)	Total (N = 383)
Total AEs	311 (56.6)	157 (60.6)	398 (65.4)	335 (87.5)
AEs in > 5% any group				
Viral upper respiratory tract infection	68 (12.4)	35 (13.5)	96 (15.8)	100 (26.1)
Upper respiratory tract infection	33 (6.0)	13 (5.0)	45 (7.4)	62 (16.2)
Sinusitis	31 (5.6)	14 (5.4)	44 (7.2)	42 (11.0)
Injection-site pain	[redacted]	[redacted]	[redacted]	NR
Fatigue	[redacted]	[redacted]	[redacted]	NR
Influenza	[redacted]	[redacted]	[redacted]	38 (9.9)
Back pain	[redacted]	[redacted]	[redacted]	38 (9.9)
Notable harms				
Anaphylactic reaction	[redacted]	[redacted]	[redacted]	-
Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Antibody formation[a]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular events	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Orthostatic hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular events	[redacted]	[redacted]	[redacted]	2 (0.5)
Myocardial ischemia	[redacted]	[redacted]	[redacted]	1 (0.3)
Blood creatine phosphokinase MB increased	[redacted]	[redacted]	[redacted]	1 (0.3)
Total SAEs	14 (2.6)	10 (3.9)	24 (3.9)	39 (10.2)
SAEs in > 1 patient				
Migraine	[redacted]	[redacted]	[redacted]	[redacted]
Intervertebral disc protrusion	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]
Adjustment disorder	[redacted]	[redacted]	[redacted]	2 (0.5)
Syncope	[redacted]	[redacted]	[redacted]	2 (0.5)
Uterine leiomyoma	[redacted]	[redacted]	[redacted]	2 (0.5)
Breast cancer	[redacted]	[redacted]	[redacted]	2 (0.5)
Total WDAEs	[redacted]	[redacted]	[redacted]	16 (4.2)
WDAEs in > 1 patient				
Migraine	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	2 (0.5)

	Study 255			Study 178 OLTP
	ERE 70 mg (N = 549)	ERE 140 mg (N = 259)	Total (N = 609)	Total (N = 383)
Depression	[redacted]	[redacted]	[redacted]	2 (0.5)
Deaths	[redacted]	[redacted]	[redacted]	1 (0.3)

AE = adverse event; ERE = erenumab; OLTP = open-label treatment phase; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Note: Data extracted from November 2016 Interim Analysis.[61]

[a] Incidence of total antibody (binding anti-erenumab) anytime during the study.

[b] Study 255: hot flush (n = 4); angiopathy, flushing, hematoma, thrombosis (n = 1 each). Study 178: thrombosis (n = 2); arteriosclerosis, deep-vein thrombosis, flushing, hematoma, hot flush, internal hemorrhage (n = 1 each).

Source: Clinical Study Report for Study 255,[63] Ashina (2019),[58] November 2016 Interim Analysis.[61]

Efficacy Results

The efficacy results from Study 255 and Study 178 have been summarized in Table 31. Statistical analyses were not conducted for any of the efficacy outcomes.

The data suggest sustained reduction in the number of MMDs, responders with at least 50% reduction in MMD, the number of days per month when acute migraine-specific medication was taken, and the cumulative monthly headache hours, over the 52-week open-label Study 255 and up until week 64 of the OLTP of Study 178. In addition, the OLTP of Study 178 reported the numbers of responders who reached at least 75% and 100% reduction in MMD, which were 119 (41.9%) and 73 (23.7%), respectively.

[redacted] (Table 32).

Table 31: Efficacy Results (Efficacy Analysis Set, Study 255 – Secondary End Points; Study 178 – Exploratory End Points)

	Study 255	Study 178 OLTP
	Total (N = 605)	Total (N = 378)
MMD		
Double-blind trial[a] baseline, mean (SD)	18.11 (4.53)	[redacted]
Change from baseline to week 24, mean (95% CI)	−8.36 (−8.92 to −7.80) n = 481	-
Change from baseline to week 52, mean (95% CI)	−9.29 (−9.96 to −8.62) n = 383	-
Change from baseline to week 64, mean (SD)	-	[redacted]
Percent reduction in MMDs		
≥ 50% reduction		
Responders at week 24, n (%)	258 (53.6)	-
Responders at week 52, n (%)	226 (59.0)	-
Responders at week 64, n (%)	-	[redacted]
≥ 75% reduction, responders at week 64, n (%)	-	[redacted]

	Study 255	Study 178 OLTP
	Total (N = 605)	Total (N = 378)
100% reduction, responders at week 64, n (%)	-	[redacted]
Monthly acute migraine-specific medication treatment days		
Number of days at double-blind trial[a] baseline, mean (SD)	9.53 (7.26)	[redacted]
Change from baseline to week 24, mean (95% CI)	[redacted]	-
Change from baseline to week 52, mean (95% CI)	[redacted]	-
Change from baseline to week 52, mean (SD)	-	[redacted]
Cumulative monthly headache hours		
Double-blind trial[a] baseline, mean (SD)	226.84 (125.54)	[redacted]
Change from baseline to week 24, mean (95% CI)	[redacted]	[redacted]
Change from baseline to week 52, mean (95% CI)	[redacted]	[redacted]
Change from baseline to week 64, mean (SD)	[redacted]	[redacted]

CI = confidence interval; MMD = monthly migraine day; OLTP = open-label treatment phase; SD = standard deviation.

[a] Refers to the double-blind trial preceding Study 255 (Study 295) or the Study 178 double-blind treatment phase, which preceded the Study 178 OLTP.

[b] The percent value has been reported based on N1 or the number of patients at available at the time data were collected.

Source: Clinical Study Report for Study 255[63] and Clinical Study Report (November 2016) for Study 178.[61]

Table 32: Patient-Reported Outcomes (Efficacy Analysis Sets)

	Study 255	Study 178 OLTP
	Total (N = 605)	Total (N = 378)
MPFID		
HIT-6		
[redacted]	[redacted]	60.2 (6.3)
[redacted]		[redacted]
MIDAS total score		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
MSQ version 2.1		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]

	Study 255	Study 178 OLTP
	Total (N = 605)	Total (N = 378)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
PROMIS Pain Interference Scale		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

DBT = double-blind trial; EF = emotional function; HIT-6 = six-item Headache Impact Test; MIDAS = Migraine Disability Assessment Scale; MSQ = Migraine Specific Questionnaire; NR = not reported; OLTP = open-label treatment phase; PROMIS = Patient-Reported Outcomes Measurement Information System; RFR = role function – restrictive; RPR = role function – preventive.

[a] Refers to the double-blind trial preceding Study 255 (Study 295) or the Study 178 double-blind treatment phase, which precedes the Study 178 OLTP.

Source: Clinical Study Report for Study 255[63] and Clinical Study Report (November 16, 2016) for Study 178.[61]

Additional Safety and Efficacy Results

In addition to the information summarized in the preceding section, the sponsor provided a presentation slide deck that included an overview of safety and efficacy data from the OLTP of Study 178 for patients who had completed at least four years of treatment.[62] Of the 383 patients enrolled in the OLTP, 250 had continued following the increase in the dose to 140 mg, and 221 patients remained in the study at the time of the interim analysis. Reasons for discontinuation include patient request (n = 16; 4.2%), AE (n = 3; 0.8%), pregnancy (n = 2; 0.5%), noncompliance, decision by sponsor, lost to follow-up, requirement for alternative therapy (n = 1; 0.3%), or other reasons (n = 4; 1.0%).

The median (first to third quartile) total exposure to erenumab at both the 70 mg and 140 mg doses was 4.9 (1.4 to 5.2) years. At month 60, the mean (standard error) change from baseline in MMDs was −5.8 (0.31), and a reduction in MMDs by at least 50%, at least 75%, and 100% was reported for 76.5%, 55.7%, and 32.9% of patients, respectively, although the denominator used for the latter statistics was unclear. The change from baseline in acute migraine-specific medication was also reported at month 60, at −4.6 (0.3) days. The change in cumulative monthly headache hours was not provided. Additionally, by month 60, a total of 339 patients (88.5%) had reported an AE, 46 (12.0%) reported an SAE, and 18 (4.7%) a WDAE, along with one fatal AE, which was considered unrelated to the investigational product by the investigator. The most frequent AEs were similar to what was previously reported, with the exception of constipation, which was previously not listed and is now reported in 24 patients (1.9%). The presentation also reported the number of patients who developed antibodies against erenumab. A total of 52 (13.6%) had a positive result for binding antibodies and 2.4% had a positive result for developing neutralizing antibodies.

Limitations

While the OLE of Study 255 and the OLTP of Study 178 provided information on the safety of erenumab when administered for up to 52 and 64 weeks, respectively, the ability to draw conclusions regarding the sustained efficacy is limited due to the lack of a control group. In addition, patients in both studies initially received 70 mg of erenumab; however, the protocol was amended part-way through to increase the dose to 140 mg where available. The available data do not provide patient-level detail about the changes to the dosing and this introduces uncertainty in the long-term results, which is further compounded by the lack of a control group. Moreover, the evaluations of efficacy were included as secondary end points in Study 255 and exploratory end points in Study 178 but did not include statistical testing, making it difficult to interpret the results. As both summarized studies were open-label, it is possible that the lack of blinding may have affected reporting of both efficacy and safety results as well as introduce reporting bias, given migraine-related outcomes are subjective and therefore difficult to measure, particularly in terms of quality of life. Despite this, there were no safety signals to report in either of the included studies.

The long-term open-label assessments of erenumab are also limited by their rates of discontinuation of investigational product, which were 23% in Study 255 and 34.5% for the ongoing Study 178. Discontinuation rates based on the number of patients entering the preceding double-blind trial or phase are higher. Further, the most common reason for discontinuation was patient request, followed by lack of efficacy and AEs, all of which may have had an impact on the reported results for safety and efficacy.

Conclusion

Overall, the safety profile of erenumab demonstrated by Study 255 and Study 178 does not highlight any safety-related signals. None of the notable harms that were experienced by patients were reported in more than 1% of patients, with the exception of hypertension, which was reported by approximately 3% of patients. More broadly, AEs were reported in 65.4% and 87.5% of patients in Study 255 and Study 178, respectively, SAEs were reported in 3.9% and 10.2% of patients, WDAEs were reported by 2.6% and 4.2% of patients, and no deaths were reported in either study. The most common AEs were viral upper respiratory tract infection, upper respiratory infections, sinusitis, injection-site pain, fatigue, influenza, and back pain, and the most common SAEs were migraine, intervertebral disc protrusion, depression, adjustment disorder, syncope, uterine leiomyoma, and breast cancer. Based on the number of MMDs, the proportion of responders, the number of monthly acute migraine-specific medication treatment days, and cumulative monthly headache hours, efficacy of erenumab appears to have been sustained for the duration of Study 255, and up until the time of analysis that was available for Study 178. However, a comparator group was not included for either study, discontinuation rates were high, and statistical testing was not performed. Interpretation of the long-term safety and efficacy results was therefore significantly limited.

Open-Label Extension of LIBERTY – Interim Analysis

A 156-week OLE of the LIBERTY study (included in the CDR systematic review) is currently ongoing; only interim data up to week 24 were available to summarize and appraise. The aim of the OLE is to assess the long-term impact of erenumab (140 mg) in patients with episodic migraine who had failed two to four preventive treatments.[65] The sponsor provided a summary of an efficacy assessment that was performed in all patients who completed the first three months of the OLE, which is reviewed here.

Results

A total of 240 patients enrolled in the OLE, 228 (95%) of whom had completed a week-24 visit during the OLE. [redacted][65]

Efficacy was evaluated based on the proportion of patients who achieved a reduction of at least 50%, at least 75%, or 100% in MMDs compared to the double-blind trial baseline; the change from baseline in MMDs and monthly acute migraine-specific medication days (Table 33); and the change from baseline in HRQoL scores, including the HIT-6 and MPFID (Table 34).[65]

The proportions of patients in the overall population who achieved a reduction of at least 50%, at least 75%, and 100% in MMDs during weeks 21 to 24 were 39.2%, [redacted] respectively. A reduction in the mean number of MMDs was also observed during weeks 21 to 24 (−2.7 MMDs for the overall population). The mean change from baseline in migraine-specific medication days was similar at each of the three time points (Table 33).[65]

Table 33: Efficacy Outcomes, Interim Analysis of the LIBERTY Open-Label Extension

	Total N = 240
Percent reduction in MMDs	
≥ 50% reduction, %	
During weeks 13 to 16	30.4
During weeks 17 to 20	34.0
During weeks 21 to 24	39.2
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
MMDs	
Mean change in MMDs from baseline, days	
During weeks 13 to 16	−2
During weeks 17 to 20	−2.6

	Total N = 240
During weeks 21 to 24	−2.7
Migraine-specific medication days	
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

MMD = monthly migraine days.

Note: Outcomes are measured as change from double-blind treatment phase baseline.

Source: Reuter et al. (2019).[65]

A reduction in the total score for the HIT-6, suggesting an improved quality of life, was sustained until week 24. Similar results were reported for the everyday activities domain of the MPFID, with a mean (SD) reduction of −4.0 (9.0) during weeks 21 to 24; however, the change from baseline reported for the physical impairment domain varied.[65]

Table 34: Quality-of-Life Outcomes, Interim Analysis of the LIBERTY Open-Label Extension

	Total N = 240
HIT-6	
Change from baseline in HIT-6 total score, total score	
During weeks 13 to 16	−6.4
During weeks 17 to 20	−7.4
During weeks 21 to 24	−7.6
MPFID	
Change from baseline in MPFID-EA score, mean (SD)	
During weeks 13 to 16	−3.2 (8.7)
During weeks 17 to 20	[redacted]
During weeks 21 to 24	[redacted]
Change from baseline in MPFID-PI score, mean (SD)	
During weeks 13 to 16	−1.9 (8.6)
During weeks 17 to 20	[redacted]
During weeks 21 to 24	[redacted]

HIT-6 = six-item Headache Impact Test; MPFID-EA = migraine physical function impact diary – everyday activities; MPFID-PI = migraine physical function impact diary – physical impairment; SD = standard deviation.

Source: Reuter et al. (2019).[65]

Limitations

The data used to summarize the efficacy of erenumab up to week 24 of the 156-week OLE of the LIBERTY trial were based on a poster presentation submitted by the sponsor. Due to the brief nature of this type of presentation, details of the study were limited. Baseline characteristics, a full summary of patient disposition, statistical methods, and details of the analyses conducted were not provided, which hinders the ability to critically appraise the results provided for this study. Moreover, measures of variability such as SD were provided for few outcomes (only the MPFID mean change data) and statistical testing was not performed, which precludes drawing conclusions regarding the long-term efficacy of erenumab based on these results. Further, the study is open-label and includes self-reported and subjective outcomes (HIT-6 and MPFID), which may lead to an overestimate of the effect of the intervention. The study also lacks a comparator arm, which adds to the difficulty in deciphering the true efficacy of erenumab based on the results provided.

Appendix 7: Summary of Other Studies, Part II

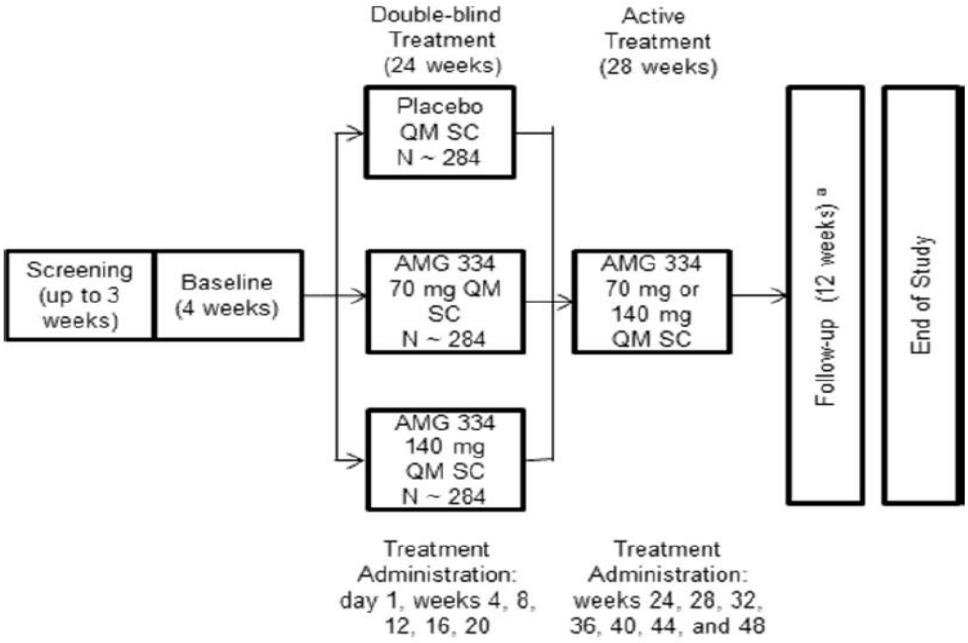
Aim

To summarize the available data of the active treatment phase of the STRIVE study, which was designed to demonstrate efficacy and safety of erenumab (70 mg or 140 mg monthly subcutaneously) in adults with episodic migraine, defined as patients who experienced at least four and fewer than 15 migraine days per month with fewer than 15 headache days per month on average across the three months prior to screening.

Findings

The STRIVE study, previously described in the main body of this report, is composed of a screening (up to three weeks) and baseline phase (four weeks), followed by a 24-week DBTP, a 28-week ATP, and finally a 12-week follow-up to conclude the study (Figure 3). This summary will focus on the 28-week ATP.

Figure 3: Study Design



AMG 334 = erenumab; QM = once monthly; SC = subcutaneous.

Source: Clinical Study Report for STRIVE.[7]

Patients who participated in the DBTP were re-randomized to receive either the 70 mg or 140 mg dose of erenumab once monthly for six months (up to week 48) during the ATP.[7] Rerandomization was stratified by region and treatment status with migraine prophylactic medication, as well as the treatment group they were assigned to during the double-blind phase. The Clinical Study Report provided by the sponsor included early data from the ongoing active treatment phase of the STRIVE study.[7] A poster presentation and slide deck were also provided, which included a more recent analysis of safety and efficacy that

includes data for 764 patients (90.5%) who completed the study.[66] While it is not stated in the presentation, the Clinical Study Report refers to an interim analysis that was to be conducted after approximately 600 patients had completed 52 weeks of the investigational product, indicating this was a pre-specified analysis.[7] Also of note, investigators and patients remained blinded to the dosage assignments during the interim analysis, and data were therefore reported for all patients regardless of the dose of erenumab received.[7]

Patient Disposition

The patient disposition table is presented by the initial dose received during the DBTP (Table 35). As per the early interim analysis, 844 patients, or 88.4% of those enrolled in the DBTP of STRIVE, received at least one dose of the investigational product during the ATP (Table 35). At the time of reporting for the interim analysis, 151 patients (15.8%) had completed the investigational product, and 650 (68.1%) were continuing treatment. Forty-three (4.5%) had discontinued, with the main reasons being due to patient request (2.4%), AEs (0.9%) and lost to follow-up (0.7%) (Table 35).

Table 35: STRIVE Active Treatment Phase – Patient Disposition

	Placebo N = 319	ERE 70 mg N = 317	ERE 140 mg N = 319	Total N = 955
Blinded active treatment phase				
Receiving investigational product	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed active treatment phase	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERE = erenumab; IP = investigational product.

Source: Clinical Study Report for STRIVE.[7]

At the time of reporting for the updated safety and efficacy data (Table 37 and Table 38), [redacted].[66]

Baseline Characteristics

The baseline characteristics and demographics of patients participating in the STRIVE study are provided in the main report and in Table 35.

Safety

The mean (SD) number of days of exposure to erenumab during the active treatment phase was 92.7 (61.8), based on the interim analysis. Information about the exposure to investigational product was not provided for the updated safety and efficacy data.

[redacted] (Table 36). [redacted]

None of the SAEs occurred in more than one patient. The SAEs that were reported included deep-vein thrombosis, diverticulitis, toxic encephalopathy, migraine, femur fracture, subdural haematoma, dehydration, gastritis, depression, dyspepsia, and optic neuritis (Table 36). [redacted]

Table 36: Harms That Occurred During the Active Treatment Phase (Safety Set, Interim Analysis)

	ERE 70 mg and ERE 140 mg [redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

	ERE 70 mg and ERE 140 mg [redacted]
[redacted]	[redacted]
Vascular disorders	5 (0.6)
Deep-vein thrombosis	1 (0.1)
Hypertension	3 (0.4)
Varicose vein	1 (0.1)
SAEs	11 (1.3)
Deep-vein thrombosis	1 (0.1)
Diverticulitis	1 (0.1)
Toxic encephalopathy	1 (0.1)
Migraine	1 (0.1)
Femur fracture	1 (0.1)
Subdural hematoma	1 (0.1)
Dehydration	1 (0.1)
Gastritis	1 (0.1)
Depression	1 (0.1)
Dyspepsia	1 (0.1)
Optic neuritis	1 (0.1)
WDAEs	11 (1.3)
WDAEs in ≥ 2 patients	
Monocytopenia	2 (0.2)
Migraine	3 (0.4)
Deaths	0

AE = adverse event; ATP = active treatment phase; ERE = erenumab; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: Clinical Study Report – STRIVE.[7]

Table 36 is a summary of the AEs at the time of the interim analysis, when approximately 11% of patients who had enrolled in the ATP had completed the study. A brief updated summary of provided safety data (Table 37) includes data from approximately 90% of patients who had completed the ATP. The proportion of patients that reported experiencing an AE or a serious AE had increased to 56.2% and 3.3%, respectively, and a single death in the 140 mg group was reported in the update. The number of withdrawals due to AEs was similar to what was reported during the interim analysis.

Table 37: Harms That Occurred During the Active Treatment Phase, by Treatment Group, Reported in the Updated Safety Analysis (Poster Presentation)

	ERE 70 mg N = 421	ERE 140 mg N = 424	ERE 70 mg/140 mg (total) N = 844
All AE, n (%)	241 (57.2)	233 (55.0)	474 (56.2)
WDAE,[a] n (%)	6 (1.4)	10 (2.4)	16 (1.9)
SAEs, n (%)	14 (3.3)	14 (3.3)	28 (3.3)
Deaths, n (%)	0	1 (0.2)	1 (0.1)

AE = adverse event; ERE = erenumab; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Discontinuation of study drug.

Source: Chou et al. (2019).[66]

Efficacy

The sponsor also provided efficacy results up to 52 weeks (24-week DBTP + 28-week ATP), which are summarized in Table 38: STRIVE – Efficacy Results up to Week 52 (Poster Presentation). At the time of reporting, 764 patients (90.4%) had completed the ATP; however, efficacy outcomes were only available for 369 (87.6%) and 368 (86.8%) patients from the 70 mg and 140 mg treatment arms, respectively. Each outcome, except for the proportion of patients with a reduction in MMD, was reported by the change from DBTP baseline and change from ATP baseline. Patients in the 70 mg and 140 mg groups reported a mean of 4.22 and 4.64 fewer MMDs at week 52, respectively, compared to the DBTP baseline, or 1.10 and 1.78 fewer MMDs, respectively, compared to the pre-ATP baseline. More than half of patients reported a reduction in MMDs of at least 50% compared to the pre-DBTP baseline (61.0% for the 70 mg group and 64.9% for the 140 mg group). The number of monthly acute migraine-specific medication days also decreased from both the DBTP baseline and ATP baseline. Quality of life was assessed using the MPFID outcome and reported by the physical impairment and everyday activities domains. Based on these measures, patients in both treatment groups reported an improved quality of life in both domains over the 52-week study.

Table 38: STRIVE – Efficacy Results up to Week 52 (Poster Presentation)

	ERE 70 mg N = 421	ERE 140 mg N = 424
MMD, mean (SD)		
Pre-DBTP baseline	8.34 (2.48)	8.23 (2.43)
Change from pre-DBTP baseline to week 52	−4.22	−4.64
Pre-ATP Baseline	5.16	5.34
Change from pre-ATP baseline to week 52	−1.10	−1.78
Reduction in MMDs from pre-DBTP baseline to week 52		
Proportion with ≥ 50% reduction, %	61.0	64.9
Proportion with ≥ 75% reduction, %	38.5	40.8
Proportion with 100% reduction, %	19.8	21.2
Monthly acute migraine-specific medication days, mean (SD)		
Pre-DBTP baseline	3.60 (3.41)	3.49 (3.49)
Change from pre-DBTP baseline to week 52	−1.75 (0.14)	−2.00 (0.15)
Pre-ATP baseline	2.60 (3.46)	2.52 (3.52)

	ERE 70 mg N = 421	ERE 140 mg N = 424
Change from Pre-ATP baseline to week 52	–0.72 (0.14)	−0.98 (0.13)
MPFID-PI, mean (SD)		
Pre-DBTP baseline	12.08 (9.31)	12.10 (9.05)
Change from Pre-DBTP baseline to week 52	−5.42 (0.51)	−5.74 (0.45)
Pre-ATP baseline	8.24 (10.77)	8.11 (9.75)
Change from pre-ATP baseline to week 52	−1.28 (0.41)	−1.90 (0.34)
MPFID-EA, mean (SD)		
Pre-DBTP baseline	13.45 (8.64)	13.31 (8.60)
Change from pre-DBTP baseline to week 52	−6.94 (0.47)	−7.05 (0.44)
Pre-ATP baseline	8.37 (10.27)	8.30 (9.48)
Change from pre-ATP baseline to week 52	−1.62 (0.39)	−2.20 (0.34)

ATP = active treatment phase; DBTP = double-blind treatment phase; EA = everyday activities; ERE = erenumab; MMD = monthly migraine day; MPFID = migraine physical function impact diary; PI = physical impairment; SD = standard deviation.

Source: Chou et al. (2019).[66]

Limitations

The data available for the ATP of the STRIVE study at the time of this review were limited. An early interim analysis in which 10.8% of patients had completed the study was available, as well as an updated safety and efficacy analysis that was provided in the form of a poster presentation and slide deck with a brief description of the methodology and statistical analyses used. As a result, it is difficult to provide a useful critical appraisal of the ATP of the STRIVE study. The ATP was randomized and double-blind, but it lacked a comparator arm, making it difficult to interpret the results. Moreover, the efficacy analyses were based on exploratory end points and statistical testing was not performed, which provides another limitation in the ability to draw conclusions regarding the safety and efficacy of erenumab. In addition, approximately one-third of the patients enrolled in the active treatment phase received placebo during the DBTP, and given that the half-life of erenumab is 28 days,[67] the seven-month duration of the study may not provide enough time to adequately capture the long-term effects of the drug related to safety and efficacy.

Conclusion

As the ATP of the STRIVE study is currently ongoing, the data presented in this summary are based on interim analyses and there are no safety signals to report. Just over half of patients (56.2%) reported experiencing an AE, 3.3% of patients reported an SAE, and one patient died during the ATP. The efficacy results available suggest a sustained effect of erenumab over the 52-week study (including the 28-week ATP), based on the number of MMD, 50% or greater reduction in MMD, and monthly acute migraine-specific medication days. However, the limitations that have been discussed must be considered. Quality of life improved over the duration of the study, but these outcomes are also subject to limitations.

Appendix 8: Summary of Indirect Comparisons

Introduction and Background

In the absence of head-to-head studies comparing erenumab with other therapies for prevention of migraine in adults who have at least four MMDs, ITCs can provide information on the comparative effectiveness and safety of erenumab to existing therapies. The objective of this appendix was to summarize and critically appraise the evidence available regarding the comparative efficacy and safety of any ITCs that compare erenumab to relevant treatment regimens (specified in the CDR review protocol) for patients who have at least four MMDs.

Methods

The sponsor submitted one ITC,[36] which was reviewed, summarized, and critically appraised. CDR conducted an independent literature search for published ITCs that compared erenumab with other relevant comparators for the treatment of migraine in adults. One relevant publication was identified in the grey literature.[37]

Description of Indirect Treatment Comparisons

The sponsor submitted an ITC that compared the efficacy of erenumab 140 mg and onabotulinum toxin A among chronic migraine patients who failed to respond to at least three prior prophylactic treatments using an unmatched, anchor-based ITC.[36]

The Institute for Clinical and Economic Review (ICER) conducted an NMA to examine the clinical effectiveness, tolerability, and safety of CGRP inhibitors compared with placebo or commonly used preventive treatments in adults with chronic or episodic migraine.[37] This appendix focuses on the NMAs that compared erenumab with onabotulinum toxin A and other preventive therapies in adults with chronic or episodic migraine.

The population, intervention, comparators, outcomes, and design of studies included in the ITCs are provided below in Table 39.

Table 39: Populations, Interventions, Comparisons, Outcomes, and Study Design Criteria for Inclusion in Network Meta-Analyses

	Sponsor-submitted ITC[36]	ICER (2018)[37]
Population	Adults with chronic migraine who failed to respond to ≥ 3 prior prophylactic treatments	Adults (≥ 18 years) with episodic or chronic migraine and eligible for preventive migraine therapy • chronic migraine defined ≥ 15 headache days per month for at least 3 months and migraine symptoms present on at least 8 days per month • episodic migraine is any migraine not subclassified as chronic migraine
Intervention	Erenumab 140 mg	CGRP inhibitors: • erenumab (70 mg, 140 mg)[a] • fremanezumab • galcanezumab

	Sponsor-submitted ITC[36]	ICER (2018)[37]
Comparators	Onabotulinum toxin A (155-195 IU)	• placebo • topiramate • propranolol • amitriptyline • onabotulinum toxin A
Outcomes	[redacted]	• Change from baseline in monthly migraine days • Change from baseline in headache days • Change from baseline in days using acute medication per month • ≥ 50% reduction in migraine days • Quality of life (MIDAS, HIT-6, MSQ) • All-cause discontinuations • Discontinuations from adverse events • Adverse events reported by ≥ 5% patients in a trial arm • SAEs
Study design	RCTs	• RCTs • Crossover studies if results prior to crossover were presented • Non-randomized comparative studies with at least 100 patients • OLEs of RCTs • Non-comparative observational studies with at least 100 patients and 6-month follow-up
Other		English language

CGRP = calcitonin gene-related peptide; HIT-6 = six-item Headache Impact Test; ICER = Institute for Clinical and Economic Review; ITC = indirect treatment comparison; IU = international units; MIDAS = Migraine Disability Assessment Scale; MSQ = Migraine-Specific Quality of Life Questionnaire; OLE = open-label extension; RCT = randomized controlled trial; SAE = serious adverse event.

[a] Focus of this appendix.

Source: Sponsor-submitted ITC[36] and ICER.[37]

Review and Appraisal of ITCs

Review of the Sponsor-Submitted ITC

Methods of the Indirect Comparison

Study Eligibility and Selection Process

No literature search was conducted. How the studies were selected was not reported. Studies included in the ITC were PREEMPT-1[68] and PREEMPT-2[69] trials for onabotulinum toxin A, and Study 295[19] for erenumab.

Data Extraction

How data were extracted and whether more than one reviewer was involved were not reported.

For erenumab 140 mg, individual patient data from the phase II, randomized, double-blind, multi-centre Study 295 were extracted. Data were based on the 12-week DBTP. Only patients with at least three prior oral prophylactic treatments were included. In the overall analysis, 99 and 68 patients were included in the placebo and erenumab 140 mg treatment groups, respectively. While in the analysis of patients who were onabotulinum toxin A–naive, 55 and 36 patient patients were included in the placebo and erenumab 140 mg treatment groups, respectively. Table 40 below presents the baseline characteristics of

patients with at least three treatment failures in Study 295. Given that patients were not stratified during randomization by number of prior failures to prophylactic treatments, there were imbalances in baseline characteristics between erenumab 140 mg and placebo treatment groups, mainly in prior migraine prophylactic medication failed patients, with more patients who had failed three prior treatments randomized into placebo, and more patients who had failed at least four prior treatments randomized into erenumab 140 mg.

For onabotulinum toxin A, aggregated data of the phase III, randomized, double-blind, multi-centre PREEMPT-1 and PREEMPT-2 trials were extracted from studies by Dodick et al.[70] and Lipton et al.[71] Efficacy data for patients with at least three prior treatment failures were obtained from a Scottish Medicines Consortium report.[72] Baseline characteristics for patients included in the PREEMPT trials who failed at least three prior treatments are not available in the public literature, and they were therefore not provided in this ITC.

Table 40: Baseline Characteristics of Patients With at Least Three Treatment Failures in Study 295

Baseline characteristics	Patients with ≥ 3 treatments failure in Study 295		Onabotulinum toxin A–naive patients with ≥ 3 treatment failures in Study 295	
	Erenumab 140 mg N = 68	Placebo N = 99	Erenumab 140 mg N = 36	Placebo N = 55
Mean (SD) age, years	[redacted]	[redacted]	[redacted]	[redacted]
Monthly headache days at baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Monthly migraine days at baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of migraine, mean (SD), years	[redacted]	[redacted]	[redacted]	[redacted]
Medication overuse, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior migraine prophylactic medication failed, n (%)				
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
> 4	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation.

Source: Sponsor-submitted ITC.[36]

Comparators

Only onabotulinum toxin A 155-195 international units administered in 31 to 39 injections was considered a comparator in this ITC.

Outcomes

The only outcome assessed in this ITC was 50% responders based on reduction in mean MHDs, defined as patients with at least a 50% reduction from baseline in MHDs.

Quality Assessment of Included Studies

No quality assessment of included studies was reported.

Evidence Network

No evidence network was provided.

Indirect Comparison Methods

An anchor-based ITC without matching baseline characteristics between erenumab 140 mg and onabotulinum toxin A was conducted using the Bucher method.[73]

The ITC was made on relative difference, relative risk, and OR. 95% CI and P values were calculated for each analysis.

Results

Table 41 and Table 42 presented results for the ITC between erenumab 140 mg and onabotulinum toxin A, and the ITC for onabotulinum toxin A–naive patients treated with erenumab 140 mg compared to onabotulinum toxin A, respectively.

[redacted]

Table 41: Indirect Treatment Comparison Between Erenumab 140 mg and Onabotulinum toxin A

	Study 295		PREEMPT-1 and PREEMPT-2	
	Erenumab 140 mg N = 68	Placebo N = 99	Onabotulinum toxin A N = 189	Placebo N = 207
50% responder based on reduction in monthly headache days[ab]	[redacted]	[redacted]	[redacted]	[redacted]
Relative difference (95% CI) P value	[redacted]			
Relative risk (95% CI) P value	[redacted]			
OR (95% CI) P value	[redacted]			

CI = confidence interval.

[a] 50% responder rate based on reduction in monthly headache days assessed at week 12 for erenumab 140 mg and week 24 for onabotulinum toxin A.

[b] The percentage was calculated based on the patients with response recorded without imputation of missing values.

Source: Sponsor-submitted indirect treatment comparison.[36]

Table 42: ITC for Onabotulinum toxin A–naive Patients Treated with Erenumab 140 mg Compared to Onabotulinum toxin A

	Study 295[a]		PREEMPT-1 and PREEMPT-2	
	Erenumab 140 mg N = 36	Placebo N = 55	Onabotulinum toxin A N = 189	Placebo N = 207
50% responder based on reduction in monthly headache days[bc]	[redacted]	[redacted]	[redacted]	[redacted]
Relative difference (95% CI) P value	[redacted]			
Relative risk (95% CI) P value	[redacted]			
Odds ratio (95% CI) P value	[redacted]			

CI = confidence interval.

[a] Patients without prior use of onabotulinum toxin A were included in the analysis.

[b] 50% responder rate based on reduction in monthly headache days assessed at week 12 for erenumab 140 mg and week 24 for onabotulinum toxin A.

[c] The percentage was calculated based on the patients with response recorded without imputation of missing values.

Source: Sponsor-submitted ITC.[36]

Critical Appraisal

No literature search was conducted to identify the appropriate trials to be included in this ITC. It is not clear how the studies identified in this ITC were selected.

There were substantial differences in the placebo effect [redacted] between the trials (similar to those with onabotulinum toxin A–naive patients included in Study 295), which signal the potential difference in background therapies in the patient population between the trials (reflecting a change over time); the transitivity or homogeneity assumption therefore may not hold.

The baseline characteristics of patients in the PREMMPT trials in the subgroup who had failed three previous treatments were not available to the sponsor. It is therefore uncertain whether the patient populations compared were similar enough, and erenumab 140 mg may not have the same effect as it would in the patient population in the PREEMPT trial, leading to a biased estimate of the relative effect between the two drugs.

In Study 295 and the PREEMPT trials, patients were not stratified by previous prophylactic treatment failure at randomization. The subgroup comparison therefore breaks randomization, and patient characteristics may be imbalanced between treatment arms.

The time point for assessment in the PREEMPT (onabotulinum toxin A) trials was 24 weeks, while that in Study 295 (erenumab 140 mg) was 12 weeks. The clinical expert consulted for this review indicated that, given the different mechanism of action between the two different treatments, comparing efficacy results for the erenumab 140 mg treatment group at 12 weeks with those for the onabotulinum toxin A treatment group at 24 weeks is acceptable. The expert also indicated that this comparison might be biased in favour of onabotulinum toxin A.

An ITC comparing erenumab 140 mg with onabotulinum toxin A was conducted, but erenumab 70 mg was not compared with onabotulinum toxin A. The clinical expert indicated that physicians are divided on the starting dose of erenumab in patients with chronic

migraine. The expert stated that half of physicians would start treating patients with chronic migraine with a 70 mg dose of erenumab, and if it does not work then the dose would be increased to 140 mg, while others would treat patients with chronic migraine with erenumab 140 mg, and if patients respond well to that dose then the dose would be reduced. The sponsor indicated that the ITC was conducted only on the 140 mg dose. While it was assumed that the results of a comparison of erenumab 70 mg and onabotulinum toxin A would be similar to that comparing erenumab 140 mg with onabotulinum toxin A, no rationale was provided for this assumption.

Review of the Institute for Clinical and Economic Review ITC

Methods of the Indirect Comparison

Study Eligibility and Selection Process

Two reviewers screened abstracts and full texts independently and studies were selected based on the eligibility criteria outlined in Table 39. Published RCTs of any sample size were included. Non-randomized comparative studies with at least 100 patients and crossover studies were eligible if data were reported prior to the crossover period. To assess long-term efficacy and safety, OLEs of RCTs of any size and duration were considered in the ICER review, as were non-comparative observational studies with at least 100 patients and six months of follow-up. However, these studies are not described here. The population of interest for this appendix was adult patients (≥ 18 years of age) with migraine who experience at least four headache days per month and were eligible for preventive therapy. Studies of patients with other types of headache conditions, such as tension-type, cluster, or secondary headaches, were excluded. The primary intervention was CGRP inhibitors, which included subcutaneous injections of erenumab, fremanezumab, and galcanezumab, (only erenumab is currently available in Canada) at any dose or frequency. For both episodic and chronic migraine populations, the included preventive therapies were topiramate, propranolol, and amitriptyline. For chronic migraine patients, onabotulinum toxin A was also included.

Key outcomes were change from baseline in MMDs, change from baseline in headache days, change from baseline in days using acute medication per month, a 50% or greater reduction in migraine days, quality of life as assessed by the MIDAS, MSQ, or HIT-6, all-cause discontinuations, discontinuations from AEs, and AEs reported by at least 5% of patients in a trial arm.

Data Extraction

One reviewer extracted data on patient population, sample size, duration of follow-up, funding source, study design, intervention, outcome assessment (definition, timing, and method of assessment), and results. A second reviewer independently verified the extracted data.

For patients with chronic migraine, Table 43, Table 44, and Table 45 provide sample sizes, doses, and selected baseline population characteristics for the included onabotulinum toxin A, topiramate, and CGRP-inhibitor studies, respectively. Table 46 provides the design features of the studies.

For patients with chronic migraine, 14 trials were included for the assessment of clinical benefit of onabotulinum toxin A, topiramate, and CGRP inhibitors in chronic migraine. In the three CGRP-inhibitor trials (Tepper,[19] Bigal,[74] and Silberstein[75]) and two of the

onabotulinum toxin A trials (Aurora[68] and Diener[69]), patients who showed at least 80% compliance with a daily electronic headache diary and who continued to meet the criteria for chronic migraine during the four-week baseline phase continued to the randomized phase. Criteria related to compliance with a daily headache diary were not reported in the other trials. One topiramate trial and both fremanezumab trials permitted concomitant preventive migraine therapy, which was not permitted in the other trials. Both factors, compliance with headache diary and use of concomitant preventive migraine therapy, are sources of potential heterogeneity in the NMAs. The average age was approximately 40 years, and more than 80% of the patients were female. The included patients had a history of chronic migraine for an average of 20 years. Four trials reported the proportion of patients with medication-overuse headache, which ranged from 41% to 68%, and five trials excluded patients with medication-overuse headaches. None of the fremanezumab trials reported this information. The mean number of migraine days per month ranged from 15 to 25 at baseline across the 14 trials of onabotulinum toxin A, topiramate, and CGRP inhibitors. The time point of analysis ranged from 12 to 26 weeks.

Table 43: Selected Baseline Patient Characteristics of Calcitonin Gene-Related Peptide Inhibitor Trials in Chronic Migraine

Study	Arm	N	Mean age (SD)	Mean years since onset (SD)	Mean migraine days per month (SD)	Mean headache days per month (SD)	Mean days of acute medication use per month (SD)
Erenumab							
Tepper (2017) (phase II)	Erenumab 70 mg per month	191	41.4 (11.3)	20.7 (12.8)	17.9 (4.4)	20.5 (3.8)	8.8 (7.2)
	Erenumab 140 mg per month	190	42.9 (11.1)	21.9 (11.8)	17.8 (4.7)	20.7 (3.8)	9.7 (7.0)
	Placebo	286	42.1 (11.3)	22.2 (12.6)	18.2 (4.7)	21.1 (3.9)	9.5 (7.6)
Fremanezumab							
Bigal (2015) (phase II)	Fremanezumab 675 mg/225 mg per month	88	40.0 (11.6)	15.8 (11.2)	17.2 (5.4)	16.5 (6.7)	15.1 (7.0)
	Fremanezumab 900 mg per month	87	41.5 (12.9)	18.8 (12.2)	16.4 (5.3)	15.9 (6.5)	16.2 (6.7)
	Placebo	89	40.7 (11.5)	20.4 (13.1)	16.8 (5.0)	16.5 (6.3)	15.7 (6.2)
Silberstein (2017) (phase III)	Fremanezumab 675 mg every 3 months	376	42 (12.4)	19.7 (12.8)	16.2 (4.9)	20.4 (3.9)	13.1 (6.8)
	Fremanezumab 675 mg/225 mg per month	379	40.6 (12.0)	20.1 (12.0)	16.0 (5.2)	20.3 (4.3)	13.1 (7.2)
	Placebo	375	41.4 (12.0)	19.9 (12.9)	16.4 (5.2)	20.3 (4.2)	13.0 (6.9)

SD = standard deviation.

Source: Institute for Clinical and Economic Review.[37]

Table 44: Selected Baseline Patient Characteristics in Studies of Onabotulinum Toxin A Versus Placebo and Onabotulinum Toxin A Versus Topiramate in Chronic Migraine

Study	Arm	N	Mean age (SD)	Mean years since onset (SD)	Mean migraine days per month (SD)	Mean headache days per month (SD)	Mean days of acute medication use per month (SD)
Aurora (2010) (PREEMPT-1)	Ona A 155 U	341	41.2 (NR)	20.3 (NR)	19.1 (4.0)	20.0 (3.7)	NR
	Placebo	338	42.1 (NR)	20.6 (NR)	19.1 (4.1)	19.8 (3.7)	NR
Diener (2010) (PREEMPT-2)	Ona A 155 U	347	41.0 (NR)	18.5 (NR)	19.2 (3.9)	19.9 (3.6)	NR
	Placebo	358	40.9 (NR)	17.6 (NR)	18.7 (4.1)	19.7 (3.7)	NR
Cady (2014)	Ona A 155 U	10	NR	NR	23.4 (1.9)[a]	NR	NR
	Placebo	10	NR	NR	24.8 (1.9)[a]	NR	NR
Freitag (2008)	Ona A 100 U	30	42.2 (NR)	NR	NR	23 (NR)	NR
	Placebo	30	42.4 (NR)	NR	NR	23 (NR)	NR
Sandrini (2011)	Ona A 100 U	33	48.5 (9.2)	19.7 (NR)	NR	24.2 (5.0)	22.7 (6.4)
	Placebo	35	49.0 (10.1)	20.3 (NR)	NR	25.5 (5.6)	23.6 (6.6)
Cady (2011)	Ona A 200 U	29	NR	NR	11.9 (NR)	21.8 (NR)	13.9 (NR)
	Topiramate 200 mg/day	30	NR	NR	10.3 (NR)	20.5 (NR)	15.1 (NR)
Mathew (2009)	Ona A 200 U	30	NR	NR	NR	15.6 (7.0)	NR
	Topiramate 100 mg/day	30	NR	NR	NR	15.5 (7.2)	NR

NR = not reported; Ona A = onabotulinum toxin A; NR = not reported; SD = standard deviation; U = units.

[a] Standard error.

Source: Institute for Clinical and Economic Review.[37]

Table 45: Selected Baseline Patient Characteristics in Studies of Topiramate Versus Placebo in Chronic Migraine

Study	Arm	N	Mean age (SD)	Mean years since onset (SD)	Mean migraine days per month (SD)	Mean headache days per month (SD)	Mean days of acute medication use per month (SD)
Silberstein (2007)	Topiramate 100 mg/day	165	37.8 (12.4)	9.3 (10.5)	17.1 (5.4)	20.4 (4.8)	11.9 (7.0)
	Placebo	163	38.6 (11.8)	9.1 (10.6)	17.0 (5.0)	20.8 (4.6)	11.4 (6.6)
Diener (2007)	Topiramate 100 mg/day	32	47.8 (9.4)	NR	15.5 (4.6)	NR	NR
	Placebo	27	44.4 (9.6)	NR	16.4 (4.4)	NR	NR
Mei (2006)	Topiramate 100 mg/day	30	45.8 (9.1)	5.0 (1.9)	NR	24.4 (3.9)	NR
	Placebo	20	45.9 (8.4)	5.0 (2.2)	NR	23.5 (3.7)	NR

Study	Arm	N	Mean age (SD)	Mean years since onset (SD)	Mean migraine days per month (SD)	Mean headache days per month (SD)	Mean days of acute medication use per month (SD)
Silvestrini (2003)	Topiramate 50 mg/day	14	43 (NR)	3 (NR)	NR	20 (NR)	NR
	Placebo	14	44 (NR)	3 (NR)	NR	20 (NR)	NR

NR = not reported; SD = standard deviation.

Source: Institute for Clinical and Economic Review.[37]

Table 46: Design Features of Studies in Patients with Chronic Migraine

Study	Number of centres funding	Location	Baseline (weeks)	Intervention (weeks)	Total follow-up (weeks)	Inclusion: migraine history Exclusion: prior failures	Ongoing preventive therapy
Ona A vs. placebo							
Aurora (2010) (PREEMPT-1) (RCT)	Multi-centre Industry	North America	4	24	56	ICHD-II NA	Not allowed
Diener (2010) (PREEMPT-2) (RCT)	Multi-centre Industry	North America; Europe	4	24	56	ICHD-II NA	Not allowed
Cady (2014) (RCT crossover)	Multi-centre Industry	US	NR	16	28	ICHD-II NA	Allowed
Freitag (2008) (RCT)	Unclear Industry	US	4	16	16	ICHD-I NA	Allowed
Sandrini (2011) (RCT)	Multi-centre Industry	Italy	4	12	24	ICHD-II NA	Not allowed
Ona A vs. topiramate							
Cady (2011) (RCT)	Multi-centre NR	US	4	12	24	ICHD-II NA	Allowed
Mathew (2009) (RCT)	Single-centre Industry	US	4	36	38	NR NA	Not allowed
Topiramate vs. placebo							
Silberstein (2007) (RCT)	Multi-centre Industry	US	4	16	18	≥ 15 headache days per month with ≥ 8 days migraine	Not allowed

Study	Number of centres funding	Location	Baseline (weeks)	Intervention (weeks)	Total follow-up (weeks)	Inclusion: migraine history Exclusion: prior failures	Ongoing preventive therapy
						> 2 preventive medications or topiramate	
Diener (2007) (RCT)	Multi-centre Industry	Europe	4	16	23	ICHD-II NA	Allowed
Mei (2006) (RCT)	Unclear NR	Italy	4	12	12	ICHD-II NA	Not allowed
Silvestrini (2003) (RCT)	Single-centre NR	Italy	8	9	9	NR < 4 preventive medications	Not allowed
CGRP vs. placebo							
Tepper (2017) (RCT)	Multi-centre Industry	North America, Europe	4	12	24	≥ 15 headache days per month with ≥ 8 days migraine > 3 preventive medications	Not allowed
Bigal (2015) (RCT)	Multi-centre Industry	US	4	12	12	ICHD-III beta > 2 medication categories or > 3 preventive medications	Allowed
Silberstein (2017) (RCT)	Multi-centre Industry	Global	4	12	12	ICHD-III beta > 2 preventive medication categories	Allowed

CGRP = calcitonin gene-related peptide; ICHD-I = International Classification of Headache Disorders, first edition; ICHD-II = International Classification of Headache Disorders, second edition; ICHD-III = International Classification of Headache Disorders, third edition; NA = not applicable; NR = not reported; Ona A = onabotulinum toxin A; RCT = randomized controlled trial; vs. = versus.

Source: Institute for Clinical and Economic Review.[37]

For patients with episodic migraine, Table 47 and Table 48 provide sample sizes, doses, and selected baseline population characteristics for the included CGRP-inhibitor, amitriptyline, propranolol, and topiramate studies, respectively. Table 49 provides the design features of the studies.

For patients with episodic migraine, nine trials were included for the assessment of clinical benefit of CGRP inhibitors: three trials for erenumab (Sun,[76] STRIVE,[14] and ARISE[21]), two trials for fremanezumab (Bigal[77] and HALO-EM[78]), and four trials for galcanezumab (Dodick,[79] Skljarevski,[80] EVOLVE-1,[81] and EVOLVE-2[82]). All were industry-funded and

multi-centre trials conducted predominately in North America and Europe. All trials were double-blinded and included a four-week baseline period followed by a 12-week randomized, placebo-controlled treatment phase. At baseline, the average age was 40 years, and patients had been diagnosed with migraine for approximately 20 years, with an average number of migraine days per month of eight to nine, except in patients in Bigal[77] (fremanezumab), who experienced a higher frequency at baseline, with approximately 12 MMD. Across the trials, the number of days using any acute medication was approximately seven to 10.

Of the 24 trials assessing a comparator of interest (amitriptyline, propranolol, or topiramate) in the episodic migraine population, 17 compared active therapy versus placebo (four RCTs assessed amitriptyline,[83-86] four RCTs[87-90] and one crossover assessed propranolol,[91] and eight RCTs assessed topiramate[92-99]) and seven head-to-head studies (three RCTs of topiramate versus propranolol,[100-102] one RCT of topiramate versus amitriptyline,[103] one RCT of propranolol versus amitriptyline,[104] one RCT of topiramate versus amitriptyline versus topiramate plus amitriptyline,[105] and one RCT of propranolol versus amitriptyline versus propranolol plus amitriptyline).[106] Most trials were industry-funded. Ten were single-centre trials, whereas 10 others were multi-centred and four were unclear. Where reported, the trials were conducted in the US and Europe, except for four conducted in Turkey and one in Singapore. Baseline phases were typically four weeks in length, followed by randomized phases of four weeks to 26 weeks. At baseline, the average number of migraine days ranged from five to 12 days per month. The percentage of patients who experienced prior failure of at least one preventive treatment was not reported in any of the oral preventive therapy trials.

Table 47: Selected Baseline Patient Characteristics in Calcitonin Gene-Related Peptide Inhibitor Trials in Episodic Migraine

Study	Arm	N	Mean age (SD)	Mean years since onset (SD)	Mean migraine days per month (SD)	Mean headache days per month (SD)	Mean days of acute medication use per month (SD)
Erenumab							
Sun (2016)[76] (phase II)	Erenumab 7 mg/month	108	40.3 (10.9)	19.0 (11.4)	8.6 (2.8)	9.8 (2.7)	7.0 (2.9)
	Erenumab 21 mg/month	108	39.9 (12.3)	20.1 (12.5)	8.9 (2.9)	10.1(2.7)	6.9 (2.8)
	Erenumab 70 mg/month	107	42.6 (9.9)	21.5 (11.7)	8.6 (2.5)	9.9 (2.5)	6.9 (2.9)
	Placebo	160	41.4 (10.0)	20.7 (11.5)	8.8 (2.7)	9.7 (2.7)	7.1 (3.0)
Goadsby (2017) (STRIVE[14]) (phase III)	Erenumab 70 mg/month	317	41.1 (11.3)	NR	8.3 (2.5)	9.1 (2.6)	3.2 (3.4)
	Erenumab 140 mg/month	319	40.4 (11.1)	NR	8.3 (2.5)	9.3 (2.5)	3.4 (3.5)
	Placebo	319	41.3 (11.2)	NR	8.2 (2.5)	9.3 (2.6)	3.4 (3.4)
Dodick (2018) (ARISE[21]) (phase III)	Erenumab 70 mg/month	286	42 (11)	22 (13)	8.1 (2.7)	9.1 (2.7)	3.7 (3.6)
	Placebo	291	42(12)	20 (12)	8.4(2.6)	9.3 (2.7)	3.4 (3.6)

Study	Arm	N	Mean age (SD)	Mean years since onset (SD)	Mean migraine days per month (SD)	Mean headache days per month (SD)	Mean days of acute medication use per month (SD)
Fremanezumab							
Bigal (2015)[77] (phase II)	Fremanezumab 225 mg/month	96	40.8 (12.4)	18.9 (12.9)	11.5 (1.9)	12.6 (3.1)	10.4 (3.6)
	Fremanezumab 675 mg/month	97	40.7 (12.6)	16.9 (12.3)	11.3 (2.2)	12.5 (2.65)	9.8 (4.0)
	Placebo	104	42 (11.6)	21.1 (14.1)	11.5(2.24)	12.4 (2.3)	10.4 (3.6)
Dodick (2018) (HALO-EM[78]) (phase III)	Fremanezumab 225 mg/month	290	42.9 (12.7)	20.7 (12.9)	8.9 (2.6)	6.8 (2.9)	7.7 (3.4)
	Fremanezumab 675 mg every 3 months	291	41.1 (11.4)	20.0 (12.1)	9.3 (2.7)	7.2 (3.1)	7.8 (3.7)
	Placebo	294	41.3 (12.0)	19.9 (11.9)	9.1 (2.7)	6.9 (3.1)	7.7 (3.6)
Galcanezumab							
Dodick (2014)[79] (phase II)	Galcanezumab 150 mg every 2 weeks	108	40.9 (11.4)	NR	8.1 (2.9)	NR	NR
	Placebo	110	41.9 (11.7)	NR	8.4 (2.9)	NR	NR
Skljarevski (2018)[80] (phase II)	Galcanezumab (all doses)	273	40.6(11.9)	NR	8.4(3.2)	NR	NR
	Placebo	137	39.5 (12.1)	NR	8.0(3.1)	NR	NR
Stauffer (2018) (EVOLVE-1[81])	Galcanezumab 120 mg/month	213	40.9 (11.9)	21.1 (13.0)	9.2 (3.1)	NR	7.4 (3.7)
	Galcanezumab 240 mg/month	212	39.1 (11.5)	19.3 (11.9)	9.1 (2.9)	NR	7.3 (3.3)
	Placebo	433	41.3 (11.4)	19.9(12.3)	9.1 (3.0)	NR	7.4 (3.5)
Skljarevski (2018) (EVOLVE-2[82])	Galcanezumab 120 mg/month	233	40.9 (11.2)	19.93(11.7)	9.07 (2.9)	10.56 (3.4)	7.47 (3.3)
	Galcanezumab 240 mg/month	226	41.9 (10.8)	20.01(12.1)	9.06 (2.9)	10.74 (3.7)	7.47 (3.3)
	Placebo	463	42.3 (11.3)	21.2 (12.8)	9.2 (3.0)	10.7(3.5)	7.6 (3.4)

NR = not reported; SD = standard deviation.

Source: Institute for Clinical and Economic Review.[37]

Table 48: Selected Baseline Patient Characteristics for other Preventive Therapy Trials in Episodic Migraine

Study	Arm	N	Mean age (SD)	Mean years since onset (SD)	Mean migraine days per month (SD)	Mean headache days per month (SD)	Mean days of acute medication use per month (SD)
Amitriptyline							
Couch (1979)[83]	Amitriptyline 100 mg/day	NR	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR
Couch (2011)[84]	Amitriptyline 100 mg/day	194	34.1 (NR)	NR	NR	NR	NR
	Placebo	197	35.7 (NR)	NR	NR	NR	NR
Lampl (2009)[85]	Amitriptyline 25 mg/day	66	Median: 32 (19 to 53)	NR	Median: 7 (4 to 14)	NR	NR
	Amitriptyline 50 mg/day	66	Median: 33 (19 to 51)	NR	Median: 7 (4 to 14)	NR	NR
	Amitriptyline 25 mg/day	66	37.2 (11.2)	24.1 (9.1)	7.2 (2.5)	NR	NR
Gonçalves (2016)[86] (phase III)	Placebo	65	36.6 (13.7)	20.2 (10.6)	7.3 (3.1)	NR	NR
	Amitriptyline 100 mg/day	NR	NR	NR	NR	NR	NR
Propranolol							
Diener (1996)[87]	Propranolol 120 mg/day	78	40(13)	21 (13)	NR	NR	NR
	Placebo	55	39 (11)	19 (11)	NR	NR	NR
Jafarpour (2016)[88]	Propranolol 60 mg/day	30	37.74 (12.39)	14.04 (11.23)	NR	NR	NR
	Placebo	30	41.73 (11.92)	11.10 (8.85)	NR	NR	NR
Pradalier (1989)[89]	Propranolol 160 mg/day	40	37.1 (1.7)	NR	NR	NR	NR
	Placebo	34	37.7 (1.8)	NR	NR	NR	NR
Sargent (1985)[90]	Total	161	30 (16 to 62)	20	NR	NR	NR
Weber (1972)[91]	Total	25	40.6 (19-61)	NR	NR	NR	NR
Topiramate							
Lipton (2011)[92]	Topiramate 100 mg/day	188	39.6 (10.6)	19.8 (10)	11.6 (2.0)	13.0 (2.5)	8.6 (3.2)
	Placebo	197	40.9 (11.2)	20.8 (10.8)	11.8 (2.2)	13.1(2.6)	8.6 (3.5)
Brandes (2004)[93] (phase III)	Topiramate 50 mg/day	120	39 (12.09)	NR	6.4 (2.88)	NR	5.7 (2.72)
	Topiramate 100 mg/day	122	39.1 (12.58)	NR	6.9 (3)	NR	6.2 (2.13)
	Topiramate 200 mg/day	121	39.1 (12.71)	NR	6.1 (2.54)	NR	5.8 (2.52)

Study	Arm	N	Mean age (SD)	Mean years since onset (SD)	Mean migraine days per month (SD)	Mean headache days per month (SD)	Mean days of acute medication use per month (SD)
	Placebo	120	38.3 (11.96)	NR	6.7 (2.84)	NR	5.8 (2.67)
Silberstein (2004)[94] (phase III)	Topiramate 50 mg/day	125	40.2 (11.5)	NR	6.4 (2.7)	NR	5.8 (2.5)
	Topiramate 100 mg/day	128	40.6 (11.0)	NR	6.4 (2.7)	NR	5.9 (2.5)
	Topiramate 200 mg/day	117	40.5 (11.4)	NR	6.6 (3.1)	NR	6.1 (2.6)
	Placebo	117	40.4 (11.5)	NR	6.4 (2.6)	NR	6.1 (3.0)
Gode (2010)[95]	Topiramate 50 mg/day	15	37.1 (NR)	NR	NR	NR	NR
	Topiramate 100 mg/day	15	40 (NR)	NR	NR	NR	NR
Lo (2010)[96]	Topiramate 25 mg/day	10	NR	NR	NR	10.2 (5.1)	NR
	Topiramate 50 mg/day	10	NR	NR	NR	6.9 (2.6)	NR
	Topiramate 75 mg/day	10	NR	NR	NR	8.8 (4.4)	NR
	Topiramate 100 mg/day	10	NR	NR	NR	8.0 (2.5)	NR
Mei (2004)[97]	Topiramate 100 mg/day	58	39.74 (12.02)	NR	NR	NR	6.17 (1.8)
	Placebo	57	38.7 (11.04)	NR	NR	NR	6.49 (1.29)
Silberstein (2006)[98]	Topiramate 200 mg/day	138	39.9 (11.8)	NR	NR	NR	NR
	Placebo	73	41.7 (9.4)	NR	NR	NR	NR
Storey (2001)[99]	Topiramate 200 mg/day	19	38.3 (19-62)	NR	NR	NR	NR
	Placebo	21	38.1 (24-56)	NR	NR	NR	NR
Head-to-head							
Diener (2004)[100]	Propranolol 160 mg/day	144	40.6 (11.13)	NR	6.1 (2.70)	NR	5.4 (2.54)
	Topiramate 100 mg/day	141	39.8 (10.88)	NR	5.8 (2.21)	NR	5.0 (2.21)
	Topiramate 200 mg/day	144	42.6 (11.29)	NR	6.2 (2.76)	NR	5.5 (2.62)
	Placebo	146	40.4 (10.11)	NR	6.1 (2.60)	NR	5.3 (2.52)
Ashtari (2008)[101]	Topiramate 50 mg/day	31	31.7 (8)	NR	NR	NR	NR
	Propranolol 80 mg/day	31	29.93 (9)	NR	NR	NR	NR

Study	Arm	N	Mean age (SD)	Mean years since onset (SD)	Mean migraine days per month (SD)	Mean headache days per month (SD)	Mean days of acute medication use per month (SD)
Dodick (2009)[103]	Topiramate 100 mg/day	178	39.7 (10.7)	NR	7.4 (2.9)	8.7 (3.1)	6.5 (3.0)
	Amitriptyline 100 mg/day	169	37.9 (11.3)	NR	7.1 (2.6)	8.4 (2.9)	6.1 (3.1)
Dogan (2015)[102]	Propranolol 80 mg/day	26	32.0 (11.8)	NR	NR	NR	NR
	Topiramate 50 mg/day	25	34.2 (8.7)	NR	NR	NR	NR
Duman (2015)[104]	Total	108	34.2 (9.3)	5.9 (3.9)	NR	NR	NR
	Amitriptyline		NR	NR	NR	NR	NR
	Propranolol		NR	NR	NR	NR	NR
Keskinbora (2008)[105]	Topiramate 200 mg/day	24	35.25 (9.39)	NR	NR	NR	NR
	Amitriptyline 150 mg/day	28	37.86 (8.67)	NR	NR	NR	NR
	Topiramate 200 mg/day + amitriptyline 150 mg/day	23	39.14 (9.13)	NR	NR	NR	NR
Mathew (1981)[106]	Propranolol 160 mg/day	44	35 (NR)	NR	NR	NR	NR
	Amitriptyline 75 mg/day	42	36 (NR)	NR	NR	NR	NR
	Amitriptyline 75 mg/day + propranolol 160 mg/day	41	31 (NR)	NR	NR	NR	NR
	Placebo	45	32 (NR)	NR	NR	NR	NR

NR = not reported; SD = standard deviation.

Source: Institute for Clinical and Economic Review.[37]

Table 49: Design Features of Studies in Patients with Episodic Migraine

Study	Number of centres funding	Location	Baseline (weeks)	Intervention (weeks)	Total follow-up (weeks)	Inclusion: migraine history Exclusion: prior failures	Ongoing preventive therapy
Erenumab							
Sun (2016)[76] (phase II)	Multi-centre Industry	North America, Europe	4	12	280	ICHD-II Previously failed > 2 preventive medication categories	Not allowed
Goadsby, (2017) (STRIVE[14]) (phase III)	Multi-centre Industry	North America, Europe	4	24	64	ICHD-III beta Previously failed > 2 preventive medication categories	Allowed
Dodick (2018) (ARISE[21]) (phase III)	Multi-centre Industry	North America, Europe	4	12	40	ICHD-III beta Previously failed > 2 preventive medication categories	Allowed
Fremanezumab							
Bigal (2015)[77] (phase II)	Multi-centre Industry	US	4	12	12	ICHD-III beta Previously failed > 2 medication categories or > 3 preventive medication	Allowed
Dodick (2018) (HALO-EM)[78] (phase III)	Multi-centre Industry	Global	4	12	12	ICHD-III beta Previously failed ≥ 2 preventive medication categories	Allowed
Galcanezumab							
Dodick (2014)[79] (phase II)	Multi-centre Industry	US	4 to 5	12	24	ICHD-II Previously failed > 2 preventive medications	Not allowed
Skljarevski (2018)[80] (phase II)	Multi-centre Industry	US	4 to 5	12	24	4 to 14 migraine headache days Previously failed >2 preventive medications	Not allowed

Study	Number of centres funding	Location	Baseline (weeks)	Intervention (weeks)	Total follow-up (weeks)	Inclusion: migraine history Exclusion: prior failures	Ongoing preventive therapy
Stauffer (2018) (EVOLVE-1[81])	Multi-centre Industry	North America	4 to 6	24	40	ICHD-III beta Previously failed ≥ 3 classes of migraine-preventive treatments	Not allowed
Skljarevski (2018) (EVOLVE-2[82])	Multi-centre Industry	Global	4 to 6	24	40	ICHD-III beta Previously failed ≥ 3 classes of migraine-preventive treatments	Not allowed
Amitriptyline							
Couch (1979)[83]	Single-centre NR	US	4	4	12	Not specified NA	NR
Couch (2011)[84]	Unclear Industry	US	4	16	20	≥ 2 moderate or worse migraine headaches per month NA	Not allowed
Lampl (2009)[85]	Multi-centre NR	NR	NR	16	24	ICHD-II NA	Allowed
Gonçalves (2016)[86] (phase III)	Multi-centre Government, non-profit, academic	Brazil	4	12	12	ICHD-III beta NA	Not allowed
Propranolol							
Diener (1996)[87]	Multi-centre NR	NR	4	14	16	ICHD-I NA	Not allowed
Jafarpour (2016)[88]	Single-centre NR	Iran	NR	4	4	ICHD-II NA	Not allowed
Pradalier (1989)[89]	Multi-centre NR	NR	4	12	12	ICHD-I Previously failed ≥ 2 preventive medication categories	Not allowed

Study	Number of centres funding	Location	Baseline (weeks)	Intervention (weeks)	Total follow-up (weeks)	Inclusion: migraine history Exclusion: prior failures	Ongoing preventive therapy
Sargent (1985)[90]	Unclear NR	NR	NR	14	17	Average of 12 migraine headache days over at least six migraine attacks NA	Not allowed
Weber (1972)[91]	Unclear Industry provided supplies	US	NR	12	24	NIH Ad Hoc Committee on Classification of Headache, 1962 NA	Not allowed
Topiramate							
Lipton (2011)[92]	Multi-centre Industry	US	4	26	26	ICHD-II Previously failed > 2 preventive medication categories	Not allowed
Brandes (2004)[93] (phase III)	Multi-centre Industry	US	4	26	33	ICHD-I Previously failed > 2 preventive medications	Allowed
Silberstein, (2004)[94] (phase III)	Multi-centre Industry	US	4	26	26	ICHD-I Previously failed > 2 preventive medications	Not allowed
Gode (2010)[95]	Single-centre NR	Turkey	4	24	24	ICHD-II NA	Not allowed
Lo (2010)[96]	Single-centre Industry	Singapore	4	12	12	ICHD-II NA	Not allowed
Mei (2004)[97]	Single-centre NR	Italy	4	16	16	ICHD-I NA	Not allowed
Silberstein (2006)[98]	Multi-centre Industry	US	4	20	20	ICHD-I NA	Not allowed
Storey (2001)[99]	Single-centre Industry	US	4	16	16	ICHD-I NA	Allowed

Study	Number of centres funding	Location	Baseline (weeks)	Intervention (weeks)	Total follow-up (weeks)	Inclusion: migraine history Exclusion: prior failures	Ongoing preventive therapy
Head-to-Head							
Diener (2004)[100]	Multi-centre Industry	Global	4	26	52	ICHD-I Previously failed > 2 preventive medications	Not allowed
Ashtari (2008)[101]	Single-centre NR	Iran	NR	8	8	ICHD-II NA	Not allowed
Dodick (2009)[103]	Multi-centre Industry	US	4	26	26	ICHD-I Previously failed > 2 preventive medications	Not allowed
Dogan (2015)[102]	Single-centre NR	Turkey	NR	4	4	ICHD-II NA	Not allowed
Duman (2015)[104]	Single-centre NR	Turkey	4	12	12	ICHD-II NA	Not allowed
Keskinbora (2008)[105]	Single-centre NR	Turkey	NR	12	12	ICHD-I NA	Not allowed
Mathew (1981)[106]	Unclear NR	US	4	24	24	Not specified NA	NR

ICHD-I = International Classification of Headache Disorders, first edition; ICHD-II = International Classification of Headache Disorders, second edition; ICHD-III = International Classification of Headache Disorders, third edition; NR = not reported; NA = not applicable.

Source: Institute for Clinical and Economic Review.[37]

Quality Assessment of Included Studies

The quality of crossover studies and comparative non-randomized studies was assessed based on the US Preventive Services Task Force criteria, which assess comparability of groups, non-differential follow-up, patient and physician blinding, clear definitions of intervention and outcomes, and approach to missing data.

Of RCTs conducted in patients with chronic migraine, an overall rating of "good," "fair," or "poor" was given to each study. The onabotulinum toxin A studies were rated as good (the PREEMPT-1 and PREEMPT-2 trials of Aurora[68] and Diener,[69] respectively), fair (Sandrini[107]), and poor (Cady[108] and Freitag[109]). Sandrini was rated as fair because the approach to missing data was not described. In Cady and Freitag, there were insufficient data to assess the comparability of groups. The topiramate trials were rated as good (Silberstein[110]), fair (Mei[111]), and poor (Diener[112] and Silvestrini[113]). Mei was rated as fair because the approach to missing data was not described. In Diener, groups were not comparable, there was non-differential follow-up, and outcomes were not clearly defined. In Silvestrini, there was insufficient information to assess patient and/or physician blinding and approach to missing data, and outcomes were not clearly defined. The CGRP-inhibitor

studies[19,74,75] were rated to be of good quality. The head-to-head studies that compared onabotulinum toxin A with topiramate were rated as fair (Mathew[114]; groups were not comparable), and poor (Cady[115]; no imputation of missing data and outcomes were not clearly defined).

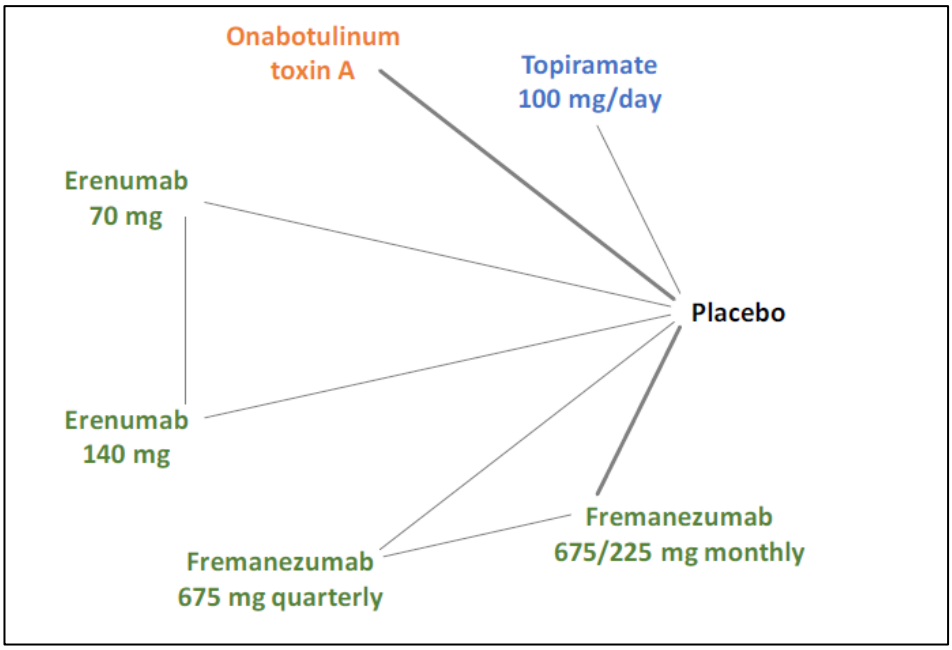
Of the RCTs conducted in patients with episodic migraine, an overall rating of "good," "fair," or "poor" was given to each study. The CGRP-inhibitor studies were rated to be of good quality.[14,21,76-82] The amitriptyline studies were rated as poor (Couch[83]), fair (Couch[84] and Lampl[85]), and good (Gonçalves[86]). The propranolol studies were rated as good (Diener[87]), fair (Pradalier[89]), and poor (Jafarpour,[88] Sargent,[90] and Weber[91]). The topiramate studies were rated as good (Silberstein[98]), fair (Lipton,[92] Brandes,[93] Silberstein,[94] Mei,[97], and Storey[99]), and poor (Gode[95] and Lo[96]). The head-to-head trials were rated as fair (Diener,[100], Dogan,[102], and Keskinbora[105]), and poor (Ashtari,[101] Dodick,[103] Duman,[104] and Mathew[106]).

Evidence Network

The relevant networks available for erenumab in patients with chronic migraine are shown in Figure 4, Figure 5, and Figure 6. These networks describe change from baseline in MMDs, days using acute medication, and all-cause discontinuation, respectively. Limited data were available for change from baseline in monthly headache days, at least 50% reduction in migraine days, and quality of life; networks were therefore not available for these outcomes.

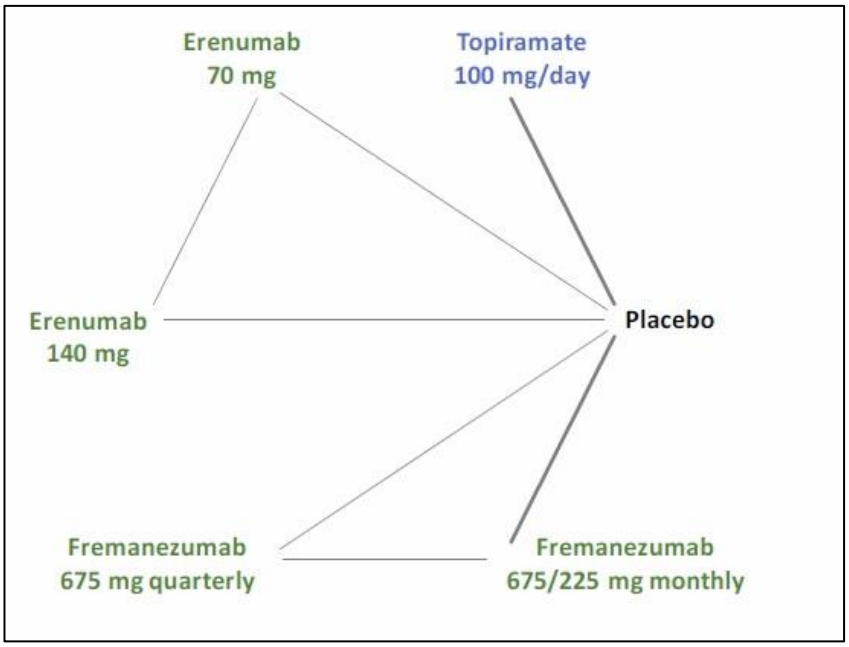
The relevant networks available for erenumab in patients with episodic migraine are shown in Figure 7, Figure 8, Figure 9, and Figure 10. These networks describe change from baseline in MMDs, at least 50% reduction in migraine days, days using acute medication, and all-cause discontinuation, respectively. Limited data were available for change from baseline in monthly headache days and quality of life; networks were therefore not available for these outcomes. Networks for discontinuations due to AEs and SAEs were available for the chronic and episodic patient population combined, and they are shown in Figure 11 and Figure 12.

Figure 4: Network of Studies in Chronic Migraine Patients – Monthly Migraine Days (Extracted from ICER [2018], page 197)



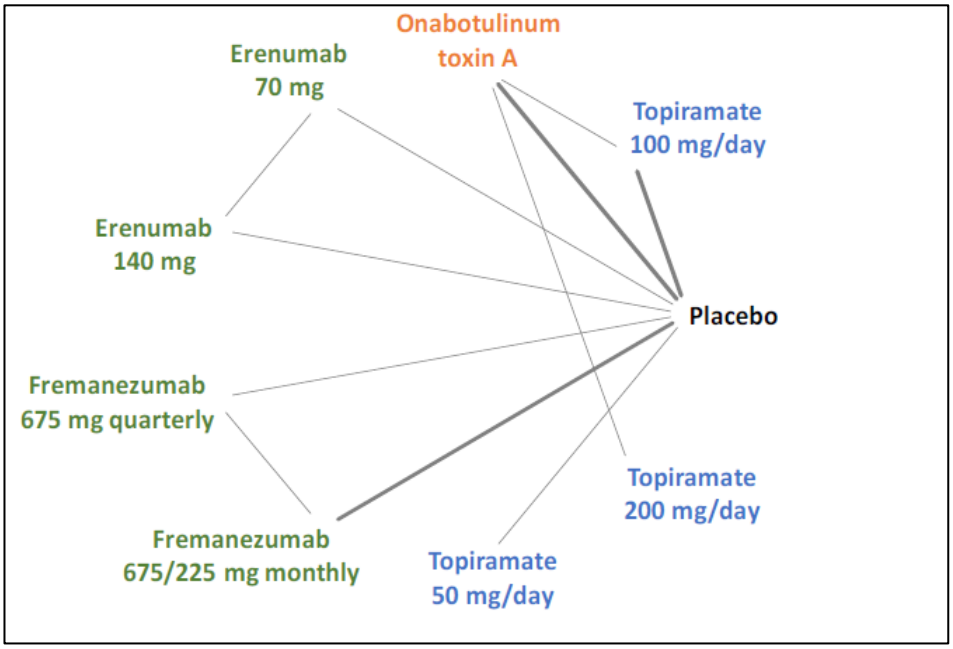
Source: Institute for Clinical and Economic Review.[37]

Figure 5: Network of Studies in Chronic Migraine Patients – Monthly Headache Days



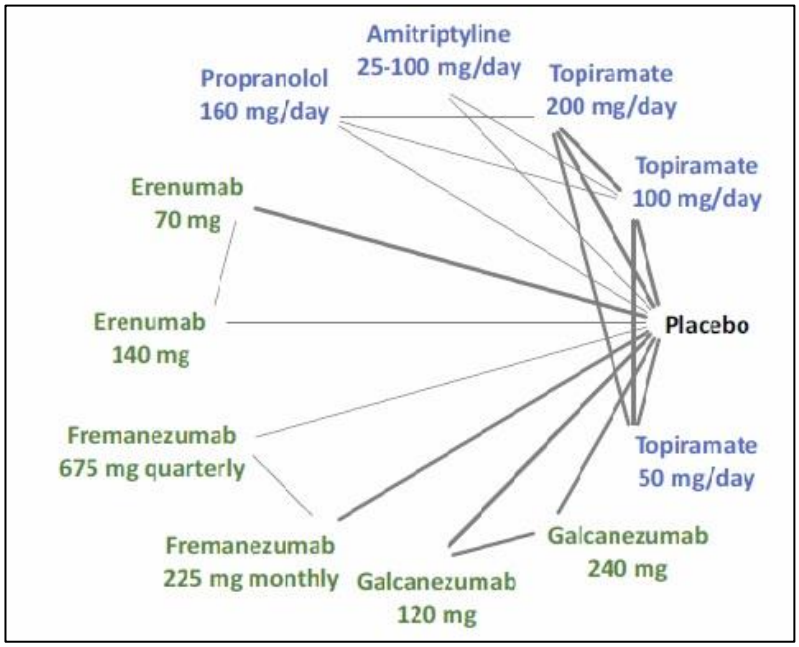
Source: Institute for Clinical and Economic Review.[37]

Figure 6: Network of Studies in Chronic Migraine Patients – All-Cause Discontinuation



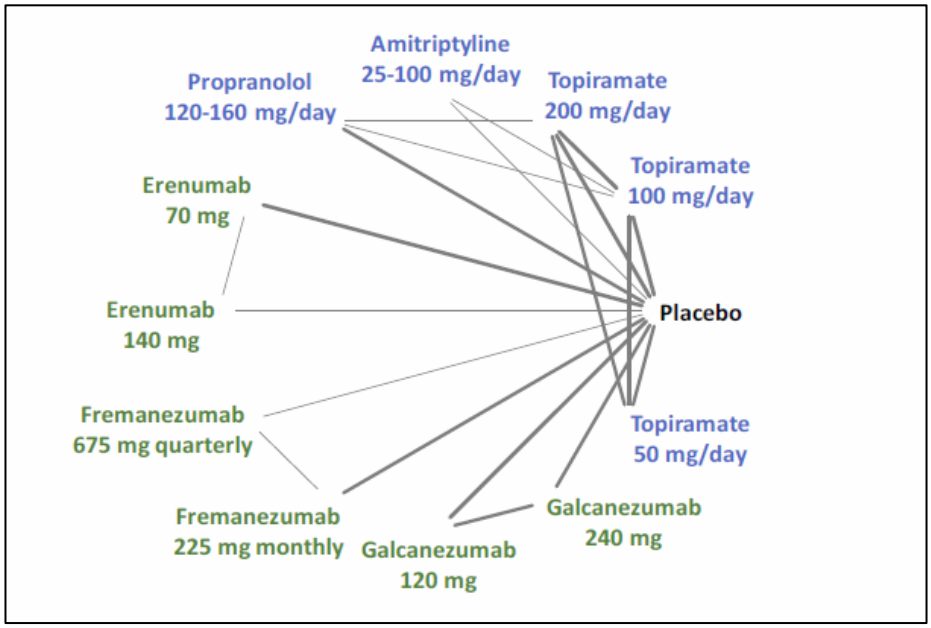
Source: Institute for Clinical and Economic Review.[37]

Figure 7: Network of Studies in Episodic Migraine Patients – Monthly Migraine Days



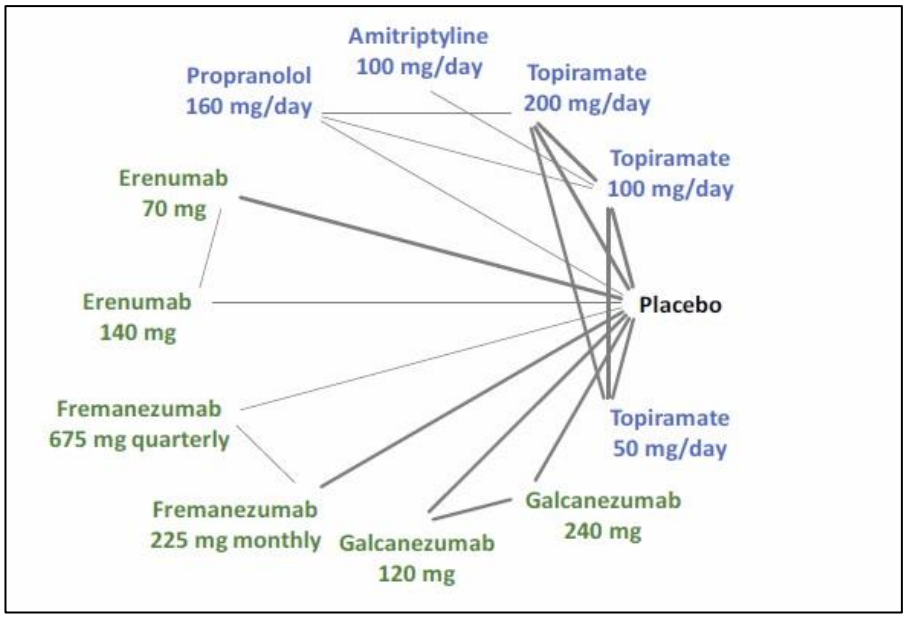
Source: Institute for Clinical and Economic Review.[37]

Figure 8: Network of Studies in Episodic Migraine Patients – Assessing 50% Response



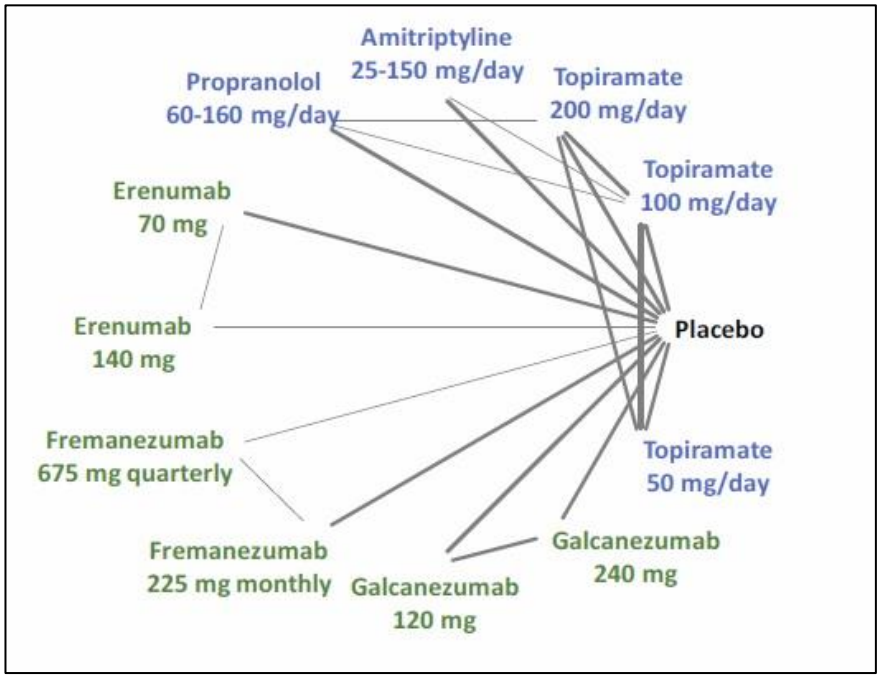
Source: Institute for Clinical and Economic Review.[37]

Figure 9: Network of Studies in Episodic Migraine Patients – Days Using Acute Medication



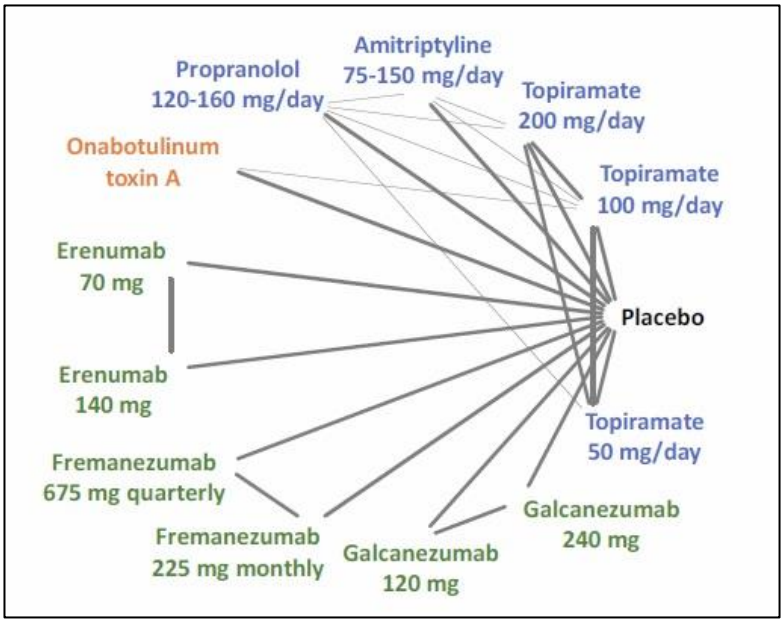
Source: Institute for Clinical and Economic Review.[37]

Figure 10: Network of Studies in Episodic Migraine Patients – All-Cause Discontinuation



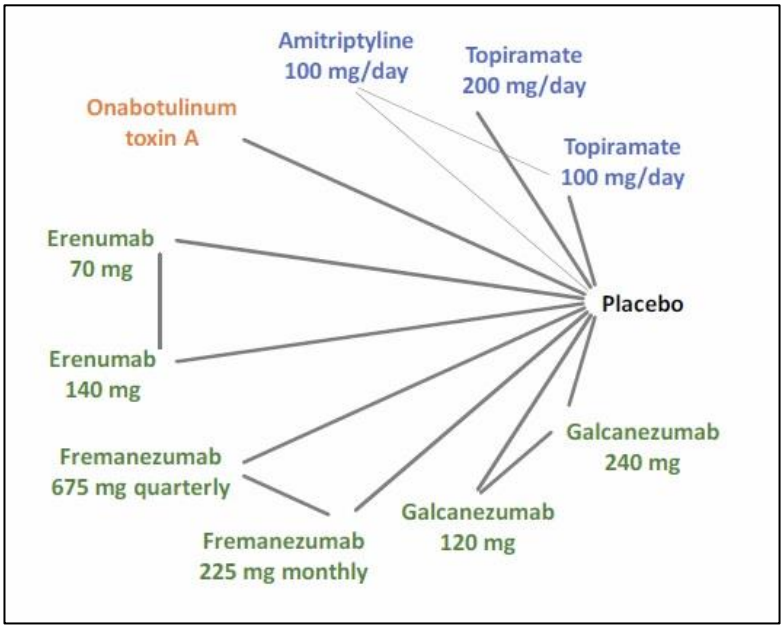
Source: Institute for Clinical and Economic Review.[37]

Figure 11: Network of Studies in Episodic or Chronic Migraine Patients – Discontinuations From Adverse Events



Source: Institute for Clinical and Economic Review.[37]

Figure 12: Network of Studies in Episodic Migraine Patients – Serious Adverse Events



Source: Institute for Clinical and Economic Review.[37]

Indirect Comparison Methods

An NMA was conducted if data were available from at least three similar studies with respect to characteristics such as population, intervention, outcome, and time point. Sufficient data were available for the following outcomes in the chronic migraine population: change from baseline in MMDs, change from baseline in MHDs, change from baseline in days per month using acute medications, and all-cause discontinuations. Aside from monthly acute medication use, the networks for these outcomes (Figure 4, Figure 5, and Figure 6) included onabotulinum toxin A, with comparisons against placebo, topiramate, and CGRP inhibitors. There were insufficient data to conduct an NMA of a reduction of at least 50% in migraine days or quality of life (MIDAS, MSQ, or HIT-6). In addition, NMAs for discontinuations due to AEs, AEs reported by at least 5% of patients in a trial arm, and SAEs were not available for patients with chronic migraine. A meta-regression with a covariate for time points was also conducted. A treatment was concluded to favour another if the credible interval (CrI) excluded the null.

The NMAs used a Bayesian framework with random effects on the treatment parameters, and between-study variance was assumed to be constant across treatment comparisons. Continuous outcomes were analyzed with a normal likelihood and identity link while binary outcomes used a binomial likelihood and logit link. The treatment effects were presented as mean differences with 95% CrIs for continuous outcomes and as ORs with 95% CrIs for binary outcomes. Non-informative prior distributions were used for all model parameters. The first 50,000 iterations were discarded as "burn-in," base inferences were made on an additional 50,000 iterations using three chains, and chain convergence was assessed visually with trace plots. If studies reported multiple time points, the NMAs included the latest time-point data. Separate NMAs were conducted at monthly time points (e.g., four

weeks, eight weeks, 12 weeks, and 26 weeks) where data were available. A subgroup of patients who had failed at least one prior preventive treatment was also analyzed.

Results

Results for Chronic Migraine Patients

A total of 14 trials were available in patients with chronic migraine. Of these, four RCTs and one crossover trial compared onabotulinum toxin A with placebo (Table 44), two RCTs compared onabotulinum toxin A with topiramate (Table 44), four RCTs compared topiramate with placebo (Table 45), and three RCTs compared CGRP inhibitors (erenumab and fremanezumab) with placebo (Table 43). Sample sizes, baseline characteristics, and treatment doses in these trials are provided in Table 44, Table 45, and Table 43.

Six trials (Tepper,[19] Bigal,[74] Silberstein,[75] Aurora,[68] Diener,[69] and Silberstein[110]) were included in the NMA for the mean change from baseline in MMDs. The time-point of analysis was the full 16-week period for the topiramate trial, the full 24-week period for the two onabotulinum toxin A trials, and the last four weeks of the 12-week randomization period for the three CGRP-inhibitor trials. This difference presented a potential source of heterogeneity if the treatment effect varied by the duration of time. An average change from baseline of 3.8 to 6.3 fewer migraine days per month was reported in patients receiving placebo across the individual trials.

Eight trials (Bigal,[74] Cohen,[116] Aurora,[68] Diener,[69] Cady,[108] Freitag,[109] Silberstein,[117] and Cady[115]) were included in the NMA for the mean change in monthly headache days. The analysis time point was the last four weeks of the randomization period for two of the onabotulinum toxin A trials (Freitag 2008[109] and Cady 2014[108]) and the two fremanezumab trials,[74,116] the full 12-week period for the head-to-head onabotulinum toxin A and topiramate trial,[115] and the full 24-week period for the two PREEMPT trials,[68,69] and is a potential source of heterogeneity. An average change from baseline of 3.3 to 8.0 fewer headache days per month was reported in patients receiving placebo across the individual trials.

Five trials reported the change from baseline in days using acute medications (one trial assessing erenumab, two trials assessing fremanezumab, and two trials assessing topiramate. The time point of the analysis was the last four weeks of the randomization period (9 to 12 weeks) for erenumab trials, 12 weeks for the fremanezumab trial, and 16 weeks for both topiramate trials. The results reported for the erenumab trial were days using migraine-specific acute medication, and the results for the two fremanezumab and two topiramate trials were days of any acute medication. Across the trials, patients receiving placebo experienced an average of 0.7 to 3.4 fewer days per month using acute medications.

The results for change from baseline in MMDs, change from baseline in monthly headache days, and all-cause discontinuation, respectively, for erenumab from NMAs are shown in Table 50, Table 51, and Table 52. No treatment was favoured for MMDs or days using acute medication per month. In comparison with placebo, both erenumab 140 mg and erenumab 70 mg were favoured for change from baseline in MMDs, and only erenumab 140 mg was favoured in days using acute medication per month. No significant difference was found for all-cause discontinuation compared with placebo, onabotulinum toxin A, topiramate, or other CGRP inhibitors.

Table 50: Network Meta-Analysis Results for Change from Baseline in Monthly Migraine Days in Patients with Chronic Migraine

Comparison	Mean difference (95% CrI)
Erenumab 140 mg vs. erenumab 70 mg	0.00 (−2.40 to 2.41)
Erenumab 140 mg vs. Ona A	−0.45 (−3.34 to 2.47)
Erenumab 140 mg vs. topiramate 100 mg daily	−0.70 (−4.13 to 2.75)
Erenumab 140 mg vs. fremanezumab 675 mg/225 mg	−0.74 (−3.7 to 2.28)
Erenumab 140 mg vs. fremanezumab 675 mg quarterly	−1.10 (−4.35 to 2.18)
Erenumab 140 mg vs. placebo	−2.40 (−4.77 to 0.00)
Erenumab 70 mg vs. Ona A	−0.45 (−3.35 to 2.48)
Erenumab 70 mg vs. topiramate 100 mg daily	−0.71 (−4.14 to 2.77)
Erenumab 70 mg vs. fremanezumab 675 mg/225 mg	−0.74 (−3.73 to 2.27)
Erenumab 70 mg vs. fremanezumab 675 mg quarterly	−1.11 (−4.37 to 2.18)
Erenumab 70 mg vs. placebo	−2.40 (−4.79 to 0.00)

CrI = credible interval; Ona A = onabotulinum toxin A; vs. = versus.

Source: Institute for Clinical and Economic Review.[37]

Table 51: Network Meta-Analysis Results for Change from Baseline in Days Using Acute Medication per Month in Patients with Chronic Migraine

Comparison	Mean difference (95% CrI)
Erenumab 140 mg vs. erenumab 70 mg	−0.59 (−3.10 to 1.90)
Erenumab 140 mg vs. topiramate 100 mg daily	−1.23 (−4.25 to 2.21)
Erenumab 140 mg vs. fremanezumab 675 mg/225 mg	−0.32 (−3.41 to 2.79)
Erenumab 140 mg vs. fremanezumab 675 mg quarterly	−1.10 (−4.52 to 2.35)
Erenumab 140 mg vs. placebo	−2.49 (−4.95 to −0.01)
Erenumab 70 mg vs. topiramate 100 mg daily	−0.63 (−3.66 to 2.79)
Erenumab 70 mg vs. fremanezumab 675 mg quarterly	−0.50 (−3.91 to 2.91)
Erenumab 70 mg vs. placebo	−1.90 (−4.34 to 0.57)

CrI = credible interval; Ona A = onabotulinum toxin A; vs. = versus.

Source: Institute for Clinical and Economic Review.[37]

Table 52: Network Meta-Analysis Results for All-Cause Discontinuation in Patients with Chronic Migraine

Comparison	Odds ratio (95% CrI)
Erenumab 140 mg vs. erenumab 70 mg	0.76 (0.21 to 2.65)
Erenumab 140 mg vs. Ona A	0.50 (0.14 to 1.76)
Erenumab 140 mg vs. topiramate 100 mg daily	0.60 (0.16 to 2.13)
Erenumab 140 mg vs. topiramate 200 mg daily	0.43 (0.07 to 2.93)
Erenumab 140 mg vs. fremanezumab 675 mg/225 mg	0.46 (0.11 to 1.67)
Erenumab 140 mg vs. fremanezumab 675 mg quarterly	0.66 (0.15 to 2.66)
Erenumab 140 mg vs. placebo	0.55 (0.17 to 1.67)
Erenumab 70 mg vs. Ona A	0.66 (0.20 to 2.24)
Erenumab 70 mg vs. topiramate 100 mg daily	0.79 (0.23 to 2.72)

Comparison	Odds ratio (95% CrI)
Erenumab 70 mg vs. topiramate 200 mg daily	0.57 (0.09 to 3.83)
Erenumab 70 mg vs. fremanezumab 675 mg/225 mg	0.61 (0.16 to 2.11)
Erenumab 70 mg vs. fremanezumab 675 mg quarterly	0.87 (0.21 to 3.39)
Erenumab 70 mg vs. placebo	0.73 (0.23 to 2.13)

CrI = credible interval; Ona A = onabotulinum toxin A; vs. = versus.

Source: Institute for Clinical and Economic Review.[37]

An NMA was conducted at multiple time points (i.e., four weeks, eight weeks, and 12 weeks) and a network meta-regression was performed with study duration as a covariate. The results for MMDs and MHDs by time point were available for onabotulinum toxin A 155 units versus placebo and are provided in Table 53.

The results showed a trend of onabotulinum toxin A favoured over placebo for monthly headache or migraine days at any point, although statistical significance was not achieved at the change from baseline in MHDs over all the time points, as was the change in MMDs at week 12.

Table 53: Network Meta-Analysis Results by Time Point (Onabotulinum Toxin A 155 Units Versus Placebo)

Time point	Change from baseline in monthly migraine days (Mean difference, 95% CrI)	Change from baseline in monthly headache days (Mean difference, 95% CrI)
4 weeks	−2.10 (−3.99 to −0.20)	−1.25 (−2.68 to 0.05)
8 weeks	−1.80 (−3.57 to −0.04)	−1.84 (−5.05 to 0.42)
12 weeks	−1.40 (−2.94 to 0.13)	−1.46 (−4.65 to 0.39)
Covariate for time point	−2.15 (−21.39 to 8.62)	−2.40 (−5.38 to 0.47)
No covariate for time point	−1.95 (−3.88 to −0.02)	−2.06 (−3.48 to −0.63)

CrI = credible interval.

Source: Institute for Clinical and Economic Review.[37]

Results for Episodic Migraine Patients

Fourteen trials were included in the NMA of change from baseline in MMD. Two trials compared topiramate with either amitriptyline or propranolol, and 12 of the trials compared an active therapy to placebo only. Across the trials, patients receiving placebo experienced an average reduction from baseline of 1.1 to 5.3 migraine days per month.

Eighteen trials reported on the proportion of patients who experienced a reduction in migraine frequency or migraine days of at least 50%. The definitions were considered sufficiently similar to analyze. The trials assessed response between 12 weeks and 26 weeks of treatment. Across the trials, 10% to 62% of patients on placebo were responders, as defined by a reduction in migraine days of at least 50%.

Twelve of the 14 trials reporting on the change from baseline in MMDs also reported on the change in the number of days per month using acute medications during follow-up. Across the trials, patients on placebo experienced an average reduction from baseline of 0.6 to 3.8 days using acute medications.

Data on all-cause discontinuations were available from 26 trials. Discontinuations among patients on placebo ranged from 0% to 54% between four weeks and 26 weeks. Discontinuations among patients on a CGRP inhibitor ranged from 5% to 17% between 12 weeks and 24 weeks. Discontinuations among patients on other preventive therapies ranged from 0% to 62% between four weeks and 26 weeks.

Table 54 presents results from the NMA for the change from baseline in MMDs in patients with episodic migraine. Erenumab 140 mg was compared with erenumab 70 mg, propranolol 160 mg/day, topiramate 100 mg/day, amitriptyline 25 mg to 100 mg/day, topiramate 200 mg/day, topiramate 50 mg/day, placebo, and other CGRP inhibitors (results not presented). Erenumab 140 mg was favoured only when compared with topiramate 200 mg/day, topiramate 50 mg/day, and placebo. Erenumab 70 mg was favoured only when compared with topiramate 50 mg/day and placebo.

Table 54: Network Meta-Analysis Results for Change From Baseline in Monthly Migraine Days in Patients with Episodic Migraine

Comparison	Mean difference (95% CrI)
Erenumab 140 mg vs. erenumab 70 mg	−0.65 (−1.40 to 0.10)
Erenumab 140 mg vs. propranolol 160 mg/day	−0.74 (−1.81 to 0.37)
Erenumab 140 mg vs. topiramate 100 mg/day	−0.78 (−1.66 to 0.13)
Erenumab 140 mg vs. amitriptyline 25 mg/day to 100 mg/day	−0.87 (−2.25 to 0.52)
Erenumab 140 mg vs. topiramate 200 mg/day	**−0.99 (−1.89 to −0.02**)
Erenumab 140 mg vs. topiramate 50 mg/day	**−1.77 (−2.85 to −0.66)**
Erenumab 140 mg vs. placebo	**−1.95 (−2.68 to −1.19)**
Erenumab 70 mg vs. propranolol 160 mg/day	−0.10 (−1.01 to 0.86
Erenumab 70 mg vs. topiramate 100 mg/day	−0.13 (−0.81 to 0.58)
Erenumab 70 mg vs. amitriptyline 25 mg/day to 100 mg/day	−0.23 (−1.50 to 1.06)
Erenumab 70 mg vs. topiramate 200 mg/day	−0.34 (−1.06 to 0.44)
Erenumab 70 mg vs. topiramate 50 mg/day	**−1.12 (−2.05 to −0.17)**
Erenumab 70 mg vs. placebo	**−1.30 (−1.79 to −0.79)**

CrI = credible interval; vs. = versus.

Source: Institute for Clinical and Economic Review.[37]

Table 55 presents results from the NMA for the 50% response in patients with episodic migraine. When erenumab 140 mg or erenumab 70 mg was compared with active treatment, no significant difference was found. Both erenumab 140 mg and erenumab 70 mg were favoured when compared with placebo.

Table 55: Network Meta-Analysis Results for 50% Response in Patients with Episodic Migraine

Comparison	Odds ratio (95% CrI)
Topiramate 100 mg/day vs. erenumab 140 mg	1.24 (0.77 to 2.03)
Topiramate 200 mg/day vs. erenumab 140 mg	1.06 (0.64 to 1.77)
Propranolol 120 mg/day to 160 mg/day vs. erenumab 140 mg	1.25 (0.68 to 2.22)
Erenumab 140 mg vs. erenumab 70 mg	1.27 (0.70 to 2.31)
Erenumab 140 mg vs. amitriptyline 25 mg/day to 100 mg/day	1.01 (0.54 to 1.87)

Comparison	Odds ratio (95% CrI)
Erenumab 140 mg vs. topiramate 50 mg/day	1.37 (0.78 to 2.40)
Erenumab 140 mg vs. placebo	**2.16 (1.45 to 3.26)**
Topiramate 100 mg/day vs. erenumab 70 mg	1.42 (0.97 to 2.11)
Topiramate 100 mg/day vs. erenumab 70 mg	1.22 (0.81 to 1.84)
Propranolol 120-160 mg/day vs. erenumab 70 mg	1.43 (0.85 to 2.35)
Amitriptyline 25-100 mg/day vs. erenumab 70 mg	1.04 (0.60 to 1.85)
Erenumab 70 mg vs. topiramate 50 mg/day	1.19 (0.74 to 1.94)
Erenumab 70 mg vs. placebo	**1.88 (1.43 to 2.51)**

CrI = credible interval; vs = versus.

Source: Institute for Clinical and Economic Review.[37]

Table 56 present results from the NMA for change from baseline in acute medication use per month in patients with episodic migraine. Erenumab 140 mg was compared with erenumab 70 mg, amitriptyline 100 mg/day, propranolol 160 mg/day, topiramate 100 mg/day, topiramate 200 mg/day, topiramate 50 mg/day, placebo, and other CGRP inhibitors (results not presented). Erenumab 140 mg was favoured only when compared with topiramate 50 mg/day and placebo. Erenumab 70 mg was favoured only when compared with placebo.

Table 56: Network Meta-Analysis Results for Change from Baseline in Days Using Acute Medication per Month in Patients with Episodic Migraine

Comparison	Mean difference (95% CrI)
Erenumab 140 mg vs. erenumab 70 mg	−0.77 (−1.46 to 0.00)
Erenumab 140 mg vs. amitriptyline 100 mg/day	−0.48 (−1.90 to 0.93)
Erenumab 140 mg vs. propranolol 160 mg/day	−0.55 (−1.59 to 0.50)
Erenumab 140 mg vs. topiramate 100 mg/day	−0.68 (−1.55 to 0.19)
Erenumab 140 mg vs. topiramate 200 mg/day	−0.92 (−1.79 to 0.00)
Erenumab 140 mg vs. topiramate 50 mg/day	**−1.20 (−2.33 to −0.05)**
Erenumab 140 mg vs. placebo	**−1.63 (−2.37 to −0.92)**
Amitriptyline 100 mg/day vs. erenumab 70 mg	−0.28 (−1.57 to 1.04)
Propranolol 160 mg/day vs. erenumab 70 mg	−0.22 (−1.08 to 0.71)
Topiramate 100 mg/day vs. erenumab 70 mg	−0.08 (−0.73 to 0.63)
Erenumab 140 mg vs. topiramate 200 mg/day	−0.15 (−0.87 to 0.55)
Erenumab 140 mg vs. topiramate 50 mg/day	−0.43 (−1.45 to 0.55)
Erenumab 70 mg vs. placebo	**−0.86 (−1.40 to −0.44)**

CrI = credible interval; vs. = versus.

Source: Institute for Clinical and Economic Review.[37]

Table 57 present results from the NMA for all-cause discontinuation in patients with episodic migraine. Erenumab 140 mg and erenumab 70 mg were compared with propranolol 60 mg/day to 160 mg/day, topiramate 100 mg/day, topiramate 200 mg/day, topiramate 50 mg/day, amitriptyline 75 mg/day to 100 mg/day, placebo, and other CGRP inhibitors (results not presented). Erenumab 140 mg and erenumab 70 mg were favoured only when compared with topiramate 200 mg/day.

Table 57: Network Meta-Analysis Results for All-Cause Discontinuation in Patients with Episodic Migraine

Comparison	Odds ratio (95% CrI)
Erenumab 140 mg vs. erenumab 70 mg	0.90 (0.39 to 2.08)
Erenumab 140 mg vs. propranolol 60 mg/day to 160 mg/day	0.68 (0.24 to 1.67)
Erenumab 140 mg vs. topiramate 100 mg/day	0.64 (0.25 to 1.50)
Erenumab 140 mg vs. topiramate 200 mg/day	**0.37 (0.15 to 0.90)**
Erenumab 140 mg vs. topiramate 50 mg/day	0.57 (0.22 to 1.52)
Erenumab 140 mg vs. amitriptyline 75 mg/day to 100 mg/day	0.60 (0.22 to 1.45)
Erenumab 140 mg vs. placebo	0.63 (0.27 to 1.39)
Erenumab 70 mg vs. propranolol 60 mg/day to 160 mg/day	0.75 (0.30 to 1.66)
Erenumab 70 mg vs. topiramate 100 mg/day	0.71 (0.31 to 1.47)
Erenumab 70 mg vs. topiramate 200 mg/day	**0.41 (0.18 to 0.88)**
Erenumab 70 mg vs. topiramate 50 mg/day	0.63 (0.27 to 1.49)
Erenumab 70 mg vs. amitriptyline 75 mg/day to 100 mg/day	0.67 (0.28 to 1.44)
Erenumab 70 mg vs. placebo	0.70 (0.34 to 1.34)

CrI = credible interval; vs. = versus.

Source: Institute for Clinical and Economic Review.[37]

Results for Chronic Episodic Migraine Patients

For discontinuations due to AEs, data were available from 33 trials of patients with either episodic or chronic migraine. Discontinuations due to AEs among patients on placebo ranged from 0% to 30% between four weeks and 26 weeks. Discontinuations due to AEs among patients on a CGRP inhibitor ranged from 0% to 5% between 12 weeks and 24 weeks. Discontinuations due to AEs among patients on other preventive therapies ranged from 0% to 49%.

Reports of SAEs were included in 19 trials. Between 12 weeks and 26 weeks, SAEs with placebo ranged from 0% to 5%, between 12 weeks and 24 weeks, SAEs with a CGRP inhibitor ranged from 0% to 3%, and SAEs with other preventive therapies ranged from 1% to 15%.

Table 58 presents results from the NMA for discontinuations from AEs in chronic or episodic migraine. Erenumab 140 mg and erenumab 70 mg were compared with onabotulinum toxin A quarterly, propranolol 120 mg/day to 160 mg/day, topiramate 100 mg/day, topiramate 200 mg/day, topiramate 50 mg/day, amitriptyline 75 mg/day to 100 mg/day, placebo, and other CGRP inhibitors (results not presented). Erenumab 140 mg and erenumab 70 mg were not favoured in any comparison.

Table 58: Network Meta-Analysis Results for Discontinuations from Adverse Events in Chronic or Episodic Migraine

Comparison	Odds ratio (95% CrI)
Erenumab 70 mg vs. erenumab 140 mg	1.01 (0.30 to 3.27)
Erenumab 140 mg vs. onabotulinum toxin A quarterly	0.52 (0.12 to 2.27)
Propranolol 120 mg/day to 160 mg/day vs. erenumab 140 mg	1.04 (0.24 to 4.09)
Erenumab 140 mg vs. topiramate 100 mg/day	0.53 (0.15 to 1.88)
Erenumab 140 mg vs. topiramate 200 mg/day	0.37 (0.10 to 1.39)
Erenumab 140 mg vs. Topiramate 50 mg/day	0.85 (0.22 to 3.56
Erenumab 140 mg vs. amitriptyline 75 mg/day to 100 mg/day	0.49 (0.12 to 1.94)
Placebo vs. erenumab 140 mg	0.74 (0.22 to 2.39)
Erenumab 70 mg vs. onabotulinum toxin A quarterly	0.53 (0.15 to 1.88)
Erenumab 70 mg vs. propranolol 120 mg/day to 160 mg/day	0.97 (0.30 to 3.33)
Erenumab 70 mg vs. topiramate 100 mg/day	0.53 (0.19 to 1.49)
Erenumab 70 mg vs. topiramate 200 mg/day	0.37 (0.13 to 1.11)
Erenumab 70 mg vs. topiramate 50 mg/day	0.85 (0.27 to 2.88)
Erenumab 70 mg vs. amitriptyline 75 mg/day to 100 mg/day	0.49 (0.15 to 1.57)
Placebo vs. erenumab 70 mg	0.71 (0.34 to 1.53)

CrI = credible interval; vs. = versus.

Source: Institute for Clinical and Economic Review.[37]

Table 59 presents results from the NMA for SAEs in chronic or episodic migraine. Erenumab 140 mg and erenumab 70 mg were compared with onabotulinum toxin A quarterly, topiramate 100 mg/day, topiramate 200 mg/day, amitriptyline 100 mg/day, placebo, and other CGRP inhibitors (results not presented). Erenumab 70 mg was not favoured in any comparison. Erenumab 140 mg was favoured only when compared with amitriptyline 100 mg/day.

Table 59: Network Meta-Analysis Results for Serious Adverse Events in Chronic or Episodic Migraine

Comparison	Odds ratio (95% CrI)
Erenumab 140 mg vs. erenumab 70 mg	0.56 (0.18 to 1.55)
Erenumab 140 mg vs. onabotulinum toxin A quarterly	0.29 (0.07 to 1.13)
Erenumab 140 mg vs. topiramate 100 mg/day	0.59 (0.12 to 2.91)
Erenumab 140 mg vs. topiramate 200 mg/day	0.53 (0.04 to 5.4)
Erenumab 140 mg vs. amitriptyline 100 mg/day	**0.20 (0.04 to 0.89)**
Erenumab 140 mg vs. placebo	0.59 (0.12 to 2.91)
Erenumab 70 mg vs. onabotulinum toxin A quarterly	0.52 (0.15 to 1.74)
Erenumab 70 mg vs. topiramate 200 mg/day	0.95 (0.09 to 8.96)
Erenumab 70 mg vs. amitriptyline 100 mg/day	0.36 (0.10 to 1.39)
Topiramate 100 mg/day vs. erenumab 70 mg	0.96 (0.21 to 3.83)
Placebo vs. erenumab 70 mg	0.90 (0.38 to 2.03)

CrI = credible interval; vs. = versus.

Source: Institute for Clinical and Economic Review.[37]

Critical Appraisal

The NMAs were based on a systematic review of the literature to identify all relevant published trials from multiple databases, with the focus of the review on CGRP inhibitors as the intervention. While the patient population (i.e., adults with chronic migraine and eligible for preventive migraine therapy) was in alignment with the indication for erenumab, limited data were available for patients who failed previous therapies. The CGRP-inhibitor trials excluded patients who experienced failures with two or three previous treatments and the applicability of the evidence to the patient population of interest is therefore limited. The Health Canada–approved dosing for onabotulinum toxin A is 155 units up to 195 units. While the main trials in the NMA (i.e., PREEMPT-1 and PREEMPT-2) followed the Health Canada–approved dosing, several trials used either a smaller dose (i.e., 100 units) or a higher dose (200 units). This also limits the applicability of the NMA results to the patient population of interest and is a source of heterogeneity. A comprehensive set of safety and efficacy outcomes was evaluated and included quality-of-life scales, such as MIDAS, MSQ, and HIT-6. However, the data available for quality of life were insufficient for an NMA, and follow-up on all outcomes was limited from 12 weeks to 26 weeks.

The ICER report did not present the direct and indirect estimates separately when available, and the consistency of the direct and indirect estimates is therefore unclear. However, the report did indicate that for networks that had loops, the assumption of consistency among indirect and direct estimates was examined empirically using a node-splitting approach, and that no evidence of inconsistency was observed.

The report did not discuss whether the transitivity assumption was met in the networks of trials. Table 43, Table 44, Table 45, Table 47, and Table 48 show that there were differences among the trials in the mean number of years since onset. There were also differences among the trials in the exclusion of previous treatment failures, whether ongoing preventive therapy was allowed, and the percentage of patients with medication-overuse headache (trials either excluded these patients or prevalence ranged from 41% to 68%). These factors may be important effect modifiers, but they were not examined in analyses.

The NMA considered time points in a meta-regression, and attempted a subgroup analysis of patients who had failed previous therapies; however, no other sources of potential heterogeneity were considered, such as number of previous treatment failures, use of concomitant migraine-preventive therapy, compliance with headache diary, onabotulinum toxin A dose, or study quality.

The clinical expert consulted for this review indicated that placebo response would be expected to vary based on the route of administration (i.e., injection versus oral tablets) and that placebo response is typically higher when it is received as an injection. Across the trials included in the NMA, the placebo response was different between trials. While adjusting for placebo response may be the preferred approach, there are limitations to the approach, because there is an assumption that study and patient characteristics (which are effect modifiers of the relative treatment effect) are also prognostic factors of the outcome with placebo.[118,119] Given the unclear extent to which placebo response is an adequate proxy for specific characteristics or effect modifiers, uncertainty remains in such an analysis.

The strength of the network for chronic migraine patients was low, with only six studies of seven treatment options (for change from baseline in MMD) and only eight studies for seven treatment options (change in MHDs). The networks were centred on placebo, and most comparisons were indirect. While all of the studies included in the analysis for change from baseline in MMDs were of good quality, three of the eight studies included in the analysis for

the mean change in MHDs were of poor quality. A sensitivity analysis based on study quality was not conducted.

The ITC did not include any HRQoL data, patient-reported symptoms, key safety outcomes, SAEs, or WDAEs.

As with all NMAs, inclusion of the null value in the 95% CrIs of the difference between treatments does not necessarily imply that the treatments are equivalent or noninferior.

Discussion and Conclusion

The sponsor submitted an ITC comparing erenumab 140 mg with onabotulinum toxin A in patients with chronic migraine who failed at least three previous prophylactic treatments. No statistically significant results were found between erenumab 140 mg and onabotulinum toxin A. However, these results are highly uncertain because it was impossible to confirm whether the patient populations were similar, in addition to many other limitations.

The ICER conducted NMAs to compare CGRP inhibitors with placebo or commonly used preventive treatments in adults with chronic or episodic migraine. For patients with chronic migraine, relevant data were available to indirectly compare erenumab with onabotulinum toxin A, topiramate, and other CGRP inhibitors. Although several efficacy and safety outcomes were evaluated, NMAs could be performed only for change from baseline in MMD, change from baseline in days using acute medication, and all-cause discontinuation. In a Bayesian NMA, erenumab was not favoured over onabotulinum toxin A, topiramate, or CGRP inhibitors on these outcomes. Several potential sources of heterogeneity were not systematically evaluated and generalizability to the patient population of interest was limited. In clinical practice, onabotulinum toxin A is likely to be used in patients who have failed several lines of previous treatments. However, the CGRP-inhibitor trials in the NMAs excluded patients who failed as few as two or three previous therapies, and insufficient data were available to conduct subgroup analyses for patients who failed at least one prior preventive therapy. Generalizability was also limited because the trials did not consistently align with Health Canada–approved onabotulinum toxin A dosing and the NMAs did not incorporate longer-term follow-up data.

For patients with episodic migraine, erenumab was compared with topiramate, propranolol, amitriptyline, and other CGRP inhibitors. Although efficacy and safety outcomes were evaluated, NMAs could be performed only for change from baseline MMD, 50% response, change from baseline in days using acute medication, and all-cause discontinuation. In a Bayesian NMA, for the change from baseline in MMD, erenumab 140 mg was favoured only when compared with topiramate 200 mg/day, topiramate 50 mg/day, and placebo, and erenumab 70 mg was favoured only when compared with topiramate 50 mg/day and placebo. For the 50% response, both erenumab 140 and erenumab 70 mg were favoured when compared with placebo only. For the change from baseline in acute medication use per month, erenumab 140 mg was favoured only when compared with topiramate 50 mg/day and placebo, and erenumab 70 mg was favoured only when compared with placebo. For all-cause discontinuation, erenumab 140 mg and erenumab 70 mg were favoured only when compared with topiramate 200 mg/day. Several potential sources of heterogeneity were not systematically evaluated, and generalizability to the patient population of interest was limited. In addition, many of the included studies were of poor quality.

For patients with chronic or episodic migraine, further data on quality of life, safety, and patients who failed previous therapies are needed to fully characterize benefits and harms.

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