CADTH

CADTH COMMON DRUG REVIEW

# Clinical Review Report

## FREMANEZUMAB (AJOVY)

**(Teva Canada Innovation)**

**Indication:** For the prevention of migraine in adults who have at least 4 migraine days monthly


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# Abbreviations

| | |
|---|---|
| **ADA** | antidrug antibody |
| **AE** | adverse event |
| **ANCOVA** | analysis of covariance |
| **ANOVA** | analysis of variance |
| **BDI** | Beck Depression Inventory |
| **CGRP** | calcitonin gene–related peptide |
| **CI** | confidence interval |
| **CM** | chronic migraine |
| **CrI** | credible interval |
| **DBTP** | double-blind treatment period |
| **eC-SSRS** | electronic Columbia-Suicide Severity Rating Scale |
| **ECG** | electrocardiogram |
| **EM** | episodic migraine |
| **EOT** | end of treatment |
| **EQ-5D-5L** | EuroQol 5-Dimensions 5-Levels |
| **FAS** | full analysis set |
| **HIT-6** | 6-item Headache Impact Test |
| **HRQoL** | health-related quality of life |
| **ICER** | Institute of Clinical and Economic Reviews |
| **ICHD-3** | International Classification of Headache Disorders |
| **IRT** | interactive response technology |
| **ITC** | indirect treatment comparison |
| **ITT** | intention-to-treat |
| **LSM** | least squares mean |
| **LTS** | long-term study |
| **mAb** | monoclonal antibody |
| **MID** | minimal important difference |
| **MIDAS** | Migraine Disability Assessment |
| **mITT** | modified intention-to-treat |

| | |
|---|---|
| **MMD** | monthly migraine day |
| **MSQoL** | Migraine-Specific Quality of Life questionnaire |
| **NMA** | network meta-analysis |
| **NSAID** | nonsteroidal anti-inflammatory drug |
| **OLTP** | open-label treatment period |
| **OnaA** | onabotulinumtoxin A |
| **PGIC** | Patients' Global Impression of Change |
| **PHQ** | Patient Health Questionnaire |
| **PP** | per protocol |
| **RCT** | randomized controlled trial |
| **RR** | relative risk |
| **SAE** | serious adverse event |
| **SC** | subcutaneous |
| **SD** | standard deviation |
| **SE** | standard error |
| **VAS** | visual analogue scale |
| **WPAI** | Work Productivity and Activity Impairment |

# Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

## Table 1: Submitted for Review

| Item | Description |
|---|---|
| **Drug product** | Fremanezumab (Ajovy), solution for subcutaneous injection (150 mg/mL), 225 mg once a month or 675 mg every 3 months |
| **Indication** | For the prevention of migraine in adults who have had at least 4 migraine days monthly |
| **Reimbursement request** | As per indication |
| **Health Canada approval status** | NOC |
| **Health Canada review pathway** | Standard |
| **NOC date** | April 9, 2020 |
| **Sponsor** | Teva Canada Innovation |

NOC = Notice of Compliance.

## Introduction

Migraine is a neurological disease characterized by recurrent attacks of pulsating headache pain of at least moderate severity.[1] Migraine episodes may last from 4 to 74 hours and can be accompanied by associated symptoms, such as photophobia, phonophobia, nausea, and vomiting.[2] The type of migraine can be refined based on the average monthly migraine days (MMDs) and monthly headache days.[1] The third edition of the International Classification of Headache Disorders (ICHD-3) described a chronic migraine (CM) as a headache (tension-type–like or migraine-like) occurring on 15 or more days per month for more than 3 months, with the features of migraine headaches on at least 8 days per month.[3] In episodic migraine (EM), individuals experience headaches on 14 or fewer days per month for more than 3 months, with the features of migraine headaches on at least 4 days per month.[3,4] In Canada, at least 2.6 million adult women and almost 1 million adult men suffer from migraine, although this may be an underestimation, as some of those who suffer from migraine may not seek medical help and therefore may not have a medical diagnosis.[2,5,6] Approximately three-quarters of patients experiencing migraine report impaired function, and one-third require bed rest during a migraine attack. Patients may transition between experiencing EM to CM, with an estimated 2.5% of patients with EM transitioning to CM.[7]

Preventive treatments are considered an important part of the overall approach for a proportion of individuals with migraine.[8] Erenumab and topiramate are indicated in adults for the prophylaxis of migraine headache, and erenumab was previously reviewed by CADTH.[9] Onabotulinumtoxin A (OnaA) has a Health Canada indication for prophylaxis of CM (more than 15 headache days per month) and was previously reviewed by CADTH.[10] Many therapies used for migraine prophylaxis are used off-label, as they lack an official indication for this purpose from Health Canada. Aside from OnaA, 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.[11] Approximately 87% of patients with migraine have an inadequate response to 2 or more preventive therapies.[12,13]

Fremanezumab is a fully humanized monoclonal antibody (mAb) 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.[14] Fremanezumab is administered by subcutaneous (SC) injection at a dosage of either 225 mg monthly or 675 mg quarterly.[14] It can also be used as monotherapy or with a concomitant preventive medication.[14] Fremanezumab received a Notice of Compliance on April 9, 2020, with an indication for the prevention of migraine in adults who have had at least 4 migraine days monthly.[15]

The objective of this review is to perform a systematic review of the beneficial and harmful effects of fremanezumab for the preventive treatment of migraine in adults who have at least 4 migraine days per month.

## Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from the clinical expert consulted by CADTH for the purpose of this review.

### Patient Input

CADTH received 1 patient input submission, which was a joint effort between Migraine Canada and Migraine Quebec. Patient input was gathered through an online survey that was promoted through Migraine Canada's Facebook and Twitter platforms as well as in migraine clinics across Canada. Migraine Canada designed the survey and analyzed the results from a total of 597 participants.

According to survey respondents, migraines had the greatest impact on their ability to work, causing financial repercussions and added pressure on their spouse. In addition, respondents reported requiring help with childcare, being unable to attend social events (which also affects family members), and suffering effects on their personal relationships related to a lack of understanding and support from those around them. Responses from family members focused on how migraines negatively affected family activities. Some couples had decided not to have children, and some were financially restricted to 1 spouse's income.

Adverse reactions are a key consideration when deciding among treatment options. From the survey responses, 7% of respondents reported having no side effects and 25% stated that side effects they experienced were tolerable; however, 68% had discontinued a medication because of side effects. Patients are often told that, while there is no cure for migraine, a 50% improvement in frequency and intensity should be acceptable. However, 74% of surveyed patients had not seen at least a 50% improvement with treatments they had tried. Migraine Canada noted the value to patients of the availability of an injectable monoclonal antibody treatment for migraines in preference to oral medications. Of survey respondents, 73% indicated that they would prefer a monthly injection to a daily pill, and many expressed interest in a medication that could be taken less frequently.

When asked about meaningful and successful preventive therapies, patients were looking for "something that has minimal mental side effects," "something that will reduce frequency and intensity so that [they] can resume professional activities," and "anything that would

allow [them] to live a fruitful life — return to work, keep a relationship, to see friends and family on a regular basis, to go to events." Treatment affordability was another concern.

## Clinician Input

The clinical expert consulted by CADTH for the purposes of this review identified that anti-CGRP mAbs are indicated for the treatment of episodic, frequent, and chronic migraine. Anti-CGRP mAbs are the first treatment of a prophylactic nature specifically designed to treat migraine rather than being found to be effective in a serendipitous manner. The side effects of anti-CGRP mAbs are more tolerable than those of other medications currently available for migraine prevention. According to the clinical expert, migraine management includes treating acute attacks and using prophylactic drug therapy to reduce attack frequency or severity. Acute attacks can be treated with acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen or naproxen), and triptans.[8] The clinical expert stated that one would use a prophylactic medication in patients experiencing more than 4 headaches a month, even if they respond well to acute treatment; if patients do not respond well to acute treatment; or if patients have a contraindication to acute treatments.[8,16]

The clinical expert indicated that fremanezumab could be considered for first-line daily prophylaxis of migraines in clinical practice. However, based on current practice, it would be appropriate to recommend that patients try other treatments before initiating treatment with fremanezumab. The clinical expert noted that there is limited high-quality evidence on sequencing of preventive medications for migraines.

The clinical expert stated that patients with EM or CM, and patients in whom their headaches are having a severe impact on their ability to function, would be best suited for fremanezumab treatment. Patients who have more than 4 migraine headache days per month but not more than 14 migraine headache days per month as a group tend to be more responsive to treatment. However, patients with CM often respond well to fremanezumab and should be able to receive the treatment medication. Patients whose headaches have a severe impact on their ability to function most need an intervention. The clinical expert indicated there are no disease characteristics (e.g., presence or absence of certain symptoms, stage of disease) that would identify those patients who are most likely to exhibit a response to treatment. Patients who are pregnant or who are contemplating getting pregnant in the next 6 months are least suitable for treatment with fremanezumab.

The clinical expert stated that validated tools that measure migraine disability can be used to assess whether patients are benefiting from treatment. For example, a reduction in the Migraine Disability Assessment (MIDAS) score or the 6-item Headache Impact Test (HIT-6) score would be appropriate. Reduction in medication use for acute treatments could also be used to assess benefit of the treatment.

The clinical expert consulted on this review identified that the goal of treatment is to improve health-related quality of life by reducing the impact of migraine headaches on the patient's ability to function at work, school, home, or in social settings. Early treatment may prevent individuals from becoming disabled and unable to function in the workforce.

## Clinical Evidence

### Pivotal Studies and Protocol Selected Studies

*Description of Studies*

Three phase III, multinational, double-blind, randomized, placebo-controlled trials funded by the sponsor are included in the systematic review section of this review. HALO CM (N = 1,130) was conducted in patients with CM randomized into 3 groups (1:1:1 ratio): fremanezumab 675 mg as 3 active injections of 225 mg/1.5 mL followed by 2 monthly treatments of fremanezumab 225 mg/1.5 mL as 1 active injection (675 mg/225 mg/225 mg [monthly]), fremanezumab 675 mg as 3 active injections of 225 mg/1.5 mL followed by 2 monthly treatments of placebo as a single 1.5 mL injection (675 mg/placebo/placebo [quarterly]), and a placebo group that received three 1.5 mL placebo injections followed by 2 monthly single 1.5 mL placebo injections (placebo).[17] The primary objectives of this study were to demonstrate the efficacy of 2-dose regimens of fremanezumab, as assessed by the decrease in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug, relative to the baseline period; and to evaluate the safety and tolerability of 2-dose regimens of fremanezumab in the preventive treatment of CM.

HALO EM (N = 875), was conducted in patients with EM randomized into 3 groups (1:1:1 ratio): fremanezumab 225 mg as 1 active injection of 225 mg/1.5 mL and 2 placebo injections of 1.5 mL followed by monthly treatments of 225 mg of fremanezumab as 1 active injection of 225 mg/1.5 mL (225 mg/225 mg/225 mg [monthly]), fremanezumab 675 mg as 3 active injections of 225 mg/1.5 mL followed by 2 monthly treatments of placebo as a single 1.5 mL injection (675 mg/placebo/placebo [quarterly]), and a placebo group that received three 1.5 mL placebo injections followed by 2 monthly single 1.5 mL placebo injections (placebo).[18] The primary objectives of this study were to demonstrate the efficacy of 2-dose regimens of fremanezumab, as assessed by the decrease in MMDs during the 12-week period after the first dose of study drug relative to the baseline period and to evaluate the safety and tolerability of 2-dose regimens of fremanezumab in the preventive treatment of EM. A total of 132 centres participated in HALO CM and 123 centres in HALO EM, including sites in Canada. For HALO CM and HALO EM, randomization was performed using electronic interactive response technology (IRT). Patients were stratified based on sex, country, and baseline preventive migraine medication use (yes, no). The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses), and patients were blinded to treatment assignment. The double-blinded treatment period was 12 weeks for both studies.

In FOCUS (N = 838), patients with CM or EM were randomized 1:1:1 to the following groups.

For patients with CM:

- Fremanezumab 675 mg as 3 active injections of 225 mg/1.5 mL followed by 2 monthly treatments of 225 mg of fremanezumab as a single active injection of 225 mg/1.5 mL (675 mg/225 mg/225 mg [monthly])
- Fremanezumab 675 mg as 3 active injections of 225 mg/1.5 mL followed by 2 monthly treatments of placebo as a single 1.5 mL injection (675 mg/placebo/placebo [quarterly])
- Placebo

For patients with EM:

- Fremanezumab 225 mg as 3 active injections 225 mg/1.5 mL plus 2 matching placebo injections followed by 2 monthly treatments of 225 mg of fremanezumab as a single active injection of 225 mg/1.5 mL (225 mg/225 mg/225 mg [monthly])
- Fremanezumab 675 mg as 3 active injections of 225 mg/1.5 mL followed by 2 monthly treatments of placebo as a single 1.5 mL injection (675 mg/placebo/placebo [quarterly])
- Placebo[19]

The primary objective of the study was to demonstrate the efficacy of fremanezumab, as compared with placebo, administered as monthly and quarterly subcutaneous injections to adult patients with migraine and with documented inadequate response to 2 to 4 classes of prior preventive treatments. A total of 98 centres with sites in Canada, US, and Europe participated. FOCUS included a double-blind 12-week treatment period, followed by a 12-week open-label period, with patients followed for up to 46 weeks. Randomization to the double-blind treatment period was stratified based on CM or EM, sex, country, and a special treatment failure group, defined as patients who had documented inadequate response to valproic acid. Patients were allocated to treatment groups using IRT. The objectives of the open-label period were to provide the patients treated with placebo during the double-blind period with the opportunity to receive fremanezumab, and to provide longer-term efficacy and tolerability data.

*Efficacy Results*

In HALO CM, the difference in mean change from baseline in the MMDs at 12 weeks was –1.8 days (95% confidence interval [CI], –2.61 to –1.09; P < 0.0001) for the monthly fremanezumab group and –1.7 days (95% CI, –2.48 to –0.97, P < 0.0001) for the quarterly fremanezumab group, compared with the placebo group. In HALO EM, there was a reduction in MMDs from baseline at 12 weeks of –1.5 days (95% CI, –2.01 to –0.93; P < 0.0001) for the monthly fremanezumab group and –1.3 days (95% CI, –1.79 to –0.72, P < 0.0001) for the quarterly fremanezumab treatment group versus the placebo group. In FOCUS, the difference in mean change from baseline in the MMDs at 12 weeks during the double-blind treatment period (DBTP) was –3.5 days (95% CI, –4.19 to –2.78), between the monthly fremanezumab and placebo groups, and–3.1 days (95% CI, –3.84 to –2.42) between the quarterly fremanezumab and placebo groups. The outcome of change from baseline in headache days was adjusted for multiplicity. The clinical expert consulted by CADTH indicated that these changes may be clinically important; however, there is no established minimal important difference (MID) to evaluate clinical significance in difference in MMD. The proportion of patients reaching at least 50% reduction in the MMD during the 12-week DBTP after the first dose of fremanezumab was 95 patients (34%) in the quarterly fremanezumab treatment group and 97 patients (34%) in the monthly fremanezumab treatment group, in comparison with 24 patients (9%) in the placebo treatment group.

In HALO CM, the mean reduction in headache days of at least moderate severity at 12 weeks favoured quarterly fremanezumab (–1.8 days; 95% CI, –2.46 to –1.15; P < 0.0001) and monthly fremanezumab (–2.1 days; 95% CI, –2.76 to –1.45; P < 0.0001), compared with placebo. In the FOCUS study, the mean reduction in headache days of at least moderate severity in quarterly fremanezumab compared with placebo was –3.2 days (95% CI, –3.93 to –2.52; P < 0.0001) and –3.6 days (95% CI, –4.30 to –2.91; P < 0.0001) for monthly fremanezumab compared with placebo. The outcome of change from baseline in headache days was adjusted for multiplicity.

There was an improvement in MIDAS disability scores in the HALO EM study, with the mean change from baseline in MIDAS disability scores at 4 weeks after the last dose of study drug of –5.4 (95% CI, –8.90 to –1.93; P = 0.0023) for quarterly fremanezumab and –7.0 (95% CI, –10.51 to –3.53; P < 0.0001) for monthly fremanezumab, favouring the fremanezumab treatment groups compared with placebo. HALO CM demonstrated an improvement in the HIT-6 disability scores at 4 weeks after the last dose of study drug, with –1.9 (95% CI, –2.90 to –0.96; P < 0.0001) for quarterly fremanezumab, and –2.4 (95% CI, –3.32 to –1.38; P < 0.0001) for monthly fremanezumab, compared with placebo. In the FOCUS study, exploratory analysis of the mean change from baseline in disability score, as measured by the HIT-6 at 4 weeks after administration of the sixth dose of study drug, showed an improvement in disability score among patients across double-blind treatment groups during the open-label treatment period (OLTP).

In the HALO CM study, the monthly average number of days of use of any acute headache medication at 12 weeks after the first dose of study drug decreased from baseline by –1.8 days (95% CI, –2.43 to –1.12; P < 0.0001) for quarterly fremanezumab and –2.3 days (95% CI, –2.61 to –1.09; P < 0.0001) for monthly fremanezumab compared with the placebo group. In the HALO EM study, the monthly average number of days of use of any acute headache medication at 12 weeks after the first dose of study drug decreased from baseline by –1.3 days (95% CI, –1.76 to –0.82; P < 0.0001) for quarterly fremanezumab and –1.4 days (95% CI, –1.84 to –0.89; P < 0.0001) for monthly fremanezumab compared with placebo. In the FOCUS study, the monthly average number of days of use of any acute headache medications during the 12-week DBTP changed from baseline (28-day run-in period) compared with placebo by –3.1 days (95% CI, –3.75 to –2.41) for quarterly fremanezumab and by –3.4 days (95% CI, –4.03 to –2.69) for monthly fremanezumab.

Health-related quality of life was measured using several outcome measures, both migraine-specific (e.g., Migraine-Specific Quality of Life Questionnaire [MSQoL]) and general (e.g., EuroQol 5-Dimensions 5-Levels [EQ-5D-5L]). While fremanezumab appeared to be associated with numerical improvements in health-related quality of life across all 3 studies, the outcomes were evaluated as exploratory analyses and are considered supportive of a general benefit; a definitive conclusion regarding its comparative effects on this outcome cannot be made.

Similarly, other patient-valued outcomes, such as treatment satisfaction (measured with the Patient Global Impression of Change) and productivity (measured with the Work Productivity and Activity Impairment scale) were evaluated as exploratory outcomes in the trials and were interpreted as supportive evidence.

### *Harms Results*

The majority of patients in HALO CM and HALO EM experienced at least 1 adverse event (AE), with the fewest events occurring in the placebo groups (64% and 58% in HALO CM and HALO EM, respectively) as compared with the fremanezumab groups (66% to 71%). Injection-site reactions, primarily injection-site–related pain, were the most frequent AEs. Most reactions were mild to moderate and occurred from within hours to 1 month after administration. One patient in the placebo group of HALO EM experienced a serious injection-site reaction. During the DBTP of FOCUS, 49% of patients in the fremanezumab 675 mg/225 mg/225 mg treatment group, 40% of patients in the fremanezumab 225 mg/225 mg/225 mg treatment group, 55% of patients in the fremanezumab 675 mg/placebo/placebo treatment group, and 48% of patients in the placebo treatment group reported at least 1 AE. As in the other 2 studies, injection-site reactions were the most

common AEs. During the OLTP and follow-up period of FOCUS, 60% of patients in the fremanezumab 675 mg/225 mg/225 mg double-blind treatment group, 51% of patients in the fremanezumab 225 mg/225 mg/225 mg double-blind treatment group, 55% of patients in the fremanezumab 675 mg/placebo/placebo double-blind treatment group, and 52% of patients in the placebo double-blind treatment group reported at least 1 AE. Withdrawals due to AEs occurred in 2% or less of patients across all 3 studies. Other notable AEs (antidrug antibody formation, vascular events, constipation, and development of hypertension) were unremarkable and occurred in 1% or less of patients.

Serious AEs (SAEs) occurred in 2% or less of patients in all 3 studies, except in the OLTP and follow-up period of FOCUS, in which they occurred in 3% of patients in the fremanezumab 675 mg/225 mg/225 mg double-blind treatment group, 3% of patients in the fremanezumab 675 mg/placebo/placebo double-blind treatment group, 3% of patients in the placebo double-blind treatment group, and less than 1% of patients in the fremanezumab 225 mg/225 mg/225 mg double-blind treatment group.

Two patients died, 1 in the HALO CM 675 mg/placebo/placebo treatment group and the other in the HALO EM study 675 mg/placebo/placebo treatment group. The causes of death were assessed by the investigators as unrelated to the study drug. No deaths occurred in the FOCUS study.

## Table 2: Summary of Key Results From Pivotal and Protocol Selected Studies — HALO CM and HALO EM

| | HALO CM | | | HALO EM | | |
|---|---|---|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg (N = 379) | Fremanezumab 675 mg/PB/PB (N = 376) | Placebo (N = 375) | Fremanezumab 225 mg/225 mg/225 mg (N = 290) | Fremanezumab 675 mg/PB/PB (N = 291) | Placebo (N = 294) |
| **Mean change from baseline in MMDs during 12-week period after the first dose of study drug** | | | | | | |
| Number of patients contributing to the analysis | 375 | 375 | 371 | 287 | 288 | 290 |
| Baseline, mean (SD) | 16.0 (5.19) | 16.2 (4.88) | 16.4 (5.15) | 8.9 (2.63) | 9.3 (2.65) | 9.1 (2.65) |
| Change from baseline, mean (SE) (95% CI) | –4.6 (0.30) (–5.16 to –3.97) | –4.3 (0.31) (–4.87 to –3.66) | –2.5 (0.31) (–3.06 to –1.85) | –3.7 (–4.15 to –3.18) | –3.4 (–3.94 to –2.96) | –2.2 (–2.68 to –1.71) |
| Treatment group difference versus control (95% CI) | –1.8 (–2.61 to –1.09) | –1.7 (–2.48 to –0.97 | | –1.5 (–2.01 to –0.93) | –1.3 (–1.79 to –0.72) | |
| P value | P < 0.0001 | P < 0.0001 | | P < 0.0001 | P < 0.0001 | |
| **Mean reduction in headache days of at least moderate severity** | | | | | | |
| Number of patients contributing to the analysis | 375 | 375 | 371 | 287 | 288 | 290 |
| Baseline, mean (SD) | 68.0 (53.88) | 66.4 (58.83) | 68.5 (57.03) | 31.7 (23.65) | 33.3 (25.41) | 31.6 (23.21) |
| Change from baseline, mean (SE) (95% CI) | –4.6 (0.30) (–5.16 to –3.97) | –4.3 (0.31) (–4.87 to –3.66) | –2.5 (0.31) (–3.06 to –1.85) | –2.9 (0.21) (–3.34 to –2.51) | –3.0 (0.22) (–3.39 to –2.55) | –1.5 (0.21) (–1.88 to –1.06) |
| Treatment group difference versus control (95% CI) | –2.1 (–2.76 to –1.45) | –1.8 (–2.46 to –1.15) | – | –1.5 (0.24) (–1.92 to –0.99) | –1.5 (0.24) (–1.96 to –1.04) | – |
| P value | P < 0.0001 | P < 0.0001 | – | P < 0.0001 | P < 0.0001 | – |
| **Proportion of patients with ≥ 50% reduction in monthly average number of headache days of at least moderate severity** | | | | | | |
| Number of patients contributing to the analysis | 374 | 375 | 370 | – | – | – |
| Yes, n (%) | 153 (40.8) | 141 (37.6) | 67 (18.1) | – | – | – |
| P value compared to placebo | P < 0.0001 | P < 0.0001 | | – | – | – |

| | HALO CM | | | HALO EM | | |
|---|---|---|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg (N = 379) | Fremanezumab 675 mg/PB/PB (N = 376) | Placebo (N = 375) | Fremanezumab 225 mg/225 mg/225 mg (N = 290) | Fremanezumab 675 mg/PB/PB (N = 291) | Placebo (N = 294) |
| **Proportion of patients with ≥ 50% reduction in MMDs** | | | | | | |
| Number of patients contributing to the analysis | 375 | 375 | 371 | 287 | 288 | 290 |
| Yes, n (%) | 125 (33.3) | 115 (30.7) | 74 (19.9) | 137 (47.7) | 128 (44.4) | 81 (27.9) |
| P value compared to placebo | P < 0.0001 | P = 0.0008 | | P < 0.0001 | P < 0.0001 | |
| **HIT-6 score** | | | | | | |
| Number of patients contributing to the analysis | 375 | 375 | 371 | NR | NR | NR |
| Baseline, mean (SD) | 64.6 (4.42) | 64.3 (4.74) | 64.1 (4.80) | NR | NR | NR |
| Change from baseline, mean (SE) (95% CI) | –6.8 (–7.71 to –5.97) | –6.4 (–7.31 to –5.52) | –4.5 (–5.38 to –3.60) | NR | NR | NR |
| Treatment group difference versus control (95% CI) | –2.4 (–3.32 to –1.38) | –1.9 (–2.90 to –0.96) | – | NR | NR | NR |
| P value | P < 0.0001 | P < 0.0001 | – | NR | NR | NR |
| **Change from baseline in monthly average number of days of use of any acute headache medication** | | | | | | |
| Number of patients contributing to the analysis | 375 | 375 | 371 | 287 | 288 | 290 |
| Baseline, mean (SD) | 11.1 (5.99) | 11.3 (6.18) | 10.7 (6.30) | 7.7 (3.37) | 7.8 (3.74) | 7.7 (3.60) |
| Change from baseline, mean (SE) (95% CI) | –4.1 (–4.74 to –3.47) | –3.6 (–4.27 to –2.98) | –1.8 (–2.41 to –1.13) | –3.0 (–3.41 to –2.56) | –2.9 (–3.34 to –2.48) | –1.6 (–2.04 to –1.20) |
| Treatment group difference versus control (95% CI) | –2.3 (–3.02 to –1.64) | –1.8 (–2.43 to –1.12) | – | –1.4 (–1.84 to –0.89) | –1.3 (–1.76 to –0.82) | – |
| P value | P < 0.0001 | P < 0.0001 | – | P < 0.0001 | P < 0.0001 | – |
| **Harms, n (%) (FAS)** | | | | | | |
| AEs | 270 (71) | 265 (70) | 240 (64) | 192 (66) | 193 (66) | 171 (58) |

| | HALO CM | | | HALO EM | | |
|---|---|---|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg (N = 379) | Fremanezumab 675 mg/PB/PB (N = 376) | Placebo (N = 375) | Fremanezumab 225 mg/225 mg/225 mg (N = 290) | Fremanezumab 675 mg/PB/PB (N = 291) | Placebo (N = 294) |
| SAEs | 5 (1) | 3 (< 1) | 6 (2) | 3 (1) | 3 (1) | 7 (2) |
| WDAE (from study treatment) | 7 (2) | 5 (1) | 8 (2) | 5 (2) | 5 (2) | 5 (2) |
| Deaths | 0 | 1 (< 1) | 0 | 0 | 1 (< 1) | 0 |
| **Notable harms, n (%)** | | | | | | |
| Hypersensitivity (SAE) | NR | NR | NR | 0 | 0 | 1 (< 1) |
| Hypertension | NR | NR | NR | 0 | 3 (1) | 2 (< 1) |
| Investigations | 5 (< 1) | 5 (< 1) | 3 (< 1) | NR | NR | NR |

AE = adverse event; CI = confidence interval; CM = chronic migraine; EM = episodic migraine; FAS = full analysis set; HIT-6 = 6-Item headache impact test; MMD = monthly migraine day; PB = placebo; NR = not reported; SAE = serious adverse event; SD = standard deviation; SE = standard error; WDAE = withdrawal due to adverse event.

Note: For MIDAS total score, larger scores reflect greater disability. Baseline refers to the 28-day run-in period for headache variables and visit 2 (day 0) for all other variables.

[a] P value for the treatment comparison is from an analysis of variance (ANOVA) with treatment group as a factor.

Source: Clinical Study Reports for HALO CM[17] and HALO EM.[18]

## Table 3: Summary of Key Results From Pivotal and Protocol Selected Studies — FOCUS

| | FOCUS | | |
|---|---|---|---|
| | Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 285) | Fremanezumab 675 mg/PB/PB (N = 276) | Placebo (N = 279) |
| **Mean change from baseline in MMDs during 12-week period after the first dose of study drug DBTP** | | | |
| Number of patients contributing to the analysis | 283 | 276 | 277 |
| Baseline, mean (SD) | 14.1 (5.58) | 14.1 (5.61) | 14.3 (6.12) |
| End-of-treatment time point | End of DBTP | End of DBTP | End of DBTP |
| Change from baseline, mean (95% CI) | –4.1 (–4.73 to –3.41) | –3.7 (–4.38 to –3.05) | –0.6 (–1.25 to 0.07) |
| Treatment group difference versus control (95% CI) | –3.5 (–4.19 to –2.78) | –3.1 (–3.84 to –2.42) | – |
| P value | P < 0.0001 | P < 0.0001 | – |

| | FOCUS | | |
|---|---|---|---|
| | Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 285) | Fremanezumab 675 mg/PB/PB (N = 276) | Placebo (N = 279) |
| **Mean reduction of headache days of at least moderate severity** | | | |
| Number of patients contributing to the analysis | 283 | 275 | 279 |
| Baseline, mean (SD) | 12.7 (5.2) | 12.4 (5.84) | 12.8 (5.92) |
| End-of-treatment time point | End of DBTP | End of DBTP | End of DBTP |
| Change from baseline, mean (95% CI) | –4.2 (–4.89 to –3.58) | –3.9 (–4.51 to –3.19) | –0.6 (–1.28 to 0.03) |
| Treatment group difference versus control (95% CI) | –3.6 (–4.30 to –2.91) | –3.2 (–3.93 to –2.52) | – |
| P value | P < 0.0001 | P < 0.0001 | – |
| **Proportion patients ≥ 50% reduction in average monthly migraine days** | | | |
| **Double-blind treatment period** | | | |
| Number of patients contributing to the analysis | 283 | 276 | 278 |
| Responders, n (%) | 97 (34) | 95 (34) | 24 (9) |
| Responder common OR (95% CI and P value) versus placebo[b] | 5.82 (3.56 to 9.51) P < 0.0001 | 5.84 (3.57 to 9.55) P < 0.0001 | – |
| **Open-label treatment period** | | | |
| Number of patients contributing to the analysis | 272 | 271 | 263 |
| Responder, n (%) | 125 (46) | 123 (45) | 100 (38) |
| **HIT-6 score** | | | |
| Number of patients contributing to the analysis | 283 | 275 | 278 |
| Baseline, mean (SD) | 63.9 (4.47) | 64.2 (4.28) | 64.1 (4.95) |
| End-of-treatment time point | End of DBTP | End of DBTP | End of DBTP |
| Change from baseline, mean (95% CI) | –6.1 (–7.12 to –4.99) | –5.2 (–6.29 to –4.13) | –2.2 (–3.31 to –1.17) |
| Treatment group difference versus control (95% CI) | –3.8 (–4.95 to –2.69) | –3.0 (0.58) (–4.10 to –1.83) | – |
| P value | P < 0.0001 | P < 0.0001 | – |
| **Use of acute headache medications (subgroup)** | | | |
| Number of patients contributing to the analysis | 283 | 276 | 278 |

| | FOCUS | | |
|---|---|---|---|
| | Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 285) | Fremanezumab 675 mg/PB/PB (N = 276) | Placebo (N = 279) |
| Baseline, mean (SD) | NR | NR | NR |
| Change from baseline, mean (95% CI) | –3.9 (–4.58 to –3.32) | –3.7 (–4.30 to –3.03) | –0.6 (–1.21 to 0.04) |
| Treatment group difference versus control (95% CI) | –3.4 (–4.03 to –2.69) | –3.1 (–3.75 to –2.41) | – |
| P value | P < 0.0001 | P < 0.0001 | – |
| **Harms, n (%) (double-blind safety analysis set)** | | | |
| AEs | 129 (45) | 151 (55) | 134 (48) |
| SAEs | 4 (2) | 2 (< 1) | 4 (1) |
| WDAE (from study treatment) | 4 (2) | 1 (< 1) | 3 (1) |
| Deaths | 0 | 0 | 0 |
| **Notable harms, n (%)** | | | |
| Injection-site erythema | 12 (7) | 4 (4) | 19 (7) |
| Injection-site induration | 10 (6) | 3 (3) | 12 (4) |
| Nasopharyngitis | 6 (3) | 1 (< 1) | 13 (5) |

AE = adverse event; CI = confidence interval; DBTP = double-blind treatment period; HIT-6 = 6-Item headache impact test; MMD = monthly migraine day; NR = not reported; OR = odds ratio; PB = placebo; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

Note: The analysis of covariance (ANCOVA) model includes treatment, gender, region, special group of treatment failure (yes/no), migraine classification (EM/CM) and treatment × migraine classification as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates.

Note: Fremanezumab monthly is 675 mg/225 mg/225 mg for CM patients and 225 mg/225 mg/225 mg for EM patients. Fremanezumab quarterly is 675 mg/placebo/placebo for both CM and EM patients.

Note: Baseline refers to the 28-day run-in period for headache variables and visit 2 (day 0) for all other variables.

Source: Clinical Study Report for FOCUS.[19]

*Critical Appraisal*

The baseline demographic and disease characteristics were balanced. In addition, the randomization procedures and blinding methods were appropriate in all the trials. No significant concerns were identified with the validity of key outcome measures (e.g., MMD) in the conduct of the trial. The clinical expert noted a reasonable discontinuation rate of participants (10%) in the migraine population. The number of AEs and withdrawals due to AEs was low across all studies. The FOCUS study included an open-label extension phase of up to 46 weeks after the end of the 12-week randomized treatment period to monitor the long-term effects of the drug, introducing potential bias in the patients' reporting of headache or migraine, or related subjective outcome measures, such as HIT-6, MIDAS, and MSQoL. All the study patients were trained in the proper use of the diary to record their migraine days. Missing data were still likely a concern, particularly when missingness differed between the 2 comparison arms. A multiple imputation method was applied, in which all continuous efficacy outcomes were analyzed by an analysis of covariance (ANCOVA) method or the Wilcoxon rank sum test. The efficacy results were confirmed by mixed-effects repeated measures (MMRM), which could have accounted for missing data, under the missing-at-random assumption. Multiplicity was adjusted for analyses of primary and secondary efficacy outcomes. The validity, reliability, and responsiveness of outcome measures, including the use of MSQoL, HIT-6, and MIDAS, were considered of moderate to high reliability and valid in measuring the impact of CM or EM on the patient's disability and quality of life under a double-blind and controlled setting. Overall, the quality of the 3 included trials was considered reasonable.

The high selectivity of the study populations of the included studies, based on a stringent list of eligibility criteria, may restrict generalizability to the general migraine population. Although restricting eligibility helped to prevent previous preventive treatments from influencing the results, all the 3 studies excluded patients who had prior experience in use of OnaA (for migraine or other indication) within the previous few months or prior exposure to a monoclonal antibody with CGRP pathway, as well as many other treatments for migraine. Patients with major cardiovascular and other major comorbid diseases, including psychiatric disorders, or unfavourable test results for liver function, for example, were excluded from this study, thus limiting full extrapolation of the safety data to the general population. The clinical expert indicated that patients with CM commonly experience psychiatric disorders such as depression. Since patients with a history of psychiatry disorders were excluded from these trials, the generalizability of the study results to the migraine population may be limited. In the FOCUS trial, the presence of EM and CM during the baseline period was evaluated by the use of triptans or ergot derivatives to treat an established headache, which is not an established ICHD-3 criterion. This may restrict the comparability of the FOCUS results to the results of other trials. Despite the strict inclusion and exclusion criteria, the clinical expert indicated that the study population was representative of the general migraine population. Patients in all of the studies could continue to use acute headache medications, in agreement with headache guidelines that allow preventive migraine therapy in combination with acute treatment. The use of concomitant medications was diverse across the trials. Finally, the included trials could not assess the long-term effects of fremanezumab beyond 3 months. No direct comparative effect between fremanezumab and other available CGRP medications was studied.

## Indirect Comparisons

### *Description of Studies*

Two indirect treatment comparisons (ITCs) were summarized for this review. A sponsor-submitted ITC was conducted of drugs for CM or EM. Another ITC of fremanezumab versus other migraine therapies for patients with CM and EM, conducted and published by the Institute of Clinical and Economic Reviews (ICER), was also included. Both ITCs included adults (≥ 18 years) with EM or CM who were eligible for preventive migraine therapy. Both ITCs had a similar approach to data synthesis using Bayesian network meta-analysis (NMA).

### *Efficacy Results*

The overall results from both ITCs show that fremanezumab has favourable clinical efficacy versus placebo in most of the outcomes analyzed. Similarly, and throughout the various networks in both ITCs, fremanezumab did not show a clearly favourable, or unfavourable, effect versus other prophylaxis medications for migraine (including OnaA in a sensitivity analysis).

In the sponsor-submitted ITC, favourable effects were demonstrated: monthly and quarterly fremanezumab appeared more efficacious in reducing MMDs at 12 weeks than erenumab 70 mg and in reducing use of acute migraine-specific medication at 12 weeks than erenumab 70 mg and 140 mg in EM patients who had inadequate response to 2 or more previous treatments. This result should be considered in light of the FOCUS trial that was included in this network, which incorporated both CM and EM patients receiving fremanezumab.

In the sponsor-submitted ITC, monthly and quarterly fremanezumab appeared more efficacious in terms of the percentage of patients who had a 50% response at 12 weeks than erenumab 140 mg (monthly: relative risk [RR] = 1.83; 95% credible interval [CrI], 1.15 to 3.08; quarterly: RR = 1.71; 95% CrI, 1.07 to 2.89) in CM patients who had inadequate response to less than 2 previous treatments. In these results, there is uncertainty stemming from the variable definition of responders in the included studies; the sponsor-submitted ITC did not elaborate on how such differences in the outcome definition were handled. In the sponsor-submitted ITC, monthly fremanezumab also appeared more efficacious in reducing the days using acute migraine-specific medication at 12 weeks than erenumab 70 mg and 140 mg in the CM patients who had inadequate response to less than 2 previous treatments. Potential uncertainty in this result stems from the small size of the network (3 studies) and the lack of an assessment of inconsistency.

In the ICER ITC, monthly fremanezumab appeared to be more efficacious in reducing MMDs at 12 weeks than topiramate 50 mg/day in EM patients (mean difference = –1.42; 95% CrI, –2.59 to –0.29). Uncertainty in this result mainly stems from clinical heterogeneity in the included studies.

AEs were not analyzed.

### *Critical Appraisal*

Both ITCs shared similar inclusion and exclusion criteria. However, 1 noticeable difference is that the sponsor-submitted ITC included only studies that had clearly indicated the proportion of the included patient population with CM, EM, and the number of previous

inadequate treatments. The results of the outcomes in the sponsor-submitted ITC were reported based on migraine type (CM or EM) and the number of inadequate previous treatments (less than 2 or 2 or more). In contrast, the ICER ITC provided only the results stratified by migraine type. This variation in the approach to data synthesis meant that the sponsor-submitted ITC would be more homogeneous than the ICER ITC, albeit with smaller networks. The smaller network sizes mean the ITC has less precision (wide 95% CrI); it is unable to test the consistency assumption; and it needs to use a fixed-effects model, which adds another layer of unverifiable assumptions to the model. The sponsor-submitted ITC included the FOCUS trial in the networks with 2 or more inadequate previous treatments, without separating the CM patients from EM patients. This approach violated the eligibility criteria for the sponsor-submitted ITC analysis, in which many other trials were excluded for not providing data separately for each migraine type, and, more concerning, introduced considerable clinical heterogeneity into these networks. This likely biased the results in favour of fremanezumab in the EM networks and against fremanezumab in the CM networks, assuming a potentially larger treatment effect in the CM population. There is no way, based on current data, to quantify the exact magnitude that this bias may have had on the results.

## Other Relevant Evidence

### *Description of Studies*

The HALO long-term study (LTS) (N = 1,890) was a multi-centre, randomized, double-blind, parallel-group, phase III study of SC administration of fremanezumab for the preventive treatment of migraine in adults. Patients who had completed the pivotal efficacy studies, HALO CM and HALO EM, were enrolled in HALO LTS, as were new patients (16.5%) who had not participated in the pivotal efficacy studies. Patients who received placebo during the pivotal studies and newly enrolled patients were randomized 1:1 to either monthly or quarterly fremanezumab treatment. Patients who had received fremanezumab as either monthly or quarterly dosing in the pivotal studies continued with the same dosage regimen for 12 months, along with a 6.5-month post-treatment follow-up. Patients with EM on monthly treatment received fremanezumab 225 mg every month for a total 12 doses, while those with CM received the same treatment but with a loading dose of fremanezumab 675 mg the first month. New patients with EM or CM on quarterly treatment received fremanezumab 675 mg every 3 months, for a total of 4 doses. Once assigned, patients did not switch between the dosage regimens.

### *Efficacy Results*

For both migraine classifications and both treatment groups, the mean number of headache days per month and MMDs of at least moderate severity decreased from baseline and remained stable for the duration of the study. From baseline to month 6 and month 12, the mean number of MMDs in patients with CM decreased by 7.6 and 8.1 days, respectively, in the 225 mg monthly treatment group compared with a decrease of 6.5 and 7.2 days, respectively, in the 675 mg quarterly treatment group. For the EM group, the mean decrease in the number of MMDs was 4.9 and 5.1 days from baseline to month 6 and month 12, respectively, in the 225 mg monthly treatment group and a decrease in 5.0 and 5.2 days, respectively, in the 675 mg quarterly treatment group. The use of acute headache medication followed a similar decreasing trend during the LTS.

HIT-6 and MIDAS scores for CM and EM patients, respectively, showed a decrease for both dosage groups over time, indicating patients experienced reduced migraine-related

disability. Quality of life measures (MSQoL and EQ-5D-5L) and patient-reported assessment of clinical change after treatment (through the Patients' Global Impression of Change [PGIC]) showed improvements in most patients during the HALO LTS. Patient Health Questionnaire (PHQ)-9 scores (for assessing depression in patients) and Work Productivity and Activity Impairment (WPAI) scores (for assessing how migraine affects work and daily life) both decreased from baseline to end of treatment, suggesting improved patient outcomes during the LTS.

*Harms Results*

Most patients (85%) experienced an AE, and 10% experienced an SAE. Injection-site induration, pain, and erythema were the 3 most common AEs, occurring in 619 (33%), 580 (31%), and 497 (26%) patients, respectively. The 2 most common SAEs were status migrainosus and basal cell carcinoma, both occurring in 4 patients (< 1%) each. Seventy-six (4%) patients discontinued the study due to AE, which occurred at a similar frequency (3% to 5%) across the 3 groups. One death occurred in the fremanezumab 675 mg quarterly group, approximately 300 days after the last dose of the study drug. The patient had a brain aneurysm and multiple strokes.

*Critical Appraisal*

HALO LTS did not contain a placebo arm or other comparator; patients were randomized to different dosages of fremanezumab. Nearly 20% of the overall intention-to-treat (ITT) population discontinued the study. Only 30% of rollover patients completed the study at the data cut-off date, compared with 75% of newly enrolled patients, although overall withdrawal frequency was similar across treatment arms. Discontinuation due to AEs was slightly greater in the group of newly randomized patients compared to patients who had rolled over from the pivotal studies, while withdrawal by subject was more common in the rollover patients versus those newly randomized.

As part of the eligibility criteria for the LTS, patients had to complete 1 of the pivotal studies, potentially allowing for selection bias. Not all patients who completed the pivotal studies rolled over to the LTS, and there was no clear explanation given for those who did not. Additionally, there was potential for survival bias, since any patients who discontinued the pivotal studies due to AEs were excluded. This could result in a greater enrolment of patients who were better able to tolerate fremanezumab and fewer AEs being reported. Finally, no statistical testing was performed, making interpretation of the results uncertain.

## Conclusions

Three clinical trials (HALO CM, HALO EM, and FOCUS) with double-blind treatment periods were included in this review. HALO CM included adult patients with CM, HALO EM included adult patients with EM, and FOCUS included adult patients with either CM or EM. All studies demonstrated that fremanezumab reduced the mean MMDs and average number of headache days of at least moderate severity from baseline compared with placebo, which was considered clinically meaningful by the clinical expert and patient groups. However, the lack of a validated MID in these outcomes limits the interpretation of the clinical significance of fremanezumab compared with placebo in the frequency of migraine and headache days. HIT-6 scores improved for fremanezumab treatment groups after adjustment for multiplicity, but the clinical significance of the changes for patients with CM are uncertain. Likewise, while MIDAS scores improved for fremanezumab treatment groups, there is no established MID to help determine the clinical significance of the

differences versus placebo. Numerical improvements in work and daily life, as well as health-related quality of life, were shown in the fremanezumab treatment groups; however, the outcomes were assessed as exploratory, precluding definitive conclusions. No clear safety issues or tolerability issues emerged from the 3 included studies. Generally, neither the sponsor-submitted nor ICER ITCs identified a difference in effects of fremanezumab compared with active comparators with any certainty.

# Introduction

## Disease Background

Migraine is a neurological disease characterized by recurrent attacks of pulsating headache pain of at least moderate severity.[1] Migraine episodes may last from 4 to 74 hours and can be accompanied by associated symptoms, such as photophobia, phonophobia, nausea, and vomiting.[2] The type of migraine can be refined based on the frequency of MMDs and monthly headache days.[1] The third edition of the ICHD-3 described CM as a headache (tension-type–like or migraine-like) occurring on 15 or more days per month for more than 3 months with the features of migraine headaches on at least 8 days per month.[3] In EM, individuals experience headaches on 14 or fewer days per month for more than 3 months with the features of migraine headaches on at least 4 days per month.[3]

In Canada (2010 to 2011), 9.6% of the population older than 18 years of age experienced migraine attacks, with more women (13.8%) than men (5.3%) having suffered from migraine.[5] In a longitudinal web-based panel study of migraine in the US (N = 16,789), 91.2% of patients had EM and 8.8% had CM.[20] An estimated 2.5% of patients with EM transition to having CM.[7]

Among those that suffered from migraine in Canada (aged ≥ 15 years, 2010 to 2011), 38.2% reported that migraine at least moderately affected their life and 25.5% reported that the pain prevented them from engaging in activities.[21] In a cross-sectional, web-based observational survey of patients with migraine (N = 8,726), nearly half of all respondents reported moderate or severe disability, with more headache days per month being associated with more severe disability.[12] Among the respondents, 5.7% had CM and 94.3% had EM.[12] Patients with CM reported longer, more painful headaches, and more comorbidities than those with EM.[12] Additionally, patients with CM reported worse headache-related disability compared with those with EM, as measured by the MIDAS, a validated tool that measures disability in patients with migraine.[12] Migraine attacks are often disabling. Indeed, headache disorders are among the 3 highest causes of years lived with disability worldwide (1990 to 2017), with migraine accounting for 47,245,400 years lived with disability globally in 2017.[22]

Migraine is associated with missed activities at work, school, and/or at home.[21] Additionally, prevalence is highest during peak productive years (i.e., around 30 to 64 years of age),[4] which maximizes impact on the sufferer, family, and society.[6,21,23,24] Migraine reduces productivity, leading to missed work days and substantial economic costs. Loss of productivity accounts for up to 70% of total migraine-related annual costs.[25] In Canada (2010 to 2011), 34% of individuals with migraine reported limitations in job opportunities due to migraine, 36% of those currently employed reported missing at least 1 day of work in the past 3 months due to migraine, and 18% who had previously been employed reported that they had changed their work activities (hours, type of work, or stopped work) for 3 months or more owing to migraine.[21]

## Standards of Therapy

Comprehensive migraine therapy includes management of lifestyle factors and triggers, acute and preventive (or prophylactic) medications, and migraine self-management strategies.[2,8] The goals of migraine treatments are to relieve pain, restore function, improve health-related quality of life, reduce headache frequency, and prevent the progression of

EM to CM.[26] The Canadian Headache Society has guidelines for the acute treatment of migraine and for preventing attacks.[2]

Preventive medications include a variant of the botulinum toxin (OnaA), inhibitors of the CGRP (erenumab), blood pressure medications (e.g., beta-blockers [e.g., propranolol, metoprolol], calcium-channel blockers [e.g., flunarizine or verapamil]), tricyclic antidepressants (e.g., amitriptyline or nortriptyline), antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors), anticonvulsants (e.g., topiramate, gabapentin, or divalproex), and a serotonin antagonist (pizotifen). Only topiramate, OnaA, and the CGRP inhibitors have been approved by Health Canada for the prevention of migraines, and, of these, OnaA is only indicated for the prevention of CM. Migraine prophylaxis is an important part of the overall approach for a proportion of individuals with migraine.[8] Of patients with migraine who have received preventive medications, 87% have an inadequate response to 2 or more preventive therapies.[13]

## Drug

Fremanezumab is a fully humanized mAb that binds to and inhibits the 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.[14]

Fremanezumab is administered by SC injection at a dosage of either 225 mg monthly or 675 mg quarterly.[14] It can also be used as monotherapy or with a concomitant preventive medication.[14] Fremanezumab received Health Canada Notice of Compliance on April 9, 2020, with an indication for the prevention of migraine in adults who have had at least 4 migraine days monthly.[15]

The sponsor requested reimbursement of fremanezumab per the indication, for the prevention of migraine in adults who have 4 or more migraine days per month.[15]

### Table 4: Key Characteristics of Fremanezumab, Erenumab, OnaA, Beta-Blockers, Anticonvulsants, TCAs and SNRIs, CCBs, ACE Inhibitors and ARBs, and Pizotifen

| | Fremanezumab | Erenumab | OnaA |
|---|---|---|---|
| **Mechanism of action** | Binds to CGRP ligand | Binds to CGRP receptor | Inhibits presynaptic release of CGRP and other neurotransmitters |
| **Indication[a]** | For prevention of migraine in patients who have at least 4 migraine days monthly | For prevention of migraine in patients who have at least 4 migraine days monthly | For prophylaxis of headaches in adults with chronic migraine (≥ 15 days/month with headache lasting ≥ 4 hours per day |
| **Route of administration** | Subcutaneous injection | Subcutaneous injection | Intramuscular injection |
| **Recommended dosage** | 675 mg quarterly, 675 mg followed by 225 mg monthly (patients with CM), or 225 mg monthly (patients with EM) | 70 mg or 140 mg once monthly | 5 units to 31 different sites, across 7 different head-and-neck muscle areas |
| **Serious adverse effects or safety issues** | Hypersensitivity reactions | Hypersensitivity reactions | Spread of toxin beyond injection site (e.g., breathing difficulties) |
| **Other** | None | None | None |

| | Beta-blockers | Anticonvulsants | TCAs and SNRIs |
|---|---|---|---|
| **Mechanism of action** | Beta1-receptor antagonists | Multiple mechanisms of action | Inhibits reuptake of serotonin, norepinephrine |
| **Indication[a]** | Migraine prophylaxis: propranolol, timolol<br>Others:<br>None for migraine<br>Various cardiovascular indications | Topiramate:<br>migraine prophylaxis<br>Topiramate/others:<br>epilepsy | None for migraine<br>Depression<br>Anxiety |
| **Route of administration** | Oral | Oral | Oral |
| **Recommended dose** | Varies by drug | Varies by drug | Varies among drugs |
| **Serious adverse effects or safety issues** | Rebound syndrome<br>Bronchospasm | Valproic acid:<br>Hepatotoxicity | Hypertension<br>Serotonin syndrome<br>Conditions that may be exacerbated by anticholinergic effects (TCA mainly) |
| **Other** | Drugs: Propranolol<br>Timolol<br>Nadolol<br>Metoprolol | Drugs: Topiramate<br>Gabapentin<br>Valproic acid | Drugs: Amitriptyline<br>Nortriptyline<br>Venlafaxine |
| | **CCBs** | **ACE inhibitors and ARBs** | **Pizotifen** |
| **Mechanism of action** | Blocks L-type calcium channels | Inhibits effects of angiotensin 2 | Blocks 5HT-2 receptors, histamine ($H_1$) receptors |
| **Indication[a]** | Flunarizine:<br>Migraine prophylaxis<br>Others:<br>None for migraine<br>Various cardiovascular indications | None for migraine<br>Hypertension<br>Heart failure | Prevention of migraine: recommended for those with ≥ 3 attacks monthly who fail to respond to symptomatic treatment and have reduced quality of life |
| **Route of administration** | Oral | Oral | Oral |
| **Recommended dose** | Varies among drugs | Varies among drugs | 1 mg/day to 6 mg/day, up to 3 mg in a single dose |
| **Serious adverse effects or safety issues** | Heart block | Angioedema | Conditions that may be exacerbated by anticholinergic effects |
| **Other** | Drugs: Flunarizine<br>Verapamil | Drugs: Lisinopril<br>Candesartan | None |

5HT-2 = serotonin-2; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CCB = calcium-channel blocker; CGRP = calcitonin gene–related peptide; CM = chronic migraine; EM = episodic migraine; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

[a] Health Canada–approved indication.

Source: Product monographs from e-CPS, and CADTH clinical review of erenumab.[9]

# Stakeholder Engagement

## Patient Group Input

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

### About the Patient Groups and Information Gathered

CADTH received 1 patient input submission, which was a joint effort between Migraine Canada and Migraine Quebec. Migraine Canada is a national not-for-profit organization whose mission is to provide support and education as well as raise awareness about the impact of migraines. It advocates for the optimal care of those living with migraines and supports research toward a cure.

A disclosure of any conflicts of interest for the organization is available on the CADTH website.

Patient input was gathered through an online survey, which was promoted through Migraine Canada's Facebook and Twitter platforms as well as in migraine clinics across Canada. Migraine Canada designed the survey and analyzed the results from a total of 597 respondents, of which 93% were women, 5% were 25 years or younger, 34% were from 26 to 39 years old, 46% were from 40 to 54 years old, and 15% were age 55 years or older. The survey results showed that 26% had 1 to 6 migraines per month, 32% had 7 to 14 migraines per month, and 42% had at least 15 migraines per month.

### Disease Experience

Between migraines, patients live in fear of the next attack, dread potential triggers, and have difficulty planning for future events, limiting both personal and professional activities.

Symptoms can include severe, throbbing, recurring pain; nausea; vomiting; dizziness; vertigo; loss of balance; extreme sensitivity to sound, light, touch, and smell; visual disturbances; loss of vision, speech, sensation, or muscle strength; and tingling or numbness in the extremities or face. Migraines can also be associated with slowed thinking, lack of focus, and difficulty reading and speaking, all of which affect the patient's ability to perform work tasks and socialize with others. Eighty percent of respondents also noted that their migraines have led to anxiety or depression.

The burden on day-to-day life can be illustrated by the following patient comments:

> "I'm just done. It is hard to be positive or see any end to the constant pain. I can't plan my future or even my day-to-day and I hate asking for help all the time."
>
> "Migraine is slowly destroying my life. I suffer from depression, an anxiety disorder and I often think of ending my life because I am so tired of being in pain, nauseated, vomiting, not sleeping, constantly tired."
>
> "Migraines control every aspect of my life. Not an hour goes by where I don't think about pain. Migraines have affected my family and friends and work as I am always in pain. It has caused serious depression including suicidal thoughts that have been treated with medication... not the root problem."

According to survey respondents, migraines had the greatest impact on their ability to work, causing financial repercussions and added pressure on their spouse. In addition,

respondents reported requiring help with childcare. Respondents also noted that they were often unable to attend social events, which affected family members and their personal relationships due to a lack of understanding and support from those around them.

When asked about how migraines had affected their ability to work, 45% responded they had missed at least 1 day per month from work, while 25% were disabled and not working. Those who are able to may try to make up for lost time by working harder on good days, but the extra effort takes away from their rest and recovery.

From the survey, 3% indicated that their migraines had not affected their family or intimate relationships, 48% and 40% responded that there was a minor and major impact, respectively, and 9% listed migraines as the main reason they had no family or intimate relationships. One patient stated, “Made the decision long ago to not have any relationship or children because I believed that it wouldn’t be fair to either one. I also did not want it on my conscience that my child would be crippled with migraine.”

When family members were asked for input, their responses tended to focus on how migraines negatively affected family activities. Some couples had decided not to have children, and some were financially restricted to 1 spouse’s income. Children of patients with migraines responded, “We do not do fun things because mommy can’t do it,” and “I wish I had my old life back with my normal fun mom who can do anything and everything and is always happy.” Partners also shared the burden and stated, “Her migraines have an intimately personal impact on my life because I care so much about her, and I don't want to see her hurting, and I feel powerless to help. I just wish there was something more to offer her, so she wasn't suffering all the time” and “A lot of extra pressure to be the major breadwinner of the family. A lot of frustration at being helpless to help a partner, a lot of frustration at the inefficiencies of the health care system that fail to help migraine patients, a lot of frustration that my wife’s health isn’t better both for her and us and our family.”

From this survey, 27% of respondents had been to the emergency department at least 4 times since the start of their disease, although they felt stigmatized and blamed for wasting health care resources and the time of health care providers. Furthermore, patients felt they were often met with skepticism from social and work networks as well as health care providers since there are no objective diagnostic tests for migraines. This can lead to feelings of guilt and shame, which can prevent patients from getting much-needed support, as well as to isolation. One respondent shared their difficulties of living with migraines as follows: “It is invisible. It is stigmatized. It isolates and diminishes you.”

## Experience With Treatment

When asked about oral preventive treatments, 11% of respondents had not tried any, 22% had tried 1 or 2 preventives, 22% had tried 3 or 4, and 45% had tried at least 5. Adverse reactions are a key consideration when deciding among treatment options. From the survey responses, 7% of respondents reported having no side effects, 25% stated that side effects they experienced were tolerable, and 68% had discontinued a medication because of side effects. The most common side effects from using preventive medications reported in this survey were somnolence (76%), dizziness (58%), weight gain (54%), cognitive difficulties (53%), gastrointestinal upset (45%), and mood difficulties (44%).

Loved ones also witness the hardships that patients have experienced with ineffective treatments: “She has tried so hard over the years trying countless medications and seeing

the best specialists without much success," and "Watching him try treatment after treatment with no real relief is sad."

Migraine Canada was not aware of any Canadian patients who had experience with fremanezumab through a clinical trial.

### Improved Outcomes

Access to care was also noted as limited, with 27% of respondents reporting having to wait more than a year to see a neurologist or headache specialist. In addition to wait times, 54% indicated that they were dissatisfied or very dissatisfied with the current care they were receiving from their physicians (general practitioner or neurologist). Respondents indicated they are often told that, while there is no cure for migraines, a 50% improvement in frequency and intensity should be acceptable, although 74% of surveyed patients had not seen at least a 50% improvement with treatments they had tried.

Migraine Canada noted that the availability of an injectable mAb treatment for migraines versus oral medications would be valuable to patients. Of survey respondents, 73% indicated that they would prefer a monthly injection to a daily pill, and several expressed interest in a medication that could be taken less frequently, with 1 commenting that they "would love to be able to stop having to take so many pills."

When asked about meaningful and successful preventive therapies, patients were looking for "something that has minimal mental side effects," "something that will reduce frequency and intensity so that [they] can resume professional activities," and "anything that would allow [them] to live a fruitful life — return to work, keep a relationship, to see friends and family on a regular basis, to go to events." Treatment affordability was another concern.

Migraine Canada noted that "new treatment options may allow patients the ability to return to work, interact with their family and friends and feel like they are contributing to society" and emphasized that "the migraine population is a younger pain population and a strong contributor to the workforce."

## Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of migraines.

### Unmet Needs

The clinical expert consulted by CADTH noted that, although several medications are available for the prevention of migraine, most are used off-label. Only fremanezumab and erenumab have been specifically developed for use in migraine prophylaxis. The clinical expert indicated that patients with migraines seem to be sensitive to medication adverse effects, and currently available oral medications used for the prevention of migraine are associated with numerous adverse effects that patients with migraine find difficult to tolerate. For example, the hypotension caused by beta-blockers, the mental slowing caused by topiramate, or the weight gain caused by amitriptyline are notable among 3 of the most

used types of medications. Many patients are unable to take these medications at a high enough dose for long enough to achieve prophylactic benefit, and they stop therapy prematurely. As well, the clinical expert noted that less one-third of patients respond to their first prophylactic treatment. As a result, there remains a need for drugs that are effective in preventing migraines with minimal adverse effects.

The clinical expert indicated the lack of access to expert treatment providers is an important barrier for patients. The clinical expert noted there is particularly limited access to health care providers in Canada who are expert in administering OnaA for the prevention of migraines.[27]

### Place in Therapy

The clinical expert indicated that anti-CGRP mAbs, including fremanezumab, could be considered first-line daily preventive medications in clinical practice. However, at present, patients with EM or with CM would try 1 or 2 of the oral prophylactic medications before fremanezumab. Anti-CGRP mAbs cannot be used in women intending pregnancy in the following 6 months.

### Patient Population

The clinical expert stated that patients with EM or CM for whom headaches have a severe impact on their ability to function would be best suited for fremanezumab treatment. Patients who have more than 4 migraine headache days per month but not more than 14 migraine headache days per month as a group tend to be more responsive to treatment. Patients most in need of an intervention are those in whom headaches have a severe impact on their ability to function. The clinical expert indicated there are no disease characteristics (e.g., presence or absence of certain symptoms, stage of disease) that would identify those patients who are most likely to exhibit a response to treatment. Patients who are pregnant or who are contemplating getting pregnant in the next 6 months are least suitable for treatment with fremanezumab.

According to the clinical expert, migraines are accurately diagnosed in more than 80% of cases. However, misdiagnosis is possible, and 80% of patients who are diagnosed with chronic sinus headache actually have migraine.

### Assessing Response to Treatment

The clinical expert stated that validated tools that measure migraine disability can be used to assess patients to determine whether they are benefiting from the treatment. For example, a reduction in the MIDAS score or the HIT-6 score would be appropriate. The clinical expert indicated that reduction in medication use for acute treatments could also be used to assess benefit of the treatment. However, the clinical expert indicated that patients with very frequent or daily headaches may begin using acute medications once mAbs reduce the total number of headache days.

According to the clinical expert, a global assessment in clinical practice, consisting of the questions “Are you feeling better? Do you want to continue with the medication?” is the most important assessment. The definition of effective response is variable from patient to patient. The clinical expert stated that selected patients feel that a 2 day to 3 day reduction in the number of headache days per month is likely meaningful. The clinical expert stated that some patients experience the same number of headache days per month yet

experience improved daily functioning. The improvement in function can be reflected in the HIT-6 score, with a 20% reduction in a HIT-6 score being considered meaningful.

The clinical expert stated there is no universal timeline for the assessment of treatment response. The clinical expert stated that they assess treatment response at 2 weeks after the third dose and 2 weeks after the sixth dose by asking the patient their preferences for continuation of the drug. It is unclear whether patients with a meaningful reduction in the number of headache days per month can discontinue the medication. The clinical expert indicated that patients experiencing stability after 1 year of treatment can discontinue the drug to determine the lasting effects, and re-start fremanezumab if symptoms return or worsen.

## Discontinuing Treatment

Fremanezumab should be discontinued in patients who are pregnant or who are contemplating getting pregnant in the next 6 months. Therapy discontinuation would be considered if there was no effect after 3 months at the highest tolerated dose, or there was loss of effect for 3 consecutive months, or a patient has 4 or fewer headache days per month for at least 9 months and these headaches can be readily treated with an acute therapy (i.e., triptan or NSAID).

## Prescribing Conditions

Because of the limited availability of headache specialists in Canada, the clinical expert stated that fremanezumab could be prescribed by primary care physicians in the community, by community neurologists, and by headache specialists. The clinical expert indicated specialist monitoring is not necessary.

### Additional Considerations

The clinical expert stated that fremanezumab is expected to be similar to erenumab in terms of efficacy and safety, based on its similar mechanism of action.

# Clinical Evidence

The clinical evidence included in the review of fremanezumab is presented in 3 sections. The first section, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence from the sponsor and indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes sponsor-submitted long-term extension studies that were considered to address important gaps in the evidence included in the systematic review.

## Systematic Review (Pivotal and Protocol Selected Studies)

### Objectives

To perform a systematic review of the beneficial and harmful effects of fremanezumab at 225 mg (1 SC injection) once a month in patients with EM, or 675 mg (3 separate SC injections of 225 mg, one after another) followed by 225 mg (1 SC injection) once a month in patients with CM, or 675 mg (3 separate SC injections of 225 mg, one after another) every 3 months, for the prevention of migraine in adults who have at least 4 migraine days per month.

### Methods

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

**Table 5: Inclusion Criteria for the Systematic Review**

| | |
|---|---|
| **Patient population** | Adult patients with migraine who have at least 4 migraine days per month<br><br>**Subgroups of interest:**<br>• Patients with episodic migraine (EM) who experience 14 or fewer headache days per month<br>• Patients with chronic migraine (CM) who experience 15 or more headache days per month<br>• Patients who have received ≥ 2 prior preventive migraine therapies<br>• Patients who have received < 2 prior preventive migraine therapies<br>• Patients who exhibit signs of medication overuse. Medication overuse is defined as use of simple analgesics (those without narcotics) for ≥ 15 days/month for ≥ 3 months, or other acute medications (triptans, combination analgesics, simple narcotics) for ≥ 9 days/month for ≥3 months |
| **Intervention** | Fremanezumab 225 mg (1 subcutaneous injection) once a month (monthly dosing), or<br>Fremanezumab 675 mg (3 separate subcutaneous injections of 225 mg, one after another) every 3 months (quarterly dosing) |
| **Comparators** | Pharmacologic interventions<br>• Erenumab<br>• Galcanezumab<br>• Onabotulinum toxin A (CM only)<br>• Beta-blockers (propranolol, metoprolol, atenolol, and bisoprolol)<br>• Anticonvulsants (topiramate, valproic acid)<br>• Tricyclics (amitriptyline) |

| | |
|---|---|
| | • Calcium-channel blockers (flunarizine)<br>• Angiotensin II receptor antagonists (candesartan)<br>• Other oral small molecule (pizotifen, gabapentin, divalproex, atogepant, frovatriptan, naratriptan)<br><br>Placebo |
| **Outcomes** | **Key outcomes:**<br>• Mean number and frequency of migraine days per month, changes from baseline[a]<br>• Mean number and frequency of headache days per month, changes from baseline[a]<br>• Migraine-related disability scores, as measured by the MIDAS<br>• Headache symptoms[a]<br>• Headache-related disability, as measured by the 6-item headache impact test (HIT-6)<br>• Health-related quality of life, as measured by validated scales (e.g., EQ-5D-5L, HRQoL, MSQoL)<br>• Acute headache pain medication intake<br>• Patient satisfaction, ease of use[a]<br>• Work productivity, loss of work days (e.g., Work Productivity and Activity Impairment scale)[a]<br>• Adherence<br>• Health care resource utilization (e.g., hospitalizations)[a]<br>• Reduction in medication use<br><br>**Harms outcomes:**<br>AEs, SAEs, WDAEs, AEs of special interest (e.g., injection-site reactions, anaphylaxis/hypersensitivity reactions, antibody formation, vascular events, constipation, development of hypertension) |
| **Study design** | Published and unpublished phase III and phase IV RCTs |

AE = adverse event; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; HRQoL = health-related quality of life; MIDAS = Migraine Disability Assessment Score; MSQoL = Migraine-Specific Quality of Life Questionnaire; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[28]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. 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 Ajovy (fremanezumab). Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

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 October 6, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on February 17, 2021.

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.[29] Health Technology Assessment

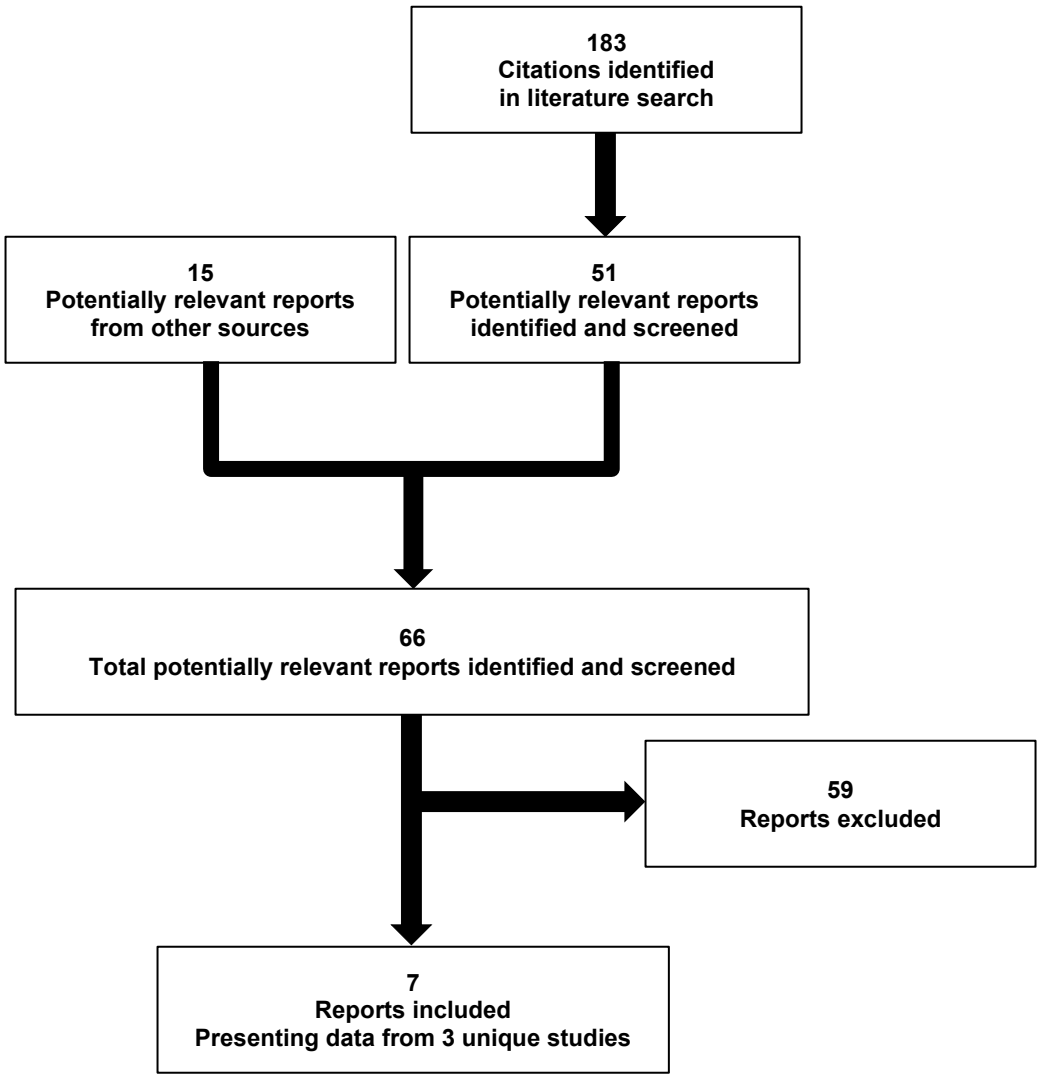
Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers. 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 CADTH 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 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

## Findings From the Literature

A total of 3 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 6. A list of excluded studies is presented in Appendix 2.

## Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



## Table 6: Details of Included Pivotal and Protocol Selected Studies

| | | HALO CM | HALO EM | FOCUS |
|---|---|---|---|---|
| DESIGNS AND POPULATIONS | **Study design** | DB RCT, placebo-controlled, multi-centre, parallel-group | DB RCT, placebo-controlled, multi-centre, parallel-group | DB RCT, placebo-controlled, multi-centre, parallel-group |
| | **Locations** | 132 centres: US, Canada, Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain | 123 sites: US, Canada, Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain | 98 centres: Canada, US, Europe |
| | **Randomized (N)** | 1,130 | 875 | 838 |
| | **Inclusion criteria** | • Adults ≥ 18 to ≤ 70 years of age<br>• Migraine onset at ≤ 50 years of age<br>• History of migraine (according to ICHD-3 criteria [Headache Classification Committee of the IHS 2013]) or clinical judgment suggests a migraine diagnosis for ≥ 12 months before screening<br>• Fulfills criteria for CM during the 28-day run-in period:<br>○ Headache occurring ≥ 15 days<br>○ Any of the following for ≥ 8 days: migraine with or without aura, probable migraine, use of a triptan or ergot<br>• Using ≤ 1 preventive medication for migraine or other medical conditions<br>• BMI between 17.5 and 37.5 kg/m$^2$ and total body weight between 45 and 120 kg, inclusive<br>• Nonchildbearing potential or use of contraception<br>• Approximately 85% adherence to the electronic headache diary during the run-in period by entry of headache data on minimum 24 of 28 days<br>• In good health, as determined by medical and psychiatric history, medical examination, 12-lead ECG, serum | • Adults ≥ 18 to ≤ 70 years of age<br>• Migraine onset at ≤ 50 years of age<br>• Patient has history of migraine (according to ICHD-3 criteria [Headache Classification Committee of the IHS 2013]) or clinical judgment suggests a migraine diagnosis for ≥ 12 months before screening<br>• Fulfills criteria for EM during the 28-day run-in period:<br>○ Headache occurring on ≥ 6 and ≤ 14 days during the 28-day run-in period<br>○ On ≥ 4 days, fulfilling any of the following: migraine with and without aura, probable migraine, use of a triptan or ergot<br>• Not using preventive medications or using ≤ 1 preventive medication for migraine or other medical conditions<br>• BMI of 17.5 to 37.5 kg/m$^2$ and a total body weight between 45 and 120 kg, inclusive<br>• Nonchildbearing potential or use of contraception<br>• Adherence to the electronic headache diary during the run-in period by entry of headache data on a minimum of 24 out of 28 days (approximately 85% diary adherence) | • Adults ≥ 18 to ≤ 70 years of age<br>• Migraine with onset at ≤ 50 years of age<br>• Patient has history of migraine (according to ICHD-3 criteria [Headache Classification Committee of the IHS 2013]) or clinical judgment suggests a migraine diagnosis for ≥ 12 months prior to screening<br>• For patients with CM:<br>○ Headache occurring on ≥ 15 days during the 28-day run-in period<br>○ On ≥ 8 days during the run-in period, the patient fulfills any of the following: migraine with or without aura, or probable migraine, use of a triptan or ergot to treat a headache<br>• For patients with EM:<br>○ Headache occurring on ≥ 6 and < 15 days during the 28-day run-in period<br>○ On ≥ 4 days during the run-in period, the patient fulfills any of the following: migraine with or without aura, probable migraine, use of a triptan or ergot to treat a headache<br>• Inadequate response to 2 to 4 classes of prior preventive migraine medications within the past 10 years (e.g., valproic acid, OnaA) |

| | | HALO CM | HALO EM | FOCUS |
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| | | chemistry, hematology, coagulation, and urinalysis | • In good health, as determined by a medical and psychiatric history, medical examination, 12-lead ECG, serum chemistry, hematology, coagulation, and urinalysis | • Body weight ≥ 45 kg and body mass index within the range 17.5 to 34.9 kg/m$^2$ (inclusive)<br>• Women who had no childbearing potential, as well as women with childbearing potential who were using effective birth control<br>• Adherence to the electronic headache diary during the run-in period on a minimum of 24 days (approximately 85% diary adherence)<br>• In good health, as determined by a medical and psychiatric history, medical examination, 12-lead ECG, serum chemistry, hematology, coagulation, and urinalysis |
| | **Exclusion criteria** | • Use of onabotulinum toxin A for migraine, medical, or cosmetic reasons, requiring injections in the head, face, or neck in 4 months before screening visit<br>• Use of medications containing opioids or barbiturates on > 4 days per month for migraine or any other reason<br>• Previously failed ≥ 2 of the following medications for treatment of EM or CM after use for ≥ 3 months:<br>○ Cluster A: divalproex sodium, sodium valproate<br>○ Cluster B: flunarizine, pizotifen<br>○ Cluster C: amitriptyline, nortriptyline, venlafaxine, duloxetine<br>○ Cluster D: atenolol, nadolol, metoprolol, propranolol, timolol<br>• Patient has used an intervention/device (e.g., scheduled nerve blocks and transcranial magnetic stimulation) for migraine within 2 months before screening | • Received onabotulinum toxin A for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck in prior 4 months before screening visit<br>• Using medications containing opioids or barbiturates on > 4 days per month for the treatment of migraine or for any other reason<br>• Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the following medications for treatment of EM or CM after use for at least 3 months at accepted migraine therapeutic doses:<br>○ Cluster A: divalproex sodium and sodium valproate<br>○ Cluster B: flunarizine and pizotifen<br>○ Cluster C: amitriptyline, nortriptyline, venlafaxine, and duloxetine<br>○ Cluster D: atenolol, nadolol, metoprolol, propranolol, and timolol | • Use of any preventive migraine medications for > 5 days and expected to continue with the medications<br>• Received onabotulinum toxin A for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck in prior 3 months before screening visit<br>• Used medications containing opioids or barbiturates on > 4 days during the run-in period for the treatment of migraine or for any other reason<br>• Used an intervention/device (e.g., scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the 2 months prior to screening<br>• Used triptans/ergots as preventive therapies for migraine<br>• Patient used NSAIDs as preventive therapy for migraine on nearly daily basis. Note: Low-dose Aspirin (e.g., 81 mg) used |

| | | HALO CM | HALO EM | FOCUS |
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| | | • Suffers from unremitting headaches (> 80% of awake time) and < 4 days without headache per month. Daily headache was acceptable if patient has headaches < 80% of the time they are awake on most days<br><br>Any of the following medical conditions or clinical findings:<br>• Clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, or clinical abnormality, at the discretion of the investigator<br>• Evidence or medical history of clinically significant psychiatric issues<br>• History of clinically significant cardiovascular disease or vascular ischemia or thromboembolic events<br>• Known infection or history of HIV, tuberculosis, or chronic hepatitis B or C infection<br>• History of cancer in the past 5 years, except non-melanoma skin carcinoma<br>• Pregnant or nursing women<br>• History of hypersensitivity reactions to injected proteins, including monoclonal antibodies<br>• Prior exposure to a monoclonal antibody targeting the CGRP pathway<br>• Hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) > 1.5 × ULN after confirmation in a repeat test or suspected hepatocellular damage that fulfills criteria for Hy's law | • Patient has used an intervention/device (e.g., scheduled nerve blocks and transcranial magnetic stimulation) for migraine within 2 months before screening.<br><br>Any of the following medical conditions or clinical findings:<br>• Clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, or clinical abnormality, at the discretion of the investigator<br>• Evidence or medical history of clinically significant psychiatric issues<br>• History of clinically significant cardiovascular disease or vascular ischemia or thromboembolic events, such as cerebrovascular accident, deep vein thrombosis, or pulmonary embolism<br>• Known infection or history of HIV, tuberculosis, or chronic hepatitis B or C infection<br>• History of cancer in the past 5 years, except non-melanoma skin carcinoma<br>• Pregnant or nursing women<br>• History of hypersensitivity reactions to injected proteins, including monoclonal antibodies<br>• Prior exposure to a monoclonal antibody targeting the CGRP pathway (AMG 334, ALD304, LY2951742, or fremanezumab)<br>• Hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) > 1.5 × ULN after confirmation in a repeat test or suspected | for cardiovascular disease prevention was allowed<br>• Patient suffered from unremitting headaches, defined as having headaches for > 80% of awake time, and < 4 days without headache per month. Daily headache was acceptable if patient has headaches < 80% of the time they are awake on most days<br><br>Any of the following medical conditions or clinical findings:<br>• Clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, or clinical abnormality, at the discretion of the investigator<br>• Evidence or medical history of clinically significant psychiatric issues, including major depression, panic disorder, or generalized anxiety disorder, any suicide attempt in the past or suicidal ideation with a specific plan the past 2 years before screening, or current suicidal ideation as measured by electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)<br>• History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological (e.g., cerebral ischemia), peripheral extremity ischemia, or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events), such as cerebrovascular accident (including transient ischemic attacks), |

| | | HALO CM | HALO EM | FOCUS |
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| | | • Serum creatinine > 1.5 × ULN, clinically significant proteinuria, or evidence of renal disease<br>• History of alcohol or drug abuse during the past 2 years or dependence during the past 5 years | hepatocellular damage that fulfills criteria for Hy's law<br>• Serum creatinine > 1.5 × ULN, clinically significant proteinuria, or evidence of renal disease<br>• History of alcohol or drug abuse during the past 2 years, or alcohol or drug dependence during the past 5 years | deep vein thrombosis, or pulmonary embolism<br>• History of HIV, tuberculosis, or chronic hepatitis B or C infection<br>• History of cancer, except non-melanoma skin carcinoma<br>• Pregnant or breastfeeding women, or women planning a pregnancy<br>• Prior exposure to a monoclonal antibody targeting the CGRP pathway (such as AMG334, ALD304, LY2951742, or fremanezumab)<br>• Hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) > 1.5 × ULN after confirmation in a repeat test or suspected hepatocellular damage that fulfilled criteria for Hy's law at screening<br>• Serum creatinine > 1.5 × ULN, clinically significant proteinuria, or evidence of renal disease at screening<br>• History of alcohol or drug abuse during the past 2 years or drug dependence during the past 5 years |
| Drugs | **Intervention** | Fremanezumab 675 mg as 3 active injections (225 mg/1.5 mL), followed by 2 monthly treatments of fremanezumab 225 mg as 1 active injection (225 mg/1.5 mL), or<br><br>Fremanezumab 675 mg as 3 active injections (225 mg/1.5 mL), followed by 2 monthly treatments of placebo as a single 1.5 mL injection | Fremanezumab 225 mg as 1 active injection (225 mg/1.5 mL), and 2 placebo injections (1.5 mL), followed by monthly treatments of 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL), or<br><br>Fremanezumab 675 mg as 3 active injections (225 mg/1.5 mL), followed by 2 monthly treatments of placebo as a single 1.5 mL injection | For patients with CM:<br>• Fremanezumab 675 mg as 3 active injections (225 mg/1.5 mL), followed by 2 monthly treatments of 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL), or<br>• Fremanezumab 675 mg as 3 active injections (225 mg/1.5 mL), followed by 2 monthly treatments of placebo as a single 1.5-mL injection. |

| | | HALO CM | HALO EM | FOCUS |
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| | | | | For patients with EM:<br>• Fremanezumab 225 mg as 3 active injections (225 mg/1.5 mL) plus 2 matching placebo injections, followed by 2 monthly treatments of 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL), or<br>• Fremanezumab 675 mg as 3 active injections (225 mg/1.5 mL), followed by 2 monthly treatments of placebo as a single 1.5-mL injection.<br><br>OLTP: All patients received 225 mg of fremanezumab monthly for 3 months |
| | **Comparator(s)** | Placebo group received three 1.5 mL placebo injections, followed by 2 monthly single 1.5 mL placebo injections | Placebo group received three 1.5 mL placebo injections, followed by 2 monthly single 1.5 mL placebo injection | DBTP:<br>Placebo group received three 1.5 mL placebo injections, followed by 2 monthly single 1.5 mL placebo injection.<br><br>OLTP:<br>No placebo arm |
| DURATION | **Phase** | | | |
| | Run-in | Screening visit with a 28-day run-in period | Screening visit with a 28-day run-in period | Screening visit and 28 days run-in period |
| | Double-blind | 12-week (84-day) treatment period | 12-week (84-day) treatment period | 12-week, double-blind, placebo-controlled treatment period |
| | Follow-up | EOT visit, approximately 4 weeks (28 days) after the final dose of study drug | EOT visit, approximately 4 weeks (28 days) after the final dose of study drug | 12-week OLTP; and a follow-up visit 6 months |
| OUTCOMES | **Primary end point** | Monthly average number of headache days of at least moderate severity | Change from baseline in the MMDs | Mean change from baseline in the average number of MMDs in the 12-week period after the initial dose of fremanezumab |
| | **Secondary and exploratory end points** | Secondary<br><br>*Efficacy*<br>• Mean change from baseline in the MMDs during the 12-week period after the first dose of study drug | Secondary<br><br>*Efficacy*<br>• Proportion of patients reaching at least 50% reduction in the MMDs during the | Secondary<br><br>*Efficacy*<br>• Proportion of patients reaching at least 50% reduction in the average number of monthly migraine days during the 12-week |

| | | HALO CM | HALO EM | FOCUS |
|---|---|---|---|---|
| | | • Proportion of patients reaching at least 50% reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the number of headache days of at least moderate severity during the 4-week period after the first dose of study drug<br>• Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug in patients not receiving concomitant migraine preventive medications<br>• Mean change from baseline (day 0) in HIT-6 score at 4 weeks after administration of the last (third) dose of study drug<br>• Evaluate immunogenicity and impact of antidrug antibodies on efficacy and safety during 12 weeks of treatment<br><br>*Safety*<br>• AEs, WDAEs<br>• Clinical laboratory values, vital signs, and 12-lead ECG findings, physical examination findings<br>• Injection-site assessment<br>• Suicidal ideations and behaviours (eC-SSRS scores)<br>• Concomitant medication use | 12-week period after the first dose of study drug<br>• Mean change from baseline in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the number of migraine days during the 4-week period after the first dose of the study drug<br>• Mean change from baseline in the MMDs during the 12-week period after the first dose of study drug in patients not receiving concomitant migraine preventive medications<br>• Mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (third) dose of study drug<br><br>*Safety*<br>• AEs, WDAEs<br>• Clinical laboratory values, vital signs, and 12-lead ECG findings<br>• Immunogenicity<br>• Local injection-site assessments<br>• Suicidal ideations and behaviours (eC-SSRS scores)<br>• Physical examination findings (including body weight measurements)<br>• Concomitant therapy or medication usage<br>• Evaluate immunogenicity and impact of antidrug antibodies on efficacy and safety during 12 weeks of treatment | period after the first dose of fremanezumab<br>• Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of fremanezumab<br>• Mean change from baseline in the MMDs during the 4-week period after the first dose of fremanezumab<br>• Proportion of patients reaching at least 50% reduction in the MMDs during the 4-week period after the first dose of fremanezumab<br>• Mean change from baseline in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of fremanezumab<br>• Mean change from baseline in the number of headache days of at least moderate severity during the 4-week period after the first dose of fremanezumab<br><br>*Safety*<br>• AEs, WDAEs<br>• Clinical laboratory values and vital signs<br>• Severe hypersensitivity/anaphylaxis reactions<br>• Suicidal ideations and behaviours<br><br>Exploratory<br>DBTP<br>• Proportion of patients reaching at least 75% reduction in the MMDs<br>• Proportion of patients reaching total (100%) response (no headache) |

| | | HALO CM | HALO EM | FOCUS |
|---|---|---|---|---|
| | | • Immunogenicity<br><br>Exploratory<br>• Mean change from baseline in the weekly number of headache days of at least moderate severity during the 4-week period after the first dose of study drug<br>• Proportion of patients reaching at least 75% reduction and total (100%) reduction in the monthly average number of headache days of at least moderate severity<br>• Proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of headache days of at least moderate severity during the 4-week period after the first dose of study drug for whom this level of effect is sustained throughout the 12-week period after the first dose of study drug<br>• Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug in patients who used topiramate for migraine in the past<br>• Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug in patients who used onabotulinum toxin A for migraine in the past<br>• Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 4-week period after the second dose of study drug | Exploratory<br>• Mean change from baseline in the number of headache days of at least moderate severity during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the weekly number of migraine days during the 4-week period after the first dose of study drug<br>• Proportion of patients reaching at least 75% reduction and total (100%) reduction in the MMDs during the 12-week period after the first dose of study drug<br>• Proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of migraine days during the 4-week period after the first dose of study drug for whom this level of effect is sustained throughout the 12-week period after the first dose of study drug<br>• Mean change from baseline in the MMDs during the 12-week period after the first dose of study drug in patients who used topiramate for migraine in the past<br>• Mean change from baseline in the number of migraine days during the 12-week period after the first dose of study drug for patients who used onabotulinum toxin A for migraine in the past<br>• Mean change from baseline in the number of migraine days during the 4-week period after the second dose of the study drug<br>• Mean change from baseline in the number of migraine days during the 4-week period after the last (third) dose of the study drug | During the 12-week period after the first dose of study drug:<br>• Proportion of patients reaching total (100%) response (no headache) for at least 1 month<br>• Mean change from baseline in the monthly average number of headache hours of at least moderate severity<br>• Proportion of patients reaching at least 50% reduction in the number of migraine days during the 4-week period after the first dose of study drug for whom this level of effect was sustained throughout<br>• Proportion of patients reaching at least 75% reduction in the number of migraine days during the 4-week period after the first dose of study drug for whom this level of effect was sustained throughout<br>• Mean change from baseline in the monthly average number of days with nausea or vomiting<br>• Mean change from baseline in the monthly average number of days with photophobia and phonophobia<br>• Mean change from baseline in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds)<br>• Mean change from baseline in the number of migraine days for patients who failed topiramate for migraine in the past<br>• Mean change from baseline in the number of migraine days for patients who failed onabotulinum toxin A for migraine in the past |

| | | HALO CM | HALO EM | FOCUS |
|---|---|---|---|---|
| | | • Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 4-week period after the last (third) dose of study drug<br>• Mean change from baseline in the monthly average number of headache days of any severity during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the MMDs during the 4-week period after each dose of study drug<br>• Mean change from baseline in the weekly number of migraine days during the 4-week period after the first dose of study drug<br>• Proportion of patients reaching at least 50% reduction, at least 75% reduction, and total (100%) reduction in the MMDs during the 12-week period after the first dose of study drug<br>• Proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of migraine days during the 4-week period after the first dose of study drug for whom this level of effect is sustained throughout the 12-week period after the first dose of study drug<br>• Mean change from baseline in the number of migraine days during the 12-week period after the first dose of study drug for patients not receiving concomitant preventive migraine medications<br>• Mean change from baseline in the number of migraine days during the 12-week period after the first dose of study | • Mean change from baseline in the monthly average number of headache days of any severity during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the number of headache days of at least moderate severity during the 4-week period after each dose of study drug<br>• Mean change from baseline in the weekly number of headache days of at least moderate severity during the 4-week period after the first dose of study drug<br>• Proportion of patients reaching at least 50% reduction, at least 75% reduction, and total (100%) reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug<br>• Proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of headache days of at least moderate severity during the 4-week period after the first dose of study drug for whom this level of effect is sustained throughout the 12-week period after the first dose of study drug<br>• Mean change from baseline in the number of headache days of at least moderate severity during the 12-week period after the first dose of study drug for patients not receiving concomitant migraine preventive medications<br>• Mean change from baseline in the number of headache days of at least moderate severity during the 12-week period after the first dose of study drug | • Mean change from baseline in the number of migraine days for patients who failed valproic acid for migraine in the past<br>• Mean change from baseline in the number of migraine days for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past<br>• Proportion of patients reaching at least 50% reduction in the MMDs for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past<br><br>At 4 weeks after administration of the third dose of study drug:<br>• Mean change from baseline (day 0) in disability score, as measured by the HIT-6<br>• Mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire<br>• Mean change from baseline (day 0) in quality of life, as measured by the MSQoL questionnaire<br>• Mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire<br>• Mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9<br>• Mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire<br>• Mean change from baseline (day 0) of patient satisfaction, as measured by the PGIC scale |

| | | HALO CM | HALO EM | FOCUS |
|---|---|---|---|---|
| | | drug for patients who used topiramate for migraine in the past<br>• Mean change from baseline in the number of migraine days during the 12-week period after the first dose of study drug for patients who used onabotulinum toxin A for migraine in the past<br>• Mean change from baseline in the monthly average number of headache hours of any severity during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the monthly average number of headache hours of at least moderate severity during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the monthly average number of days with nausea or vomiting during the 12-week period after the first dose of the study drug<br>• Mean change from baseline in the monthly average number of days with photophobia and phonophobia during the 12-week period after the first dose of study drug<br>• Mean change from baseline (day 0) in quality of life, as measured by the MSQoL questionnaire, at 4 weeks after administration of the last (third) dose of study drug | for patients who used topiramate for migraine in the past<br>• Mean change from baseline in the number of headache days of at least moderate severity during the 12-week period after the first dose of study drug for patients who used onabotulinum toxin A for migraine in the past<br>• Mean change from baseline in the monthly average number of headache hours of any severity during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the monthly average number of headache hours of at least moderate severity during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the monthly average number of days with nausea or vomiting during the 12-week period after the first dose of study drug<br>• Mean change from baseline in the monthly average number of days with photophobia and phonophobia during the 12-week period after the first dose of study drug questionnaire<br>• Mean change from baseline (day 0) in quality of life, as measured by the MSQoL questionnaire, at 4 weeks after administration of the last (third) dose of study drug | OLTP<br>• Change from baseline in the mean monthly number of migraine days<br><br>During the 12-week period after the fourth dose of study drug:<br>• Proportion of patients reaching at least 50% reduction from baseline in the MMDs<br>• Mean change from baseline in the monthly average number of headache days of at least moderate severity<br>• Mean change from baseline in the monthly average number of days of use of any acute headache medications<br>• Proportion of patients reaching at least 75% reduction from baseline in the MMDs<br>• Proportion of patients reaching total (100%) response (no headache)<br>• Proportion of patients reaching total (100%) response (no headache) for at least 1 month<br>• Mean change from baseline in the monthly average number of headache hours of at least moderate severity<br>• Proportion of patients reaching at least 50% reduction from baseline in the number of migraine days during the 4-week period after the fourth dose of study drug for whom this level of effect was sustained throughout<br>• Proportion of patients reaching at least 75% reduction from baseline in the number of migraine days during the 4-week period after the fourth dose of study drug for whom this level of effect was sustained throughout |

| | | HALO CM | HALO EM | FOCUS |
|---|---|---|---|---|
| | | • Mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire, at 4 weeks after administration of the last (third) dose of study drug<br>• Mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and the PHQ-9, at 4 weeks after administration of the last (third) dose of study drug<br>• Mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at 4 weeks after administration of the last (third) dose of study drug<br>• Assessment of patient satisfaction, as measured by the PGIC scale, at 4 weeks after administration of the first dose of study drug, at 4 weeks after administration of the second dose of study drug, and at 4 weeks after administration of the last (third) dose of study drug | • Mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire at 4 weeks after administration of the last (third) dose of study drug<br>• Mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9, at 4 weeks after administration of the last (third) dose of study drug<br>• Mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at 4 weeks after administration of the last (third) dose of study drug<br>• Assessment of patient satisfaction, as measured by the PGIC scale, at 4 weeks after administration of the first dose of study drug, at 4 weeks after the second dose of study drug, and at 4 weeks after the last (third) dose of study drug | • Mean change from baseline in the monthly average number of days with nausea or vomiting<br>• Mean change from baseline in the monthly average number of days with photophobia and phonophobia<br>• Mean change from baseline in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds)<br>• Mean change from baseline in the number of migraine days for patients who failed topiramate for migraine in the past<br>• Mean change from baseline in the number of migraine days for patients who failed onabotulinum toxin A for migraine in the past<br>• Mean change from baseline in the number of migraine days for patients who failed valproic acid for migraine in the past<br>• Mean change from baseline in the number of migraine days for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past<br>• Proportion of patients reaching at least 50% reduction from baseline in the MMDs for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past<br><br>At 4 weeks after administration of the sixth dose of study drug:<br>• Mean change from baseline (day 0) in disability score, as measured by the HIT-6 |

| | | HALO CM | HALO EM | FOCUS |
|---|---|---|---|---|
| | | | | • Mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire<br>• Mean change from baseline (day 0) in quality of life, as measured by the MSQoL questionnaire<br>• Mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire<br>• Mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9<br>• Mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire<br>• Mean change from baseline (day 0) of patient satisfaction, as measured by the PGIC scale |
| NOTES | **Publications** | Silberstein et al. (2017)[30] | Dodick et al. (2018)[31] | Ferrari et al. (2019)[32] |

AE = adverse event; BMI = body mass index; CGRP = calcitonin gene–related peptide; CM = chronic migraine; DB = double-blind; DBTP = double-blind treatment period; ECG = electrocardiogram; EOT = end of treatment; EM = episodic migraine; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; HIT-6 = 6-item headache impact test; ICHD-3 = International Classification of Headache Disorders, third edition; IHS = International Headache Society; MIDAS = migraine disability assessment score; MMD = monthly migraine day; MSQoL = Migraine-Specific Quality of Life Questionnaire; NSAID = nonsteroidal anti-inflammatory drug; OLTP = open-label treatment period; PGIC = Patients' Global Impression of Change; PHQ = Patient Health Questionnaire; RCT = randomized controlled trial; ULN = upper limit of the normal range; WDAE = withdrawal due to adverse events; WPAI = Work Productivity and Activity Impairment.

Note: The baseline period of the DBTP refers to the 28-day run-in period. Two additional reports were included (Health Canada reviewer's report and sponsor's submission).[15,33]

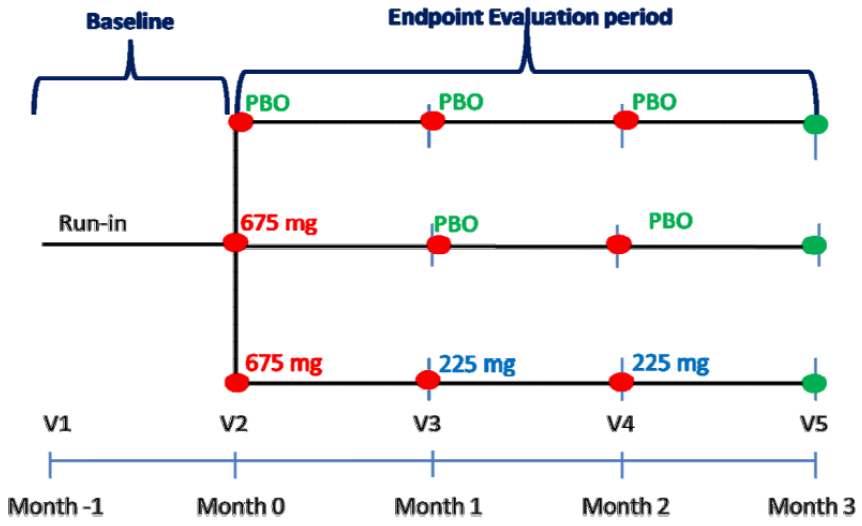
Source: Silberstein et al. (2017),[30] Dodick et al. (2018),[31] Ferrari et al. (2019),[32] and Clinical Study Reports for HALO CM,[17] HALO EM,[18] and FOCUS.[19]

## Description of Studies

Three phase III, multinational, double-blind, randomized, placebo-controlled trials funded by the sponsor are included in the Systematic Review section of this report. HALO CM (N = 1,130, 1:1:1 ratio, fremanezumab 675 mg/225 mg/225 mg and fremanezumab 675 mg/placebo/placebo, and placebo) (Table 6 and Figure 2) was conducted in patients with CM.[17] A total of 132 centres participated, including sites in the US, Canada, Czech Republic, Finland, Israel, Poland, Russia, and Spain. Randomization was performed using electronic IRT. Patients were stratified based on sex, country, and baseline preventive migraine medication use (yes, no). There was no stratification by baseline frequency of migraines or headaches. The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses), and patients were blinded to treatment assignment. The primary objectives of this study were to demonstrate the efficacy of 2 dosage regimens of fremanezumab, as assessed by the decrease in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug relative to the baseline period; and to evaluate the safety and tolerability of 2 dosage regimens of fremanezumab in the preventive treatment of CM.

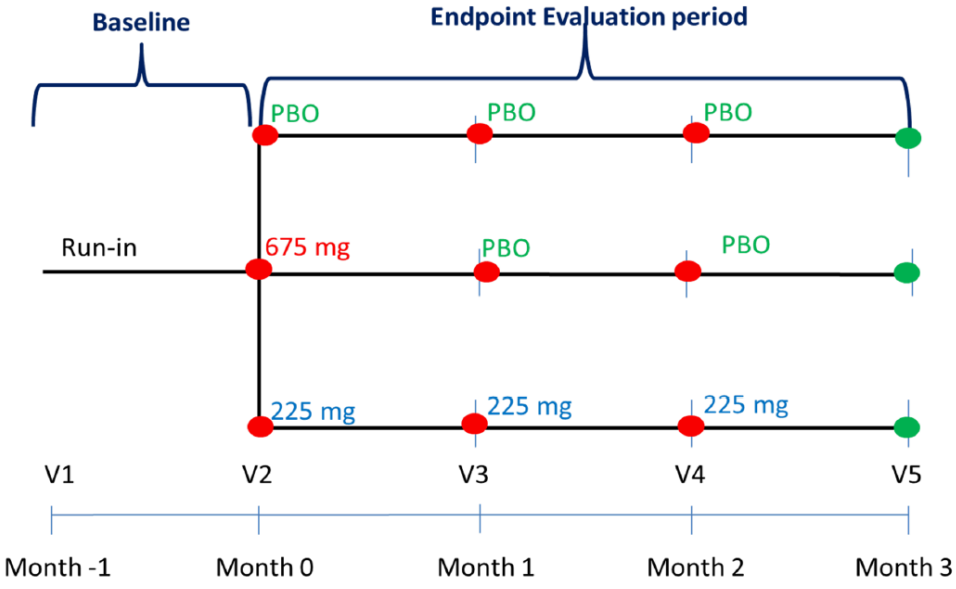
HALO EM (N = 875, 1:1:1 ratio, fremanezumab 675 mg/225 mg/225 mg and fremanezumab 675 mg/placebo/placebo, and placebo) (Table 6 and Figure 3) was conducted in patients with EM.[18] A total of 123 centres participated in the US, Canada, Czech Republic, Finland, Israel, Poland, Russia, and Spain. The double-blind treatment period lasted 12 weeks. Patients were randomized with stratification based on sex, country, and baseline preventive migraine medication use. Patients were stratified based on sex, country, and baseline preventive migraine medication use (yes, no). There was no stratification by baseline frequency of migraines or headaches. Treatment groups were assigned by IRT. The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses), and patients were blinded to treatment assignment. The primary objectives of this study were to demonstrate the efficacy of 2 dosage regimens of fremanezumab, as assessed by the decrease in MMDs during the 12-week period after the first dose of study drug relative to the baseline period; and to evaluate the safety and tolerability of 2 dosage regimens of fremanezumab in the preventive treatment of EM.

## Figure 2: Overall Study Schema of HALO CM




PBO = placebo; V = visit.
Note: Baseline refers to the 28-day run-in period for headache variables and visit 2 (day 0) for all other variables.
Source: Clinical Study Report for HALO CM.[17]

## Figure 3: Overall Study Schema of HALO EM



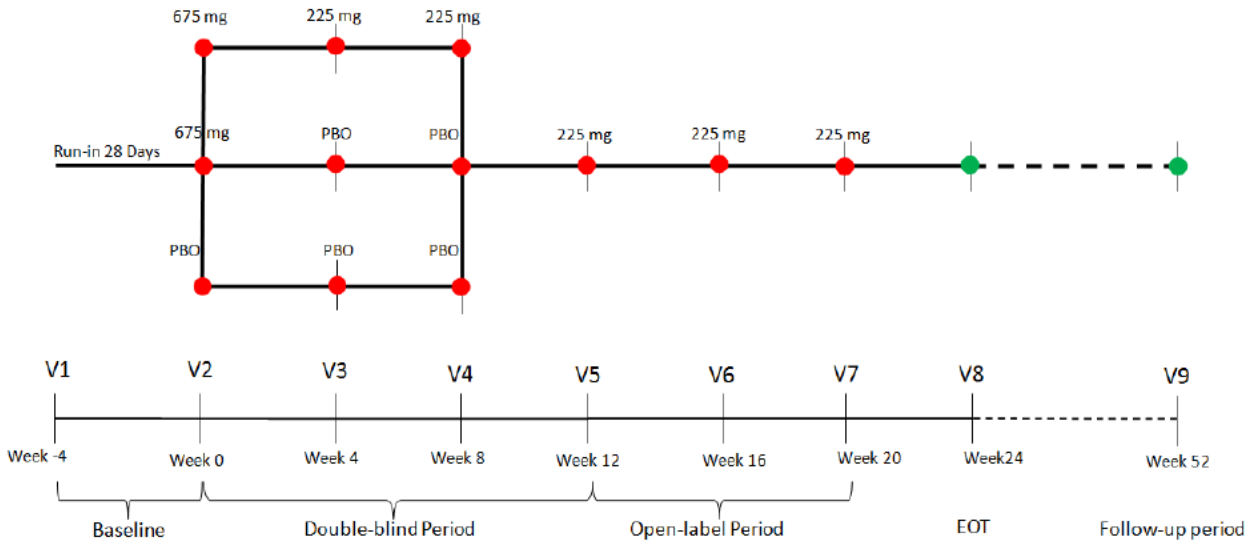

PBO = placebo; V = visit.
Note: Baseline refers to the 28-day run-in period for headache variables and visit 2 (day 0) for all other variables.
Source: Clinical Study Reports for HALO EM.[18]

In FOCUS (N = 838), patients with EM or CM were randomized 1:1:1 to either monthly fremanezumab (675 mg/225 mg/225 mg in patients with CM or 225 mg/225 mg/225 mg in patients with EM), fremanezumab 675 mg/placebo/placebo, or placebo.[19] The primary objective of the study was to demonstrate the efficacy of fremanezumab, as compared with placebo, administered as monthly and quarterly SC injections in adult patients with migraine and with documented inadequate response to 2 to 4 classes of prior preventive treatments. A total of 98 centres with sites in Canada, US, and Europe participated. FOCUS included a double-blind 12-week treatment period, followed by a 12-week open-label period, with patients followed for up to 46 weeks. Randomization into the DBTP was stratified based on CM or EM, sex, country, and a special treatment failure group, defined as patients who had documented inadequate response to valproic acid. Patient were allocated to treatment groups using IRT.

The objective of the open-label period was to provide the placebo-treated patients from the double-blind period with the opportunity to receive fremanezumab, and to provide longer-term efficacy and tolerability data.

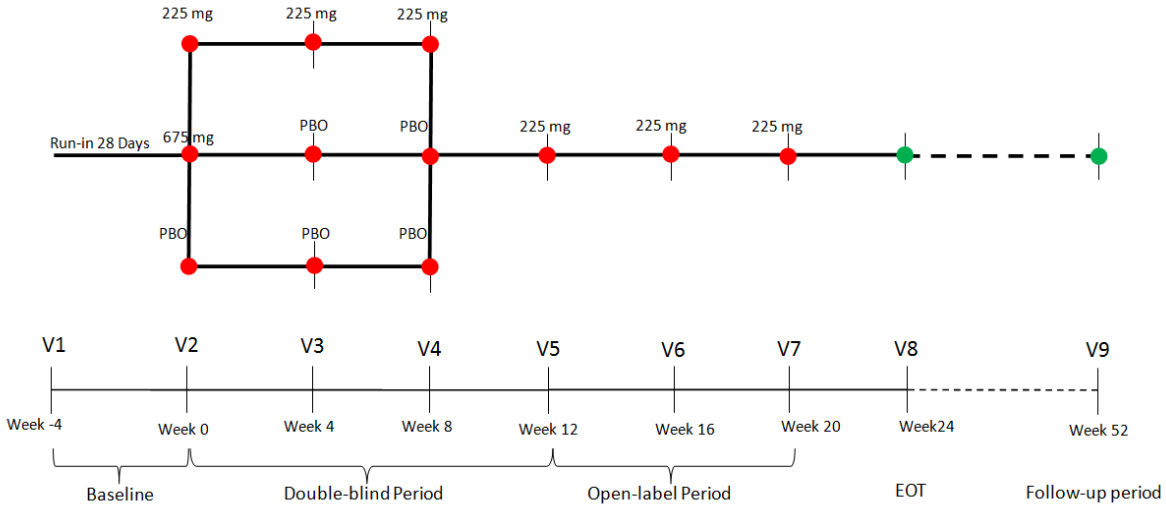
All 3 studies included a 28-day run-in period to ensure electronic headache diary adherence and to collect baseline measurements. In the FOCUS study, at least 75% adherence was needed for randomization. The HALO CM and HALO EM studies required at least 85% compliance for eligibility and randomization.

## Figure 4: Overall Study Schema for FOCUS — Patients With CM




CM = chronic migraine; EOT = end of treatment; PBO = placebo; V = visit.
Note: Baseline refers to the 28-day run-in period for headache variables and visit 2 (day 0) for all other variables.
Source: Clinical Study Reports for FOCUS.[19]

## Figure 5: Overall Study Schema for FOCUS — Patients With EM




EM = episodic migraine; EOT = end of treatment; PBO = placebo; V = visit.
Note: Baseline refers to the 28-day run-in period for headache variables and visit 2 (day 0) for all other variables.
Source: Clinical Study Report for FOCUS.[19]

### Populations

#### *Inclusion and Exclusion Criteria*

All 3 studies enrolled adults with a history of migraine for at least 1 year, according to the ICHD-3 classification system (Table 6). In all studies, adults aged 18 to 70 years were included. All studies excluded patients older than 50 years at first onset of migraine. In HALO CM and FOCUS, patients with CM were defined as those having at least 8 migraine days and at least 15 headache days per month. In HALO EM and FOCUS, patients with EM were defined as those having headache between 6 and 14 days per month and at least 4 MMDs. FOCUS additionally stipulated that patients must have failed 2 to 4 classes of prior preventive migraine therapies (e.g., valproic acid, OnaA) within the previous 10 years. HALO CM and HALO EM excluded patients who had failed 2 or more clusters of migraine prophylaxis medications (cluster A: divalproex sodium and sodium valproate; cluster B: flunarizine and pizotifen; cluster C: amitriptyline, nortriptyline, venlafaxine, and duloxetine; cluster D: atenolol, nadolol, metoprolol, propranolol, and timolol).

The 3 studies excluded patients who received OnaA for migraine or other medical or cosmetic reasons in the head, face, or neck in the 4 months (HALO CM and HALO EM) or 3 months (FOCUS) before the study, or who had a history (within 12 months) of cardiovascular or cerebrovascular disease, or psychiatric issues.

#### *Baseline Characteristics*

In the HALO studies, the mean age of enrolled patients was between 40 and 43 years, and most patients were women (> 80%) and White (> 75%) (Table 7). Patients enrolled in FOCUS had a mean age of 45 to 47 years, a similar proportion of women, and a greater proportion of participants who were White (> 93%) (Table 8). Patients had migraine for

approximately 20 years, on average, in HALO CM and HALO EM, with patients in FOCUS having migraines for approximately 24 years, on average.

For all studies, for efficacy outcomes derived from headache information collected using the electronic headache diary, “baseline” referred to the 28-day run-in period. If the run-in period was greater or less than 28 days, the baseline values for calculating the change from baseline of the monthly values of the efficacy outcomes were normalized to 28 days. Patients enrolled in FOCUS had a mean of approximately 14 MMDs, which involved patients with CM, with an average of 17 MMDs, and patients with EM, with an average of 9 MMDs. Approximately 85% of patients in FOCUS had reported higher triptan or ergot use during baseline compared with approximately 50% in the HALO studies. Previous OnaA use was reported in 15% of patients in HALO CM and 5% of patients in HALO EM. The majority of patients in FOCUS (> 47%) had failed 2 prior classes of preventive migraine therapies. Baseline for all other efficacy outcomes and safety outcomes was the last observation before the first dose of study drug.

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

## Table 7: Summary of Baseline Characteristics of HALO CM and HALO EM — ITT Analysis

| | HALO CM | | | HALO EM | | |
|---|---|---|---|---|---|---|
| **Baseline characteristics** | **Fremanezumab 675 mg/225 mg/225 mg (N = 379)** | **Fremanezumab 675 mg/PB/PB (N = 376)** | **Placebo (N = 375)** | **Fremanezumab 225 mg/225 mg/225 mg (N = 290)** | **Fremanezumab 675 mg/PB/PB (N = 291)** | **Placebo (N = 294)** |
| **Age, years** | | | | | | |
| n | 379 | 376 | 375 | 290 | 291 | 294 |
| Mean (SD) | 40.6 (11.95) | 42.0 (12.37) | 41.4 (12.03) | 42.9 (12.67) | 41.1 (11.41) | 41.3 (12.04) |
| **Sex, n (%)** | | | | | | |
| Male | 49 (13) | 45 (12) | 45 (12) | 46 (16) | 40 (14) | 47 (16) |
| Female | 330 (87) | 331 (88) | 330 (88) | 244 (84) | 251 (86) | 247 (84) |
| **Race, n (%)** | | | | | | |
| White | 297 (78) | 293 (78) | 303 (81) | 243 (84) | 232 (80) | 225 (77) |
| Black | 37 (10) | 33 (9) | 29 (8) | 18 (6) | 28 (10) | 40 (14) |
| Asian | 41 (11) | 40 (11) | 40 (11) | 25 (9) | 27 (9) | 25 (9) |
| American Indian or Alaskan Native | 2 (< 1) | 4 (1) | 0 | 3 (1) | 1 (< 1) | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 2 (< 1) | 1 (< 1) | 0 | 1 (< 1) | 0 |
| Other | 2 (< 1) | 4 (1) | 2 (< 1) | 1 (< 1) | 2 (< 1) | 4 (1) |
| **Weight (kg)** | | | | | | |
| n | 377 | 376 | 375 | 290 | 291 | 294 |
| Mean (SD) | 72.5 (16.36) | 72.4 (15.79) | 72.6(15.58) | 72.1 (15.77) | 74.2 (15.42) | 75.3 (16.01) |
| Median (min, max) | 69.8 (44, 119) | 70.5 (45, 132) | 71.2 (45, 119) | 69.3 (45, 119) | 73.0 (45, 120) | 74.3 (43, 118) |
| **Time since initial migraine diagnosis (years)** | | | | | | |
| n | 379 | 376 | 375 | 290 | 291 | 294 |
| Mean (SD) | 20.1 (11.98) | 19.7 (12.84) | 19.9(12.86) | 20.7 (12.85) | 20.0 (12.14) | 19.9 (11.87) |
| Median (min, max) | 18.0 (1, 55) | 18.0 (1, 61) | 17.0 (1, 57) | 19.0 (0, 58) | 19.0 (1, 65) | 17.5 (1, 51) |

| | HALO CM | | | HALO EM | | |
|---|---|---|---|---|---|---|
| **Baseline characteristics** | **Fremanezumab 675 mg/225 mg/225 mg (N = 379)** | **Fremanezumab 675 mg/PB/PB (N = 376)** | **Placebo (N = 375)** | **Fremanezumab 225 mg/225 mg/225 mg (N = 290)** | **Fremanezumab 675 mg/PB/PB (N = 291)** | **Placebo (N = 294)** |
| **Preventive medication use during baseline period, n (%)** | | | | | | |
| Yes | 85 (22) | 77 (20) | 77 (21) | 62 (21) | 58 (20) | 62 (21) |
| No | 294 (78) | 299 (80) | 298 (79) | 228 (79) | 233 (80) | 232 (79) |
| **Previous topiramate use for migraine, n (%)** | | | | | | |
| Yes | 117 (31) | 106 (28) | 117 (31) | 64 (22) | 51 (18) | 53 (18) |
| No | 262 (69) | 270 (72) | 258 (69) | 226 (78) | 240 (82) | 241 (82) |
| **Previous onabotulinumtoxin A use for migraine, n (%)** | | | | | | |
| Yes | 50 (13) | 66 (18) | 49 (13) | 16 (6) | 15 (5) | 9 (3) |
| No | 329 (87) | 310 (82) | 326 (87) | 274 (94) | 276 (95) | 285 (97) |
| **Triptans/ergots use during baseline period, n (%)** | | | | | | |
| Yes | 187 (49) | 208 (55) | 192 (51) | 148 (51) | 152 (52) | 137 (47) |
| No | 192 (51) | 168 (45) | 183 (49) | 142 (49) | 139 (48) | 157 (53) |
| **Any acute headache medication use during baseline period, n (%)** | | | | | | |
| Yes | 360 (95) | 359 (95) | 358 (95) | 279 (96) | 281 (97) | 280 (95) |
| No | 19 (5) | 17 (5) | 17 (5) | 9 (3) | 10 (3) | 13 (4) |
| Missing | NR | NR | NR | 2 (< 1) | 0 | 1 (< 1) |
| **Total number of headache days of any duration and any severity** | | | | | | |
| n | 379 | 376 | 375 | 288 | 291 | 293 |

| Baseline characteristics | HALO CM | | | HALO EM | | |
|---|---|---|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg (N = 379) | Fremanezumab 675 mg/PB/PB (N = 376) | Placebo (N = 375) | Fremanezumab 225 mg/225 mg/225 mg (N = 290) | Fremanezumab 675 mg/PB/PB (N = 291) | Placebo (N = 294) |
| Mean (SD) | 20.3 (4.26) | 20.4 (3.93) | 20.3 (4.19) | 11.0 (2.49) | 11.1 (2.42) | 11.2 (2.45) |
| Median (min, max) | 19.0 (8, 28) | 20.0 (13, 28) | 19.3 (11, 28) | 11.2 (6, 17) | 11.0 (6, 18) | 11.7 (6, 16) |
| **Number of headache days of at least moderate severity** | | | | | | |
| n | 379 | 376 | 375 | 288 | 291 | 293 |
| Mean (SD) | 12.8 (5.80) | 13.2 (5.47) | 13.3 (5.82) | 6.8 (2.90) | 7.2 (3.14) | 6.9 (3.12) |
| Median (min, max) | 12.0 (0, 28) | 13.0 (1, 28) | 12.6 (0, 28) | 6.5 (0, 15) | 7.0 (0, 16) | 7.0 (0, 15) |
| **Number of migraine days** | | | | | | |
| n | 379 | 376 | 375 | 288 | 291 | 293 |
| Mean (SD) | 16.0 (5.19) | 16.2 (4.88) | 16.4 (5.15) | 8.9 (2.63) | 9.3 (2.65) | 9.1 (2.65) |
| Median (min, max) | 15.4 (5, 28) | 15.9 (7, 28) | 15.5 (7, 28) | 9.0 (3, 16) | 9.0 (4, 17) | 9.0 (4, 15) |
| **Number of headache hours of any severity** | | | | | | |
| n | 379 | 376 | 375 | 288 | 291 | 293 |
| Mean (SD) | 129.0 (88.62) | 119.1 (73.23) | 127.2 (86.03) | 57.1 (30.04) | 57.1 (29.97) | 55.7 (26.47) |
| Median (min, max) | 108.0 (21, 672) | 104.1 (24, 672) | 103.6 (22, 672) | 51.7 (9, 211) | 50.0 (8, 206) | 50.0 (9, 192) |
| **Number of headache hours of at least moderate severity** | | | | | | |
| n | 379 | 376 | 375 | 288 | 291 | 293 |
| Mean (SD) | 68.0 (53.88) | 66.4 (58.83) | 68.5 (57.03) | 31.7 (23.65) | 33.3 (25.41) | 31.6 (23.21) |
| Median (min, max) | 52.4 (0, 494) | 54.0 (0, 672) | 52.0 (0, 454) | 26.2 (0, 190) | 27.0 (0, 179) | 26.1 (0, 178) |
| **Number of days of use of any acute headache medications** | | | | | | |
| n | 379 | 376 | 375 | 288 | 291 | 293 |
| Mean (SD) | 13.1 (7.20) | 13.1 (6.79) | 13.0 (6.92) | 7.7 (3.37) | 7.8 (3.74) | 7.7 (3.60) |
| Median (min, max) | 13.6 (0, 28) | 14.0 (0, 28) | 13.5 (0, 28) | 7.7 (0, 15) | 8.0 (0, 16) | 8.0 (0, 15) |

| | HALO CM | | | HALO EM | | |
|---|---|---|---|---|---|---|
| **Baseline characteristics** | **Fremanezumab 675 mg/225 mg/225 mg (N = 379)** | **Fremanezumab 675 mg/PB/PB (N = 376)** | **Placebo (N = 375)** | **Fremanezumab 225 mg/225 mg/225 mg (N = 290)** | **Fremanezumab 675 mg/PB/PB (N = 291)** | **Placebo (N = 294)** |
| **Number of days of use of migraine-specific acute headache medications** | | | | | | |
| n | 187 | 208 | 192 | 148 | 152 | 137 |
| Mean (SD) | 11.1 (5.99) | 11.3 (6.18) | 10.7 (6.30) | 6.1 (3.09) | 6.6 (3.07) | 7.1 (2.99) |
| Median (min, max) | 10.3 (1, 27) | 11.0 (1, 28) | 10.0 (1, 28) | 6.0 (1, 14) | 7.0 (1, 14) | 7.0 (1, 14) |
| **Headache impact test (HIT-6) score** | | | | | | |
| n | 377 | 370 | 373 | NR | NR | NR |
| Mean (SD) | 64.6 (4.42) | 64.3 (4.74) | 64.1 (4.80) | NR | NR | NR |
| Median (min, max) | 64.0 (50, 78) | 65.0 (42, 78) | 64.0 (48, 78) | NR | NR | NR |
| **Migraine disability assessment score (MIDAS)** | | | | | | |
| n | NR | NR | NR | 287 | 287 | 290 |
| Mean (SD) | NR | NR | NR | 38.0 (33.19) | 41.7 (32.96) | 37.3 (27.59) |
| Median (min, max) | NR | NR | NR | 33.0 (0, 306) | 33.0 (0, 206) | 32.5 (0, 156) |

CM = chronic migraine; EM = episodic migraine; ITT = intention-to-treat; max = maximum; min = minimum; NR = not reported; PB = placebo; SD = standard deviation.

Note: Baseline values refer to the 28-day run-in period.
Source: Clinical Study Reports for HALO CM,[17] HALO EM,[18] and FOCUS.[19]

## Table 8: Summary of Baseline Characteristics of FOCUS: Double-Blind Safety Analysis Set

| | FOCUS | | |
|---|---|---|---|
| **Baseline characteristics** | **Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 285)** | **Fremanezumab 675 mg/PB/PB (N = 276)** | **Placebo (N = 277)** |
| **Age, years** | | | |
| n | 285 | 276 | 277 |
| Mean (SD) | 46.0 (11.03) | 45.8 (10.97) | 46.8 (11.13) |
| **Sex, n (%)** | | | |
| Men | 45 (16) | 47 (17) | 46 (17) |
| Women | 240 (84) | 229 (83) | 231 (83) |
| **Race, n (%)** | | | |
| White | 264 (93) | 262 (95) | 260 (94) |
| Black or African-American | 4 (1) | 2 (< 1) | 2 (< 1) |
| Asian | 3 (1) | 0 (0) | 1 (< 1) |
| American Indian or Alaskan Native | 1 (< 1) | 0 (0) | 0 (0) |
| Native Hawaiian or other Pacific Islander | 0 (0) | 0 (0) | 0 (0) |
| Other | 1 (< 1) | 2 (< 1) | 1 (< 1) |
| Not reported | 12 (4) | 10 (4) | 13 (5) |
| **Weight, kg** | | | |
| n | 285 | 276 | 277 |
| Mean (SD) | 70.89 (13.68) | 70.68 (13.44) | 71.51 (13.75) |
| **Time since initial migraine diagnosis (years)** | | | |
| n | 285 | 275 | 277 |
| Mean (SD) | 24.1 (13.68) | 24.3 (12.83) | 24.2 (13.64) |

| Baseline characteristics | FOCUS | | |
|---|---|---|---|
| | Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 285) | Fremanezumab 675 mg/PB/PB (N = 276) | Placebo (N = 277) |
| **Migraine classification (as randomized), n (%)** | | | |
| Episodic | 111 (39) | 107 (39) | 111 (40) |
| Chronic | 174 (61) | 169 (61) | 166 (60) |
| **Migraine classification (as per CRF), n (%)** | | | |
| Episodic | 112 (39) | 109 (39) | 111 (40) |
| Chronic | 173 (61) | 167 (61) | 166 (60) |
| **Migraine preventive medications failed in the past 10 years, n (%)** | | | |
| Beta-blockers | 167 (59) | 146 (53) | 158 (57) |
| Anticonvulsants | 218 (76) | 213 (77) | 184 (66) |
| Tricyclics | 127 (45) | 124 (45) | 137 (49) |
| Flunarizine | 46 (16) | 41 (15) | 58 (21) |
| Candesartan | 46 (16) | 53 (19) | 51 (18) |
| Onabotulinumtoxin A | 71 (25) | 75 (27) | 76 (27) |
| Valproic acid | 92 (32) | 86 (31) | 83 (30) |
| **Triptans/ergots use during baseline, n (%)** | | | |
| Yes | 247 (87) | 235 (85) | 236 (85) |
| No | 38 (13) | 41 (15) | 41 (15) |
| **Prior preventive medications failed, n (%)** | | | |
| 2 | 134 (47) | 140 (51) | 141 (51) |

| | FOCUS | | |
|---|---|---|---|
| **Baseline characteristics** | **Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 285)** | **Fremanezumab 675 mg/PB/PB (N = 276)** | **Placebo (N = 277)** |
| 3 | 99 (35) | 85 (31) | 81 (29) |
| 4 | 50 (18) | 49 (18) | 54 (19) |
| **Headache impact test (HIT-6) score** | | | |
| n | 283 | 275 | 278 |
| Mean (SD) | 63.9 (4.47) | 64.2 (4.28) | 64.1 (4.95) |

CRF = Case Report Form; PB = placebo; SD = standard deviation.

Note: Fremanezumab monthly is 675 mg/225 mg/225 mg for patients with CM and 225 mg/225 mg/225 mg for patients with EM. Fremanezumab quarterly is 675 mg/placebo/placebo for both CM and Patients with EM.

Note: Other = Persian Arabic (1), White (Amerindian) (1), Gypsy (1), and Maghrebin (1). Baseline values refer to the 28-day run-in period.

Source: Clinical Study Reports for HALO CM,[17] HALO EM,[18] and FOCUS.[19]

## Interventions

In HALO CM and HALO EM, blinded treatment was administered by qualified study personnel as SC injections approximately every 28 days for a total of 3 doses. In HALO CM, patients who were randomized (1:1:1) to receive fremanezumab 675 mg/225 mg/225 mg received 675 mg of fremanezumab as 3 active injections at visit 2 and 225 mg of fremanezumab as 1 active injection at visits 3 and 4. In HALO EM, patients who were randomized (1:1:1) to receive fremanezumab 225 mg/225 mg/225 mg received 225 mg of fremanezumab as 1 active injection along with 2 placebo injections at visit 2 and 225 mg of fremanezumab as 1 active injection at visits 3 and 4. For both studies, patients who were randomized to receive fremanezumab 675 mg/placebo/placebo received 675 mg of fremanezumab as 3 active injections at visit 2 and placebo as a single 1.5 mL injection at visits 3 and 4. For both studies, patients who were randomized to receive placebo received three 1.5 mL placebo injections at visit 2 and a single 1.5 mL placebo injection at visits 3 and 4. The 4-week (28-day) period was determined relative to the planned dosing day, provided the patient returned to the study centre within 3 days. If the patient returned to the study centre more than 3 days late, then the 4-week period was determined from the actual dosing day rather than the planned dosing day.

For the DBTP of FOCUS, patients were randomly assigned to a treatment group with fremanezumab (2 different dosage regimens) or placebo in a 1:1:1 ratio at the baseline visit (visit 2). For patients with CM, the dosage regimen was SC administration of fremanezumab 675 mg at visit 2 followed by monthly SC administration of fremanezumab 225 mg for 2 months, or SC administration of fremanezumab 675 mg at visit 2 followed by monthly SC administration of matching placebo for 2 months, or 3 monthly doses of matching placebo. For patients with EM, the dosage regimen was SC administration of fremanezumab 225 mg plus 2 matching placebo injections as a first dose followed by monthly SC administration of fremanezumab 225 mg for 2 months, or SC administration of fremanezumab 675 mg as a first dose followed by monthly SC administration of matching placebo for 2 months, or 3 monthly doses of matching placebo. After visit 4, all patients completing the double-blind period entered the open-label period. All patients (CM and EM) received SC administration of fremanezumab 225 mg monthly for 3 months (visits 5, 6, and 7). The open-label period was not randomized, as all patients received the same monthly dose (fremanezumab 225 mg). The open-label treatment was administered for a total of 3 doses (visits 5, 6, and 7). Final study assessments were performed at visit 8 (end-of-treatment [EOT] visit), approximately 4 weeks after administration of the last dose of fremanezumab. All injections were administered by study staff.

In HALO CM, a subset of patients (specified not to exceed 30% of all participants) was allowed to use 1 concomitant migraine preventive medication, and no changes in these medications were allowed until the last study assessments were completed. All other patients were not using concomitant preventive migraine medications at the time of the screening visit, and they were not allowed to initiate these medications after study start. In HALO EM, concomitant medication use was allowed and monitored throughout the study. In FOCUS, patients must not have been on any migraine preventive medications at the time of screening, and they were not permitted to initiate migraine preventive medications during the run-in and treatment periods. All studies allowed for the use of acute medications to treat migraines, as needed, with the exception of medications containing opioids and barbiturates, which could not be used more than 4 times per month before study entry.

## Outcomes

Table 9 lists the efficacy end points assessed in the clinical trials that were identified in the CADTH review protocol and included in this review. These end points are further summarized following the table. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

### Table 9: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

| Outcome measure | HALO CM | HALO EM | FOCUS |
|---|---|---|---|
| MMDs | Secondary | Primary | Primary |
| Headache days per month | Primary | Exploratory | Secondary |
| ≥ 50% responder analysis | Exploratory | Secondary | Secondary |
| Headache symptoms (nausea, vomiting, photophobia, phonophobia) | Exploratory | Exploratory | Exploratory |
| MIDAS | Not assessed | Secondary | Exploratory |
| HIT-6 | Secondary | Not assessed | Exploratory |
| Acute pain medication intake | Secondary | Secondary | Exploratory |
| WPAI | Exploratory | Exploratory | Exploratory |
| EQ-5D-5L | Exploratory | Exploratory | Exploratory |
| MSQoL | Exploratory | Exploratory | Exploratory |
| PHQ-2/PHQ-9 | Exploratory | Exploratory | Exploratory |
| PGIC | Exploratory | Exploratory | Exploratory |
| Harms | Primary | Primary | Secondary |

CM = chronic migraine; EM = episodic migraine; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; HIT-6 = 6-item headache impact test; MIDAS = migraine disability assessment score; MMD = monthly migraine day; MSQoL = Migraine-Specific Quality of Life questionnaire; PGIC = Patients' Global Impression of Change; PHQ = Patient Health Questionnaire; WPAI = Work Productivity and Activity Impairment.

The primary outcome of the HALO EM and FOCUS studies was the change from baseline in MMDs. The primary efficacy outcome for HALO CM was monthly average number of headache days of at least moderate severity, which was a secondary efficacy for HALO EM and an exploratory outcome for FOCUS. Monthly use of acute migraine medication was a secondary outcome in all included studies. The MID for reduction in MMDs, monthly average number of headache days, and reduction in use of acute migraine medication is unclear.

Patients received comprehensive training from study personnel on the use of the electronic headache diary device to record onset and severity of migraine and headache in general, symptoms experienced, as well as medication use.

Migraine-related disability was measured using the HIT-6 and was a secondary efficacy outcome in the HALO CM study and an exploratory outcome in the other studies. The HIT-6 measures pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress on a 5-point Likert scale.[34] 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. For patients with EM, the within-group MID was −2.5 and the between-group MID was −1.5, and, for chronic daily headaches, it was −2.3.[35,36] The MIDAS questionnaire was used to assess migraine-related disability as a secondary efficacy outcome in the HALO EM study and as an exploratory outcome in the other studies. It evaluates headache-related disability through 5 questions regarding the number of days lost and days with significant limitations

for work or schoolwork, housework or chores, and family, social, or leisure activities.[37] Two additional questions, which are not included in the scoring, ask about the frequency of headaches and intensity of headache pain. An overall score for the questionnaire is calculated by summing the lost days recorded in the 5 questions. No MID was identified for this instrument.

Additional exploratory outcomes included changes in health-related quality of life, health status, depression status, work productivity and activity impairment, and patient satisfaction with treatment.

For health-related quality of life, the MSQoL (version 2.1) questionnaire was used to assess the impact of migraine and migraine treatment on a patient's quality of life during the previous 4 weeks by measuring limitations on normal activities and emotional effects of migraine. Scores range from 0 to 100, with higher scores indicating better health-related quality of life. MIDs are provided for each section of the questionnaire for patients with 15 or more headache days per month and for patients with CM.[38,39] The EQ-5D-5L questionnaire includes a descriptive system of 5 dimensions and a visual analogue scale (VAS) assessed at monthly visits. The descriptive system assesses mobility, self -care, usual activities, pain/discomfort, and anxiety/depression.[40] Results from the EQ-5D-5L descriptive system can be converted into a single index score ranging from 0 to 1.0, with the possibility of negative scores for societal health states, using a scoring algorithm that takes the local patient and population preferences into account. The nonspecific MID estimate was 0.056 (standard deviation [SD] = 0.011) for the Canadian population.[41] For depression status, the PHQ-9 quick depression assessment score was used to evaluate the frequency of 9 diagnostic criteria for depressive disorders over the previous 2 weeks as an exploratory outcome. A score of 0 to 4 represents no or minimal depression, 5 to 9 mild depression, 10 to 14 moderate depression,15 to 19 moderately severe depression, and 20 to 27 severe depression. To rapidly screen for depression, the PHQ-2 was developed, consisting of the first 2 questions from the PHQ-9. If the PHQ-2 was positive (i.e., a score of ≥ 3), patients completed questions 3 through 9 (unique questions) of the PHQ-9.[42]

The WPAI score is an exploratory outcome that was assessed via an electronic diary to measure impairments in work and activities during the previous 7 days.[43] The score assesses absenteeism; presenteeism (impairment at work or reduced on-the-job effectiveness); work productivity loss; activity impairment (through the number of days or hours missed from work); days or hours worked; days during which performing work was challenging, and the extent to which the patient was limited at work (work impairment). No migraine-specific MID was found for this instrument. Work productivity was indicated as an important outcome in the patient input. The PGIC scale was assessed as an exploratory outcome. The PGIC is a global assessment of the change in clinical status to assess change in activity limitations, symptoms, emotions, and overall quality of life related to the patient's condition.[44] A 7-point scale and a VAS ranging from 0 to 10 were used. No migraine-specific MIDs were found for these instruments.

Safety was assessed by qualified study personnel by evaluating reported AEs, clinical laboratory test results, vital signs measurements, 12-lead electrocardiogram (ECG) findings, physical examination findings (including body weight measurements), electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) scores, local injection-site assessments, and concomitant medication usage.[45] AEs in the form of treatment-emergent AEs, SAEs, withdrawals due to AEs, and notable AEs (i.e., AEs of particular interest to this review) were reported in all studies.

Refer to Appendix 4 for more information on the validity of the outcome measures described in this section.

## Statistical Analysis

### *HALO CM*

The power calculation of the HALO CM study assumed a treatment difference of 1.7 days of monthly average headache days of at least moderate severity between the monthly fremanezumab and placebo treatment groups, based on results from the phase IIb study.[46] A sample size of 867 patients (i.e., 289 evaluable patients completing the study per treatment group) provides at least 90% power for the study to succeed (assuming a common SD of 6.29 days) at an alpha level of 0.05. Assuming a 15% discontinuation rate, 340 patients per treatment group were required.

A multiple imputation method was applied to the primary outcome as sensitivity analyses. All continuous efficacy outcomes were analyzed using an ANCOVA method (primary analysis), with treatment, sex, region, and baseline preventive migraine medication as fixed effects and the baseline number of headache days of at least moderate severity and years since onset of migraine as covariables. When the normality of residuals from the ANCOVA model had a P value ≤ 0.01 when checked using Shapiro-Wilk's normality test, the Wilcoxon rank sum test was conducted as the primary analysis, and the ANCOVA analysis was performed as a supportive analysis. The least square means (LSMs) for the treatment groups, LSMs and corresponding 95% CIs for the treatment differences (fremanezumab – placebo), and associated P values were provided.

An MMRM analysis model was used to estimate the mean change from baseline in the monthly average number of headache days of at least moderate severity for the overall 3-month treatment period and by each month to support the primary analysis. Each patient's monthly number of headache days of at least moderate severity during the 4-week period was calculated based on the e-diary responses for that month. If a patient prematurely withdrew and had less than 20 days of e-diary entries after the last injection, the last month's value was used. The MMRM model included baseline value, treatment, sex, region, baseline preventive migraine medication use (yes/no), years since onset of migraines, month and treatment-by-month interaction as fixed effects, and patient in the repeated statement as a random effect. The unconstructed covariance structure was used for the repeated observations within a patient. LSMs for the treatment groups, LSMs for the treatment differences (fremanezumab – placebo) and corresponding 95% CIs and associated P values were calculated by month and for the overall treatment period.

The ANCOVA and MMRM methods were applied to pre-specified subgroup analyses of the mean change from baseline in the monthly average number of headache days of at least moderate severity and the mean change from baseline in the MMDs. Analyzed subgroups were concomitant preventive migraine medication use (yes, no), patients who used topiramate for migraine in the past, patients who used OnaA for migraine in the past, age (18 to 45 years, 45 to 65 years, > 65 years), race (White, non-White), and sex (female, male) subgroups. Of these, only subgroups related to concomitant preventive migraine medication use (yes, no), patients who used topiramate for migraine in the past, and patients who used OnaA for migraine in the past were relevant to this review per the protocol (Table 5). Cochran-Mantel-Haenszel test stratified by baseline preventive migraine medication use (yes/no) was used to analyze the responder type of efficacy end points.

Analysis methods were those specified in the statistical analysis plan that was approved before the unblinding of the data. A fixed-sequence (hierarchical) testing procedure was implemented to control the type I error rate at 0.05 for the primary and secondary efficacy end points. No adjustments for multiplicity were applied to the analyses of exploratory efficacy end points.

The sequence was:

- Change in monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug for monthly fremanezumab versus the placebo treatment group
- Change in MMDs during the 12-week period after the first dose of study drug for monthly fremanezumab versus placebo, change in the number of headache days of at least moderate severity during the 4-week period after the first dose of study drug for both monthly and quarterly fremanezumab groups versus the placebo treatment group
- Proportion of patients reaching at least 50% reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug for the fremanezumab 675 mg/225 mg/225 mg treatment group versus the placebo treatment group
- Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug for the fremanezumab 675 mg/placebo/placebo treatment group versus the placebo treatment group
- Mean change from baseline in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug for the fremanezumab 675 mg/225 mg/225 mg treatment group versus the placebo treatment group
- Proportion of patients reaching at least 50% reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug for the fremanezumab 675 mg/placebo/placebo treatment group versus the placebo treatment group
- Mean change from baseline in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug for the fremanezumab 675 mg/placebo/placebo treatment group versus the placebo treatment group
- Mean change from baseline (28-day run-in period) in the average number of MMDs during the 12-week period after the first dose of study drug for the fremanezumab 675 mg/placebo/placebo treatment group versus the placebo treatment group
- Mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug for the fremanezumab 675 mg/225 mg/225 mg treatment group versus the placebo treatment group in patients not receiving concomitant migraine preventive medications
- Mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug for the fremanezumab 675 mg/placebo/placebo treatment group versus the placebo treatment group in patients not receiving concomitant migraine preventive medications
- Mean change from baseline (day 0) in disability score, as measured by the HIT-6 at 4 weeks after administration of the last (third) dose of study drug for the fremanezumab 675 mg/225 mg/225 mg treatment group versus the placebo treatment group

- Mean change from baseline (day 0) in disability score, as measured by the HIT-6 at 4 weeks after administration of the last (third) dose of study drug for the fremanezumab 675 mg/placebo/placebo treatment group versus the placebo treatment group

In calculating a patient's monthly number of days/hours of efficacy outcomes during the 4-week period after each dose of study drug for months 1, 2, and 3, the following method was used to handle the missing data. If a patient had at least 10 days of e-diary data for a month, the monthly number of days/hours of efficacy outcomes was prorated to 28 days for that month. If a patient had fewer than 10 days of e-diary data for a month, the monthly number of days/hours of efficacy outcomes were considered as missing.

*HALO EM*

A total of 768 patients needed to be randomized in HALO EM to have 675 completers (225 completers per treatment group), given a 12% dropout rate. A sample size of 675 patients (i.e., 225 evaluable patients completing the study per treatment group) would provide 90% power to detect a 1.6-day difference in migraine days between a fremanezumab treatment arm and placebo at an alpha level of 0.05, assuming a common SD of 5.2 days.

The same statistical analysis plan was used as in HALO CM. The hierarchical sequence was:

- Mean change from baseline in the average number of MMDs during the 12-week period after the first dose of study drug for the fremanezumab 225 mg/225 mg/225 mg treatment group versus the placebo treatment group
- Proportion of patients reaching at least 50% reduction in average number of MMDs during 12-week period after the first dose of study drug for the fremanezumab 225 mg/225 mg/225 mg treatment group versus the placebo treatment group
- Mean change from baseline in the average number of MMDs during the 12-week period after the first dose of study drug for the fremanezumab 675 mg/placebo/placebo treatment group versus the placebo treatment group
- Mean change from baseline in the number of migraine days during the 4-week period after the first dose of the study drug for the fremanezumab 675 mg/placebo/placebo treatment group versus the placebo treatment group
- Proportion of patients reaching at least 50% reduction in the monthly number of migraine days during 12-week period after the first dose of study drug for the fremanezumab 675 mg/placebo/placebo treatment group versus the placebo treatment group
- Mean change from baseline in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of the study drug for the fremanezumab 225 mg/225 mg/225 mg treatment group versus the placebo treatment group
- Mean change from baseline in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug for the fremanezumab 675 mg/placebo/placebo treatment group versus the placebo treatment group
- Mean change from baseline in the number of migraine days during the 4-week period after the first dose of the study drug for the fremanezumab 225 mg/225 mg/225 mg treatment group versus the placebo treatment group
- Mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (third) dose of study drug for the fremanezumab 225 mg/225 mg/225 mg treatment group versus the placebo treatment group

- Mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (third) dose of study drug for the fremanezumab 675 mg/placebo/placebo treatment group versus the placebo treatment group
- Mean change from baseline in the average number of MMDs during the 12-week period after the first dose of study drug for the fremanezumab 225 mg/225 mg/225 mg treatment group versus the placebo treatment group in patients not receiving concomitant migraine preventive medications
- Mean change from baseline in the average number of MMDs during the 12-week period after the first dose of study drug for the fremanezumab 675 mg/placebo/placebo treatment group versus the placebo treatment group in patients not receiving concomitant migraine preventive medications

The ANCOVA and MMRM methods were applied to subgroup analyses (concomitant migraine preventive medication use [yes, no], patients who used topiramate for migraine in the past, patients who used OnaA for migraine in the past, age [18 to 45 years and > 45 years], race [White, non-White], and sex [women, men] subgroups) of the change from baseline in the MMDs and the change from baseline in the monthly average number of headache days of at least moderate severity.

In calculating a patient's monthly number of days/hours of efficacy outcomes during the 4-week period after each dose of study drug for months 1, 2, and 3, the following method was used to handle the missing data. If a patient had 10 days or more of e-diary data for a month, the monthly number of days/hours of efficacy outcomes was prorated to 28 days for that month. If a patient had less than10 days of e-diary data for a month, the monthly number of days/hours of efficacy outcomes were considered as missing.

*FOCUS*

A sample size of 705 (235 patients per treatment group) evaluable patients completing the study was derived for 90% power to show a 1.8 difference in migraine days (assuming a common SD of 6 days) at an alpha level of 0.05. The study assumed a 12% discontinuation rate to indicate 268 patients per treatment group randomized in the study.

The primary efficacy end point was analyzed using an ANCOVA method. The model included treatment, sex, region, special group of treatment failure (yes or no), migraine classification (i.e., CM or EM), and treatment-by-migraine classification interaction as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. The stratification factors (as randomized) were used in the model. The treatment comparison between each fremanezumab treatment group (monthly dosage and quarterly dosage) and placebo for average MMDs was conducted under this model using the estimate statement. Ninety-five percent CIs were constructed for the LSM differences between each fremanezumab treatment group (monthly dosage and quarterly dosage) and placebo. The continuous secondary efficacy end points were analyzed similarly to the primary efficacy end point. For the proportion of responders, defined as a 50% or more reduction from baseline in the MMDs, a logistic regression model was used with the following effects: treatment, sex, region, special group of treatment failure (yes or no), and migraine classification (i.e., CM or EM). The odds ratios, 95% CIs for odds ratios, and P values were presented for each fremanezumab treatment group (monthly dosage and quarterly dosage).

A sensitivity analysis was also performed using an MMRM analysis model. If a patient's participation was terminated early or had intermittent missing days and had fewer than 10

days of e-diary entries for a month, that month's value was considered as missing. The MMRM model included treatment, sex, region, special group of treatment failure (yes or no), migraine classification (i.e., CM or EM), month, treatment-by-migraine classification interaction, and treatment-by-month interaction as fixed effects; baseline value and years since onset of migraines as covariates; and patient in the repeated statement as a random effect. The treatment comparison between each fremanezumab treatment group (monthly dosage and quarterly dosage) and placebo for average MMDs were conducted. Ninety-five percent CIs were constructed for the LSM differences between each fremanezumab treatment group (monthly dosage and quarterly dosage) and placebo. The sensitivity analysis was performed on the modified ITT analysis set. The special treatment failure group was defined as patients who had documented inadequate response to valproic acid and to 2 to 3 other classes of migraine preventive medications.

The Hochberg's method along with hierarchical testing procedure for multiple comparisons between treatment groups (2 comparisons: fremanezumab monthly dosage compared with placebo, and fremanezumab quarterly dosage compared with placebo) was applied for the primary and secondary end points. In the primary analysis, according to the Hochberg's method, if the null hypothesis was rejected for both the fremanezumab monthly and quarterly treatment groups at an alpha level of 5%, then no adjustment to the alpha level was performed, and both comparisons were declared statistically significant. The secondary outcomes were then tested for both the fremanezumab monthly and quarterly treatment groups using the same procedure as the primary analysis. If the null hypothesis was not rejected for 1 of the dosages at an alpha level of 5%, then the other dosage was tested using an alpha level of 5%/2 = 2.5%, and the sequential testing was stopped. The sequence of the hierarchical testing was not indicated in the clinical study report provided by the sponsor.

For the OLTP, the exploratory efficacy end points were summarized using descriptive statistics.

The ANCOVA and the MMRM analyses were also applied for the following subgroups for the primary end point: age group (18 to 45 years, > 45 years), sex (male, female), region (North America, Europe), country (countries with less than 20 patients were excluded from the subgroup analysis), migraine classification (CM, EM), 4 classes of migraine preventive medications failed in the past not including valproic acid (yes, no), number of classes of migraine preventive medications failed in the past (2, 3, 4), overuse of acute medication (yes, no), frequency of headache days at baseline for EM patients (4 to 9, 10 to 14). Of these subgroups, migraine classification (CM, EM), 4 classes of migraine preventive medications failed in the past not including valproic acid (yes, no), number of classes of migraine preventive medications failed in the past (2, 3, 4), overuse of acute medication (yes, no), and frequency of headache days at baseline for EM patients (4 to 9, 10 to 14) were relevant to the review per the protocol (Table 5).

An exploratory analysis for the primary end point was also performed by adding the treatment by region interaction to the primary analysis model to test whether treatment effects are homogeneous across regions.

*Analysis Populations*

**HALO CM and HALO EM**

The ITT population included all randomized patients. In this population, treatment was assigned based on the treatment to which the patients were randomized, regardless of which treatment they actually received. The safety population included all patients who took at least 1 dose of study drug. In this population, treatment was assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized. The full analysis set (FAS) included those in the ITT population who received at least 1 dose of study drug and had at least 10 days of post-baseline efficacy assessments on the primary end point. The per-protocol (PP) analysis set included all patients who completed the study without any violations of the inclusion/exclusion criteria or any violations or omissions of the drug administration.

*FOCUS*

The ITT analysis set included all randomized patients. In the ITT analysis set, treatment was assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. The modified ITT (mITT) analysis set is a subset of the ITT analysis set that included only patients who received at least 1 dose of study drug and had at least 10 days of post-baseline efficacy assessment on the primary end point. The open-label mITT analysis set is a subset of the ITT analysis set including only patients who received at least 1 dose of study drug during the OLTP and had at least 10 days of post-baseline diary entries during the OLTP.

The double-blind safety analysis set included all randomized patients who received at least 1 dose of study drug during the DBTP. The open-label safety analysis set included all patients who received at least 1 dose of study drug during the OLTP. In the safety analysis sets, treatment was assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified. The PP analysis set is a subset of the double-blind mITT analysis set, including only patients who completed the DBTP, without important protocol deviations that may affect the efficacy assessments or any deviations/omissions of the study drug administration. Patients with less than 75% diary adherence during the DBTP were excluded from the PP analysis set. Patients who received a study drug different from the study drug they were randomized to were excluded from the PP analysis set. A blinded data review meeting was conducted before the interim database lock in order to determine the exclusion of the patients from the PP analysis set.

## Results

### Patient Disposition

*HALO CM*

Of the 3,148 patients screened, 1,130 (36%) met the entry criteria, including diagnostic criteria for CM and headache diary adherence during the run-in period, and were randomized into this study. Of the 2,018 patients who were not randomized into this study, 870 patients qualified for and were randomized into the HALO EM study. An additional 5 patients who consented only to the EM study were not included in the CM study. The remaining 1,148 patients were excluded on the basis of AEs (3), inclusion criteria not met

(666), exclusion criteria met (297), loss to follow-up (49), and other reasons (133). The most frequent inclusion criteria not met were the criteria for CM during the 28-day run-in period. The most frequent exclusion criterion met was evidence or medical history of clinically significant psychiatric issues.

The percentage of discontinued patients was similar in all treatment groups (range = 7% to 9%; Table 10). The most frequent reason for study discontinuation was withdrawn consent, followed by loss to follow-up and AEs.

*HALO EM*

Of the 2,995 patients screened, 875 (29%) met entry criteria, including diagnostic criteria for EM and headache diary adherence during the run-in period, and were randomized into this study. Of the 2,120 patients who were not randomized into this study, 1,036 patients were randomized into HALO CM. An additional 94 patients who consented only to the CM study were not included in the EM study. The remaining 1,084 patients were excluded on the basis of AEs (2), inclusion criteria not met (643), exclusion criteria met (273), lost to follow-up (46), and other reasons (120). The most frequent inclusion criteria not met were the criteria for EM during the 28-day run-in period. The most frequent exclusion criterion met was evidence or medical history of clinically significant psychiatric issues.

The percentage of discontinued patients was similar in all treatment groups (range = 9% to 10%; Table 10), with the most frequent reason being withdrawn consent, followed by loss to follow-up and AEs.

*FOCUS*

A total of 1,028 patients with CM or EM were screened for enrolment, of which 838 patients (82%) met the entry criteria. Of the 190 patients who were not enrolled, 150 were excluded on the basis of inclusion/exclusion criteria, 25 patients withdrew consent, 13 patients were excluded due to “other” reasons, 1 patient was lost to follow-up before the baseline visit, and 1 patient experienced an AE. Of the 838 patients enrolled, all received at least 1 dose of study drug and were evaluated for safety in the study; 25 patients withdrew before taking any study drug.

A total of 28 (3%) patients discontinued double-blind treatment (6 [3%] receiving fremanezumab 675 mg/225 mg/225 mg treatment, 5 [5%] receiving fremanezumab 225 mg/225 mg/225 mg treatment, 5 [2%] receiving fremanezumab 675 mg/placebo/placebo treatment, and 15 [5%] receiving placebo treatment). All reasons for discontinuation from the DBTP occurred in less than 1% of the total study population.

A total of 35 (4%) patients discontinued open-label treatment (10 [6%] in the fremanezumab 675 mg/225 mg/225 mg treatment group, 2 [2%] in the fremanezumab 225 mg/225 mg/225 mg treatment group, 12 [4%] in the fremanezumab 675 mg/placebo/placebo treatment group, and 11 [4%] in the placebo treatment group). All reasons for discontinuation from the OLTP involved less than 1% of the total study population, with the exception of patient withdrawal, in 2% of the total study population.

## Table 10: Patient Disposition in HALO CM and HALO EM

| | HALO CM | | | HALO EM | | |
|---|---|---|---|---|---|---|
| **Disposition** | **Fremanezumab 675 mg/225 mg/225 mg (N = 379)** | **Fremanezumab 675 mg/PB/PB (N = 376)** | **Placebo (N = 375)** | **Fremanezumab 225 mg/225 mg/225 mg (N = 290)** | **Fremanezumab 675 mg/PB/PB (N = 291)** | **Placebo (N = 294)** |
| **Screened** | 3,148 | | | 2,995 | | |
| **Screening failures** | 2,018 | | | 2,120 | | |
| **Randomized (ITT population), N (%)** | 379 (100) | 376 (100) | 375 (100) | 290 (100) | 291 (100) | 294 (100) |
| **ITT population, not treated, n (%)** | 0 | 0 | 0 | 1 (< 1) | 0 | 0 |
| **Safety population** | 379 (100) | 376 (100) | 375 (100) | 289 (> 99) | 291 (100) | 294 (100) |
| **FAS** | 375 (99) | 375 (> 99) | 371 (99) | 287 (99) | 288 (99) | 290 (99) |
| **PP analysis set** | 317 (84) | 321 (85) | 321 (86) | 255 (88) | 245 (84) | 247 (84) |
| **Completed study** | 343 (91) | 349 (93) | 342 (91) | 262 (90) | 264 (91) | 265 (90) |
| **Continued to HALO LTS** | 314 (83) | 313 (83) | 312 (83) | 225 (78) | 229 (79) | 232 (79) |
| **Discontinued from study** | 36 (9) | 27 (7) | 33 (9) | 28 (10) | 27 (9) | 29 (10) |
| Death | 0 | 1 (< 1) | 0 | 0 | 0 | 0 |
| Adverse event | 7 (2) | 5 (1) | 8 (2) | 4 (1) | 5 (2) | 7 (2) |
| Withdrawal by patient | 11 (3) | 10 (3) | 12 (3) | 13 (4) | 8 (3) | 5 (2) |
| Protocol violation | 2 (< 1) | 2 (< 1) | 2 (< 1) | 7 (2) | 3 (1) | 2 (< 1) |
| Pregnancy | 0 | 0 | 2 (< 1) | 0 | 1 (< 1) | 2 (< 1) |
| Nonadherence to study procedures | 2 (< 1) | 1 (< 1) | 0 | 0 | 0 | 0 |
| Lost to follow-up | 10 (3) | 7 (2) | 8 (2) | 4 (1) | 9 (3) | 12 (4) |
| Lack of efficacy | 1 (< 1) | 0 | 0 | 0 | 0 | 0 |
| Other | 3 (< 1) | 1 (< 1) | 1 (< 1) | 0 | 1 (< 1) | 1 (< 1) |

CM = chronic migraine; EM = episodic migraine; FAS = full analysis set; ITT = intention-to-treat; LTS = long-term study; PB = placebo; PP = per-protocol.

Notes: The denominator for calculating percentages was the number of patients in the ITT population. The safety population included all patients who received at least 1 dose of study drug. The ITT population included all randomized patients. The FAS included all patients in the ITT population who received at least 1 dose of study drug and had at least 10 days of post-baseline efficacy assessment on primary end point. The PP analysis set included all ITT patients who completed the study without any inclusion/exclusion violations or study drug administration violations.

[a] Patient numbers based on randomization.

Source: Clinical Study Report for HALO CM[17] and HALO EM.[18]

## Table 11: Patient Disposition in FOCUS

| Disposition | FOCUS | | | |
|---|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg (N = 173) | Fremanezumab 225 mg/225 mg/225 mg (N = 110) | Fremanezumab 675 mg/PB/PB (N = 276) | Placebo (N = 279) |
| **Screened** | 1,028 | | | |
| **Randomized, n (%)** | 173 (100) | 110 (100) | 276 (100) | 279 (100) |
| **Completed double-blind treatment period** | 167 (97) | 105 (95) | 271 (98) | 264 (95) |
| **Discontinued double-blind treatment period** | 6 (3) | 5 (5) | 5 (2) | 15 (5) |
| Adverse event | 3 (2) | 1 (< 1) | 1 (< 1) | 3 (1) |
| Lack of efficacy | 0 (0) | 0 (0) | 1 (< 1) | 1 (< 1) |
| Consent withdrawn | 1 (< 1) | 2 (2) | 2 (< 1) | 2 (< 1) |
| Protocol deviation | 1 (< 1) | 2 (2) | 0 (0) | 5 (2) |
| Nonadherence to study procedures | 0 (0) | 0 (0) | 1 (< 1) | 1 (< 1) |
| Lost to follow-up | 0 (0) | 0 (0) | 0 (0) | 1 (< 1) |
| Other | 1 (< 1) | 0 (0) | 0 (0) | 2 (< 1) |
| **ITT analysis set** | 173 (100) | 110 (100) | 276 (100) | 279 (100) |
| **Double-blind safety analysis set** | 173 (100) | 110 (100) | 276 (100) | 279 (100) |
| **Double-blind mITT analysis set** | 173 (100) | 110 (100) | 276 (100) | 278 (> 99) |
| **PP analysis set** | 159 (92) | 100 (91) | 256 (93) | 250 (90) |
| **Open-label safety analysis set**[a] | 167 (97) | 105 (95) | 271 (98) | 264 (95) |
| **Open-label mITT analysis set**[a] | 167 (97) | 105 (95) | 271 (98) | 263 (94) |
| **Completed OLTP**[a] | 157 (91) | 103 (94) | 259 (94) | 253 (91) |
| **Discontinued OLTP**[a] | 10 (6) | 2 (2) | 12 (4) | 11 (4) |
| Adverse event | 1 (< 1) | 0 (0) | 1 (< 1) | 4 (1) |
| Lack of efficacy | 0 (0) | 0 (0) | 2 (< 1) | 1 (< 1) |
| Consent withdrawn | 5 (3) | 2 (2) | 5 (2) | 5 (2) |
| Protocol deviation | 1 (< 1) | 0 (0) | 1 (< 1) | 0 (0) |
| Nonadherence to study procedures | 1 (< 1) | 0 (0) | 0 (0) | 0 (0) |
| Lost to follow-up | 1 (< 1) | 0 (0) | 1 (< 1) | 0 (0) |

| Disposition | FOCUS | | | |
|---|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg (N = 173) | Fremanezumab 225 mg/225 mg/225 mg (N = 110) | Fremanezumab 675 mg/PB/PB (N = 276) | Placebo (N = 279) |
| Other | 1 (< 1) | 0 (0) | 2 (< 1) | 1 (< 1) |
| **Completed study** | 147 (85) | 99 (90) | 247 (89) | 240 (86) |
| **Discontinued study** | 26 (15) | 11 (10) | 29 (11) | 39 (14) |
| Adverse event | 4 (2) | 1 (< 1) | 2 (< 1) | 7 (3) |
| Lack of efficacy | 0 (0) | 0 (0) | 4 (1) | 2 (< 1) |
| Consent withdrawn | 12 (7) | 6 (5) | 11 (4) | 16 (6) |
| Protocol deviation | 2 (1) | 2 (2) | 1 (< 1) | 5 (2) |
| Nonadherence to study procedures | 1 (< 1) | 0 (0) | 1 (< 1) | 1 (< 1) |
| Lost to follow-up | 3 (2) | 2 (2) | 7 (3) | 4 (1) |
| Other | 3 (2) | 0 (0) | 3 (1) | 4 (1) |
| **Ongoing** | 156 (90) | 104 (95) | 260 (94) | 257 (92) |

ITT = intention-to-treat; mITT = modified intention-to-treat; OLTP = open-label treatment period; PB = placebo; PP = per-protocol.

Note: Other = patient discontinued due to breast cancer in history (1) and patient discontinued due to sponsor decision (1). Percentages are based on the number of patients randomized.

[a] All patients in the OLTP of the study received fremanezumab 225 mg monthly. The denominator for calculating percentages is the number of patients in the ITT analysis set.
Source: Clinical Study Reports for FOCUS.[19]

## Exposure to Study Treatments

In HALO CM, exposure to study drug was similar in terms of duration of treatment and proportion of patients who received all 3 doses of study drug across treatment groups. The majority of patients (> 90%) in each treatment group received all 3 doses of study drug. The mean duration of treatment was approximately 84 days across all treatment groups.

In HALO EM, exposure was similar in terms of duration of treatment and proportion of patients who received all 3 doses of study drug across the treatment groups. The majority of patients (> 90%) in each treatment group received all 3 doses of study drug. The mean duration of treatment was approximately 83 days across all treatment groups.

In FOCUS, exposure to study drug was similar across treatment groups. In the DBTP, the mean duration of exposure was more than 83 days (84.6 days for patients in the fremanezumab 675 mg/225 mg/225 mg treatment group, 83.6 days for patients in the fremanezumab 225 mg/225 mg/225 mg treatment group, 85.8 days for patients in the fremanezumab 675 mg/placebo/placebo treatment group, and 84.6 days for patients in the placebo treatment group). The median number of days of treatment was 85 days in the fremanezumab treatment groups. The majority of patients received 3 doses of study drug. For the OLTP, exposure to study drug was similar across treatment groups. In the OLTP, the mean duration of exposure was more than 83 days (83.2 days for patients in the fremanezumab 675 mg/225 mg/225 mg double-blind treatment group, 84.4 days for patients in the fremanezumab 225 mg/225 mg/225 mg double-blind treatment group, 84.8 days for patients in the fremanezumab 675 mg/placebo/placebo double-blind treatment group, and 83.7 days for patients in the placebo double-blind treatment group). The median number of days of treatment was 85 days in all treatment groups. The majority of patients received 3 doses of study drug.

### *Concomitant Medication Use*

During HALO CM, the total number of patients receiving concomitant migraine or headache medication was 93% of the total sample size of the study. The most frequently used concomitant migraine or headache medications were ibuprofen, sumatriptan, and products containing acetaminophen. Of the subset of patients who were permitted to receive concomitant migraine preventive medication during the study, the most frequently used concomitant migraine preventive medication was topiramate (approximately 7% across treatment groups).

In the HALO EM study, the most frequently used concomitant medications were similar across treatment groups and included ibuprofen (approximately 35% across treatment groups), a combination of acetaminophen-Aspirin-caffeine (approximately 30% across treatment groups), and sumatriptan (approximately 25% across treatment groups). During the study, the total number of patients receiving concomitant migraine/headache medication was 94% of the total sample size of the study. The most frequently used concomitant migraine/headache preventive medication was topiramate (approximately 7% across treatment groups) in the subset of patients permitted to use such medication.

In the FOCUS study, the 4 treatment groups were similar in their use of prior and concomitant medications. All patients had received medications before study entry.

## Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. Analyses of subgroups are found in Appendix 3.

## Migraine Frequency

### *Average Monthly Migraine Days*

In the HALO CM study, change in MMDs was assessed as a secondary efficacy outcome. The difference between monthly fremanezumab and placebo in mean change from baseline in the MMDs during the 12-week period after the first dose of study drug was –1.8 days (95% CI, –2.61 to –1.09; P < 0.0001), in favour of monthly fremanezumab (Table 12). For MMDs, the difference between quarterly fremanezumab and placebo in change from baseline was –1.7 days (95% CI, –2.48 to –0.97; P < 0.0001), in favour of quarterly fremanezumab.

In HALO EM, the ANCOVA results showed that the difference between quarterly fremanezumab and placebo in mean change from baseline in the MMDs during the 12-week period after the first dose of study drug was –1.3 days (95% CI, –1.79 to –0.72; P < 0.0001), favouring quarterly fremanezumab. The ANCOVA results showed that the difference between monthly fremanezumab and placebo in mean change from baseline in the MMDs during the 12-week period after the first dose of study drug was –1.5 days (95% CI, –2.01 to –0.93; P < 0.0001), in favour of monthly fremanezumab.

In both HALO CM and HALO EM, the exploratory MMRM analysis of the treatment effect of fremanezumab on migraine days during the 12-week period after the first dose of study drug supported the main analysis for the outcome. The MMRM analysis also showed that fremanezumab treatment resulted in larger reduction from baseline in the average number of migraine days compared with placebo treatment at month 1, and this difference was maintained at month 2 and month 3.

Within the FOCUS study, the primary efficacy outcome was the mean change from baseline (28-day run-in period) in the MMDs during the 12-week DBTP after the first dose of fremanezumab. The difference between quarterly fremanezumab and placebo in mean change from baseline in the MMDs during the 12-week DBTP after the first dose of study drug was –3.1 days (95% CI, –3.84 to –2.42), favouring quarterly fremanezumab. The difference between monthly fremanezumab and placebo in mean change from baseline in the MMDs during the 12-week DBTP after the first dose of study drug was –3.5 days (95% CI, –4.19 to –2.78), favouring monthly fremanezumab. During the 12-week OLTP after the fourth dose of fremanezumab, the mean change from baseline (28-day run-in period) in the MMDs showed that patients in the fremanezumab quarterly, fremanezumab monthly, and placebo double-blind treatment groups had 5.1, 5.5, and 4.7 fewer MMDs, respectively, at 12 weeks.

### *At Least 50% Reduction in Monthly Migraine Days*

In the HALO CM study, an exploratory analysis showed that a higher proportion of patients reached at least 50% reduction in MMDs during the 12-week period after the first dose of study drug with fremanezumab than with placebo. A higher percentage of patients treated with fremanezumab (30.7% in the 675 mg/placebo/placebo treatment group and 33.3% in

the 675 mg/225 mg/225 mg treatment group) achieved a reduction of at least 50% in MMDs compared with those in the placebo group (19.9%) (Table 12).

In HALO EM, the proportion of patients who reached at least 50% reduction in MMDs during the 12-week period after the first dose of study drug was analyzed as an exploratory outcome. More patients experienced a reduction of at least 50% in MMDs with fremanezumab than with placebo: 44.4% in the 675 mg/placebo/placebo treatment group and 47.7% in the 225 mg/225 mg/225 mg treatment group, compared with 27.9% in the placebo group.

A secondary efficacy outcome of the FOCUS study was the proportion of patients reaching at least 50% reduction in the MMDs during the 12-week DBTP after the first dose of fremanezumab. During 12 weeks of treatment after dose 1, the odds ratio of reaching at least 50% reduction in the MMDs was 5.84 (95% CI, 3.57 to 9.55) in quarterly fremanezumab compared to placebo, favouring quarterly fremanezumab. The odds ratio of reaching at least 50% reduction in the MMDs during 12 weeks of treatment after dose 1 was 5.82 (95% CI, 3.56 to 9.51) for monthly fremanezumab compared with placebo, favouring monthly fremanezumab. The secondary efficacy outcome, the proportion of patients reaching at least 50% reduction in the MMDs during the 12-week OLTP after the fourth dose of fremanezumab, showed that 45%, 46%, and 38% of patients in the fremanezumab quarterly, fremanezumab monthly, and placebo double-blind treatment groups, respectively, experienced at least 50% reduction in the MMDs.

## Headache Frequency

### *Monthly Average Number of Headache Days of at Least Moderate Severity*

In HALO CM, the analysis of the primary efficacy end point — the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug — demonstrated statistically significant differences in favour of fremanezumab over placebo. The mean reduction of headache days of at least moderate severity in quarterly fremanezumab compared with placebo was –1.8 days (95% CI, –2.46 to –1.15; P < 0.0001), in favour of quarterly fremanezumab (Table 12). The mean reduction of headache days of at least moderate severity in monthly fremanezumab compared with placebo was –2.1 days (95% CI, –2.76 to –1.45; P < 0.0001), in favour of monthly fremanezumab. The MMRM analysis of the treatment effect of fremanezumab on the primary efficacy outcome during the 12-week period after the first dose of study drug supported the results of the Wilcoxon rank sum test. A sensitivity analysis using an ANCOVA model with multiple imputation showed that the results of the primary end point remained robust. The outcome of change from baseline in MMDs was adjusted for multiplicity.

In the HALO EM study, the exploratory analysis of the proportion of patients who reached a reduction of at least 75% in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug showed that more patients experienced this reduction with fremanezumab treatment than with placebo. Overall, 55 patients (14.7%) in the quarterly 675 mg/placebo/placebo treatment group and 57 patients (15.2%) in the 675 mg/225 mg/225 mg treatment group reported a reduction of at least 75% in comparison with 26 patients (7.0%) in the placebo group.

The FOCUS study evaluated the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week DBTP after the

first dose of fremanezumab as a secondary efficacy outcome. Fremanezumab monthly and quarterly treatment groups had statistically significant greater decreases in the monthly average number of headache days of at least moderate severity during the treatment period than the placebo treatment group. The mean reduction of headache days of at least moderate severity for quarterly fremanezumab compared with placebo was –3.2 days (95% CI, –3.93 to –2.52; P < 0.0001), in favour of quarterly fremanezumab. The mean reduction of headache days of at least moderate severity in monthly fremanezumab compared with placebo was –3.6 days (95% CI, –4.30 to –2.91; P < 0.0001), in favour of monthly fremanezumab. The outcome of change from baseline in MMDs was adjusted for multiplicity.

### *At Least 50% Reduction in Monthly Headache Days*

In HALO CM, the proportion of patients who reached at least 50% reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug was an exploratory analysis. The analysis showed that more patients experienced at least 50% reduction in the monthly average number of headache days of at least moderate severity with fremanezumab treatment than with placebo. Overall, 141 patients (37.6%) in the 675 mg/placebo/placebo treatment group and 153 patients (40.8%) in the 675 mg/225 mg/225 mg treatment group reported a reduction of at least 50% compared with 67 patients (18.1%) in the placebo group (Table 12).

An exploratory analysis of the number of headache days of at least moderate severity during the 12-week period after the first dose of study drug in HALO EM demonstrated that more patients experienced a reduction of at least 50% in the monthly number of headache days of at least moderate severity overall with fremanezumab treatment compared with placebo treatment. A total of 140 patients (48.6%) in the 675 mg/placebo/placebo treatment group and 140 patients (48.8%) in the 225 mg/225 mg/225 mg treatment group reached a reduction of at least 50% overall, in comparison with 77 patients (26.6%) in the placebo treatment group. However, this outcome was not adjusted for multiplicity, and any interpretation of reported results should consider the potential for inflated type I error.

The reduction in average monthly headache days by at least 50% was not reported in the FOCUS study.

### *Migraine-Related Disability Scores as Measured by the Migraine Disability Assessment Score*

The MIDAS score was not collected in the HALO CM study.

In the HALO EM study, the secondary analysis of the mean change from baseline in disability scores at 4 weeks after the last dose of study drug showed statistically significant differences from placebo in favour of fremanezumab. The median for the overall change from baseline in MIDAS score demonstrated a LSM difference from placebo of –5.4 (95% CI, –8.90 to –1.93; P = 0.0023) for fremanezumab 675 mg/placebo/placebo and –7.0 (95% CI, –10.51 to –3.53; P < 0.0001) for fremanezumab 225 mg/225 mg/225 mg, favouring the fremanezumab treatment groups. The outcome of change from baseline in MMDs was adjusted for multiplicity.

The exploratory analysis of the mean change from baseline in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the third dose of study drug in FOCUS, favoured fremanezumab compared with placebo (Table 14). However, this outcome was not adjusted for multiplicity, and any interpretation of reported results should

consider the potential for inflated type I error. The reduction in average monthly headache days by at least 50% was not reported in the FOCUS study.

*Headache Symptoms*

The exploratory analyses of the mean change from baseline in the monthly average number of days patients experienced nausea or vomiting and the mean change from baseline in the monthly average number of days patients experienced both phonophobia and photophobia during the 12-week period after the first dose of study drug in HALO CM and HALO EM showed differences from placebo in favour of fremanezumab. The ANCOVA results were supported by the results from the MMRM analysis.

In FOCUS, the mean change from baseline in the monthly average number of days with nausea or vomiting during the 12-week DBTP after the first dose of study drug was reduced in both the quarterly fremanezumab and monthly fremanezumab treatment groups compared with placebo. During the 12-week OLTP after the fourth dose of study drug, the mean change from baseline in the monthly average number of days with nausea or vomiting showed that patients in the fremanezumab quarterly, fremanezumab monthly, and placebo double-blind treatment groups had 3.1, 3.0, and 2.3 fewer days with nausea or vomiting per month, respectively. Exploratory analysis of the mean change from baseline in the monthly average number of days with photophobia and phonophobia during the 12-week DBTP showed decreased symptoms in the fremanezumab quarterly and fremanezumab monthly groups compared with placebo.

*Headache-Related Disability as Measured by the 6-Item Headache Impact Test*

In HALO CM, the secondary efficacy analysis of the mean change from baseline in disability scores at 4 weeks after the last dose of study drug showed statistically significant differences from placebo in favour of fremanezumab. ANCOVA results showed a LSM difference from placebo of –1.9 points (95% CI, –2.90 to –0.96; P < 0.0001) for fremanezumab 675 mg/placebo/placebo and –2.4 points (95% CI, –3.32 to –1.38; P < 0.0001) for fremanezumab 675 mg/225 mg/225 mg disability scores (Table 12). The MID of the between-group difference is 2.3 points for patients with chronic daily headaches.

HIT-6 scores were not collected in the HALO EM study.

In the FOCUS study, an exploratory analysis of the mean change from baseline in disability score, as measured by the HIT-6, at 4 weeks after administration of the third dose of study drug favoured both the quarterly fremanezumab and monthly fremanezumab treatment groups compared with placebo (Table 14).

*Health-Related Quality of Life as Measured by Validated Scales (ED-5D-5L, PHQ-9, MSQoL)*

Health-related quality of life was assessed as an exploratory outcome in all 3 included studies.

In HALO CM, health-related quality of life measures showed improvements in favour of both fremanezumab treatment regimens compared with placebo (Table 12). The differences in LSMs versus placebo for the MSQoL at week 12 were 6.9 points (95% CI, 4.07 to 9.70) in favour of the fremanezumab 675 mg/225 mg/225 group and 6.1 points (95% CI, 3.25 to 8.87) in favour of the fremanezumab 675 mg/placebo/placebo group (Table 12). Likewise, the differences in LSMs versus placebo at week 12 for the change from baseline in the EQ-5D-5L VAS were 2.6 points (95% CI, 0.26 to 4.90) in favour of the fremanezumab monthly

675 mg/225 mg/225 mg group and 2.4 points (95% CI, 0.11 to 4.74) in favour of the fremanezumab 675 mg/placebo/placebo group (Table 12). Exploratory analysis results from the ANCOVA of the mean change from baseline in the PHQ-9 scores at 4 weeks after the last dose of study drug showed no difference compared with placebo for both treatment groups.

In the HALO EM study, exploratory analysis (ANCOVA) of the mean change from baseline in the MSQoL scores at 4 weeks after the last dose of study drug showed differences from placebo in favour of fremanezumab for all 3 domains (i.e., role function–restrictive, role function–preventive, and emotional state). The differences in LSMs versus placebo at week 12 for the change from baseline in the EQ-5D-5L VAS were 1.0 points (95% CI, –1.14 to 3.22) for the fremanezumab 225 mg/225 mg/225 mg group and 1.0 points (95% CI, –1.15 to 3.19) for the fremanezumab 675 mg/placebo/placebo group. Results from the ANCOVA of the mean change from baseline in the PHQ-9 scores at 4 weeks after the last dose of study drug showed no difference compared with placebo for both treatment groups.

In FOCUS, health-related quality of life measures showed improvements in favour of both fremanezumab treatment regimens compared with placebo (Table 14). The differences in LSMs versus placebo for the MSQoL at 4 weeks after administration of the third dose were 10.6 points (95% CI, 7.52 to 13.69) for the fremanezumab 675 mg/225 mg/225 group and 8.8 points (95% CI, 5.73 to 11.92) for the fremanezumab 675 mg/placebo/placebo group. Exploratory analysis of the mean change from baseline at 4 weeks after administration of the sixth dose of study drug showed an improvement in MSQoL in all 3 domains (role function–restrictive, role function–preventive, and emotional function) during the OLTP, with an average change from baseline to visit 8/EOT of approximately 20 points across domains. Change from baseline (day 0) in health status, as measured by the EQ-5D-5L questionnaire, at 4 weeks after administration of the third dose of study drug showed a difference favouring the study drug for the monthly and quarterly fremanezumab treatment groups compared with placebo. Exploratory analysis of the mean change from baseline (day 0) in health status, as measured by the EQ-5D-5L questionnaire, at 4 weeks after administration of the sixth dose of study drug showed an improvement in health status among patients across double-blind treatment groups during the OLTP.

The exploratory analysis of the mean change from baseline in patient depression status, as measured by the PHQ-9, in the FOCUS study at 4 weeks after administration of the third dose of study drug favoured the quarterly and monthly fremanezumab treatment groups compared with placebo. Exploratory analysis of the mean change from baseline in patient depression status, as measured by the PHQ-9, at 4 weeks after administration of the sixth dose of study drug showed an improvement in patient depression status among patients across double-blind treatment groups during the OLTP.

### *Acute Headache Pain Medication Intake*

In the HALO CM study, the secondary efficacy analysis of the mean change from baseline in the monthly average number of days of use of any acute headache medication during the 12-week period after the first dose of study drug showed statistically significant differences from placebo in favour of fremanezumab for both active treatment groups. The LSM differences for the overall change from baseline from placebo was –1.8 days (95% CI, –2.43 to –1.12; $P < 0.0001$) for fremanezumab 675 mg/placebo/placebo and –2.3 days (95% CI, –2.61 to –1.09; $P < 0.0001$) for fremanezumab 675 mg/225 mg/225 mg. The MMRM analysis of the treatment effect of fremanezumab on monthly average number of days of

use of any acute headache medication during the 12-week period after the first dose of study drug supported the results of the Wilcoxon rank sum test.

In the HALO EM study, the secondary efficacy analysis of the mean change from baseline in the monthly average number of days of use of any acute headache medication during the 12-week period after the first dose of study drug demonstrated statistically significant differences from placebo in favour of fremanezumab. The LSM difference from placebo of –1.3 days (95% CI, –1.76 to –0.82; P < 0.0001) for fremanezumab 675 mg/placebo/placebo and –1.4 days (95% CI, –1.84 to –0.89; P < 0.0001) for fremanezumab 225 mg/225 mg/225 mg. The MMRM analysis of the treatment effect of fremanezumab on the number of days of use of any acute headache medication during the 12-week period after the first dose of study drug supported the results of the Wilcoxon rank sum test.

In the FOCUS study, the secondary efficacy outcome, the mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of fremanezumab showed statistically significant differences from placebo in favour of study drug. Fremanezumab monthly and quarterly treatment groups had significantly greater decreases in the monthly average number of days of use of any acute headache medications during the 12-week treatment period after the first dose of fremanezumab than the placebo treatment group. The treatment differences of quarterly and monthly fremanezumab compared with placebo were –3.1 days (95% CI, –3.75 to –2.41) and –3.4 days (95% CI, –4.03 to –2.69), respectively. The change from baseline in monthly average number of days of use of any acute headache medications was similar, whether patients received quarterly or monthly fremanezumab. The secondary efficacy outcome, the mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the fourth dose of fremanezumab showed that patients in the fremanezumab quarterly, fremanezumab monthly, and placebo double-blind treatment groups had 4.9, 4.8, and 4.3 fewer days of use of any acute headache medications per month, respectively, at 12 weeks after the fourth dose of fremanezumab.

### *Patient Satisfaction and Ease of Use*

In the HALO CM and HALO EM studies, the PGIC responder analysis results indicated that patients in both fremanezumab treatment groups were more likely to be responders than patients who received placebo at all time points. In the FOCUS study, the PGIC responder analysis results indicated that patients in both fremanezumab treatment groups were more likely to be responders than patients who received placebo at visit 3/month 1 and at visit 5/month 3. PGIC responder analysis results indicated an improvement in patient satisfaction among patients across double-blind treatment groups at 4 weeks after the sixth dose of fremanezumab, with the majority of patients reporting feeling “better” or “a great deal better” at both visit 8/EOT and last assessment.

### *Work Productivity and Loss of Workdays (Work Productivity and Activity Impairment Scale)*

In the HALO CM study, the mean change from baseline in the WPAI scores at 4 weeks after the last dose of study drug showed general improvement in work productivity for patients on fremanezumab treatment. In the HALO EM study, the mean change from baseline in the WPAI scores at 4 weeks after the last dose of study drug showed no difference compared with placebo for both treatment groups.

In the FOCUS study, results from the ANCOVA of the mean change from baseline in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at 4 weeks after administration of the third dose of study drug showed general improvement in work productivity for patients on fremanezumab treatment. Differences from placebo in favour of study drug were observed in 3 of the 4 domains (percent impairment while working due to health, percent overall work impairment due to health, and percent activity impairment due to health). Results from the analysis of the mean change from baseline in the WPAI questionnaire at 4 weeks after administration of the sixth dose of study drug showed an improvement in all 4 domains (percent work item missed due to health, percent impairment while working due to health, percent overall work impairment due to health, and percent activity impairment due to health) among patients across double-blind treatment groups during the OLTP.

### *Adherence*

The clinical study reports provided by the sponsor did not report data on adherence.

### *Health Care Resource Utilization (Hospitalizations)*

Health care resource utilization was not reported in the included studies.

## Table 12: Key Efficacy Findings — HALO CM

| | HALO CM | | |
|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg (N = 375) | Fremanezumab 675 mg/PB/PB (N = 375) | Placebo (N = 371) |
| **Monthly average number of headache days of at least moderate severity (primary)** | | | |
| Change from baseline in mean monthly number of headache days of at least moderate severity during the 12-week period after the first dose — ANCOVA (FAS) | N = 375 | N = 375 | N = 371 |
| LSM estimates (95% CI) | –4.6 (–5.16 to –3.97) | –4.3 (–4.87 to –3.66) | –2.5 (–3.06 to –1.85) |
| Difference in LSM versus placebo (95% CI)[a] | –2.1 (–2.76 to –1.45), P < 0.0001 | –1.8 (–2.46 to –1.15), P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.3 (–0.96 to 0.36) | – | – |
| Proportion of patients with at least 50% reduction in monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug (FAS) | N = 374 | N = 375 | N = 370 |
| Yes, n (%) | 153 (40.8) | 141 (37.6) | 67 (18.1) |
| P value compared to placebo | P < 0.0001 | P < 0.0001 | |
| **Average monthly migraine days (MMDs) (secondary)** | N = 375 | N = 375 | N = 371 |
| Change from baseline (28-day run-in period) in the MMDs during the 12-week period after the first dose of study drug — ANCOVA results (FAS) | | | |
| LSM estimate (95%CI) | –5.0 (–5.70 to –4.33) | –4.9 (–5.59 to –4.20) | –3.2 (–3.86 to –2.47) |
| Difference in LSM versus placebo (95% CI)[a] | –1.8 (–2.61 to –1.09) P < 0.0001 | –1.7 (–2.48 to –0.97) P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.1 (–0.88 to 0.63) | – | – |
| Proportion of patients with ≥ 50% reduction in MMDs during the 12-week period after the first dose of study drug (FAS) (exploratory) | | | |

| | HALO CM | | |
|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg (N = 375) | Fremanezumab 675 mg/PB/PB (N = 375) | Placebo (N = 371) |
| Yes, n (%) | 125 (33.3) | 115 (30.7) | 74 (19.9) |
| P value compared to placebo | P < 0.0001 | P = 0.0008 | |
| **Use of acute headache medications (secondary)** | N = 375 | N = 375 | N = 371 |
| Change from baseline in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug – ANCOVA results and Wilcoxon rank sum test (FAS) | | | |
| LSM estimates (95% CI) | –4.2 (–4.79 to –3.61) | –3.7 (–4.25 to –3.06) | –1.9 (–2.48 to –1.28) |
| Difference in LSM versus placebo (95% CI)[a] | –2.3 (–2.97 to –1.67) P < 0.0001 | –1.8 (–2.43 to –1.12) P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.5 (–1.19 to 0.11) | – | – |
| **Monthly number of headache hours (exploratory)** | N = 375 | N = 375 | N = 370 |
| Change from baseline (28-day run-in period) in the monthly number of headache hours of any severity –MMRM results (FAS) | | | |
| LSM estimates (95% CI) | –42.5 (–49.03 to –35.91) | –37.6 (–44.26 to –30.96) | –23.9 (–30.56 to –17.25) |
| Difference in LSM versus placebo (95% CI)[a] | –18.6 (–25.96 to –11.17) P < 0.0001 | –13.7 (–21.10 to –6.31) P = 0.0003 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –4.9 (3.76) (–12.23 to 2.52) | – | – |
| **Headache symptoms (nausea, vomiting, photophobia, phonophobia) (exploratory)** | N = 287 | N = 288 | N = 290 |
| Change from baseline in the monthly average number of days with nausea or vomiting during the 12-week period after the first dose – ANCOVA (FAS) | | | |
| LSM estimate (95% CI) | –3.2 (–3.78 to –2.66) | –3.3 (–3.85 to –2.72) | –2.2 (–2.81 to –1.68) |

| | HALO CM | | |
|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg (N = 375) | Fremanezumab 675 mg/PB/PB (N = 375) | Placebo (N = 371) |
| Difference in LSM versus placebo (95% CI)[a] | –1.0 (–1.59 to –0.36)<br>P = 0.0019 | –1.0 (–1.66 to –0.43)<br>P = 0.0009 | – |
| Difference in LSM versus quarterly (95% CI)[a] | 0.1 (–0.55 to 0.68) | – | – |
| Change from baseline in monthly average number of days with photophobia and phonophobia during the 12-week treatment period – ANCOVA (FAS) | | | |
| LSM estimate (95% CI) | –3.7<br>(–4.36 to –3.11) | –3.5<br>(–4.09 to –2.82) | –2.4<br>(–3.02 to –1.75) |
| Difference in LSM versus placebo (95% CI)[a] | –1.3<br>(–2.04 to –0.66)<br>P = 0.0001 | –1.1<br>(–1.76 to –0.37)<br>P = 0.0025 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.3<br>(–0.97 to 0.40) | – | – |
| **Patient-reported outcomes** | | | |
| **HIT-6 (secondary)** | N = 375 | N = 375 | N = 371 |
| Change from baseline (day 0) in migraine-related disability score, as measured by the HIT-6, at 4 weeks after the last (third) dose of study drug – ANCOVA results and Wilcoxon rank sum test (FAS) | | | |
| LSM estimate (95% CI) | –6.8<br>(–7.71 to –5.97) | –6.4<br>(–7.31 to –5.52) | –4.5<br>(–5.38 to –3.60) |
| Difference in LSM versus placebo (95% CI)[a] | –2.4<br>(–3.32 to –1.38)<br>P < 0.0001 | –1.9<br>(–2.90 to –0.96)<br>P < 0.0001 | – |
| Wilcoxon rank sum test (versus placebo) P value | P < 0.0001 | P = 0.0004 | |
| Difference in LSM versus quarterly (95% CI)[a] | –0.4 (–1.39 to 0.55) | – | – |
| **MSQoL (exploratory)** | N = 375 | N = 375 | N = 371 |
| Change from baseline in MSQoL during the 4 weeks after the third dose of study drug – ANCOVA (FAS) | | | |
| LSM estimate (95% CI) | 21.5 | 20.7 | 14.7 |

| | HALO CM | | |
|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg (N = 375) | Fremanezumab 675 mg/PB/PB (N = 375) | Placebo (N = 371) |
| | (19.01 to 24.08) | (18.13 to 23.31) | (12.07 to 17.24) |
| Difference in LSM versus placebo (95% CI)[a] | 6.9<br>(4.07 to 9.70)<br>P < 0.0001 | 6.1<br>(3.25 to 8.87)<br>P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | 0.8<br>(–1.97 to 3.63) | – | – |
| **EQ–5D–5L (exploratory)** | N = 375 | N = 375 | N = 371 |
| Change from baseline in EQ-5D-5L visual analogue scale ANCOVA results (FAS) | | | |
| LSM estimate (95% CI) | 4.8<br>(2.70 to 6.87) | 4.6<br>(2.50 to 6.75) | 2.2<br>(0.08 to 4.32) |
| Difference in LSM versus placebo (95% CI)[a] | 2.6<br>(0.26 to 4.90)<br>P = 0.0291 | 2.4<br>(0.11 to 4.74)<br>P = 0.0402 | – |
| Difference in LSM versus quarterly (95% CI)[a] | 0.2<br>(–2.15 to 2.47) | – | – |
| **PHQ-9 (exploratory)** | N = 375 | N = 375 | N = 371 |
| Change from baseline in Patient Health Questionnaire (PHQ-9) – ANCOVA (FAS) | | | |
| LSM estimate (95% CI) | –2.3<br>(–2.82 to –1.79) | –2.7<br>(–3.22 to –2.17) | –2.0<br>(–2.52 to –1.47) |
| Difference in LSM versus placebo (95% CI)[a] | –0.3<br>(–0.88 to 0.26)<br>P = 0.2921 | –0.7<br>(–1.27 to –0.13)<br>P = 0.0165 | – |
| Difference in LSM versus quarterly (95% CI)[a] | 0.4<br>(–0.18 to 0.96) | – | – |
| **WPAI (exploratory)** | N = 375 | N = 375 | N = 371 |
| Change from baseline in Work Productivity and Activity Impairment Questionnaire (WPAI) – ANCOVA (FAS) | | | |

| | HALO CM | | |
|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg (N = 375) | Fremanezumab 675 mg/PB/PB (N = 375) | Placebo (N = 371) |
| LSM estimate (95% CI) | –2.1 (–5.07 to 0.81) | –0.1 (–3.16 to 2.91) | 0.8 (–2.17 to 3.71) |
| Difference in LSM versus placebo (95% CI)[a] | –2.9 (–6.23 to 0.43) P = 0.0873 | –0.9 (–4.19 to 2.39) P = 0.5918 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –2.0 (–5.34 to 1.33) | – | – |
| **PGIC[b] (exploratory)** | N = 375 | N = 375 | N = 371 |
| Responder analysis by visit (FAS) | | | |
| Month 1 responder, n (%)<br>P value difference versus placebo | 201 (54)<br>P < 0.0001 | 197 (53)<br>P < 0.0001 | 114 (31) |
| Month 2 responder, n (%)<br>P value difference versus placebo | 203 (54)<br>P < 0.0001 | 198 (53)<br>P < 0.0001 | 135 (36) |
| End of treatment (visit 5) responder, n (%)<br>P value difference versus placebo | 204 (54)<br>P < 0.0001 | 206 (55)<br>P < 0.0001 | 137 (37) |

ANCOVA = analysis of covariance; CI = confidence interval; CM = chronic migraine; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; FAS = full analysis set; HIT-6 = 6-item headache impact test; LSM = least squares mean; MMD = monthly migraine day; MMRM = mixed-effects model for repeated measures; MSQoL = Migraine-Specific Quality of Life questionnaire; PB = placebo; PGIC = Patients' Global Impression of Change; PHQ = Patient Health Questionnaire; WPAI = Work Productivity and Activity Impairment.

Note: For MIDAS total score, larger scores reflect greater disability.

[a] P value for the treatment comparison is from an ANOVA with treatment group as a factor.

[b] P value based on Cochran-Mantel-Haenszel test stratified by baseline preventive medication use (yes/no).

Source: Clinical Study Reports for HALO CM.[17]

## Table 13: Key Efficacy Findings — HALO EM

| Efficacy | HALO EM | | |
|---|---|---|---|
| | Fremanezumab 225 mg/225 mg/225 mg (N = 287) | Fremanezumab 675 mg/PB/PB (N = 288) | Placebo (N = 290) |
| **Average monthly migraine days (MMDs) (primary)** | N = 287 | N = 288 | N = 290 |
| Change from baseline in the MMDs during the 12-week period after the first dose of study drug – ANCOVA results and Wilcoxon rank sum test (FAS) | | | |
| LSM estimates (95% CI) | –3.7 (–4.15 to –3.18) | –3.4 (–3.94 to –2.96) | –2.2 (–2.68 to –1.71) |
| Difference in LSM versus placebo (95% CI)[a] | –1.5 (–2.01 to –0.93) P < 0.0001 | –1.3 (–1.79 to –0.72) P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.2 (–0.75 to 0.33) | – | – |
| Wilcoxon rank sum test (versus placebo) P value | P < 0.0001 | P < 0.0001 | |
| Proportion of patients with ≥ 50% reduction in MMDs during the 12-week period after the first dose of study drug (FAS) | | | |
| Yes, n (%) | 137 (47.7) | 128 (44.4) | 81 (27.9) |
| P value compared to placebo | P < 0.0001 | P < 0.0001 | |
| **Monthly average number of headache days (exploratory)** | N = 287 | N = 288 | N = 290 |
| Monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug – ANCOVA results (FAS) | | | |
| LSM estimate (95% CI) | –2.9 (–3.34 to –2.51) | –3.0 (–3.39 to –2.55) | –1.5 (–1.88 to –1.06) |
| Difference in LSM versus placebo (95% CI)[a] | –1.5 (–1.92 to –0.99) P < 0.0001 | –1.5 (–1.96 to –1.04) P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | 0.0 (–0.42 to 0.51) | – | – |
| **Monthly number of headache hours (exploratory)** | N = 287 | N = 288 | N = 290 |
| Change from baseline in the monthly number of headache hours of any severity – MMRM results (FAS) | | | |

| | HALO EM | | |
|---|---|---|---|
| **Efficacy** | **Fremanezumab 225 mg/225 mg/225 mg (N = 287)** | **Fremanezumab 675 mg/PB/PB (N = 288)** | **Placebo (N = 290)** |
| LSM estimates (95% CI) | –23.5 (2.04)<br>(–27.50 to –19.49) | –19.8 (2.07)<br>(–23.85 to –15.72) | –11.0 (2.02)<br>(–14.95 to –7.02) |
| Difference in LSM versus placebo (95% CI)[a] | –12.5<br>(–16.99 to –8.03)<br>P < 0.0001 | –8.8<br>(–13.28 to –4.32)<br>P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –3.7<br>(–8.20 to 0.78) | – | – |
| **Use of acute headache medications (secondary)** | N = 255 | N = 245 | N = 247 |
| Change from baseline in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug – ANCOVA results and Wilcoxon rank sum test (PP) | | | |
| LSM estimate (95% CI) | –3.0<br>(–3.41 to –2.56) | –2.9<br>(–3.34 to –2.48) | –1.6<br>(–2.04 to –1.20) |
| Difference in LSM versus placebo (95% CI)[a] | –1.4<br>(–1.84 to –0.89)<br>P < 0.0001 | –1.3<br>(–1.76 to –0.82)<br>P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.1<br>(–0.55 to 0.40) | – | – |
| Wilcoxon rank sum test (versus placebo) P value | P < 0.0001 | P < 0.0001 | |
| **Headache symptoms (nausea, vomiting, photophobia, phonophobia) (exploratory)** | N = 287 | N = 288 | N = 290 |
| Change from baseline in monthly average number of days with nausea or vomiting during the 12-week treatment period – ANCOVA (FAS) | | | |
| LSM estimate (95% CI) | –2.1<br>(–2.48 to –1.74) | –1.9<br>(–2.24 to –1.48) | –1.4<br>(–1.77 to –1.03) |
| Difference in LSM versus placebo (95% CI)[a] | –0.7<br>(–1.12 to –0.29)<br>P = 0.0008 | –0.5<br>(–0.87 to –0.04)<br>P = 0.0314 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.3<br>(–0.67 to 0.16) | – | – |

| | HALO EM | | |
|---|---|---|---|
| **Efficacy** | **Fremanezumab 225 mg/225 mg/225 mg (N = 287)** | **Fremanezumab 675 mg/PB/PB (N = 288)** | **Placebo (N = 290)** |
| Change from baseline in monthly average number of days with photophobia and phonophobia during the 12-week treatment period – ANCOVA (FAS) | | | |
| LSM estimate (95% CI) | –2.4 (–2.85 to –2.02) | –2.2 (–2.62 to –1.79) | –1.5 (–1.94 to –1.12) |
| Difference in LSM versus placebo (95% CI)[a] | –0.9 (–1.36 to –0.45) P = 0.0001 | –0.7 (–1.13 to –0.22) P = 0.0038 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.2 (–0.69 to 0.23) | – | – |
| **Patient-reported outcomes** | | | |
| **EQ-5D-5L (exploratory)** | N = 287 | N = 288 | N = 290 |
| Change from baseline in EQ-5D-5L visual analogue scale ANCOVA results (FAS) | | | |
| LSM estimate (95% CI) | 3.4 (1.44 to 5.34) | 3.4 (1.40 to 5.34) | 2.3 (0.43 to 4.26) |
| Difference in LSM versus placebo (95% CI)[a] | 1.0 (–1.14 to 3.22) P = 0.3481 | 1.0 (–1.15 to 3.19) P = 0.3555 | – |
| Difference in LSM versus quarterly (95% CI)[a] | 0.0 (–2.16 to 2.20) | – | – |
| **PGIC (exploratory)** | N = 287 | N = 288 | N = 290 |
| Responder analysis by visit (FAS) | | | |
| Month 1 responder, n (%)<br>P value difference versus placebo | 178 (62)<br>P < 0.0001 | 179 (62)<br>P < 0.0001 | 113 (39)<br>— |
| Month 2 responder, n (%)<br>P value difference versus placebo | 203 (71)<br>P < 0.0001 | 187 (65)<br>P < 0.0001 | 142 (49)<br>— |
| Month 3 responder, n (%)<br>P value difference versus placebo | 206 (72)<br>P < 0.0001 | 183 (64)<br>P = 0.0018 | 147 (51)<br>— |
| **MIDAS (secondary)** | N = 287 | N = 288 | N = 290 |
| MIDAS disability scores at 4 weeks after the last dose of study drug ANCOVA results and Wilcoxon rank sum test (FAS) | | | |

| | HALO EM | | |
|---|---|---|---|
| **Efficacy** | **Fremanezumab 225 mg/225 mg/225 mg (N = 287)** | **Fremanezumab 675 mg/PB/PB (N = 288)** | **Placebo (N = 290)** |
| LSM estimate (95% CI) | –24.6 (–27.68 to –21.45) | –23.0 (–26.10 to –19.82) | –17.5 (–20.62 to –14.47) |
| Difference in LSM versus placebo (95% CI)[a] | –7.0 (–10.51 to –3.53) P < 0.0001 | –5.4 (–8.90 to –1.93) P = 0.0023 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –1.6 (–5.09 to 1.89) | – | – |
| Wilcoxon rank sum test (versus placebo) P value | P = 0.0021 | P = 0.0023 | |
| **WPAI (exploratory)** | N = 287 | N = 288 | N = 290 |
| Change from baseline in WPAI questionnaire – ANCOVA (FAS) | | | |
| LSM estimate (95% CI) | –2.9 (1.21) (–5.27 to –0.52) | –2.0 (–4.28 to 0.23) | –3.1 (–5.31 to –0.88) |
| Difference in LSM versus placebo (95% CI)[a] | 0.2 (–2.46 to 2.87) P = 0.8813 | 1.1 (–1.50 to 3.65) P = 0.4127 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.9 (–3.54 to 1.80) | – | – |
| **PHQ-9 (exploratory)** | N = 287 | N = 288 | N = 290 |
| Change from baseline in Patient Health Questionnaire (PHQ-9) – ANCOVA (FAS) | | | |
| LSM estimate (95% CI) | –1.0 (–1.31 to –0.63) | –0.6 (–0.91 to –0.23) | –0.7 (–1.03 to –0.35) |
| Difference in LSM versus placebo (95% CI)[a] | –0.3 (–0.67 to 0.10) P = 0.1473 | 0.1 (–0.26 to 0.50) P = 0.5380 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.4 (–0.78 to –0.02) | – | – |
| **MSQoL (exploratory)** | N = 287 | N = 288 | N = 290 |
| Change from baseline in MSQoL during the 4 weeks after the third dose of study drug – ANCOVA (FAS) | | | |

| Efficacy | HALO EM<br>Fremanezumab 225 mg/225 mg/225 mg (N = 287) | HALO EM<br>Fremanezumab 675 mg/PB/PB (N = 288) | HALO EM<br>Placebo (N = 290) |
|---|---|---|---|
| LSM estimate (95% CI) | 24.6<br>(22.21 to 27.00) | 21.8<br>(19.37 to 24.20) | 19.2<br>(16.88 to 21.59) |
| Difference in LSM versus placebo (95% CI)[a] | 5.4<br>(2.69 to 8.05)<br>P < 0.0001 | 2.5<br>(–0.13 to 5.22)<br>P = 0.0619 | – |
| Difference in LSM versus quarterly (95% CI)[a] | 2.8<br>(0.15 to 5.50) | – | – |

ANCOVA = analysis of covariance; CI = confidence interval; EM = episodic migraine; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; FAS = full analysis set; LSM = least squares mean; MIDAS = migraine disability assessment score; MMD = monthly migraine day; MMRM = mixed-effects model for repeated measures; MSQoL = Migraine-Specific Quality of Life questionnaire; PB = placebo; PGIC = Patients' Global Impression of Change; PHQ = Patient Health Questionnaire; PP = per-protocol; WPAI = Work Productivity and Activity Impairment.

[a] P value for the treatment comparison is from an ANOVA with treatment group as a factor.

Note: For MIDAS total score, larger scores reflect greater disability.
Source: Clinical Study Reports for HALO EM.[18]

## Table 14: Key Efficacy Results — FOCUS

| Efficacy | FOCUS<br>Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 283) | FOCUS<br>Fremanezumab 675 mg/PB/PB (N = 276) | FOCUS<br>Placebo (N = 278) |
|---|---|---|---|
| **Average MMDs (primary)** | | | |
| Change from baseline in MMDs during the 12-week double-blind treatment period – ANCOVA (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| LSM estimate (95% CI) | –4.1<br>(–4.73 to –3.41) | –3.7<br>(–4.38 to –3.05) | –0.6<br>(–1.25 to 0.07) |
| Difference in LSM versus placebo (95% CI)[a] | –3.5<br>(–4.19 to –2.78)<br>P < 0.0001 | –3.1<br>(–3.84 to –2.42)<br>P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.4<br>(–1.06 to 0.35) | – | – |

| | FOCUS | | |
|---|---|---|---|
| **Efficacy** | **Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 283)** | **Fremanezumab 675 mg/PB/PB (N = 276)** | **Placebo (N = 278)** |
| Change from baseline in MMDs during month 6 (open-label mITT analysis set) | N = 261 | N = 259 | N = 253 |
| Month 6 change from baseline, mean (SD) | –5.8 (5.59) | –5.8 (5.18) | –5.0 (5.68) |
| Change from baseline in MMDs 12 weeks after fourth dose (open-label mITT analysis set) | N = 272 | N = 271 | N = 263 |
| 12 weeks after dose 4 change from baseline, mean (SD) | –5.5 (4.96) | –5.1 (4.71) | –4.7 (5.41) |
| **Proportion patients ≥ 50% reduction in average MMDs (secondary)** | N = 283 | N = 276 | N = 278 |
| Proportion of patients reaching ≥ 50% reduction in the MMDs during the 12-week period after the first dose of fremanezumab (double-blind mITT analysis set) | | | |
| Responders, n (%) | 97 (34) | 95 (34) | 24 (9) |
| Responder common OR (95% CI) versus placebo[b] | 5.82 (3.56 to 9.51)<br>P < 0.0001 | 5.84 (3.57 to 9.55)<br>P < 0.0001 | – |
| Proportion of patients reaching ≥ 50% reduction in the MMDs 12 weeks after fourth dose (open-label mITT analysis set) | N = 272 | N = 271 | N = 263 |
| Responder, n (%) | 125 (46) | 123 (45) | 100 (38) |
| **Monthly average number of headache days of at least moderate severity (secondary)** | | | |
| Change from baseline in monthly average number of headache days of at least moderate severity during the 12-week double-blind treatment period (ANCOVA results) (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| LSM estimate (95% CI) | –4.2<br>(–4.89 to –3.58) | –3.9<br>(–4.51 to –3.19) | –0.6<br>(–1.28 to 0.03) |
| Difference in LSM versus placebo (95% CI) [a] | –3.6<br>(–4.30 to –2.91)<br>P < 0.0001 | –3.2<br>(–3.93 to –2.52)<br>P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI) [a] | –0.4<br>(–1.08 to 0.32) | – | – |

| | FOCUS | | |
|---|---|---|---|
| **Efficacy** | **Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 283)** | **Fremanezumab 675 mg/PB/PB (N = 276)** | **Placebo (N = 278)** |
| Change from baseline in monthly average number of headache days of at least moderate severity during the 12-week OLTP (open-label mITT analysis set) | N = 261 | N = 259 | N = 253 |
| Month 6 change from baseline, mean (SD) | –5.3 (5.29) | –5.3 (5.02) | –4.7 (5.32) |
| **Monthly average number of days of use of any acute headache medication (secondary)** | | | |
| Change from baseline in monthly average number of days of use of any acute headache medication during the 12-week double-blind treatment period (ANCOVA results) (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| LSM estimate (95% CI) | –3.9 (–4.58 to –3.32) | –3.7 (–4.30 to –3.03) | –0.6 (–1.21 to 0.04) |
| Difference in LSM versus placebo (95% CI)[a] | –3.4 (–4.03 to –2.69) P < 0.0001 | –3.1 (–3.75 to –2.41) P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.3 (–0.96 to 0.39) | – | – |
| Change from baseline in monthly average number of days of use of any acute headache medication during the 12-week OLTP (open-label mITT analysis set) | N = 250 | N = 246 | N = 248 |
| Month 6 change from baseline, mean (SD) | –4.7 (5.37) | –5.2 (4.98) | –4.4 (5.32) |
| **Headache symptoms (nausea, vomiting, photophobia, phonophobia) (exploratory)** | | | |
| Change from baseline in monthly average number of days with nausea or vomiting during the 12-week treatment period – ANCOVA (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| LSM estimate (95% CI) | –2.6 (–3.14 to –2.08) | –2.5 (–3.00 to –1.94) | –0.5 (–1.06 to –0.01) |
| Difference in LSM versus placebo (95% CI)[a] | –2.1 (–2.64 to –1.52) | –1.9 (–2.50 to –1.37) P < 0.0001 | – |

| Efficacy | FOCUS | | |
|---|---|---|---|
| | Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 283) | Fremanezumab 675 mg/PB/PB (N = 276) | Placebo (N = 278) |
| | P < 0.0001 | | |
| Difference in LSM versus quarterly (95% CI)[a] | –0.1 (–0.71 to 0.42) | – | – |
| Change from baseline in monthly average number of days with photophobia and phonophobia during the 12-week double-blind treatment period – ANCOVA (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| LSM estimate (95% CI) | –3.1 (–3.77 to –2.51) | –2.6 (–3.26 to –1.99) | –0.4 (–1.02 to 0.24) |
| Difference in LSM versus placebo (95% CI)[a] | –2.8 (–3.42 to –2.08) P < 0.0001 | –2.2 (–2.91 to –1.56) P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.5 (–1.19 to 0.16) | – | – |
| Changes from baseline 12-weeks after dose 4 in monthly number of days with nausea or vomiting (open-label mITT analysis set) | N = 271 | N = 270 | N = 261 |
| Mean (SD) | –3.0 (4.44) | –3.1 (4.46) | –2.3 (4.55) |
| Changes from baseline 12-weeks after dose 4 in monthly number of days with photophobia or phonophobia (open-label mITT analysis set) | N = 271 | N = 270 | N = 261 |
| Mean (SD) | –4.0 (5.19) | –3.4 (5.27) | –3.1 (5.27) |
| **Patient-reported outcomes** | | | |
| **HIT-6 (exploratory)** | | | |
| Change from baseline at in HIT-6, at 4 weeks after administration of the third dose (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| LSM estimate (95% CI) | –6.1 (–7.12 to –4.99) | –5.2 (–6.29 to –4.13) | –2.2 (–3.31 to –1.17) |
| Difference in LSM versus placebo (95% CI) [a] | –3.8 (–4.95 to –2.69) P < 0.0001 | –3.0 (–4.10 to –1.83) P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.8 | – | – |

| Efficacy | FOCUS | | |
|---|---|---|---|
| | Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 283) | Fremanezumab 675 mg/PB/PB (N = 276) | Placebo (N = 278) |
| | (–1.98 to 0.28) | | |
| Change from baseline to end of treatment (visit 8) in HIT-6 (open-label mITT analysis set) | N = 258 | N = 255 | N = 251 |
| Mean (SD) | –8.3 (7.38) | –8.4 (8.02) | –7.6 (8.12) |
| **MIDAS (exploratory)** | | | |
| Change from baseline in disability score as measured by the MIDAS during the 4 weeks after the third dose of study drug (ANCOVA results) (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| LSM estimate (95% CI) | –24.7 (–31.09 to –18.38) | –19.7 (–26.19 to –13.30) | –7.0 (–13.39 to –0.66) |
| Difference in LSM versus placebo (95% CI)[a] | –17.7 (–24.45 to –10.97) P < 0.0001 | –12.7 (–19.48 to –5.95) P = 0.0002 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –5.0 (–11.73 to 1.75) | – | – |
| Change from baseline to end of treatment (visit 8) in MIDAS (open-label mITT analysis set) | N = 258 | N = 255 | N = 251 |
| Mean (SD) | –33.9 (43.73) | –29.9 (42.43) | –27.3 (48.18) |
| **WPAI (exploratory)** | | | |
| Change from baseline in Work Productivity and Activity Impairment Questionnaire (WPAI) during the 4 weeks after the third dose – ANCOVA (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| LSM estimate (95% CI) | –5.3 (–9.47 to –1.19) | –4.7 (–8.96 to –0.49) | –0.5 (–4.72 to 3.80) |
| Difference in LSM versus placebo (95% CI)[a] | –4.9 (–9.26 to –0.47) P = 0.0302 | –4.3 (–8.67 to 0.15) P = 0.0584 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.6 (–4.96 to 3.75) | – | – |

| | FOCUS | | |
|---|---|---|---|
| **Efficacy** | **Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 283)** | **Fremanezumab 675 mg/PB/PB (N = 276)** | **Placebo (N = 278)** |
| Changes from baseline to end of treatment (visit 8) in WPAI (open-label mITT analysis set) | N = 176 | N = 174 | N = 159 |
| Mean (SD) | –6.9 (23.33) | –4.9 (28.28) | –4.0 (22.54) |
| **PHQ-9 (exploratory)** | | | |
| Change from baseline in PHQ-9 during the 4 weeks after the third dose of study drug – ANCOVA (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| LSM estimate (95% CI) | –1.8 (–2.42 to –1.08) | –1.3 (–2.01 to –0.65) | –0.7 (–1.37 to –0.03) |
| Difference in LSM versus placebo (95% CI)[a] | –1.1 (–1.76 to –0.34) P = 0.0037 | –0.6 (–1.34 to 0.08) P = 0.0823 | – |
| Difference in LSM versus quarterly (95% CI)[a] | –0.4 (–1.13 to 0.29) | – | – |
| Change from baseline to end of treatment (visit 8) in PHQ-9 (open-label mITT analysis set) | N = 258 | N = 255 | N = 251 |
| Mean (SD) | –1.6 (5.52) | –2.4 (5.26) | –2.0 (4.89) |
| **MSQoL (exploratory)** | | | |
| Change from baseline in MSQoL during the 4 weeks after the third dose – ANCOVA (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| LSM estimate (95% CI) | 17.5 (14.59 to 20.40) | 15.7 (12.77 to 18.66) | 6.9 (3.99 to 9.80) |
| Difference in LSM versus placebo (95% CI)[a] | 10.6 (7.52 to 13.69) P < 0.0001 | 8.8 (5.73 to 11.92) P < 0.0001 | – |
| Difference in LSM versus quarterly (95% CI)[a] | 1.8 (–1.31 to 4.86) | – | – |
| Changes from baseline to end of treatment (visit 8) in MSQoL role function–restrictive (open-label mITT analysis set) | N = 258 | N = 255 | N = 251 |
| Mean (SD) | 22.9 (21.26) | 24.6 (21.91) | 20.8 (20.46) |

| Efficacy | FOCUS | | |
|---|---|---|---|
| | Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 283) | Fremanezumab 675 mg/PB/PB (N = 276) | Placebo (N = 278) |
| **EQ-5D-5L (exploratory)** | | | |
| Change from baseline in EQ-5D-5L VAS during the 4 weeks after the third dose – ANCOVA (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| LSM estimate (95% CI) | 7.2<br>(4.50 to 9.95) | 4.7<br>(1.88 to 7.42) | 1.6<br>(–1.08 to 4.37) |
| Difference in LSM versus placebo (95% CI)[a] | 5.6<br>(2.69 to 8.47)<br>P = 0.0002 | 3.0<br>(0.10 to 5.91)<br>P = 0.0426 | – |
| Difference in LSM versus quarterly (95% CI)[a] | 2.6<br>(–0.31 to 5.46) | – | – |
| Changes from baseline to end of treatment (visit 8) EQ-5D-5L VAS (open-label mITT analysis set) | N = 258 | N = 255 | N = 251 |
| Mean (SD) | 7.3 (21.05) | 8.0 (19.64) | 6.6 (20.99) |
| **PGIC (exploratory)** | | | |
| Responder analysis by visit (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| Month 1 responder, n (%)<br>P value difference versus placebo | 168 (59)<br>P < 0.0001 | 162 (59)<br>P < 0.0001 | 76 (27) |
| Month 3 responder, n (%)<br>P value difference versus placebo | 182 (64)<br>P < 0.0001 | 160 (58)<br>P < 0.0001 | 81 (29) |
| End of treatment (visit 8) OLTP, n (%) | 205 (75) | 209 (77) | 181 (69) |
| **MIDAS (exploratory)** | | | |
| Change from baseline in MIDAS during the 4 weeks after the third dose – ANCOVA (double-blind mITT analysis set) | N = 283 | N = 276 | N = 278 |
| LSM estimate (95% CI) | –24.7<br>(–31.09 to –18.38) | –19.7<br>(–26.19 to –13.30) | –7.0<br>(–13.39 to –0.66) |
| Difference in LSM versus placebo (95% CI)[a] | –17.7<br>(–24.45 to –10.97)<br>P < 0.0001 | –12.7<br>(–19.48 to –5.95)<br>P = 0.0002 | – |

| | FOCUS | | |
|---|---|---|---|
| **Efficacy** | **Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 283)** | **Fremanezumab 675 mg/PB/PB (N = 276)** | **Placebo (N = 278)** |
| Difference in LSM versus quarterly (95% CI)[a] | –5.0 (–11.73 to 1.75) | – | – |
| Changes from baseline to end of treatment (visit 8) MIDAS (open-label mITT analysis set) | N = 258 | N = 256 | N = 252 |
| Mean (SD) | 27.9 (47.43) | 32.7 (50.15) | 36.0 (49.77) |

ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; HIT-6 = 6-item headache impact test; LSM = least squares mean; MIDAS = migraine disability assessment score; mITT = modified intention-to-treat; MMD = monthly migraine day; MSQoL = Migraine-Specific Quality of Life questionnaire; OLTP = open-label treatment period; OR = odds ratio; PB = placebo; PGIC = Patients' Global Impression of Change; PHQ = Patient Health Questionnaire; SD = standard deviation; VAS = visual analogue scale; WPAI = Work Productivity and Activity Impairment.

Note: The ANCOVA model includes treatment, gender, region, special group of treatment failure (yes/no), migraine classification (EM/CM), and treatment × migraine classification as fixed effects and baseline number of HIT-6 and years since onset of migraine as covariates.

Note: Fremanezumab monthly is 675 mg/225 mg/225 mg for CM patients and 225 mg/225 mg/225 mg for EM patients. Fremanezumab quarterly is 675 mg/placebo/placebo for both CM and EM patients.

[a] P value for the treatment comparison is from an ANOVA with treatment group as a factor.

Source: Clinical Study Reports for FOCUS.[19]

## Harms

Only those harms identified in the review protocol are reported in this section. See Table 15 and Table 16 for detailed harms data.

### *Adverse Events*

Most patients in HALO CM and HALO EM experienced at least 1 AE, with the fewest events occurring in the placebo groups (64% and 58% in HALO CM and HALO EM, respectively) as compared with the fremanezumab groups (66% to 71%, respectively) (Table 35). The most frequent AEs were injection-site reactions, primarily injection-site–related pain.

During the DBTP of FOCUS, 49% of patients in the fremanezumab 675 mg/225 mg/225 mg treatment group, 40% of patients in the fremanezumab 225 mg/225 mg/225 mg treatment group, 55% of patients in the fremanezumab 675 mg/placebo/placebo treatment group, and 48% of patients in the placebo treatment group reported at least 1 AE (Table 16). As in the other 2 studies, injection-site reactions were the most common AEs.

During the OLTP and follow-up period of FOCUS, 60% of patients in the fremanezumab 675 mg/225 mg/225 mg double-blind treatment group, 51% of patients in the fremanezumab 225 mg/225 mg/225 mg double-blind treatment group, 55% of patients in the fremanezumab 675 mg/placebo/placebo double-blind treatment group, and 52% of patients in the placebo double-blind treatment group reported at least 1 AE.

### *Serious Adverse Events*

SAEs occurred in 2% or less of patients in all 3 studies, except in the OLTP and follow-up period of FOCUS, in which they occurred in 3% of patients in the fremanezumab 675 mg/225 mg/225 mg double-blind treatment group, 3% of patients in the fremanezumab 675 mg/placebo/placebo double-blind treatment group, 3% of patients in the placebo double-blind treatment group, and < 1% of patients in the fremanezumab 225 mg/225 mg/225 mg double-blind treatment group.

### *Withdrawals Due to Adverse Events*

Withdrawals due to AEs occurred in 2% or less patients across all 3 studies.

### *Mortality*

In the HALO CM study, 1 patient in the 675 mg/placebo/placebo treatment group died on study day 69. The cause of death was chronic obstructive pulmonary disease, as indicated by the autopsy report. The investigator assessed the AE as unrelated to the study drug.

In the HALO EM study, 1 patient in the 675 mg/placebo/placebo treatment group died 110 days after administration of the first dose of study drug. In the opinion of the medical examiner, the patient died as a result of the toxic effect of a markedly elevated level of diphenhydramine in the blood (most consistent with an intentional overdose [suicide]).

No deaths occurred in the FOCUS study.

*Notable Harms*

AEs of interest to the review were pre-specified in the review protocol and are listed in Table 15 and Table 16. One patient in the placebo group of HALO EM experienced a serious injection-site reaction. Otherwise, the other notable AEs were unremarkable and occurred in 1% or less of patients.

## Table 15: Summary of Harms — HALO CM and HALO EM

| | HALO CM | | | HALO EM | | |
|---|---|---|---|---|---|---|
| **Harms** | **Fremanezumab 675 mg/225 mg/225 mg (N = 379)** | **Fremanezumab 675 mg/PB/PB (N = 376)** | **Placebo (N = 375)** | **Fremanezumab 225 mg/225 mg/225 mg (N = 290)** | **Fremanezumab 675 mg/PB/PB (N = 291)** | **Placebo (N = 293)** |
| **Adverse events** | | | | | | |
| ≥1 AE, n (%) | 270 (71) | 265 (70) | 240 (64) | 192 (66) | 193 (66) | 171 (58) |
| Death | 0 | 1 (< 1) | 0 | 0 | 1 | 0 |
| AEs reported in > 2% of patients in any group, n (%) | | | | | | |
| Injection-site reactions | | | | | | |
| Pain | 99 (26) | 114 (30) | 104 (28) | 87 (30) | 86 (30) | 76 (26) |
| Induration | 90 (24) | 74 (20) | 68 (18) | 71 (24) | 57 (20) | 45 (15) |
| Erythema | 75 (20) | 80 (21) | 60 (16) | 52 (18) | 55 (19) | 41 (14) |
| Hemorrhage | 8 (2) | 7 (2) | 10 (3) | 3 (1) | 9 (3) | 6 (2) |
| Infections | | | | | | |
| Nasopharyngitis | 15 (4) | 19 (5) | 20 (5) | 11 (4) | 11 (4) | 9 (3) |
| Upper respiratory tract infection | 16 (4) | 18 (5) | 15 (4) | 16 (6) | 11 (4) | 15 (5) |
| Sinusitis | 4 (1) | 10 (3) | 10 (3) | 4 (1) | 2 (< 1) | 8 (3) |
| Urinary tract infection | 5 (1) | 4 (1) | 7 (2) | 7(2) | 10 (3) | 4 (1) |
| Nervous system disorders | | | | | | |
| Dizziness | 11 (3) | 9 (2) | 5 (1) | 3 (1) | 0 | 4 (1) |
| Gastrointestinal disorders | | | | | | |
| Nausea | 6 (2) | 4 (1) | 11 (3) | 4 (1) | 7 (2) | 5 (2) |
| **Serious adverse events** | | | | | | |
| Patients with a SAE, n (%) | 5 (1) | 3 (< 1) | 6 (2) | 3 (1) | 3 (1) | 7 (2) |
| Occurring in > 1 patient | | | | | | |
| Respiratory, thoracic, and mediastinal disorders | 0 | 1 (< 1) | 2 (< 1) | NR | NR | NR |

| Harms | HALO CM | | | HALO EM | | |
|---|---|---|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg (N = 379) | Fremanezumab 675 mg/PB/PB (N = 376) | Placebo (N = 375) | Fremanezumab 225 mg/225 mg/225 mg (N = 290) | Fremanezumab 675 mg/PB/PB (N = 291) | Placebo (N = 293) |
| Injury, poisoning, and procedural complications | 1 (< 1) | 1 (< 1) | 1 (< 1) | 0 | 1 (< 1) | 2 (< 1) |
| Nervous system disorders | 0 | 0 | 1 (< 1) | 1 (< 1) | 0 | 2 (< 1) |
| **Withdrawal due to adverse event** | | | | | | |
| AEs leading to discontinuation, n (%) | 7 (2) | 5 (1) | 8 (2) | 5 (2) | 5 (2) | 5 (2) |
| **AEs of special interest** | | | | | | |
| Hypersensitivity (SAE) | NR | NR | NR | 0 | 0 | 1 (< 1) |
| Vascular disorders | | | | | | |
| Hypertension | NR | NR | NR | 0 | 3 (1) | 2 (< 1) |
| Investigations, n (%) | | | | | | |
| Alanine aminotransferase increased | 3 (< 1) | 2 (< 1) | 1 (< 1) | 2 (< 1) | 1 (< 1) | 0 |
| Aspartate aminotransferase increased | 2 (< 1) | 3 (< 1) | 0 | 3 (1) | 1 (< 1) | 0 |
| Blood bilirubin increased | 0 | 2 (< 1) | 0 | 1 (< 1) | 0 | 1 (< 1) |
| Liver function test abnormal | 2 (< 1) | 0 | 1 (< 1) | NR | NR | NR |
| Hepatic enzyme increased | 1 (< 1) | 0 | 0 | 2 (< 1) | 1 (< 1) | 0 |
| Eye disorders | 3 (< 1) | 0 | 1 (< 1) | NR | NR | NR |
| Infections and infestations | 1 (< 1) | 2 (< 1) | 0 | NR | NR | NR |

AE = adverse event; CM = chronic migraine; EM = episodic migraine; SAE = serious adverse event, NR = not reported; PB = placebo; SAE = serious adverse event.

Note: All patients in the OLTP received fremanezumab 225 mg monthly.
Source: Clinical Study Reports for HALO CM[17] and HALO EM.[18]

## Table 16: Summary of Harms — FOCUS

| | FOCUS | | | |
|---|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg | Fremanezumab 225 mg/225 mg/225 mg | Fremanezumab 675 mg/PB/PB | Placebo |
| **Double-blind safety analysis set** | N = 174 | N = 111 | N = 276 | N = 277 |
| **Adverse events** | | | | |
| Patients with an AE, n (%) | 85 (49) | 44 (40) | 151 (55) | 134 (48) |
| Occurring in > 5% of patients | | | | |
| Injection-site erythema | 12 (7) | 4 (4) | 19 (7) | 15 (5) |
| Injection-site induration | 10 (6) | 3 (3) | 12 (4) | 12 (4) |
| Nasopharyngitis | 6 (3) | 1 (< 1) | 13 (5) | 11 (4) |
| **Serious adverse events** | | | | |
| Patients with an SAE, n (%) | 3 (2) | 1 (< 1) | 2 (< 1) | 4 (1) |
| Deaths | 0 | 0 | 0 | 0 |
| **Withdrawal due to adverse event** | | | | |
| AE leading to discontinuation of investigational product, n (%) | 3 (2) | 1 (< 1) | 1 (< 1) | 3 (1) |
| **Open-label treatment period** | N = 168 | N = 106 | N = 271 | N = 262 |
| **Adverse events** | | | | |
| Patients with an AE, n (%) | 101 (60) | 54 (51) | 149 (55) | 137 (52) |
| Occurring in > 5% of patients | | | | |
| Injection-site erythema | 15 (9) | 7 (7) | 15 (6) | 13 (5) |
| Injection-site induration | 11 (7) | 4 (4) | 11 (4) | 13 (5) |
| Nasopharyngitis | 13 (8) | 6 (6) | 21 (8) | 23 (9) |
| Migraine | 6 (4) | 2 (2) | 12 (4) | 14 (5) |
| **Serious adverse events** | | | | |
| Patients with an SAE, n (%) | 6 (4)[a] | 1 (< 1)[a] | 7 (3) | 9 (3) |

| | FOCUS | | | |
|---|---|---|---|---|
| | Fremanezumab 675 mg/225 mg/225 mg | Fremanezumab 225 mg/225 mg/225 mg | Fremanezumab 675 mg/PB/PB | Placebo |
| Deaths | 0 | 0 | 0 | 0 |
| **Withdrawal due to adverse event** | | | | |
| AE leading to discontinuation of investigational product, n (%) | 2 (1) | 0 | 1 (< 1) | 4 (2) |

AE = adverse event; PB = placebo; SAE = serious adverse event.

Note: All patients in the OLTP of the study received fremanezumab 225 mg monthly.

[a] Two events of retinal tear (1 occurring in the fremanezumab monthly 675 mg/225 mg/225 mg double-blind treatment group and 1 occurring in the fremanezumab monthly 225 mg/225 mg/225 mg double-blind treatment group) were not included as SAEs/protocol-defined AEs of special interest in the locked database and are thus not reflected in the respective summaries and listings.

Source: Clinical Study Reports for FOCUS.[19]

## Critical Appraisal

### *Internal Validity*

Randomization procedures and blinding methods were appropriate in all the trials, and, furthermore, the baseline demographic and disease characteristics were balanced. No significant concerns were identified concerning the validity of key outcome measures (e.g., MMD) in the conduct of the trials. Approximately 10% of patients discontinued the studies, which the clinical expert noted was reasonable within the migraine population. The number of AEs and withdrawals due to AEs were low across all studies. It was unlikely that early discontinuation due to AEs would have significant impact on the assessment of treatment effect. Fremanezumab was associated with a higher incidence of injection-site reactions than placebo, but the severity of such reactions did not differ significantly between the comparison groups. Overall, the quality of the 3 included trials was considered reasonable.

The FOCUS study included an open-label extension phase of up to 46 weeks after the end of the 12-week randomized treatment period. This extension phase helped to monitor the long-term effect of the drug, particularly safety, which was largely unknown based on the other two 12-week trials. However, the observation of long-term efficacy could have been compromised owing to the unblinding, which would more likely bias patients' reporting of headache or migraine, or related subjective outcome measures, such as HIT-6, MIDAS, and MSQoL.

All study patients were trained in the proper use of the diary to record their migraine days. Missing data were still likely a concern, particularly when missingness differed between the 2 comparison arms. The included trials took the following approach to handling the missing data. If patients had less than 10 days of electronic daily diary entries per 28 days, the monthly number of days/hours of efficacy outcomes were considered as missing. If patients had at least 10 days of daily data for 28 days, the monthly number of days/hours of efficacy outcomes (e.g., MMD) versus were prorated to 28 days for that month. Overall, the 2 approaches are seemed appropriate. However, the use of the prorating method would also rely on the random missing assumption; if this assumption did not hold, it may have introduced bias. For example, patients whose symptoms worsened may have been less likely to complete the daily assessments.

A multiple imputation method was applied, in which all continuous efficacy outcomes were analyzed by an ANCOVA method or the Wilcoxon rank sum test. The efficacy results were confirmed by MMRM, which could have accounted for missing data under the missing-at-random assumption. Multiplicity was adjusted for in analyses of primary and secondary efficacy outcomes.

Various studies have assessed the validity, reliability, and responsiveness of the outcome measures, including the use of MSQoL, HIT-6, and MIDAS. In general, the scales have moderate to high reliability and are valid in measuring the impact of the CM or EM on patients' disability and quality of life under a double-blind and controlled setting. Statistical inference on those outcomes was limited for various reasons, primarily the exploratory nature of such analysis.

### *External Validity*

The high selectivity of the study population, based on a stringent list of eligibility criteria, in the included studies may restrict generalizability to the general migraine population.

Although restricting eligibility helped to prevent influence of previous preventive treatments on the results, all 3 studies excluded patients who had prior experience in use of OnaA (for migraine or other reason) within the previous few months or prior exposure to a mAb with the CGRP pathway, as well as many other treatments for migraine. Therefore, it remained unknown whether fremanezumab would have similar beneficial effects in those patients who had failed the prior treatments, particularly treatments within the same CGRP drug class (e.g., erenumab). On the other hand, the HALO trials excluded patients who had previously failed at least 2 of the selected medications (e.g., divalproex sodium, sodium valproate), whereas the FOCUS trial included only patients who had failed 2 to 4 prior treatments. It is likely the beneficial effect was consistently observed, regardless of patients' prior treatments with non-CGRP medications, particularly in those who failed the prior treatments.

The HALO trials required approximately 85% compliance with the electronic headache diary during the run-in period (defined as entry of headache data on minimum 24 of 28 days); similarly, the FOCUS study required 75% compliance. Given that a high compliance with regular treatments over years or even decades is of key to preventing migraine, the observed treatment effect may not reflect how the drug would be used in a "real world" setting, in which a high proportion of patients could miss doses, leading to less optimal effects than those observed in the controlled trial, particularly in the case of SC instead of an oral administration. Patients with major cardiovascular and other major comorbid diseases, including psychiatric disorders, or unfavourable laboratory test results on liver function, for example, were excluded from this study, thus limiting full extrapolation of the safety data to the general population. The clinical expert indicated that patients with CM commonly experience psychiatric disorders such as depression. Since patients with a history of psychiatry disorders were excluded from these trials, the generalizability of the study results to migraine population may be limited.

In the FOCUS trial, the presence of EM and CM during the baseline period was evaluated by the use of triptans or ergot derivatives to treat an established headache, which is not an established ICHD-3 criterion. This may restrict the comparability of the FOCUS results to other trials. Also, the FOCUS trial considered valproic acid as a separate class of preventive medication, rather than as an anticonvulsant. Thus, patients not responding to another anticonvulsant therapy and valproic acid were considered to have not responded to 2 classes of previous migraine preventive therapies. Despite the strict inclusion and exclusion criteria for FOCUS, the clinical expert indicated that the study population was representative of the general migraine population.

Patients in all studies were able to continue the use of acute headache medications, agreeing with headache guidelines that allow preventive migraine therapy in combination with acute treatment. In HALO CM, a subset of patients (specified not to exceed 30% of the participants) were allowed to use 1 concomitant migraine preventive medication, and no changes in these medications were allowed until the last study assessments were completed. In HALO EM, concomitant medication use was monitored throughout the study. In FOCUS, patients were required not to be receiving any migraine preventive medications at the time of screening and were not allowed to initiative any migraine preventive medications during the run-in and treatment periods. The use of concomitant medications was diverse across the trials.

Finally, the included trials could not assess the long-term effects of fremanezumab beyond 3 months. No direct comparative effect was studied between fremanezumab and other available CGRP medications.

## Indirect Evidence

### Objectives and Methods for the Summary of Indirect Evidence

The sponsor submitted an ITC because of the lack of direct evidence comparing fremanezumab with other treatments for migraine.

CADTH also conducted a literature search and identified 1 ITC of fremanezumab versus other migraine therapies that was conducted and published by the ICER.[47]

### Description of Indirect Comparisons

The sponsor-submitted ITC was conducted with a systematic review of drugs for CM or EM, and eligible studies were further analyzed under a Bayesian NMA approach. Similarly, the ICER ITC performed a systematic review of drugs for patients with CM or EM. The population, intervention, comparators, outcomes, and study design (PICOS) for study selection in both ITCs are presented in Table 17.

**Table 17: Study Selection Criteria and Methods for ITCs**

| | Sponsor-submitted NMA | ICER ITC |
|---|---|---|
| **Population** | Adults (≥ 18 to 70 years old) with a history of chronic or episodic migraine (according to the criteria of the ICHD-3) for at least 12 months before screening | Adults (≥ 18 years) with episodic or chronic migraine who are eligible for preventive migraine therapy<br>• Chronic migraine defined as ≥ 15 headache days per month for at least 3 months and migraine symptoms present on at least 8 days per month<br>• Episodic migraine defined as migraines that are not classified as chronic migraine |
| **Intervention** | Fremanezumab | CGRP inhibitors:<br>• Erenumab (70 mg, 140 mg)<br>• Fremanezumab<br>• Galcanezumab |
| **Comparator** | • Anti-CGRP<br>• Erenumab<br>• Galcanezumab<br>• Eptinezumab<br>• Propranolol or timolol maleate<br>• Topiramate<br>• Flunarizine hydrochloride<br>• Pizotifen malate<br>• Onabotulinum toxin A<br>• Amitriptyline<br>• Gabapentin<br>• Metoprolol<br>• Atenolol<br>• Divalproex/valproate<br>• Atogepant<br>• Placebo | • Placebo<br>• Topiramate<br>• Propranolol<br>• Amitriptyline<br>• Onabotulinum toxin A |
| **Outcome** | • Change from baseline in monthly migraine days | • Change from baseline in monthly migraine days<br>• Change from baseline in headache days |

| | Sponsor-submitted NMA | ICER ITC |
|---|---|---|
| | • Change from baseline in days using acute medication per month<br>• ≥ 50% reduction in migraine days<br>• ≥ 75% reduction in migraine days | • Change from baseline in days using acute medication per month<br>• ≥ 50% reduction in migraine days<br>• Quality of life (MIDAS, HIT-6, MSQoL)<br>• All-cause discontinuations<br>• Discontinuations from adverse events<br>• Adverse events reported by ≥ 5% patients in a trial arm<br>• SAEs |
| **Study design** | • Phase III RCTs<br>• Phase II RCTs for anti-CGRPs only | • RCTs<br>• Crossover studies if results before crossover were presented<br>• Nonrandomized comparative studies with at least 100 patients<br>• OLEs of RCTs<br>• Noncomparative observational studies with at least 100 patients and 6-month follow-up |
| **Publication characteristics** | • English language<br>• Published 1996 onwards | English language |
| **Exclusion criteria** | • Trials that included any patients who fall outside of the eligible age range<br>• Populations that focused on acute, cluster, tension, medication overuse, or menstrual-related headaches<br>• Use of interventions or devices for migraine (e.g., nerve blocks and transcranial magnetic stimulation) during the 2 months before screening<br>• Use of opioid or barbiturate medications on more than 4 days during the pre-intervention period<br>• Bisoprolol<br>• Nadolol<br>• Nortriptyline<br>• Candesartan<br>• Ubrogepant<br>• Rimegepant<br>• Lasmiditan<br>• Use of the interventions as combination therapy<br>• Observational studies, case studies, open-label extension, or crossover studies<br>• Studies that did not explicitly state that they were randomized<br>• Studies in languages other than English | NR |
| **Databases searched** | • MEDLINE<br>• Embase<br>• Epub Ahead of Print<br>• Cochrane library | • MEDLINE<br>• Embase<br>• Cochrane library |
| **Selection process** | Two independent reviewers with discrepancy solved through a consensus meeting | Two independent reviewers with discrepancy solved through a consensus meeting |
| **Data extraction process** | Single reviewer with a second reviewer confirming accuracy | Single reviewer with a second reviewer confirming accuracy |

| | Sponsor-submitted NMA | ICER ITC |
|---|---|---|
| **Quality assessment** | Checklist for the National Institute for Health and Care Excellence (NICE) single-technology appraisal | US Preventive Services Task Force (USPSTF) criteria |

CGRP = calcitonin gene–related peptide; HIT-6 = 6-item headache impact test; ICER = Institute for Clinical and Economic Review; ICHD-3 = International Classification of Headache Disorders, third edition; ITC = indirect treatment comparison; MIDAS = migraine disability assessment score; MSQoL = Migraine-Specific Quality of Life questionnaire; NMA = network meta-analysis; NR = not reported; OLE = open-label extension; RCT = randomized controlled trial.

Source: CDR submission: Ajovy (fremanezumab), 225 mg in 1.5 mL (150 mg/mL) solution for subcutaneous injection [CONFIDENTIAL sponsor's submission]. In: Montreal (QC): Teva Canada Innovation; 2020 Jun 3.[15] The Institute for Clinical and Economic Review.[4,7]

## Methods of Sponsor-Submitted ITC

### *Objectives*

The sponsor aimed to determine the indirect comparative efficacy of fremanezumab versus other anti-CGRPs therapies and OnaA in patients with migraine based on their previous experience with preventive treatments. The sponsor provided the following rationale for conducting this indirect assessment: the lack of direct evidence comparing the clinical effectiveness of fremanezumab versus other treatments for migraine, particularly versus anti-CGRP therapies, and the lack of indirect evidence of such comparisons based on patients' previous experience with migraine preventive treatments. Specifically, the sponsor ITC aimed to provide the comparative effectiveness of fremanezumab in EM and CM in the following patient population:

- Patients who had an inadequate response to 2 or more prior preventive migraine treatments due to efficacy, safety, or tolerability reasons
- Patients who had an inadequate response to 3 or more prior preventive migraine treatments due to efficacy, safety, or tolerability reasons
- Patients who had an inadequate response to fewer than 2 prior preventive migraine treatments due to efficacy, safety, or tolerability reasons

### *Study Selection Methods*

The sponsor-submitted ITC was more restrictive than the ICER ITC. Specifically, the sponsor-submitted ITC included only studies that provided information on whether patients had had an inadequate response to 2 or more or fewer than 2 prior preventive migraine treatment. In addition, these studies needed to present their results separately for either CM or EM.

Screening of the retrieved results was conducted by 2 reviewers, and discrepancies were solved through a consensus meeting. Data extraction was conducted by 1 reviewer, with another comparing the extracted data with the original submission for accuracy.

Study quality was assessed using the checklist for the National Institute for Health and Care Excellence single-technology appraisal. There was no description of the implications of determining that a study had poor quality.

The sponsor's ITC included studies with results on the following outcomes: MMDs, 50% response rate, 75% response rate, and acute migraine-specific medication use.

### *ITC Analysis Methods*

The sponsor-submitted ITC uses a Bayesian NMA approach with both fixed-effects and random-effects models. The model used a vague prior and a Markov chain Monte Carlo

sampling process to construct a posterior distribution. The sampling process contained 3 parallel running chains with an 80,000 burn-in and a subsequent 20,000 iterations. Convergence of chains was assessed through the use of trace plots and Gelman-Rubin diagnostic criteria. The posterior residual deviance was reported to have been used to assess model fit. In addition, the diagnostic information criterion was used to further assess model fit. Assessment of inconsistency was planned in cases where a closed loop was available.

The sponsor-submitted ITC assessed clinical heterogeneity of the included studies by summarizing and, where feasible, conducting a sensitivity analysis of the following factors: study design (blinding, randomization), inclusion and exclusion criteria, treatment duration, mean age, percent of female patients, disease duration/history of migraine, age of onset of migraine, mean MMD at baseline, definition of inadequate response to prior preventive treatment, outcome definitions, and outcome assessment time points.

The sponsor-submitted ITC considered different doses of the same drug as different interventions, with a separate constructed node. There was no pooling of interventions based on scientific active compound or drug class.

Only results of outcomes reported at 12 weeks (or 3 months) were included in the analysis. However, results for responder-based outcomes were assumed to have the same definition throughout the studies, regardless of how they were defined within each study.

## Table 18: Sponsor-Submitted ITC Analysis Methods

| | Sponsor-submitted ITC |
|---|---|
| **ITC methods** | Bayesian NMA |
| **Priors** | Vague (noninformative) |
| **Assessment of model fit** | DIC, posterior residual deviance |
| **Assessment of consistency** | Where feasible, direct versus indirect evidence |
| **Assessment of convergence** | Trace plots and Gelmen-Rubin criteria |
| **Outcomes** | Differences in mean change of MMD<br>50% responder rate at 12 weeks<br>75% responder rate at 12 weeks<br>Change from baseline in acute migraine-specific medication use |
| **Follow-up time points** | 12 weeks |
| **Construction of nodes** | The sponsor-submitted ITC considered different doses of the same drug as different interventions, with a separate constructed node. There was no pooling of interventions based on scientific active compound or drug class. |
| **Sensitivity analyses** | Where feasible: study design (blinding, randomization), inclusion and exclusion criteria, treatment duration, mean age, percent of female patients, disease duration/history of migraine, age of onset of migraine, mean MMD at baseline, inadequate response to prior preventive treatment definition, outcome definitions, outcome assessment time points |
| **Subgroup analysis** | None |
| **Methods for pairwise meta-analysis** | None |

DIC = diagnostic information criterion; ITC = indirect treatment comparison; MMD = monthly migraine day.

Source: CDR submission: Ajovy (fremanezumab), 225 mg in 1.5 mL (150 mg/mL) solution for subcutaneous injection [CONFIDENTIAL sponsor's submission]. In: Montreal (QC): Teva Canada Innovation; 2020 Jun 3.[15]

### Results of Sponsor-Submitted ITC

*Summary of Included Studies*

A total of 12 unique randomized controlled trials (RCTs) were included in the sponsor-submitted ITC. Of these, 8 trials were for the patient population with an inadequate response to 2 or more prior preventive migraine treatments, and 5 trials for the patient population with an inadequate response to less than 2 prior preventive migraine treatments. These 2 patient populations were further classified based on migraine type (CM versus EM) and reported as such. All included trials were randomized, double-blind, placebo-controlled trials. Overall, these included studies investigated the following interventions: fremanezumab quarterly, fremanezumab monthly, galcanezumab 120 mg, erenumab 70 mg, erenumab 140 mg, and OnaA.

Baseline characteristics in the included studies indicate that the mean age, when reported, ranged from 41.4 to 46.4 years across the EM trials, and from 41.1 to 45.7 years across the CM trials. The EM and CM trials consisted mainly of women (> 80%) and patients with similar durations of disease. The most noticeable imbalance is in the baseline MMD; the FOCUS trial showed relatively higher mean MMD at baseline than the EM trials (and conversely, relatively lower mean MMD at baseline than the CM trials) because FOCUS enrolled both migraine types. This is a noticeable departure from the pre-specified criteria for the analysis, as the sponsor-submitted ITC indicated that studies that do not classify their data and results by migraine type (CM versus EM) were not included in the analysis.

Another notable difference in the included studies is the variation in the definition of the responder outcome. Specifically, the main differences are in the time period after which the specified reduction is calculated and the use of either MMDs or migraine headache days. For example, the definition of 50% responder rate in the FOCUS trial is achieving a 50% or greater reduction in the average number of MMDs during the 4-week and 12-week periods after the first dose of study drug, while the definition of 50% responder rate in the EVOLVE studies is a 50% or greater reduction in the number of migraine headache days during the 6-month period of the study. The sponsor-submitted ITC assumed that all outcome definitions are sufficiently similar for the purposes of ITC analysis.

## Table 19: Assessment of Homogeneity for Sponsor-Submitted ITC

| | Description and handling of potential effect modifiers |
|---|---|
| **Disease severity** | The sponsor-submitted ITC further analyzed the outcomes separately for patients with chronic and episodic migraine, with the exception of the fremanezumab FOCUS trial, which had a population mixed between chronic and episodic migraine, in contravention of the sponsor-submitted ITC methods |
| **Treatment history** | The sponsor-submitted ITC provided separate analyses based on the number of previous inadequate treatments |
| **Clinical trial eligibility criteria** | Considering the classification of studies based on disease severity and treatment history, eligibility criteria were similar |
| **Dosing of comparators** | Each dose was treated as a separate node |
| **Definitions of end points** | There were notable variations in the determination of adequate response, variations in the use of migraine headache days or monthly migraine days, and variations in the duration for which the definition of a responder was determined. The sponsor-submitted ITC assumed that variations in the timing of the end points are sufficiently similar for analysis purposes. |
| **Timing of end point evaluation or trial duration** | While most studies had a duration of 12 weeks or 3 months, several had a duration of 6 months. The sponsor-submitted ITC indicated that only data at 12 weeks or 3 months |

| | Description and handling of potential effect modifiers |
|---|---|
| | would be extracted. However, in cases of a predefined responder outcome based on trial duration, the sponsor-submitted ITC assumed that variations in the timing of the end points are sufficiently similar for analysis purposes. |
| **Withdrawal frequency** | Not reported |
| **Clinical trial setting** | Not reported |
| **Study design** | Similar study design across included studies |

ITC = indirect treatment comparison.

Source: Source: CDR submission: Ajovy (fremanezumab), 225 mg in 1.5 mL (150 mg/mL) solution for subcutaneous injection [CONFIDENTIAL sponsor's submission]. In: Montreal (QC): Teva Canada Innovation; 2020 Jun 3.[15]

*Results*

The sponsor-submitted ITC presented the results from the fixed-effects model. This was justified based on the following: the networks for each outcome were small; most comparisons were informed through 1 study; and the difference in the diagnostic information criterion was less than 3 points between the 2 models. Indeed, the results under the random-effects model contained, many times, unrealistically large credible intervals.

A summary of the results of each outcome in the sponsor-submitted ITC are presented in Table 20, Table 21, Table 22, and Table 23. The sponsor-submitted ITC was able to analyze the comparative efficacy of fremanezumab versus erenumab, galcanezumab, and placebo.

Overall, fremanezumab was consistently significantly better than placebo in all reported outcomes throughout the various patient populations. The results for fremanezumab versus erenumab or galcanezumab did not show a result that favoured either treatment through the exclusion of the null from the 95% credible intervals, except for the following outcomes:

- Monthly and quarterly fremanezumab were significantly better in reducing the MMDs at 12 weeks than erenumab 70 mg in EM patients who had inadequate response to 2 or more previous treatments.
- Monthly and quarterly fremanezumab were significantly better in the rate of 50% responders at 12 weeks than erenumab 140 mg and galcanezumab 120 mg in CM patients who had inadequate response to fewer than 2 previous treatments.
- Monthly and quarterly fremanezumab were significantly better in reducing the days using acute migraine-specific medication at 12 weeks than erenumab 70 mg and 140 mg in EM patients who had inadequate response to 2 or more previous treatments.
- Monthly fremanezumab were significantly better in reducing the days using acute migraine-specific medication at 12 weeks than erenumab 70 mg and 140 mg in the CM patients had inadequate response to fewer than 2 previous treatments.

The studies of OnaA were excluded from the analysis because they only reported outcomes at week 24 of the trials. A sensitivity analysis was conducted that included OnaA, but the results did not show a favourable profile for OnaA versus the other drugs.

## Table 20: Sponsor-Submitted ITC — Differences in Mean Change in Monthly Migraine Days for Fremanezumab Versus Other Comparators in the Network at Week 12

| | Episodic migraine | | | | Chronic migraine | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Previous inadequate treatments: < 2 | | Previous inadequate treatments: ≥ 2 | | Previous inadequate treatments: < 2 | | Previous inadequate treatments: ≥ 2 | | Previous inadequate treatments: ≥ 3 | |
| **Treatment** | **Monthly dose** | **Quarterly dose** | **Monthly dose** | **Quarterly dose** | **Monthly dose** | **Quarterly dose** | **Monthly dose** | **Quarterly dose** | **Monthly dose** | **Quarterly dose** |
| Number of studies, model | 4 studies, fixed-effects model | | 4 studies, fixed-effects model | | 4 studies, fixed-effects model | | 3 studies, fixed-effects model | | 2 studies, fixed-effects model | |
| Erenumab 70 mg | –0.6 (–1.71 to 0.5) | –0.3 (–1.41 to 0.81) | **–2.63 (–4.96 to –0.3)** | **–2.53 (–4.85 to –0.2)** | Reverse comparison[a] –0.4 (–2.63 to 1.82) | Reverse comparison[a] –0.5 (–2.72 to 1.73) | –1.1 (–3.09 to –0.89) | –0.5 (–2.5 to 1.49) | NR | NR |
| Erenumab 140 mg | –0.1 (–1.22 to 1.02) | Reverse comparison[a] –0.2 (–1.32 to 0.92) | –1.31 (–2.88 to 0.26) | –1.21 (–2.77 to 0.36) | –1.4 (–3.63 to 0.83) | –1.3 (–3.53 to 0.93) | Reverse comparison[a] –0.5 (–2.46 to 1.47) | Reverse comparison[a] –1.1 (–3.07 to 0.87) | NR | NR |
| Galcanezumab 120 mg | –0.12 (–1.07 to 0.83) | Reverse comparison[a] –0.18 (–1.13 to 0.77) | –0.67 (–3.13 to 1.8) | –0.56 (–3.03 to 1.89) | –1.27 (–3.73 to 1.2) | –1.17 (–3.63 to 1.3) | Reverse comparison[a] –0.54 (–2.7 to 1.62) | Reverse comparison[a] –1.14 (–3.31 to 1.03) | Reverse comparison[a] –1.45 (–4.19 to 1.3) | Reverse comparison[a] –1.45 (–4.19 to 1.3) |
| Placebo | **–1.5 (–2.19 to –0.81)** | **–1.2 (–1.89 to –0.51)** | **–3.1 (–4.32 to –1.88)** | **–3.0 (–4.20 to –1.79)** | **–1.8 (–2.91 to –0.69)** | **–1.7 (–2.81 to –0.59)** | **–3.8 (–5.08 to –2.52)** | **–3.2 (–4.49 to –1.91)** | **–3.8 (–5.08 to –2.53)** | **–3.2 (–4.49 to –1.92)** |
| Fremanezumab monthly | NA | Reverse comparison[a] –0.3 (–0.99 to 0.39) | NA | Reverse comparison[a] –0.1 (–1.34 to 1.13) | NA | Reverse comparison[a] –0.1 (–1.21 to 1.01) | NA | Reverse comparison[a] –0.6 (–1.86 to 0.67) | NA | Reverse comparison[a] –0.6 (–1.86 to 0.67) |

| | Episodic migraine | | | | Chronic migraine | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Previous inadequate treatments: < 2 | | Previous inadequate treatments: ≥ 2 | | Previous inadequate treatments: < 2 | | Previous inadequate treatments: ≥ 2 | | Previous inadequate treatments: ≥ 3 | |
| Treatment | Monthly dose | Quarterly dose | Monthly dose | Quarterly dose | Monthly dose | Quarterly dose | Monthly dose | Quarterly dose | Monthly dose | Quarterly dose |
| Fremanezumab quarterly | –0.3 (–0.99 to 0.39) | NA | –0.1 (–1.34 to 1.13) | NA | –0.1 (–1.21 to 1.01) | NA | –0.6 (–1.86 to 0.67) | NA | –0.6 (–1.86 to 0.67) | NA |

CrI = credible interval; NA = not applicable.

[a] These results should be read as the comparator versus fremanezumab, and not the other way around.

Source: CDR submission: Ajovy (fremanezumab), 225 mg in 1.5 mL (150 mg/mL) solution for subcutaneous injection [CONFIDENTIAL sponsor's submission]. In: Montreal (QC): Teva Canada Innovation; 2020 Jun 3.[15]

## Table 21: Sponsor-Submitted ITC — Relative Risks in 50% Responder Rate to Fremanezumab Versus Other Comparators in the Network at Week 12

| | Episodic migraine | | | | Chronic migraine | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Previous inadequate treatments: < 2 | | Previous inadequate treatments: ≥ 2 | | Previous inadequate treatments: < 2 | | Previous inadequate treatments: ≥ 2 | | Previous inadequate treatments: ≥ 3 | |
| Treatment | Monthly dose | Quarterly dose | Monthly dose | Quarterly dose | Monthly dose | Quarterly dose | Monthly dose | Quarterly dose | Monthly dose | Quarterly dose |
| Number of studies, model | 4 studies, fixed-effects model | | 4 studies, fixed-effects model | | 3 studies, fixed-effects model | | 3 studies, fixed-effects model | | 3 studies, fixed-effects model | |
| Erenumab 70 mg | 1.2 (0.92 to 1.6) | 1.13 (0.85 to 1.51) | 1.84 (0.98 to 3.77) | 1.71 (0.9 to 3.52) | 1.47 (0.96 to 2.38) | 1.37 (0.89 to 2.24) | 1.1 (0.63 to 1.87) | Reverse comparison[a] 0.99 (0.58 to 1.64) | 1.21 (0.66 to 2.3) | 1.1 (0.6 to 2.12) |
| Erenumab 140 mg | 1.04 (0.81 to 1.34) | Reverse comparison[a] 1.16 (0.94 to 1.43) | 1.09 (0.72 to 1.61) | Reverse comparison[a] 1.0 | **1.83 (1.15 to 3.08)** | **1.71 (1.07 to 2.89)** | Reverse comparison[a] | Reverse comparison[a] | 1.08 (0.6 to 2.01) | Reverse comparison[a] 1.02 (0.54 to 1.83) |

| | Episodic migraine | | | | Chronic migraine | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Previous inadequate treatments: < 2 | | Previous inadequate treatments: ≥ 2 | | Previous inadequate treatments: < 2 | | Previous inadequate treatments: ≥ 2 | | Previous inadequate treatments: ≥ 3 | |
| Treatment | Monthly dose | Quarterly dose | Monthly dose | Quarterly dose | Monthly dose | Quarterly dose | Monthly dose | Quarterly dose | Monthly dose | Quarterly dose |
| | | | | (0.66 to 1.51) | | | 1.05 (0.58 to 1.95) | 1.17 (0.71 to 1.88) | | |
| Galcanezumab 120 mg | 1.06 (0.86 to 1.32) | Reverse comparison[a] 1.0 (0.8 to 1.25) | Reverse comparison[a] 1.26 (0.73 to 2.0) | Reverse comparison[a] 1.25 (0.75 to 1.96) | **1.75 (1.21 to 2.62)** | **1.63 (1.12 to 2.46)** | 0.98 (0.59 to 1.72) | Reverse comparison[a] 1.11 (0.63 to 1.87) | Reverse comparison[a] 1.36 (0.61 to 2.66) | Reverse comparison[a] 1.49 (0.67 to 3.76) |
| Placebo | **1.62 (1.36 to 1.92)** | **1.52 (1.26 to 1.82)** | **2.68 (2.04 to 3.5)** | **2.48 (1.87 to 3.27)** | **2.06 (1.7 to 2.48)** | **1.92 (1.57 to 2.34)** | **2.89 (2.15 to 3.88)** | **2.65 (1.95 to 3.6)** | **2.99 (2.19 to 4.1)** | **2.74 (1.98 to 3.79)** |
| Fremanezumab monthly | NA | Reverse comparison[a] 1.07 (0.92 to 1.6) | NA | Reverse comparison[a] 1.08 (0.88 to 1.33) | NA | Reverse comparison[a] 1.07 (0.92 to 1.25) | NA | Reverse comparison[a] 1.09 (0.87 to 1.37) | NA | Reverse comparison[a] 1.21 (0.66 to 2.3) |
| Fremanezumab quarterly | 1.07 (0.92 to 1.6) | NA | 1.08 (0.88 to 1.33) | NA | 1.07 (0.92 to 1.25) | NA | 1.09 (0.87 to 1.37) | NA | 1.21 (0.66 to 2.3) | NA |

CrI = credible interval; NA = not applicable.

[a] These results should be read as the comparator versus fremanezumab, and not the other way around.

Source: CDR submission: Ajovy (fremanezumab), 225 mg in 1.5 mL (150 mg/mL) solution for subcutaneous injection [CONFIDENTIAL sponsor's submission]. In: Montreal (QC): Teva Canada Innovation; 2020 Jun 3.[15]

## Table 22: Sponsor-Submitted ITC — Relative Risks in 75% Responder Rate to Fremanezumab Versus Other Comparators in the Network at Week 12

| | Episodic migraine | | | | Chronic migraine | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Previous inadequate treatments: < 2 | | Previous inadequate treatments: ≥ 2 | | Previous inadequate treatments: < 2 | | Previous inadequate treatments: ≥ 2 | | Previous inadequate treatments: ≥ 3 | |
| **Treatment** | **Monthly dose** | **Quarterly dose** | **Monthly dose** | **Quarterly dose** | **Monthly dose** | **Quarterly dose** | **Monthly dose** | **Quarterly dose** | **Monthly dose** | **Quarterly dose** |
| Number of studies, model | 4 studies, fixed-effects model | | 4 studies, fixed-effects model | | 3 studies, fixed-effects model | | 3 studies, fixed-effects model | | 2 studies, fixed-effects model | |
| Erenumab 70 mg | NR | NR | 1.14 (0.35 to 3.88) | Reverse comparison[a] 1.36 (0.38 to 4.55) | NR | NR | 1.23 (0.38 to 3.94) | Reverse comparison[a] 1.29 (0.39 to 4.34) | 1.27 (0.36 to 4.46) | Reverse comparison[a] |
| Erenumab 140 mg | NR | NR | Reverse comparison[a] 1.15 (0.47 to 2.99) | Reverse comparison[a] 1.78 (0.69 to 4.89) | NR | NR | Reverse comparison[a] 1.69 (0.62 to 4.68) | Reverse comparison[a] 2.68 (0.94 to 7.71) | Reverse comparison[a] 1.51 (0.52 to 4.54) | Reverse comparison[a] |
| Galcanezumab 120 mg | NR | NR | Reverse comparison[a] 1.4 (0.53 to 3.64) | Reverse comparison[a] 2.17 (0.78 to 5.86) | NR | NR | 1.33 (0.33 to 5.46) | Reverse comparison[a] 1.19 (0.28 to 5.01) | NR | NR |
| Placebo | NR | NR | **3.79 (2.2 to 6.63)** | **2.44 (1.34 to 4.54)** | NR | NR | **3.92 (2.25 to 7.06)** | **2.47 (1.35 to 4.71)** | **3.86 (2.22 to 47.1)** | **2.47 (1.34 to 4.8)** |
| Fremanezumab monthly | NR | NR | NA | Reverse comparison[a] **1.54 (1.02 to 2.39)** | NR | NR | NA | Reverse comparison[a] **1.58 (1.02 to 2.48)** | NA | Reverse comparison[a] **1.55 (1.03 to 2.43)** |
| Fremanezumab quarterly | NR | NR | **1.54 (1.02 to 2.39)** | NA | NR | NR | **1.58 (1.02 to 2.48)** | NA | **1.55 (1.03 to 2.43)** | NA |

CrI = credible interval; NA = not applicable; NR = not reported.

[a] These results should be read as the comparator versus fremanezumab, and not the other way around.

Source: CDR submission: Ajovy (fremanezumab), 225 mg in 1.5 mL (150 mg/mL) solution for subcutaneous injection [CONFIDENTIAL sponsor's submission]. In: Montreal (QC): Teva Canada Innovation; 2020 Jun 3.[15]

## Table 23: Sponsor-Submitted ITC — Difference in Mean Change From Baseline in Days Using Acute Migraine-Specific Medication at Week 12 of Fremanezumab Versus Other Comparators in the Network

| | Episodic migraine | | | | Chronic migraine | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Previous inadequate treatments: < 2 | | Previous inadequate treatments: ≥ 2 | | Previous inadequate treatments: < 2 | | Previous inadequate treatments: ≥ 2 | | Previous inadequate treatments: ≥ 3 | |
| **Treatment** | **Monthly dose** | **Quarterly dose** | **Monthly dose** | **Quarterly dose** | **Monthly dose** | **Quarterly dose** | **Monthly dose** | **Quarterly dose** | **Monthly dose** | **Quarterly dose** |
| Number of studies, model | 2 studies, fixed-effects model | | 3 studies, fixed-effects model (FOCUS) | | 3 studies, fixed-effects model | | 3 studies, fixed-effects model (FOCUS) | | Not analyzed | |
| Erenumab 70 mg | –0.6 (–1.31 to 0.11) | –0.5 (–1.21 to 0.22) | **–2.95 (–4.54 to –1.34)** | **–2.54 (–4.15 to –0.95)** | **–1.6 (–2.99 to –0.20)** | –1.1 (–2.5 to 0.29) | –0.4 (–1.8 to 1.01) | Reverse comparison[a] 0 (–1.4 to 1.41) | NR | NR |
| Erenumab 140 mg | –0.4 (–1.1 to 0.31) | 0.3 (–1.01 to 0.41) | **–1.46 (–2.48 to –1.45)** | **–1.06 (–2.07 to –0.05)** | **–1.6 (–3.0 to –0.21)** | –1.1 (–2.5 to 0.3) | Reverse comparison[a] –0.9 (–2.29 to 0.49) | Reverse comparison[a] –1.3 (–2.69 to 0.09) | NR | NR |
| Galcanezumab 120 mg | NR | NR | NR | NR | –1.02 (–3.04 to 1.01) | –0.52 (–2.54 to 1.5) | Reverse comparison[a]– 1.26 | Reverse comparison[a] –1.66 (–3.6 to 0.27) | NR | NR |
| Placebo | **–1.4 (–2.0 to –0.8)** | **–1.3 (–1.9 to –0.7)** | **–3.2 (–3.97 to –2.42)** | **–2.8 (–3.57 to –2.03)** | **–2.3 (–3.14 to –1.47)** | **–1.8 (–2.63 to – 0.97)** | **–3.2 (–3.98 to – 2.42)** | **–2.8 (–3.58 to –2.02)** | NR | NR |
| Fremanezumab monthly | NA | Reverse comparison[a] –0.1 (–1.31 to 0.11) | NA | Reverse comparison[a] –0.4 (–1.17 to 0.37) | NA | Reverse comparison[a] –0.5 (–1.33 to 0.33) | NA | Reverse comparison[a] –0.4 (–1.18 to 0.38) | NR | NR |
| Fremanezumab quarterly | –0.1 (–1.31 to 0.11) | NA | –0.4 (–1.17 to 0.37) | NA | –0.5 (–1.33 to 0.33) | NA | –0.4 (–1.18 to 0.38) | NA | NR | NR |

CrI = credible interval; NA = not applicable; NR = not reported; Rev comp = reverse comparison.

[a] These results should be read as the comparator versus fremanezumab, and not the other way around.

Source: CDR submission: Ajovy (fremanezumab), 225 mg in 1.5 mL (150 mg/mL) solution for subcutaneous injection [CONFIDENTIAL sponsor's submission]. In: Montreal (QC): Teva Canada Innovation; 2020 Jun 3.[15]

## Critical Appraisal of Sponsor-Submitted ITC

The sponsor-submitted ITC provided a comprehensive and transparent approach to the sponsor's systematic review, in which the sponsor provided the search strategy, conducted the search over several databases, used 2 independent reviewers for screening, and outlined a comprehensive list of inclusion and exclusion criteria.

The sponsor-submitted ITC analyzed the patient population based on migraine type and the number of previous treatments to which patients were deemed to have inadequately responded. Fremanezumab monthly versus quarterly did not show significant differences on any of the outcome measures. On the other hand, when compared with 2 other CGRP inhibitors, fremanezumab monthly or quarterly showed a significantly better effect than erenumab 70 mg on MMDs at 12 weeks in patients with EM who had inadequate response to 2 or more previous treatments. However, no such consistent effect was observed on the outcomes of 50% or 75% reduction in migraine or headache days (responder rate). In contrast, fremanezumab showed a significantly better effect than erenumab 140 mg and galcanezumab 120 mg on 50% reduction in migraine or headache days in patients with CM who had inadequate response to less than previous treatments, yet this effect was not confirmed with a significant difference on MMDs at 12 weeks.

Fremanezumab (monthly or quarterly) as compared with erenumab 70 or 140 mg showed a significant difference both in CM and EM patients, but on different outcome measures involving migraine days, regardless of the previous numbers of treatments. However, no consistent effect was documented, as measured by different outcomes involving migraine days. This indicates that the comparative efficacy between fremanezumab and other CGRP inhibitors remained highly uncertain, although the NMA showed that fremanezumab either monthly or quarterly was significantly better on all outcome measures when compared with placebo.

The methods that the sponsor-submitted ITC used were in accordance with standard and established practices for NMA, with results obtained by using a fixed model, which is deemed appropriate when a robust network is lacking.

The main limitations of the sponsor-submitted ITC are as follows:

- Small networks with a single study for pairs of comparisons: This has reduced the robustness of the network, in which wide CrIs were observed. Furthermore, the wide CrIs prevented us from being able to firmly draw a conclusion on the efficacy of fremanezumab compared with erenumab or glacanezumab, especially considering that there is no consistently significant finding across various outcomes and measures, with the exception of placebo.
- Clinical heterogeneity in the networks of patients with 2 or more inadequate previous treatments: The sponsor-submitted ITC clearly aimed to assess patients with either EM or CM, separately. To that end, the ITC excluded 1 study from the analysis for reporting only a mixed population. Yet, to provide outcomes for fremanezumab versus other comparators in the outcomes of 50% responder rate, 75% responder rate, and days using acute migraine-specific medication, the sponsor-submitted ITC included the FOCUS trial, which reports only the results of a mixed EM and CM population. This created a noticeable clinical heterogeneity in all networks that assessed patients who had inadequate response to 2 or more previous treatments in the previously mentioned outcomes. The sponsor-submitted ITC acknowledges this as a limitation that may bias the results obtained in these outcomes.

- Variations in outcome definitions: The included trials varied in how they defined a responder — specifically, variations in the period at which a responder is determined and the use of headache days as opposed to MMDs. The sponsor-submitted ITC assumed that all outcome definitions are sufficiently similar for the purposes of ITC analysis.
- Lack of pre-planned sensitivity analysis: The sponsor-submitted ITC provided a list of various factors for which the sponsor had planned to conduct sensitivity analyses. However, because of the small size of the networks, none of these analyses were conducted.

Based on these limitations, we cannot interpret any result that showed no difference as evidence of similarity in efficacy. Moreover, the current results, in which fremanezumab is significantly better than erenumab in reducing MMDs and days using acute migraine-specific treatment at 12 weeks, are biased in favour of fremanezumab, with unclear magnitude of effect. Furthermore, the lack of clarity regarding how variations in the definition of a responder in the included trials was handled increases our uncertainty in the results of the synthesized outcome.

## Methods of the Institute for Clinical and Economic Review ITC

### *Objectives*

The ICER 2018 ITC aimed to assess the comparative clinical effectiveness of CGRP inhibitors for patients with CM or EM.

### *Study Selection Methods*

A systematic review and a search strategy over several bibliographic databases were conducted. Two reviewers screened abstracts and full text independently, and studies were selected based on the eligibility criteria outlined in Table 17. Published RCTs of any sample size were included. Nonrandomized comparative studies were selected if they had at least 100 patients, and crossover studies were eligible if data were reported before the crossover period. To assess long-term efficacy and safety, open-label extension trials of RCTs of any size and duration were considered in the ICER review, as were noncomparative observational studies with at least 100 patients and 6 months of follow-up. However, these studies are not described here. The population of interest for this review was adult patients (≥ 18 years) with migraine who experienced at least 4 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 SC injections of erenumab, fremanezumab, and galcanezumab, at any dose or frequency. For both EM and CM populations, preventive therapies included were topiramate, propranolol, and amitriptyline. For CM patients, OnaA 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, 50% or greater reduction in migraine days, quality of life as assessed by the MIDAS, the Migraine-Specific Quality of Life (MSQoL) questionnaire, or the 6-item headache impact test (HIT-6), all-cause discontinuations, discontinuations due to AEs, and AEs reported by at least 5% of patients in a trial arm.

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.

### *ITC Analysis Methods*

An NMA was conducted if data were available from at least 3 similar studies, with respect to characteristics such as population, intervention, outcome, and time point.

The NMAs followed a Bayesian framework with random effects on the treatment parameters. 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 were analyzed with a binomial likelihood and logit link. The treatment effects were presented as mean differences with 95% CrIs for continuous outcomes and odd ratios with 95% CrIs for binary outcomes. Noninformative 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 3 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., 4 weeks, 8 weeks, 12 weeks, and 26 weeks), if data were available. A subgroup of patients who had failed at least 1 prior preventive treatment was also analyzed.

## Results of Institute for Clinical and Economic Review ITC

### *Summary of Included Studies*

For patients with CM, 14 trials were included for the assessment of clinical benefit of OnaA, topiramate, and CGRP inhibitors in CM. The average age was approximately 40 years, and more than 80% of the patients were female. The included patients had a history of CM for an average of 20 years. Four trials reported the proportion of patients with medication overuse headache, which ranged from 41% to 68%, and 5 trials excluded patients with medication overuse headaches. None of the fremanezumab trials reported this information. The mean number of MMDs ranged from 15 to 25 at baseline across the 14 trials of OnaA, topiramate, and CGRP inhibitors. The time point of analysis ranged from 12 to 26 weeks.

For patients with EM, 9 trials were included for the assessment of clinical benefit of CGRP inhibitors: 3 trials for erenumab (Sun et al. [2016],[48] STRIVE,[49] and ARISE[50]), 2 trials for fremanezumab (Bigal et al. [2015][51] and HALO-EM[31]), and 4 trials for galcanezumab (Dodick et al. [2014],[52] Skljarevski et al. [2018],[53] EVOLVE-1[54], and EVOLVE-2[55]). All of these trials were industry-funded and multi-centre and were conducted predominantly in North America and Europe. All trials were double-blinded and included a 4-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 the average number of MMDs 8 to 9, except that patients in Bigal et al. (2015)[51] (fremanezumab) experienced a higher frequency at baseline, with approximately 12 MMDs. Across the trials, the number of days using any acute medication was approximately 7 to 10.

Of the 24 trials assessing a comparator of interest (amitriptyline, propranolol, or topiramate) in the EM population, 17 trials compared active therapy with placebo (4 RCTs assessed amitriptyline,[56-59] 4 RCTs[60-63] and 1 crossover trial assessed propranolol,[64] and 8 RCTs involved topiramate[65-72]) and 7 were head-to-head studies (3 RCTs of topiramate versus propranolol,[73-75] 1 RCT of topiramate versus amitriptyline,[76] 1 RCT of propranolol versus

amitriptyline,[77] 1 RCT of topiramate versus amitriptyline versus topiramate plus amitriptyline,[78] and 1 RCT of propranolol versus amitriptyline versus propranolol plus amitriptyline).[79] Most trials were industry-funded. Ten of the trials were single-centre, whereas 10 other trials were multi-centre and 4 were unclear. Where reported, the trials were conducted in the US and Europe, except for 4 conducted in Turkey and 1 in Singapore. Baseline phases were typically 4 weeks, followed by randomized phases of 4 weeks to 26 weeks. At baseline, the average number of migraine days ranged from 5 to 12 days per month. The percentage of patients who experienced prior failure of at least 1 preventive treatment was not reported in any of the oral preventive therapy trials.

Of RCTs conducted in patients with CM, an overall rating of "good," "fair," or "poor" was given to each study. The OnaA studies were rated as good (the PREEMPT-1 and PREEMPT-2 trials of Aurora et al. [2010][80] and Diener et al. [2010],[81] respectively), fair (Sandrini et al. [2011][82]), and poor (Cady et al. [2014][83] and Freitag et al. [2008][84]). Sandrini et al. (2011) was rated as fair because the approach to missing data was not described. In Cady et al. (2014) and Freitag et al. (2008), there were insufficient data to assess the comparability of groups. The topiramate trials were rated as good (Silberstein et al. [2007][85]), fair (Mei et al. [2006][86]), and poor (Diener et al. [2007][87] and Silvestrini et al. [2003][88]). Mei et al. (2006) was rated as fair because the approach to missing data was not described. In Diener et al. (2007), groups were not comparable, there was nondifferential follow-up, and outcomes were not clearly defined. In Silvestrini et al. (2003),[88] there was insufficient information to assess patient/physician blinding and approach to missing data, and outcomes were not clearly defined. The CGRP inhibitor studies[30,51,89] were rated to be of good quality. The head-to-head studies that compared OnaA with topiramate were rated as fair (Mathew and Jaffri [2009][90]; groups were not comparable), and poor (Cady et al. [2011][91]; no imputation of missing data and outcomes were not clearly defined).

Of RCTs conducted in patients with EM, an overall rating of "good," "fair," or "poor" was given to each study. The CGRP inhibitor studies were rated to be of good quality.[31,48-55] The amitriptyline studies were rated as poor (Couch and Hassanein [1979][57]), fair (Couch [2011][56] and Lampl et al. [2009][59]), and good (Gonçalves et al. [2016][58]). The propranolol studies were rated as good (Diener et al. [1996][60]), fair (Pradalier et al. [1989][62]), and poor (Jafarpour et al. [2016],[61] Sargent et al. [1985],[63] and Weber and Reinmuth [1972][64]). The topiramate studies were rated as good (Silberstein et al. [2006][70]), fair (Lipton et al. [2011],[67] Brandes et al. [2004],[65] Silberstein et al. [2004],[71] Mei et al. [2004],[69] and Storey et al. [2001][72]), and poor (Gode et al. [2010][66] and Lo et al. [2010][68]). The head-to-head trials studies were rated as fair (Diener et al. [2004],[74] Dogan et al. [2015],[75] and Keskinbora and Aydinli [2008][78]), and poor (Ashtari et al. [2008],[73] Dodick et al. [2009],[76] Duman et al. [2015],[77] and Mathew [1981][79]).

An NMA was conducted if data were available from at least 3 similar studies with respect to characteristics such as population, intervention, outcome, and time point. Sufficient data were available for the following outcomes in the CM population: change from baseline in MMDs, change from baseline in monthly headache days, change from baseline in days per month using acute medications, and all-cause discontinuations.

*Results*

**Results for Chronic Migraine Patients**

A total of 14 trials were available in patients with CM. Of these, 4 RCTs and 1 crossover trial compared OnaA with placebo, 2 RCTs compared OnaA with topiramate, 4 RCTs compared topiramate with placebo, and 3 RCTs compared CGRP inhibitors (i.e., erenumab and fremanezumab) with placebo.

Six trials (Tepper et al. [2017],[89] Bigal et al. [2015],[51] Silberstein et al. [2017],[30] Aurora et al. [2010],[80] Diener et al. [2010],[81] and Silberstein et al. [2007][85]) 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 2 OnaA trials, and the last 4 weeks of the 12 weeks randomization period for the 3 CGRP inhibitor trials. This difference could be 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 et al. [2015],[51] Cohen et al. [2018],[92] Aurora et al. [2010],[80] Diener et al. [2010],[81] Cady et al. [2014],[83] Freitag et al. [2008],[84] Silberstein et al. [2009],[93] and Cady et al. [2011][91]) were included in the NMA for the mean change in monthly headache days. The analysis time point was the last 4 weeks of the randomization period for 2 of the OnaA trials (Freitag et al. [2008][84] and Cady et al. [2014][83]) and the 2 fremanezumab trials,[51,92] the full 12-week period for the head-to-head OnaA and topiramate trial,[91] and the full 24-week period for the 2 PREEMPT trials,[80,81] which was 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 (1 trial assessing erenumab, 2 trials assessing fremanezumab, and 2 trials assessing topiramate). The time point of the analysis was the last 4 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 2 fremanezumab and 2 topiramate trials were days of any acute medication. Across the trials, on average, patients receiving placebo experienced 0.7 to 3.4 fewer days per month using acute medications.

In Table 24 and Table 25, the results for change from baseline in MMDs and in monthly headache days for fremanezumab monthly and quarterly from NMAs are shown. No treatment was favoured for MMDs or days using acute medication per month. In comparison with placebo, monthly and quarterly fremanezumab were favoured in days using acute medication per month.

## Table 24: Network Meta-Analysis Results for Change From Baseline in Monthly Migraine Days in Patients With Chronic Migraine

| Comparison | Mean difference (95% CrI) |
|---|---|
| Fremanezumab monthly versus placebo | –1.66 (–3.47 to 0.12) |
| Fremanezumab monthly versus fremanezumab quarterly | –0.6 (–3.47 to 0.12) |
| Topiramate 100 mg/ day versus fremanezumab monthly | –0.03 (–3.1 to 3.04) |
| Onabotulinum toxin A quarterly versus fremanezumab monthly | –0.29 (–2.74 to 2.17) |
| Erenumab 70 mg versus fremanezumab monthly | –0.74 (–3.73 to 2.27) |
| Erenumab 140 mg versus fremanezumab monthly | –0.74 (–3.7 to 2.28) |
| Fremanezumab quarterly versus placebo | –1.3 (–3.54 to 0.93) |
| Fremanezumab monthly versus fremanezumab quarterly | –0.6 (–3.47 to 0.12) |
| Topiramate 100 mg/ day versus fremanezumab quarterly | –0.39 (–3.73 to 2.94) |
| Onabotulinum toxin A quarterly versus fremanezumab quarterly | –0.65 (–3.45 to 2.15) |
| Erenumab 70 mg versus fremanezumab quarterly | –1.11 (–4.37 to 2.18) |
| Erenumab 140 mg versus fremanezumab quarterly | –1.10 (–4.35 to 2.18) |

CrI = credible interval.

Source: The Institute for Clinical and Economic Review.[47]

## Table 25: 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) |
|---|---|
| Fremanezumab monthly versus placebo | –2.17 (–4.05 to –0.28) |
| Fremanezumab monthly versus fremanezumab quarterly | –0.78 (–3.17 to 1.61) |
| Fremanezumab monthly versus topiramate 100 mg/ day | –1.23 (–4.25 to 2.21) |
| Fremanezumab monthly versus erenumab 70 mg | –0.27 (–3.36 to 2.81) |
| Erenumab 140 mg versus fremanezumab monthly | –0.32 (–3.41 to 2.79) |
| Fremanezumab quarterly versus placebo | –1.40 (–3.77 to 1.00) |
| Fremanezumab monthly versus fremanezumab quarterly | –0.78 (–3.17 to 1.61) |
| Fremanezumab quarterly versus topiramate 100 mg/ day | –0.13 (–3.14 to 3.25) |
| Erenumab 70 mg versus fremanezumab quarterly | –0.50 (–3.91 to 2.91) |
| Erenumab 140 mg versus fremanezumab quarterly | –0.32 (–3.41 to 2.79) |

CrI = credible interval.

Source: The Institute for Clinical and Economic Review.[47]

The NMA was conducted at multiple time points (i.e., 4 weeks, 8 weeks, and 12 weeks) and, additionally, a network meta-regression was performed with study duration as a covariate. The results for MMDs and monthly headache days by time point were only available for OnaA 155 U versus placebo.

**Results for Episodic Migraine Patients**

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

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

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.

Table 26 presents results from the NMA for the change from baseline in MMDs in patients with EM. Fremanezumab monthly and quarterly were compared with erenumab 140 mg, erenumab 70 mg, propranolol 160 mg/day, topiramate 100 mg/day, amitriptyline 25 to 100 mg/day, topiramate 200 mg/day, topiramate 50 mg/day, placebo, and galcanezumab. Fremanezumab monthly was favoured only when compared with topiramate 50 mg/day and placebo, while fremanezumab quarterly was favoured only against placebo.

## Table 26: 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 versus fremanezumab monthly | –0.35 (–1.42 to 0.81) |
| Galcanezumab 240 mg versus fremanezumab monthly | –0.25 (–1.28 to 0.83) |
| Galcanezumab 120 mg versus fremanezumab monthly | –0.20 (–1.20 to 0.85) |
| Fremanezumab monthly versus erenumab 70 mg | –0.29 (–1.31 to0.64) |
| Fremanezumab monthly versus propranolol 160 mg/day | –0.02 (–1.24 to 1.22) |
| Fremanezumab monthly versus fremanezumab quarterly | –0.40 (–1.40 to 0.54) |
| Fremanezumab monthly versus topiramate 100 mg/day | –0.43 (–1.41 to 051) |
| Fremanezumab monthly versus amitriptyline 25 mg/day to 100 mg/day | –0.52 (–1.99 to 0.88) |
| Fremanezumab monthly versus topiramate 200 mg/day | –0.64 (–1.65 to 0.34) |
| Fremanezumab monthly versus topiramate 50 mg/day | –1.42 (–2.59 to –0.29) |
| Fremanezumab monthly versus placebo | –1.59 (–2.46 to –0.79) |
| Erenumab 140 mg versus fremanezumab quarterly | –0.75 (–1.94 to 0.47) |
| Galcanezumab 240 mg versus fremanezumab quarterly | –0.56 (–1.81 to 0.50) |
| Galcanezumab 120 mg versus fremanezumab quarterly | –0.61 (–1.73 to 0.52) |
| Erenumab 70 mg versus fremanezumab quarterly | –0.11 (–1.17 to 0.99) |
| Propranolol 160 mg/day versus fremanezumab quarterly | –0.02 (–1.24 to 1.22) |
| Fremanezumab quarterly versus topiramate 100 mg/day | –0.02 (–1.09 to 1.04) |
| Fremanezumab quarterly versus amitriptyline 25 mg/day to 100 mg/day | –0.11 (–1.63 to 1.38) |
| Fremanezumab quarterly versus topiramate 200 mg/day | –0.23 (–1.32 to 0.87) |
| Fremanezumab quarterly versus topiramate 50 mg/day | –1.01 (–2.27 to 0.22) |
| Fremanezumab quarterly versus placebo | –1.19 (–2.16 to –0.25) |

CrI = credible interval.

Source: The Institute for Clinical and Economic Review.[47]

Table 27 presents results from the NMA for the 50% response in patients with EM. In this analysis, monthly and quarterly fremanezumab was favoured only when compared with placebo.

## Table 27: Network Meta-Analysis Results for 50% Response in Patients With Episodic Migraine

| Comparison | OR (95% CrI) |
|---|---|
| Topiramate 100 mg/day versus fremanezumab monthly | 1.38 (0.87 to 2.18) |
| Propranolol 120 mg/day to 160 mg/day versus fremanezumab monthly | 1.38 (0.77 to 2.40) |
| Galcanezumab 240 mg versus, fremanezumab monthly | 1.29 (0.79 to 2.05) |
| Galcanezumab 120 mg versus fremanezumab monthly | 1.21(0.73 to 1.95) |
| Topiramate 200 mg/day versus fremanezumab monthly | 1.18 (0.73 to 1.90) |
| Erenumab 140 mg versus fremanezumab monthly | 1.11 (0.64 to 1.91) |
| Amitriptyline 25 to 100 mg/day versus fremanezumab monthly | 1.01 (0.54 to 1.87) |
| Fremanezumab monthly versus erenumab 70 mg | 1.03 (0.65 to 1.67) |
| Fremanezumab monthly versus fremanezumab quarterly | 1.15 (0.74 to 1.79) |
| Fremanezumab monthly versus topiramate 50 mg/day | 1.24 (0.72 to 2.12) |
| Fremanezumab monthly versus placebo | 1.95 (1.35 to 2.51) |
| Topiramate 100 mg/day versus fremanezumab quarterly | 1.58 (0.94 to 2.64) |
| Propranolol 120 mg/day to 160 mg/day versus fremanezumab quarterly | 1.58 (0.85 to 2.88) |
| Galcanezumab 240 mg versus fremanezumab quarterly | 1.48 (0.86 to 2.47) |
| Galcanezumab 120 mg versus fremanezumab quarterly | 1.39 (0.80 to 2.35) |
| Topiramate 200 mg/day versus fremanezumab quarterly | 1.36 (0.79 to 2.28) |
| Erenumab 140 mg versus fremanezumab quarterly | 1.27 (0.70 to 2.31) |
| Amitriptyline 25 mg/day 100 mg/day versus fremanezumab quarterly | 1.15 (0.60 to 2.24) |
| Erenumab 70 mg versus fremanezumab quarterly | 1.11 (0.66 to 1.87) |
| Fremanezumab quarterly versus topiramate 50 mg/day | 1.08 (0.60 to 1.93) |
| Fremanezumab quarterly versus placebo | 1.70 (1.10 to 2.66) |

CrI = credible interval; OR = odds ratio.

Source: The Institute for Clinical and Economic Review.[47]

Table 28 present results from the NMA for the change from baseline in acute medication use per month in patients with EM. In this analysis, monthly and quarterly fremanezumab was favoured only when compared with placebo.

## Table 28: 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) |
|---|---|
| Galcanezumab 120 mg versus fremanezumab monthly | –0.60(–1.58 to 0.43) |
| Galcanezumab 240 mg versus fremanezumab monthly | 0.49 (–1.48 to 0.53) |
| Erenumab 140 mg versus fremanezumab monthly | –0.42 (–1.48 to 0.64) |
| Fremanezumab monthly versus amitriptyline 100 mg/day | –0.05 (–1.52 to 1.38) |
| Fremanezumab monthly versus fremanezumab quarterly | –0.09 (–0.97 to 0.76) |
| Fremanezumab monthly versus propranolol 160 mg/day | –0.13 (–1.21 to 0.95) |
| Fremanezumab monthly versus topiramate 100 mg/day | –0.26 (–1.18 to 0.65) |
| Fremanezumab monthly versus erenumab 70 mg | –0.34 (–1.22 to 0.58) |
| Fremanezumab monthly versus topiramate 200 mg/day | –0.49 (–1.43 to 0.46) |

| Comparison | Mean difference (95% CrI) |
|---|---|
| Fremanezumab monthly versus topiramate 50 mg/day | –0.77 (–1.95 to 0.41) |
| Fremanezumab monthly versus placebo | –1.21 (–2.01 to –0.45) |
| Galcanezumab 120 mg versus fremanezumab quarterly | –0.69 (–1.76 to 0.41) |
| Galcanezumab 240 mg versus fremanezumab quarterly | –0.59 (–1.66 to 0.50) |
| Erenumab 140 mg versus fremanezumab quarterly | –0.52 (–1.65 to 0.61) |
| Amitriptyline 100 mg/day versus fremanezumab quarterly | –0.04 (–1.54 to 1.46) |
| Fremanezumab quarterly versus propranolol 160 mg/day | –0.03 (–1.19 to 1.13) |
| Fremanezumab quarterly versus topiramate 100 mg/day | –0.16 (–1.17 to 0.84) |
| Fremanezumab quarterly versus erenumab 70 mg | –0.25 (–1.21 to 0.78) |
| Fremanezumab quarterly versus topiramate 200 mg/day | –0.39 (–1.41 to 0.64) |
| Fremanezumab quarterly versus topiramate 50 mg/day | –0.68 (–1.92 to 0.57) |
| Fremanezumab quarterly versus placebo | –1.11 (–2.00 to –0.25) |

CrI = credible interval.

Source: The Institute for Clinical and Economic Review.[47]

## Critical Appraisal of ICER ITC

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. 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 to 26 weeks. While the patient population (i.e., adults with CM and eligible for preventive migraine therapy) was in alignment with the indication for fremanezumab, the ICER ITC had limited data available for patients who failed previous therapies.

There were several sources of heterogeneity in the included networks that reduce the overall applicability to the target patient population. These sources include variations in the outcome measures related to the definition of responders, the number of inadequate previous treatments, the disease duration, and the dosing of OnaA in contrast to the Health Canada–approved indication.

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

The report did not provide a discussion about whether the transitivity assumption was met in the networks of trials. This is relevant, considering the sources of heterogeneity mentioned earlier. 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; however, they were not examined in the analyses.

The NMA considered time point in meta-regression and conducted a subgroup analysis for 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, OnaA dose, or study quality.

The strength of the network for CM patients was low, with only 6 studies for 7 treatment options (for change from baseline in MMDs) and only 8 studies for 7 treatment options (change in monthly headache days). The networks were centred on placebo, and most comparisons were indirect. All studies included in the analysis for change from baseline in MMDs were of good quality; however, 3 of the 8 studies included in the analysis for the mean change in monthly headache days were of poor quality. A sensitivity analysis based on study quality was not conducted.

## Summary

Two ITCs were summarized: the sponsor-submitted ITC and an ITC by ICER. Both ITCs had a similar approach to data synthesis. The results of the outcomes in the sponsor-submitted ITC were described based on migraine type (CM or EM) and the number of inadequate previous treatments (less than 2 or 2 or more). In contrast, the ICER ITC only provided the results stratified by migraine type. This variation in the approach to data synthesis meant that the sponsor-submitted ITC is more homogeneous than the ICER ITC, albeit smaller (e.g., 3 studies in the sponsor ITC versus 6 studies in the ICER ITC). The smaller size comes with limitations on the lack of precision (wide 95% CrI), inability to test the consistency assumption, and the use of the fixed-effects model, which adds another layer of unverifiable assumptions to the model. However, the gains in homogeneity in the networks may provide improved internal validity. Unfortunately, the sponsor-submitted ITC included the FOCUS trial in the networks with 2 or more inadequate previous treatments, without separating the CM patients from EM. This approach violated the sponsor-submitted ITC's own analysis eligibility criteria, since many other trials were excluded for not providing data separately for each migraine type, and, more concerning, introduced considerable clinical heterogeneity in these networks. This limitation has likely biased the results in favour of fremanezumab in the EM networks and against fremanezumab in the CM networks. There is no way, based on current data, to quantify the exact magnitude that this bias may have had on the results.

The overall results from both ITCs show that fremanezumab has a favourable clinical efficacy versus placebo. Similarly, and throughout the various networks in both ITCs, fremanezumab did not show a favourable or unfavourable effect that would exclude the null versus other active comparators (including OnaA in a sensitivity analysis), with the exception of the following results:

- In the sponsor-submitted ITC: Monthly and quarterly fremanezumab was significantly better in reducing the MMDs at 12 weeks than erenumab 70 mg (monthly: mean difference –2.63; 95% CrI, –4.96 to –0.3; quarterly: mean difference –2.53; 95% CrI, –4.85 to –0.2) in EM patients who had an inadequate response to 2 or more previous treatments.
- In the sponsor-submitted ITC: Monthly and quarterly fremanezumab was significantly better in the rate of 50% responders at 12 weeks than erenumab 140 mg (monthly: RR 1.83; 95% CrI, 1.15 to 3.08; quarterly: RR 1.71; 95% CrI, 1.07 to 2.89) and galcanezumab 120 mg (monthly: RR 1.75; 95% CrI, 1.21 to 2.62; quarterly: RR 1.63; 95% CrI, 1.12 to 2.46) in CM patients who had inadequate response to fewer than 2 previous treatments.
- In the sponsor-submitted ITC: Monthly and quarterly fremanezumab was significantly better in reducing the days using acute migraine-specific medication at 12 weeks than

erenumab 70 mg (monthly: mean difference –2.95; 95% CrI, –4.54 to –1.34; quarterly: mean difference –2.54; 95% CrI, –4.15 to –0.95) and 140 mg (monthly: mean difference –1.46; 95% CrI, –2.48 to –1.45; quarterly: mean difference –1.06; 95% CrI, –2.07 to –0.05) in EM patients who had inadequate response to 2 or more previous treatments.

- In the sponsor-submitted ITC: Monthly fremanezumab was significantly better in reducing the days using acute migraine-specific medication at 12 weeks than erenumab 70 mg (mean difference –1.6; 95% CrI, –2.99 to –0.20) and 140 mg (mean difference –1.6; 95% CrI, –3.0 to –0.21) in the CM patients who had inadequate response to fewer than 2 previous treatments.
- In ICER ITC: Monthly fremanezumab was significantly better in reducing the MMDs at 12 weeks than topiramate 50 mg/day in EM patients (mean difference –1.42; 95% CrI, –2.59 to –0.29). Uncertainty in this result mainly stems from clinical heterogeneity in the included studies.

The majority of the results showing comparative values that include the null in their credible interval should not be interpreted as evidence of similarity or equal effect. Because of the small size of the networks and the fact that 1 study usually informed the direct evidence between 2 nodes, this ITC would not provide a statistically robust analysis with sufficient power to determine similarity.

Overall, comparative efficacy between fremanezumab and other CGRP inhibitors remains uncertain, primarily because a robust network is lacking. Furthermore, whether there is a differential treatment effect in patients with CM or EM also remained uncertain.

## Other Relevant Evidence

This section includes submitted long-term extension studies and additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review.

### Long-Term Extension Studies

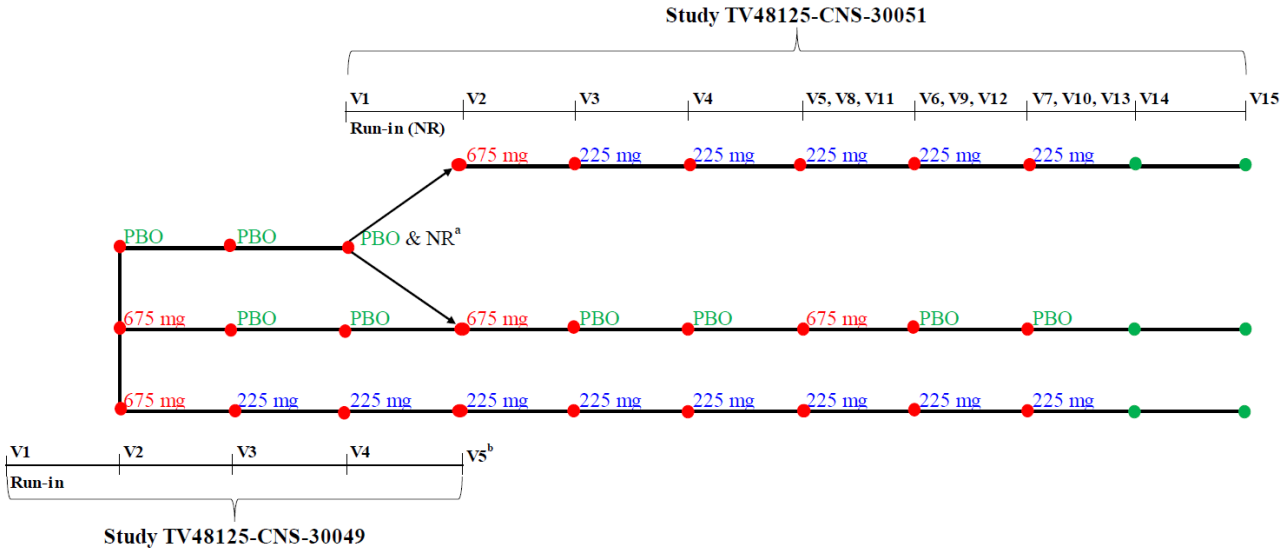
One long-term extension study was submitted by the sponsor. The HALO LTS has been summarized to provide evidence regarding the long-term safety, tolerability, and efficacy of fremanezumab 225 mg and 675 mg for monthly and quarterly dosages in patients with CM and EM. The first patient was enrolled in the HALO LTS on March 25, 2016, and the study was ongoing at the time of this review. As a result, the sponsor provided data of the interim analyses up to a cut-off date of May 30, 2018. The primary objective of this study was to evaluate the long-term safety and tolerability of fremanezumab for the preventive treatment of migraines in adult patients, and the long-term efficacy of fremanezumab was assessed as an exploratory objective.

#### *Methods*

The HALO LTS was a multi-centre, randomized, double-blind, parallel-group, phase III study of SC administration of fremanezumab for the preventive treatment of migraine in adults. It was conducted at 134 study centres in 9 countries: US, Canada, Czech Republic, Spain, Finland, Israel, Japan, Poland, and the Russian Federation. Patients who had completed the pivotal efficacy studies, HALO CM and HALO EM, were enrolled in the current HALO LTS. New patients who had not participated in the pivotal efficacy studies were also enrolled.

Patients who had received fremanezumab as either a monthly or quarterly dosage in the pivotal studies continued to receive the same dosage regimen for 12 months, along with a 6.5-month post-treatment follow-up. Patients who received placebo during the pivotal studies and newly enrolled patients were randomized 1:1 to either monthly or quarterly fremanezumab treatment. New patients who had not participated in the pivotal studies underwent screening, a 28-day run-in, and similarly received treatment for a 12-month period with a 6.5-month follow-up. During the run-in period, patients were required to complete a daily electronic headache diary and demonstrate compliance for at least 24 of 28 days. Patients with EM on monthly dosage received fremanezumab 225 mg every month for a total 12 doses, while those with CM received the same treatment but with a loading dose of fremanezumab 675 mg for the first month. New patients with EM or CM on quarterly dosage received fremanezumab 675 mg every 3 months for a total of 4 doses. Once assigned, patients did not switch between the dosage regimens. Figure 4 and Figure 5 outline the dosage regimens for patients with CM and EM during the LTS.

## Figure 6: Study Outline for HALO LTS — Patients With CM



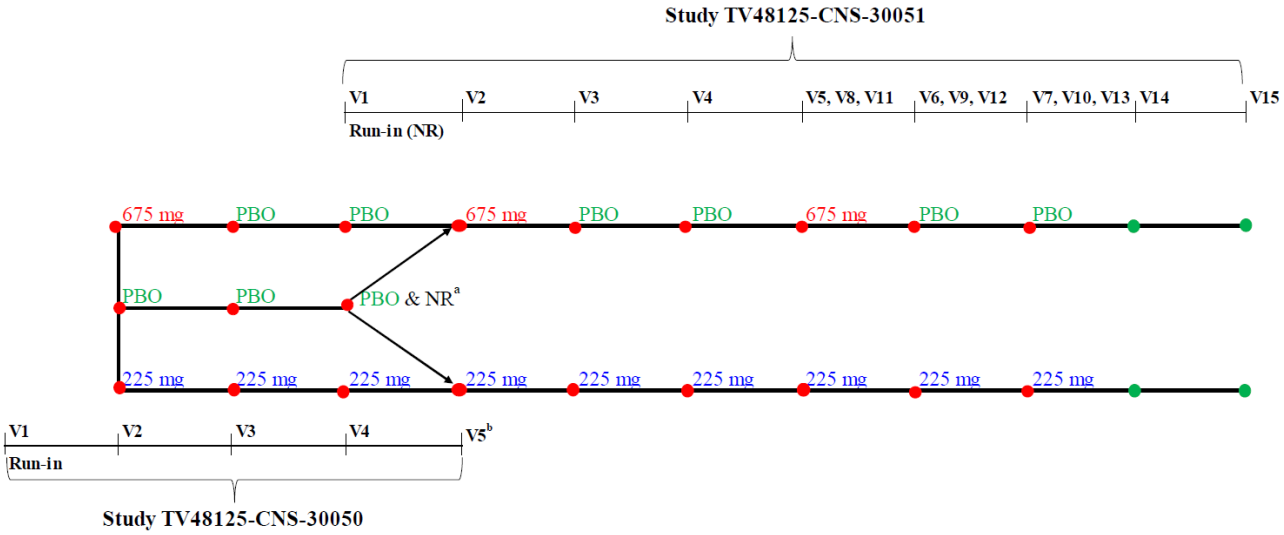

CM = chronic migraine; LTS = long-term study; NR = non-rollover patients; PBO = placebo; TV48125-CNS-30049 = HALO CM; TV48125-CNS-30051 = HALO LTS; V = visit.

[a] Patients new to the study and those rolling over from the pivotal efficacy study who received placebo were randomized in a 1:1 ratio at visit 2 to receive either a loading dose of fremanezumab 675 mg followed by monthly fremanezumab 225 mg, or quarterly fremanezumab 675 mg.

[b] For patients who began this study (visit 2) on the same day as the EOT visit (visit 5) of the pivotal efficacy studies, the EOT visit procedures/assessments for the pivotal efficacy study were completed before beginning visit 2 procedures/assessments.

Source: Clinical Study Report for HALO LTS.[94]

## Figure 7: Study Outline for HALO LTS — Patients With EM




EM = episodic migraine; LTS = long-term study; NR = non-rollover patients; PBO = placebo; TV48125-CNS-30050 = HALO EM; TV48125-CNS-30051 = HALO LTS; V = visit.

[a] Patients new to the study and those rolling over from the pivotal efficacy study who received placebo were randomized in a 1:1 ratio at visit 2 to receive either quarterly fremanezumab 675 mg or monthly fremanezumab 225 mg.

[b] For patients who began this study (visit 2) on the same day as the EOT visit (visit 5) of the pivotal efficacy study, the EOT visit procedures/assessments for the pivotal efficacy study were completed before beginning visit 2 procedures/assessments.

Source: Clinical Study Report for HALO LTS.[94]

### *Populations*

Rollover patients were eligible for the HALO LTS if they met all the following inclusion criteria:

- gave informed consent and would comply with study restrictions
- completed the pivotal efficacy study without major protocol violations
- could continue with a stable dose and regimen of the preventive medication they were taking during the pivotal efficacy studies.

Non-rollover patients were eligible for the HALO LTS if they met all the following inclusion criteria:

- gave informed consent and would comply with study restrictions
- were between 18 and 70 years old, in good health, with migraine onset before 50 years of age
- had a history of migraine or clinical assessment suggesting migraine diagnosis for at least 12 months before screening
- demonstrated at least 85% (24 of 28 days) compliance with the electronic headache diary during the run-in period
- used fewer than 2 preventive medications for migraine or other medical conditions if dose and regimen had been stable for at least 2 months before the 28-day run-in period
- had a body mass index between 17.5 kg/m$^2$ and 37.5 kg/m$^2$ and body mass between 45 kg and 120 kg

- used highly effective contraceptive methods.

Patients who completed either of the 2 pivotal trials but did not wish to participate in the LTS could be included for antidrug antibody (ADA) assessment only and were required to give informed consent.

Patients were excluded from HALO LTS if they met any of the following criteria:

- had any clinically significantly abnormal finding in the judgment of the study investigator (e.g., ECG results at baseline; clinical laboratory results; psychiatric issues; history of cardiovascular disease; known infection or history of HIV, tuberculosis, hepatitis, or cancer; contraindication to injected proteins or monoclonal antibodies)
- were pregnant or nursing, unable to participate in the opinion of the patient's health care provider or study investigator, or had a history of alcohol or drug abuse in the past 2 years or dependence in the last 5 years
- had lower than 75% compliance with the electronic headache diary during the last month of the pivotal study (for rollover patients)
- participated in another clinical study within 2 months of the LTS (for non-rollover patients)
- were employed by the study centre or sponsor, or were related to one of these.

Table 29 summarizes the baseline characteristics of the ITT population of the HALO LTS. Overall, 1,890 patients were included, with a mean age of 43.5 years (SD = 11.88, median = 44.0, range = 18 to 71). Women made up 87% of the population, and 81% were White. Forty-eight patients (3%) were from Canada, with the majority (n = 1,390, 74%) from the US. The mean time since patients had been diagnosed with migraines was 21.6 years (SD = 12.74; median = 20.0; range = 1 to 65).

## Table 29: Summary of Patient Baseline Characteristics by Treatment Group of HALO LTS — ITT Population

| | Fremanezumab 225 mg monthly | | | Fremanezumab 675 mg quarterly | | |
|---|---|---|---|---|---|---|
| | New/PBO rollover N = 419 | Active rollover N = 526 | Total N = 945 | New/PBO rollover N = 420 | Active rollover N = 525 | Total N = 945 |
| Age (years), mean (SD) | 44.1 (12.09) | 42.9 (11.97) | 43.5 (12.04) | 44.0 (11.71) | 43.2 (11.73) | 43.5 (11.72) |
| Female, n (%) | 365 (87) | 454 (86) | 819 (87) | 369 (88) | 457 (87) | 826 (87) |
| Race, n (%) | | | | | | |
| White | 351 (84) | 424 (81) | 775 (82) | 343 (82) | 412 (78) | 755 (80) |
| Black or African-American | 32 (8) | 38 (7) | 70 (7) | 38 (9) | 40 (8) | 78 (8) |
| Asian | 29 (7) | 62 (12) | 91 (10) | 36 (9) | 64 (12) | 100 (11) |
| Other (including American Indian, Alaskan Native, Native Hawaiian, Pacific Islander) | 7 (2) | 2 (< 1) | 9 (1) | 3 (1) | 9 (2) | 12 (1) |
| Mass (kg), n | 419 | 524 | 943 | 420 | 525 | 945 |
| Mean (SD) | 73.3 (15.93) | 71.8 (15.93) | 72.4 (15.94) | 73.3 (15.82) | 72.8 (15.54) | 73.0 (15.66) |
| BMI (kg/m$^2$), n | 419 | 524 | 943 | 420 | 525 | 945 |
| Mean (SD) | 26.56 (5.124) | 26.19 (5.132) | 26.35 (5.129) | 26.66 (5.151) | 26.57 (5.189) | 26.61 (5.170) |

| | Fremanezumab 225 mg monthly | | | Fremanezumab 675 mg quarterly | | |
|---|---|---|---|---|---|---|
| | New/PBO rollover N = 419 | Active rollover N = 526 | Total N = 945 | New/PBO rollover N = 420 | Active rollover N = 525 | Total N = 945 |
| Years since initial migraine diagnosis, mean (SD) | 21.8 (12.74) | 21.3 (12.08) | 21.5 (12.37) | 22.6 (13.34) | 20.9 (12.86) | 21.7 (13.10) |
| Preventive medication use, n (%) | 105 (25) | 129 (25) | 234 (25) | 105 (25) | 112 (21) | 217 (23) |
| Previous topiramate use | 149 (36) | 155 (29) | 304 (32) | 153 (36) | 140 (27) | 293 (31) |
| Previous onabotulinum toxin A use | 89 (21) | 60 (11) | 149 (16) | 80 (19) | 75 (14) | 155 (16) |
| Triptans/ergots use during baseline | 246 (59) | 301 (57) | 547 (58) | 260 (62) | 318 (61) | 578 (61) |
| Any acute headache medication use | 392 (94) | 505 (96) | 897 (95) | 405 (96) | 505 (96) | 910 (96) |
| Migraine days (days), mean (SD) | 13.9 (5.99) | 13.1 (5.49) | 13.4 (5.73) | 13.6 (5.86) | 13.2 (5.26) | 13.4 (5.53) |
| Headache days of at least moderate severity (days), mean (SD) | 11.6 (6.16) | 10.5 (5.55) | 11.0 (5.85) | 11.3 (5.94) | 10.9 (5.37) | 11.1 (5.63) |
| Headache days of any severity (days), mean (SD) | 13.6 (6.68) | 12.7 (6.20) | 13.1 (6.43) | 13.2 (6.32) | 12.9 (6.02) | 13.0 (6.15) |
| Use of acute headache medication (days), mean (SD) | 11.0 (6.64) | 11.2 (6.39) | 11.1 (6.50) | 11.4 (6.30) | 11.1 (6.19) | 11.2 (6.24) |
| Use of any migraine-specific acute headache medication, n | 246 | 301 | 547 | 260 | 318 | 578 |
| Days, mean (SD) | 9.8 (5.79) | 9.1 (5.57) | 9.4 (5.67) | 9.6 (5.48) | 9.7 (5.65) | 9.7 (5.57) |
| Headache hours of at least moderate severity (hours), mean (SD) | 61.8 (63.27) | 51.4 (42.34) | 56.0 (52.88) | 58.8 (60.27) | 52.6 (52.80) | 55.4 (56.29) |
| Headache hours of any severity (hours), mean (SD) | 111.8 (100.87) | 100.4 (79.82) | 105.5 (89.89) | 105.1 (88.86) | 93.9 (69.82) | 98.9 (79.00) |
| HIT-6 score, n | 250 | 306 | 556 | 242 | 302 | 544 |
| Mean (SD) | 64.5 (4.65) | 64.5 (4.46) | 64.5 (4.54) | 63.9 (5.01) | 64.5 (4.76) | 64.2 (4.87) |
| Median (range) | 65.0 (48 to 78) | 64.0 (50 to 78) | 65.0 (48 to 78) | 64.0 (48 to 76) | 65.0 (42 to 78) | 64.0 (42 to 78) |
| MIDAS score | 163 | 216 | 379 | 173 | 214 | 387 |
| Mean (SD) | 39.9 (30.29) | 37.4 (34.85) | 38.5 (32.95) | 34.8 (26.38) | 41.4 (31.42) | 38.4 (29.42) |
| Median (range) | 33.0 (0 to 170) | 31.0 (0 to 306) | 32.0 (0 to 306) | 31.0 (0 to 170) | 34.5 (0 to 206) | 32.0 (0 to 206) |
| MSQoL – RFR, n | 417 | 522 | 939 | 419 | 520 | 939 |
| Mean (SD) | 51.2 (18.07) | 51.8 (18.99) | 51.5 (18.58) | 52.8 (20.33) | 51.3 (18.25) | 51.9 (19.21) |
| Median (range) | 51.4 (0 to 94) | 54.3 (0 to 100) | 54.3 (0 to 100) | 57.1 (0 to 100) | 51.4 (0 to 100) | 54.3 (0 to 100) |
| MSQoL – RFP, n | 417 | 522 | 939 | 419 | 520 | 939 |

| | Fremanezumab 225 mg monthly | | | Fremanezumab 675 mg quarterly | | |
|---|---|---|---|---|---|---|
| | New/PBO rollover N = 419 | Active rollover N = 526 | Total N = 945 | New/PBO rollover N = 420 | Active rollover N = 525 | Total N = 945 |
| Mean (SD) | 67.5 (20.50) | 68.2 (21.17) | 67.9 (20.86) | 69.1 (22.44) | 68.8 (19.80) | 69.0 (21.01) |
| Median (range) | 70.0 (0 to 100) | 70.0 (0 to 100) | 70.0 (0 to 100) | 75.0 (0 to 100) | 70.0 (0 to 100) | 75.0 (0 to 100) |
| MSQoL – ES, n | 417 | 522 | 939 | 419 | 520 | 939 |
| Mean (SD) | 59.4 (25.10) | 59.6 (26.29) | 59.5 (25.75) | 60.1 (27.39) | 60.1 (25.56) | 60.1 (26.38) |
| Median (range) | 60.0 (0 to 100) | 60.0 (0 to 100) | 60.0 (0 to 100) | 66.7 (0 to 100) | 63.3 (0 to 100) | 66.7 (0 to 100) |
| EQ-5D-5L, n | 417 | 522 | 939 | 419 | 520 | 939 |
| Mean (SD) | 73.5 (18.08) | 75.7 (17.46) | 74.7 (17.76) | 76.0 (17.22) | 73.7 (18.00) | 74.7 (17.69) |
| Median (range) | 79.0 (10 to 100) | 80.0 (9 to 100) | 80.0 (9 to 100) | 80.0 (15 to 100) | 79.0 (10 to 100) | 80.0 (10 to 100) |
| PHQ-9, n | 417 | 522 | 939 | 419 | 520 | 939 |
| Mean (SD) | 3.3 (5.10) | 3.6 (5.20) | 3.5 (5.16) | 3.1 (5.15) | 3.2 (4.74) | 3.2 (4.93) |
| Median (range) | 1.0 (0 to 23) | 2.0 (0 to 24) | 1.0 (0 to 24) | 1.0 (0 to 25) | 2.0 (0 to 27) | 1.0 (0 to 27) |
| WPAI – percent work item missed due to health, n | 293 | 377 | 670 | 304 | 391 | 695 |
| Mean (SD) | 9.0 (15.18) | 8.8 (16.20) | 8.9 (15.75) | 8.3 (17.24) | 9.5 (17.15) | 9.0 (17.19) |
| Median (range) | 0.0 (0 to 100) | 0.0 (0 to 100) | 0.0 (0 to 100) | 0.0 (0 to 100) | 0.0 (0 to 100) | 0.0 (0 to 100) |
| WPAI – percent impairment while working due to health, n | 292 | 372 | 664 | 300 | 387 | 687 |
| Mean (SD) | 36.4 (22.76) | 34.9 (22.65) | 35.6 (22.69) | 35.5 (24.28) | 37.1 (23.61) | 36.4 (23.90) |
| Median (range) | 35.0 (0 to 90) | 30.0 (0 to 90) | 30.0 (0 to 90) | 30.0 (0 to 100) | 40.0 (0 to 100) | 30.0 (0 to 100) |
| WPAI – percent overall work impairment due to health, n | 292 | 372 | 664 | 300 | 387 | 687 |
| Mean (SD) | 40.8 (24.95) | 38.7 (24.39) | 39.6 (24.64) | 38.6 (26.07) | 41.5 (25.41) | 40.2 (25.72) |
| Median (range) | 40.0 (0 to 99) | 38.9 (0 to 95) | 40.0 (0 to 99) | 34.2 (0 to 100) | 40.0 (0 to 100) | 40.0 (0 to 100) |
| WPAI – percent activity impairment due to health, n | 417 | 522 | 939 | 419 | 520 | 939 |
| Mean (SD) | 42.2 (24.50) | 41.4 (23.60) | 41.8 (24.00) | 42.1 (25.33) | 41.2 (23.81) | 41.6 (24.49) |
| Median (range) | 40.0 (0 to 100) | 40.0 (0 to 100) | 40.0 (0 to 100) | 40.0 (0 to 100) | 40.0 (0 to 100) | 40.0 (0 to 100) |

BMI = body mass index; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; ES = emotional state; HIT-6 = 6-item headache impact test; ITT = intention-to-treat; LTS = long-term study; MIDAS = migraine disability assessment score; MSQoL = Migraine-Specific Quality of Life questionnaire; PBO = placebo; PHQ = Patient Health Questionnaire; RFP = role function–preventive; RFR = role function–restrictive; SD = standard deviation; WPAI = Work Productivity and Activity Impairment questionnaire.

Note: For rollover patients, baseline values have been carried forward from the 2 pivotal studies.

Note: Denominators for percentages are number of patients, N, except where otherwise stated for variables.

Source: Clinical Study Report for HALO LTS.[94]

*Interventions*

For the HALO LTS, the study drug was available in a 2.25 mL pre-filled syringe containing fremanezumab 225 mg; therefore, a dose of 675 mg required 3 injections. To maintain blinding of treatment dose volume and number of injections, all patients received 3 1.5 mL injections at quarterly visits and one 1.5 mL injection during the other visits. During the quarterly visits, the 3 injections were a combination of active drug and/or placebo, depending on which group the patient was enrolled in (Table 30). During the other visits, a single injection of either active drug or placebo was administered, depending on which group the patient was enrolled in (Table 30).

## Table 30: Study Drug Administration by Treatment Group and Visit of HALO LTS

| Treatment group | Visit 2 | Visits 5, 8, 11 | Visits 3, 4, 6, 7, 9, 10, 12, 13 |
|---|---|---|---|
| Fremanezumab 675 mg loading dose + monthly fremanezumab 225 mg | 3 injections of active drug[a] | 1 injection of active drug[a]<br>2 injections of PBO[b] | 1 injection of active drug[a] |
| Fremanezumab 225 mg monthly | 1 injection of active drug[a]<br>2 injections of PBO[b] | 1 injection of active drug[a]<br>2 injections of PBO[b] | 1 injection of active drug[a] |
| Fremanezumab 675 mg quarterly | 3 injections of active drug[a] | 3 injections of active drug[a] | 1 injection of PBO[b] |

LTS = long-term study; PBO = placebo.

[a] Active drug was fremanezumab 225 mg/1.5 mL injection.

[b] Placebo is 1.5 mL injection.

Source: Clinical Study Report for HALO LTS.[94]

Prior or concomitant treatments within 6 months of the start of the HALO LTS to the end of the study period were recorded in the case report form. Migraine preventives taken during the 2 years before the LTS were also recorded.

Rollover patients could continue taking stable doses (at least 2 months) of up to 1 preventive treatment during the LTS, while new patients could continue with up to 2 preventive medications if the medication demonstrated at least moderate evidence of efficacy. Otherwise, patients were required to discontinue use of preventive medications for at least 5 half-lives before the screening period. Patients were asked not to begin using preventive treatments de novo during the safety extension study period, although medications for acute attacks were allowed for all study arms.

Most patients (93%) in the HALO LTS were receiving medications specifically for migraines and headaches before beginning the study, with the 3 most common being ibuprofen (n = 609, 32%), sumatriptan (n = 608, 32%), and acetaminophen-Aspirin-caffeine (n = 459, 24%).

*Outcomes*

The primary objective of the HALO LTS was to assess the long-term safety and tolerability of fremanezumab for the preventive treatment of migraines in adult patients.

There were no primary or secondary efficacy end points for the HALO LTS, and all efficacy end points were exploratory.

Exploratory efficacy end points included:

- Mean change from baseline in the number of migraine days, number of headache days of at least moderate severity, number of headache days of any severity, and number of days of use of any acute headache medications
- Proportion of patients reaching at least 50%, 75%, and 100% reduction in the number of migraine days and headache days of at least moderate severity
- Proportion of patients discontinuing concomitant preventive medications during the treatment period
- Mean change from baseline for HIT-6 (patients with CM), MIDAS (patients with EM), MSQoL, EQ-5D-5L, PGIC, PHQ-2 and PHQ-9, and WPAI.

Safety outcomes included:

- AEs, SAEs, withdrawal due to AEs, and AEs of special interest
- Clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings (including body weight measurements), eC-SSRS scores, local injection-site assessments, immunogenicity, and concomitant medication usage.

*Statistical Analysis*

The ITT population (N = 1,890) consisted of all randomized patients, regardless of whether they received the study treatment. The safety population was composed of 1,888 patients who received at least 1 dose of fremanezumab. The efficacy or FAS population included 1,878 patients who had recorded at least 10 days of efficacy assessments by electronic headache diary after receiving the first injection of the study treatment. By the data cut-off date (May 30, 2018), 666 patients had completed the study.

This was an uncontrolled study with no active comparator drug or placebo group. The study sponsor, investigators, study staff (not including staff performing bioanalytical analyses), and patients were blinded to treatment assignment. The sponsor was unblinded when the pivotal studies were unblinded. Patients were stratified by sex, country, and use of preventive medication at baseline (yes or no) in the pivotal studies and this study. New patients and those who previously received placebo in the pivotal studies were randomly assigned 1:1 to 1 of the 2 dosage regimens. There were no statistical considerations for the study sample size, and no statistical testing was performed on the exploratory efficacy analyses.

Baseline values were carried forward from patients who participated in either of the pivotal studies, while new patient baseline values were based on the 28-day run-in period. AEs were recorded for the entire study period, from when the patient gave informed consent to the follow-up visit, which was approximately 7.5 months after the final dose of fremanezumab.

Efficacy results have been organized by CM and EM as well as by treatment group. Continuous variables have been summarized using descriptive statistics (number of patients [n], mean, SD, standard error [SE], median, and range). Categorical variables have been provided as frequencies and percentages.

Patients who completed the study, but who had intermittent missing data in the electronic headache diary, had their efficacy variables from months 1, 2, 3, 6, and 12 prorated to 28 days for each month. For patients who discontinued early, missing data were calculated based on the most recent information available from the headache diary.

### *Patient Disposition*

Table 31 summarizes the patient disposition of the HALO LTS. In this study, 2,033 patients were screened, 1,890 of whom were enrolled and made up the ITT population. The reasons for screening failure included not meeting inclusion or exclusion criteria (n = 51 and n = 17, respectively), loss to follow-up (n = 2), or other reason (n = 73). From the pivotal studies, 917 patients rolled over from HALO CM (81% of the randomized population), 661 from HALO EM (76% of the randomized population), and 312 were new patients (193 with CM and 119 with EM). Out of the 1,888 patients who received a dose of fremanezumab, 666 (35%) patients had completed the study as of the data cut-off date, while 20% (n = 373) had discontinued (186 and 187 patients receiving monthly and quarterly doses, respectively). The most common reasons for discontinuation were withdrawal by patient (8%), lack of efficacy (4%), and AE (4%). The group of patients who only had ADA analysis consisted of 60 patients, 28 with CM and 32 with EM.

### *Exposure to Study Treatments*

Table 32 summarizes the duration exposure to fremanezumab for the safety population. Patients who participated in the pivotal trials had exposure to fremanezumab for approximately 3 months before the HALO LTS. Overall, the mean duration of treatment was 305.4 days (SD = 87.58; median = 337.0; range = 1 to 579), which was similar across the dosage groups. In total, 89% (n = 1,671) of patients had received at least 6 doses (including both active drug and placebo) and 79% (n = 1,491) had received 12 doses.

## Table 31: Patient Disposition by Treatment Group of HALO LTS

| | New patients | | | Rollover patients | | | Overall |
|---|---|---|---|---|---|---|---|
| | Fremanezumab 225 mg monthly | Fremanezumab 675 mg quarterly | Total | Fremanezumab 225 mg monthly | Fremanezumab 675 mg quarterly | Total | |
| Screened | NR | NR | NR | NR | NR | NR | 2,033 |
| Randomized/rollover (ITT population), n (%)[a] | 156 (100) | 156 (100) | 312 (100) | 789 (100) | 789 (100) | 1,578 (100) | 1,890 (100) |
| CM, n (%) | 97 (62) | 96 (62) | 193 (62) | 462 (59) | 455 (58) | 917 (58) | 1,110 (59) |
| EM, n (%) | 59 (38) | 60 (38) | 119 (38) | 327 (41) | 334 (42) | 661 (42) | 780 (41) |
| Safety population, n (%)[b] | 156 (100) | 156 (100) | 312 (100) | 788 (> 99) | 788 (> 99) | 1,576 (> 99) | 1,888 (> 99) |
| CM, n (%) | 97 (62) | 96 (62) | 193 (62) | 461 (58) | 454 (58) | 915 (58) | 1,108 (59) |
| EM, n (%) | 59 (38) | 60 (38) | 119 (38) | 327 (41) | 334 (42) | 661 (42) | 780 (41) |
| FAS, n (%)[c] | 155 (> 99) | 156 (100) | 311 (> 99) | 781 (99) | 786 (> 99) | 1,567 (> 99) | 1,878 (> 99) |
| CM, n (%) | 97 (62) | 96 (62) | 193 (62) | 457 (58) | 453 (57) | 910 (58) | 1,103 (58) |
| EM, n (%) | 58 (37) | 60 (38) | 118 (38) | 324 (41) | 333 (42) | 657 (42) | 775 (41) |
| Completed study, n (%) | 118 (76) | 124 (79) | 242 (78) | 226 (29) | 198 (25) | 424 (27) | 666 (35) |
| CM, n (%) | 79 (51) | 75 (48) | 154 (49) | 125 (16) | 116 (15) | 241 (15) | 395 (21) |
| EM, n (%) | 39 (25) | 49 (31) | 88 (28) | 101 (13) | 82 (10) | 183 (12) | 271 (14) |
| Discontinued study, n (%) | 16 (10) | 20 (13) | 36 (12) | 93 (12) | 89 (11) | 182 (12) | 373 (20) |
| Reasons for discontinuation, n (%) | | | | | | | |
| Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adverse event | 8 (5) | 10 (6) | 18 (6) | 27 (3) | 29 (4) | 56 (4) | 74 (4) |
| Withdrawal by subject | 5 (3) | 7 (4) | 12 (4) | 70 (9) | 64 (8) | 134 (8) | 146 (8) |
| Protocol violation | 1 (< 1) | 2 (1) | 3 (< 1) | 3 (< 1) | 4 (< 1) | 7 (< 1) | 10 (< 1) |
| Pregnancy | 0 | 0 | 0 | 4 (< 1) | 2 (< 1) | 6 (< 1) | 6 (< 1) |
| Noncompliance with study procedures | 0 | 0 | 0 | 4 (< 1) | 1 (< 1) | 5 (< 1) | 5 (< 1) |
| Lost to follow-up | 5 (3) | 1 (< 1) | 6 (2) | 27 (3) | 26 (3) | 53 (3) | 59 (3) |
| Lack of efficacy | 10 (6) | 6 (4) | 16 (5) | 29 (4) | 31 (4) | 60 (4) | 76 (4) |
| Other | 0 | 1 (< 1) | 1 (< 1) | 10 (1) | 6 (< 1) | 16 (1) | 17 (< 1) |
| ADA only analysis set, n (%)[d] | – | – | – | NR | NR | 60 (4) | 60 (3) |

| | New patients | | | Rollover patients | | | Overall |
|---|---|---|---|---|---|---|---|
| | Fremanezumab 225 mg monthly | Fremanezumab 675 mg quarterly | Total | Fremanezumab 225 mg monthly | Fremanezumab 675 mg quarterly | Total | |
| CM | – | – | – | NR | NR | 28 (2) | 28 (1) |
| EM | – | – | – | NR | NR | 32 (2) | 32 (2) |

ADA = antidrug antibody; CM = chronic migraine; EM = episodic migraine; FAS = full analysis set; ITT = intention-to-treat; LTS = long-term study; NR = not reported.

[a] ITT population includes all randomized/rollover patients.

[b] Safety population includes all patients who received at least 1 dose of study drug.

[c] FAS includes all patients in ITT population who received at least 1 dose of study drug and have at least 10 days of post-baseline efficacy assessment.

[d] ADA only analysis set includes all patients rolling over from the pivotal efficacy studies for ADA assessment only.

Source: Clinical Study Report for HALO LTS.[94]

## Table 32: Duration of Exposure to Fremanezumab of HALO LTS — Safety Population

| | Fremanezumab 225 mg monthly with 675 mg loading dose[a] N = 558 | Fremanezumab 225 mg monthly[b] N = 386 | Fremanezumab 675 mg quarterly[c] N = 944 | Total N = 1,888 |
|---|---|---|---|---|
| Number of doses,[d] n (%) | | | | |
| ≥ 3 | 533 (96) | 363 (94) | 889 (94) | 1,785 (95) |
| ≥ 6 | 487 (87) | 342 (89) | 842 (89) | 1,671 (89) |
| ≥ 9 | 459 (82) | 314 (81) | 789 (84) | 1,562 (83) |
| 12 | 437 (78) | 299 (77) | 755 (80) | 1,491 (79) |
| Duration of treatment (days) | | | | |
| Mean (SD) | 305.4 (87.84) | 303.7 (89.58) | 306.1 (86.68) | 305.4 (87.58) |
| Median (range) | 338.0 (28 to 579) | 337.0 (1 to 455) | 337.0 (24 to 479) | 337.0 (1 to 579) |

LTS = long-term study; SD = standard deviation.

[a] Includes patients with CM only.

[b] Includes patients with EM only.

[c] Includes both patients with EM and patients with CM.

[d] Includes placebo doses.

Source: Clinical study report of HALO LTS.[94]

*Efficacy*

At the data cut-off date, efficacy results for about 80% of patients at month 12 were available. Table 33 and Table 34 summarize the available data for patients with CM and EM, respectively.

For both migraine classifications (CM and EM) and both dosage groups (quarterly and monthly), the mean number of MMDs, MMDs of at least moderate severity, and MMDs of any severity decreased from baseline to month 12. More specifically, the mean number of MMDs in patients with CM decreased from 16.4 days at baseline to 8.1 and 9.0 days at month 12 in the 225 mg monthly and 675 mg quarterly treatment groups, respectively. For patients with EM, the mean number of MMDs went from 9.1 days to 3.9 days from baseline to 12 months for the monthly treatment group and from 9.2 days to 3.9 days for the quarterly treatment group. The mean use of acute headache medication also decreased during the LTS from baseline to month 12. For instance, days of acute medication use went from approximately 13 days to around 7 days in patients with CM, and about 8 days to less than 4 days in patients with EM.

HIT-6 and MIDAS scores for patients with CM and EM, respectively, decreased for both dosage groups during the study. Mean HIT-6 scores for patients with CM were approximately 64 points at baseline and 56 points at the end of treatment. Mean MIDAS scores for patients with EM were around 38 points at baseline and 10 points at the end of treatment.

Quality of life measures (MSQoL and EQ-5D-5L) have been reported in this report for baseline and EOT time points. For patients with CM, mean MSQoL scores changed from about 48 to 74 points (MSQoL role function–restrictive), 66 to 85 points (MSQoL role function–preventive), and 56 to 82 points (MSQoL–emotional state) from baseline to end of treatment. For patients with EM, mean MSQoL scores showed changes from around 57 to 82 points, 71 to 91 points, and 64 to 90 points for the same respective MSQoL categories from baseline to end of treatment. Mean EQ-5D-5L VAS scores went from approximately 72 to 79 and from 79 to 84 for patients with CM and EM, respectively.

Patient-reported assessment of clinical change after treatment (PGIC) was used to estimate which patients were responders to treatment, based on a self-administered rating scale. The results of the HALO LTS suggest that around 81% of patients with CM (both monthly and quarterly dosage groups) responded to fremanezumab treatment. About 88% and 89% of patients with EM were considered responders to monthly and quarterly fremanezumab treatment, respectively.

PHQ-9 scores (for assessing depression in patients) changed from around 4 points to less than 2 points from baseline to EOT in patients with CM, while changes from approximately 2 points to less than 1 point were recorded for patients with EM. WPAI scores (how migraine affects work and daily life) started at around 42 to 46 points at baseline and decreased to about 23 to 27 points by the end of treatment for patients with CM. For patients with EM, the WPAI scores went from approximately 35 to 37 points at baseline to around 16 to 18 points at the end of treatment.

In general, there was no notable difference in efficacy between the 2 dosage regimens used in the HALO LTS.

## Table 33: Summary of Efficacy Results for CM of HALO LTS — FAS

| | Fremanezumab 225 mg monthly | | | Fremanezumab 675 mg quarterly | | |
|---|---|---|---|---|---|---|
| | New/PBO rollover[a] N = 249 | Active rollover[a] N = 305 | Total N = 554 | New/PBO rollover[a] N = 243 | Active rollover[a] N = 306 | Total N = 549 |
| **Monthly migraine days** | | | | | | |
| Baseline, mean (SD) | 17.0 (5.52) | 16.0 (5.11) | 16.4 (5.32) | 16.9 (5.41) | 16.1 (4.86) | 16.4 (5.12) |
| Month 12, n | 192 | 231 | 423 | 193 | 228 | 421 |
| Mean (SD) | 9.0 (8.13) | 7.3 (6.45) | 8.1 (7.30) | 9.3 (7.70) | 8.8 (7.24) | 9.0 (7.45) |
| **Monthly migraine days of at least moderate severity** | | | | | | |
| Baseline, mean (SD) | 14.3 (6.34) | 12.9 (5.65) | 13.5 (6.01) | 14.2 (5.80) | 13.3 (5.34) | 13.7 (5.56) |
| Month 12, n | 192 | 231 | 423 | 193 | 228 | 421 |
| Mean (SD) | 7.6 (7.62) | 5.7 (5.89) | 6.5 (6.78) | 7.4 (6.86) | 7.1 (6.53) | 7.2 (6.68) |
| **Monthly migraine days of any severity** | | | | | | |
| Baseline, mean (SD) | 16.8 (6.53) | 15.8 (5.88) | 16.3 (6.20) | 16.5 (5.91) | 15.9 (5.70) | 16.2 (5.80) |
| Month 12, n | 192 | 231 | 423 | 193 | 228 | 421 |
| Mean (SD) | 9.2 (8.69) | 7.7 (6.88) | 8.4 (7.78) | 9.2 (7.51) | 8.8 (7.54) | 9.0 (7.52) |
| **Acute headache medication use (days)** | | | | | | |
| Baseline, mean (SD) | 13.0 (7.39) | 13.4 (6.98) | 13.2 (7.16) | 13.8 (6.81) | 13.3 (6.66) | 13.5 (6.72) |
| Month 12, n | 192 | 231 | 423 | 193 | 228 | 421 |
| Mean (SD) | 7.6 (7.83) | 6.4 (6.36) | 7.0 (7.08) | 7.8 (6.40) | 7.7 (7.10) | 7.7 (6.78) |
| **HIT-6 score** | | | | | | |
| Baseline, n | 248 | 303 | 551 | 241 | 301 | 542 |
| Mean (SD) | 64.5 (4.65) | 64.5 (4.47) | 64.5 (4.55) | 63.9 (5.02) | 64.5 (4.76) | 64.2 (4.88) |
| End of treatment, n | 197 | 237 | 434 | 198 | 233 | 431 |
| Mean (SD) | 56.5 (7.98) | 55.3 (7.97) | 55.8 (7.99) | 56.5 (7.66) | 56.0 (7.80) | 56.2 (7.73) |
| **MSQoL – RFR score** | | | | | | |
| Baseline, n | 248 | 303 | 551 | 242 | 303 | 545 |
| Mean (SD) | 47.8 (19.34) | 48.5 (19.30) | 48.2 (19.30) | 48.9 (20.82) | 48.1 (18.65) | 48.5 (19.63) |
| End of treatment, n | 197 | 239 | 436 | 200 | 235 | 435 |
| Mean (SD) | 73.3 (21.86) | 75.9 (19.61) | 74.7 (20.67) | 71.9 (20.48) | 75.1 (20.05) | 73.6 (20.29) |
| **MSQoL – RFP score** | | | | | | |
| Baseline, n | 248 | 303 | 551 | 242 | 303 | 545 |
| Mean (SD) | 65.4 (21.50) | 65.9 (22.47) | 65.7 (22.02) | 66.6 (23.70) | 67.4 (20.92) | 67.0 (22.18) |
| End of treatment, n | 197 | 239 | 436 | 200 | 235 | 435 |
| Mean (SD) | 84.4 (19.07) | 86.0 (17.59) | 85.3 (18.27) | 83.7 (18.75) | 87.0 (16.02) | 85.5 (17.39) |
| **MSQoL – ES score** | | | | | | |
| Baseline, n | 248 | 303 | 551 | 242 | 303 | 545 |
| Mean (SD) | 56.0 (25.29) | 56.4 (26.20) | 56.2 (25.78) | 57.1 (28.0) | 56.8 (26.23) | 56.9 (27.04) |
| End of treatment, n | 197 | 239 | 436 | 200 | 235 | 435 |
| Mean (SD) | 80.2 (23.75) | 84.2 (19.89) | 82.4 (21.78) | 80.8 (23.29) | 83.0 (21.63) | 82.0 (22.41) |

| | Fremanezumab 225 mg monthly | | | Fremanezumab 675 mg quarterly | | |
|---|---|---|---|---|---|---|
| | New/PBO rollover[a] N = 249 | Active rollover[a] N = 305 | Total N = 554 | New/PBO rollover[a] N = 243 | Active rollover[a] N = 306 | Total N = 549 |
| **EQ-5D-5L VAS score[b]** | | | | | | |
| Baseline, n | 248 | 303 | 551 | 242 | 303 | 545 |
| Mean (SD) | 70.6 (19.48) | 72.8 (18.33) | 71.8 (18.87) | 73.0 (18.13) | 71.5 (18.40) | 72.2 (18.28) |
| End of treatment, n | 197 | 239 | 436 | 200 | 236 | 436 |
| Mean (SD) | 76.6 (18.22) | 80.9 (14.31) | 79.0 (16.31) | 79.1 (17.47) | 79.6 (15.85) | 79.4 (16.60) |
| **PGIC score** | | | | | | |
| End of treatment, n | 197 | 239 | 436 | 200 | 236 | 436 |
| Responder, n (%)[c] | 149 (76) | 202 (85) | 351 (81) | 167 (84) | 184 (78) | 351 (81) |
| **PHQ-9 score** | | | | | | |
| Baseline, n | 248 | 303 | 551 | 242 | 303 | 545 |
| Mean (SD) | 4.2 (5.89) | 4.8 (6.02) | 4.5 (5.96) | 3.9 (5.96) | 4.2 (5.44) | 4.1 (5.67) |
| End of treatment, n | 197 | 239 | 436 | 200 | 236 | 436 |
| Mean (SD) | 1.6 (3.70) | 1.6 (3.61) | 1.6 (3.64) | 1.9 (4.13) | 1.6 (3.58) | 1.7 (3.84) |
| **WPAI score – percent overall work impairment due to health** | | | | | | |
| Baseline, n | 163 | 212 | 375 | 170 | 215 | 385 |
| Mean (SD) | 43.0 (24.90) | 41.7 (24.69) | 42.3 (24.76) | 42.0 (25.97) | 45.1 (24.89) | 43.7 (25.38) |
| End of treatment, n | 146 | 178 | 324 | 143 | 183 | 326 |
| Mean (SD) | 24.7 (24.07) | 22.9 (24.42) | 23.7 (24.24) | 29.0 (27.10) | 23.3 (24.55) | 25.8 (25.82) |
| **WPAI score – percent activity impairment due to health** | | | | | | |
| Baseline, n | 248 | 303 | 551 | 242 | 303 | 545 |
| Mean (SD) | 45.6 (24.78) | 45.6 (22.94) | 45.6 (23.76) | 46.4 (25.23) | 44.7 (24.15) | 45.4 (24.63) |
| End of treatment, n | 197 | 239 | 436 | 200 | 236 | 436 |
| Mean (SD) | 27.5 (25.02) | 24.9 (23.28) | 26.1 (24.09) | 30.5 (27.17) | 23.3 (23.69) | 26.6 (25.57) |

CM = chronic migraine; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; ES = emotional state; FAS = full analysis set; HIT-6 = 6-item headache impact test; LTS = long-term study; MSQoL = Migraine-Specific Quality of Life questionnaire; PBO = placebo; PGIC = Patients' Global Impression of Change; PHQ = Patient Health Questionnaire; RFP = role function–preventive; RFR = role function–restrictive; SD = standard deviation; VAS = visual analogue scale; WPAI = Work Productivity and Activity Impairment questionnaire.

Note: Denominators for percentages are N, except where otherwise stated for variables.

[a] For rollover patients, baseline values have been carried forward from the 2 pivotal studies.

[b] VAS scores range from 0 to 100, with 0 representing the worst imaginable health state and 100 representing the best imaginable health state.

[c] A nonresponder is a score of 1 to 4 and a responder is a score of 5 to 7 on the PGIC.

Source: Clinical Study Report for HALO LTS.[94]

## Table 34: Summary of Efficacy Results for EM of HALO LTS — FAS

| | Fremanezumab 225 mg monthly | | | Fremanezumab 675 mg quarterly | | |
|---|---|---|---|---|---|---|
| | New/PBO rollover[a] N = 167 | Active rollover[a] N = 215 | Total N = 382 | New/PBO rollover[a] N = 176 | Active rollover[a] N = 217 | Total N = 393 |
| **Monthly migraine days** | | | | | | |
| Baseline, mean (SD) | 9.2 (2.74) | 9.0 (2.74) | 9.1 (2.74) | 9.2 (2.73) | 9.3 (2.54) | 9.2 (2.63) |
| Month 12, n | 124 | 173 | 297 | 138 | 173 | 311 |
| Mean (SD) | 4.6 (4.40) | 3.5 (3.78) | 3.9 (4.08) | 3.7 (3.61) | 3.9 (3.83) | 3.9 (3.73) |
| **Monthly migraine days of at least moderate severity** | | | | | | |
| Baseline, mean (SD) | 7.7 (3.02) | 7.1 (3.00) | 7.4 (3.02) | 7.3 (3.29) | 7.5 (3.06) | 7.4 (3.16) |
| Month 12, n | 124 | 173 | 297 | 138 | 173 | 311 |
| Mean (SD) | 3.7 (4.04) | 2.9 (3.38) | 3.2 (3.68) | 3.2 (3.39) | 3.0 (3.35) | 3.1 (3.36) |
| **Monthly migraine days of any severity** | | | | | | |
| Baseline, mean (SD) | 8.8 (3.02) | 8.3 (3.13) | 8.5 (3.09) | 8.5 (3.16) | 8.6 (3.21) | 8.6 (3.18) |
| Month 12, n | 124 | 173 | 297 | 138 | 173 | 311 |
| Mean (SD) | 4.4 (4.20) | 3.5 (3.64) | 3.8 (3.90) | 3.7 (3.56) | 3.7 (3.64) | 3.7 (3.60) |
| **Acute headache medication use (days)** | | | | | | |
| Baseline, mean (SD) | 8.1 (3.77) | 7.9 (3.33) | 8.0 (3.53) | 8.2 (3.61) | 8.0 (3.59) | 8.1 (3.59) |
| Month 12, n | 124 | 173 | 297 | 138 | 173 | 311 |
| Mean (SD) | 4.5 (4.57) | 3.3 (3.48) | 3.8 (4.01) | 3.6 (3.28) | 3.5 (3.37) | 3.6 (3.32) |
| **MIDAS score** | | | | | | |
| Baseline, n | 162 | 213 | 375 | 173 | 213 | 386 |
| Mean (SD) | 40.0 (30.34) | 37.4 (35.05) | 38.6 (33.08) | 34.8 (26.38) | 41.3 (31.47) | 38.4 (29.44) |
| End of treatment, n | 118 | 170 | 288 | 137 | 164 | 301 |
| Mean (SD) | 11.3 (15.45) | 8.5 (16.78) | 9.6 (16.28) | 10.1 (14.37) | 10.5 (16.05) | 10.3 (15.28) |
| **MSQoL – RFR score** | | | | | | |
| Baseline, n | 166 | 213 | 379 | 176 | 215 | 391 |
| Mean (SD) | 56.1 (14.84) | 57.0 (17.17) | 56.6 (16.18) | 58.2 (18.38) | 55.7 (16.82) | 56.8 (17.56) |
| End of treatment, n | 128 | 177 | 305 | 141 | 176 | 317 |
| Mean (SD) | 80.9 (18.71) | 84.1 (14.30) | 82.8 (16.35) | 82.6 (17.41) | 82.1 (16.49) | 82.3 (16.88) |
| **MSQoL – RFP score** | | | | | | |
| Baseline, n | 166 | 213 | 379 | 176 | 215 | 391 |
| Mean (SD) | 70.4 (18.58) | 72.1 (18.21) | 71.4 (18.37) | 72.7 (20.18) | 70.8 (18.02) | 71.7 (19.02) |
| End of treatment, n | 128 | 177 | 305 | 141 | 176 | 317 |
| Mean (SD) | 89.3 (14.07) | 92.5 (10.74) | 91.1 (12.33) | 91.4 (11.86) | 90.6 (12.49) | 90.9 (12.20) |
| **MSQoL – ES score** | | | | | | |
| Baseline, n | 166 | 213 | 379 | 176 | 215 | 391 |
| Mean (SD) | 64.1 (24.15) | 64.7 (25.41) | 64.5 (24.84) | 64.5 (25.84) | 64.5 (24.02) | 64.5 (24.82) |
| End of treatment, n | 128 | 177 | 305 | 141 | 176 | 317 |
| Mean (SD) | 88.4 (17.61) | 91.8 (13.54) | 90.4 (15.44) | 90.0 (16.32) | 89.5 (17.54) | 89.7 (16.98) |
| **EQ-5D-5L VAS score[b]** | | | | | | |
| Baseline, n | 166 | 213 | 379 | 176 | 215 | 391 |
| Mean (SD) | 77.6 (14.98) | 80.0 (15.06) | 79.0 (15.05) | 80.2 (14.99) | 76.6 (17.07) | 78.2 (16.25) |
| Month 12, n | 128 | 177 | 305 | 141 | 176 | 317 |
| Mean (SD) | 82.7 (14.73) | 85.2 (12.33) | 84.1 (13.42) | 85.7 (13.85) | 83.3 (13.63) | 84.3 (13.76) |

| | Fremanezumab 225 mg monthly | | | Fremanezumab 675 mg quarterly | | |
|---|---|---|---|---|---|---|
| | New/PBO rollover[a] N = 167 | Active rollover[a] N = 215 | Total N = 382 | New/PBO rollover[a] N = 176 | Active rollover[a] N = 217 | Total N = 393 |
| **PGIC score** | | | | | | |
| End of treatment, n | 128 | 177 | 305 | 141 | 176 | 317 |
| Responder, n (%)[c] | 111 (87) | 156 (88) | 267 (88) | 127 (90) | 155 (88) | 282 (89) |
| **PHQ-9 score** | | | | | | |
| Baseline, n | 166 | 213 | 379 | 176 | 215 | 391 |
| Mean (SD) | 2.0 (3.26) | 1.9 (3.05) | 1.9 (3.14) | 2.0 (3.42) | 1.9 (3.07) | 1.9 (3.23) |
| End of treatment, n | 128 | 177 | 305 | 141 | 176 | 317 |
| Mean (SD) | 0.7 (2.18) | 0.8 (2.08) | 0.8 (2.12) | 0.5 (1.68) | 0.9 (2.11) | 0.7 (1.94) |
| **WPAI score – percent overall work impairment due to health** | | | | | | |
| Baseline, n | 127 | 155 | 282 | 129 | 170 | 299 |
| Mean (SD) | 38.2 (25.02) | 34.3 (23.52) | 36.1 (24.24) | 33.6 (25.05) | 36.8 (25.50) | 35.4 (25.31) |
| End of treatment, n | 98 | 131 | 229 | 105 | 142 | 247 |
| Mean (SD) | 17.5 (22.45) | 17.4 (23.41) | 17.4 (22.95) | 15.7 (21.07) | 17.3 (24.28) | 16.7 (22.94) |
| **WPAI score – percent activity impairment due to health** | | | | | | |
| Baseline, n | 166 | 213 | 379 | 176 | 215 | 391 |
| Mean (SD) | 37.3 (23.42) | 35.2 (23.34) | 36.1 (23.37) | 36.0 (24.19) | 36.3 (22.59) | 36.2 (23.30) |
| End of treatment, n | 128 | 177 | 305 | 141 | 176 | 317 |
| Mean (SD) | 17.9 (21.25) | 18.2 (22.57) | 18.1 (21.99) | 16.1 (19.37) | 19.9 (24.76) | 18.2 (22.57) |

EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EM = episodic migraine; ES = emotional state; FAS = full analysis set; LTS = long-term study; MIDAS = migraine disability assessment score; MSQoL = Migraine-Specific Quality of Life questionnaire; PBO = placebo; PGIC = Patients' Global Impression of Change; PHQ = Patient Health Questionnaire; RFP = role function–preventive; RFR = role function–restrictive; SD = standard deviation; VAS = visual analogue scale; WPAI = Work Productivity and Activity Impairment questionnaire.

Note: Denominators for percentages are N, except where otherwise stated for variables.

[a] For rollover patients, baseline values have been carried forward from the 2 pivotal studies.

[b] VAS scores range from 0 to 100, with 0 representing the worst imaginable health state and 100 representing the best imaginable health state.

[c] A nonresponder is a score of 1 to 4 and a responder is a score of 5 to 7 on the PGIC.

Source: Clinical Study Report for HALO LTS.[94]

### *Harms*

Table 35 summarizes the harms outcomes from the HALO LTS. Overall, most patients (85%) experienced an AE, while 189 patients (10%) experienced an SAE. Proportionately, AEs and SAEs were slightly higher in the fremanezumab 225 mg monthly group (with loading dose of 675 mg) (89% AEs, 11% SAEs) compared with the 225 mg monthly (84% AEs, 9% SAEs) and 675 mg quarterly (83% AEs, 10% SAEs) groups. For all treatment groups, injection-site induration, pain, and erythema were the 3 most common AEs, occurring in 619 (33%), 580 (31%), and 497 (26%) patients, respectively. The 2 most common SAEs were status migrainosus and basal cell carcinoma, both occurring in 4 patients (< 1%) each. Seventy-six (4%) patients discontinued the study due to AEs, which occurred at a similar frequency (3% to 5%) across the 3 groups. Again, injection-site induration, pain, and erythema were the 3 most common reasons for patients to discontinue the study, occurring in 5 (< 1%), 4 (< 1%), and 4 (< 1%) patients, respectively. One death occurred in the fremanezumab 675 mg quarterly group, approximately 300 days after the last dose of the study drug. The patient had a brain aneurysm and multiple strokes.

## Table 35: Summary of Harms Outcomes of HALO LTS — Safety Population

| | Fremanezumab 225 mg monthly with 675 mg loading dose[a] N = 558 | Fremanezumab 225 mg monthly[b] N = 386 | Fremanezumab 675 mg quarterly[c] N = 944 | Total N = 1,888 |
|---|---|---|---|---|
| AEs with > 5% occurrence,[d] n (%) | 499 (89) | 323 (84) | 785 (83) | 1,607 (85) |
| General disorders and administration site conditions | 337 (60) | 221 (57) | 498 (53) | 1,056 (56) |
| Injection-site induration | 196 (35) | 145 (38) | 278 (29) | 619 (33) |
| Injection-site pain | 182 (33) | 123 (32) | 275 (29) | 580 (31) |
| Injection-site erythema | 171 (31) | 103 (27) | 223 (24) | 497 (26) |
| Injection-site hemorrhage | 44 (8) | 28 (7) | 59 (6) | 131 (7) |
| Injection-site pruritus | 39 (7) | 35 (9) | 41 (4) | 115 (6) |
| Infections and infestations | 278 (50) | 182 (47) | 438 (46) | 898 (48) |
| Upper respiratory tract infection | 70 (13) | 45 (12) | 133 (14) | 248 (13) |
| Nasopharyngitis | 60 (11) | 51 (13) | 102 (11) | 213 (11) |
| Sinusitis | 39 (7) | 17 (4) | 56 (6) | 112 (6) |
| Urinary tract infection | 27 (5) | 24 (6) | 60 (6) | 111 (6) |
| Musculoskeletal and connective tissue disorders | 94 (17) | 53 (14) | 152 (16) | 299 (16) |
| Gastrointestinal disorders | 98 (18) | 52 (13) | 144 (15) | 294 (16) |
| Injury, poisoning, and procedural complications | 79 (14) | 38 (10) | 119 (13) | 236 (13) |
| Nervous system disorders | 70 (13) | 39 (10) | 118 (13) | 227 (12) |
| Investigations | 66 (12) | 46 (12) | 95 (10) | 207 (11) |
| Respiratory, thoracic, and mediastinal disorder | 41 (7) | 27 (7) | 77 (8) | 145 (8) |
| Skin and subcutaneous tissue disorders | 48 (9) | 24 (6) | 73 (8) | 145 (8) |
| Psychiatric disorders | 38 (7) | 26 (7) | 72 (8) | 136 (7) |
| SAEs with > 1% occurrence, n (%) | 62 (11) | 35 (9) | 92 (10) | 189 (10) |
| Nervous system disorders | 6 (1) | 8 (2) | 8 (< 1) | 22 (1) |
| Neoplasms benign, malignant, and unspecified (including cysts and polyps) | 5 (< 1) | 1 (< 1) | 14 (1) | 20 (1) |
| Discontinued study due to AE, n (%) | 19 (3) | 18 (5) | 39 (4) | 76 (4) |
| Deaths, n (%) | 0 | 0 | 1 (< 1) | 1 (< 1) |

AE = adverse event; LTS = long-term study; SAE = serious AE.

[a] Includes patients with CM only.

[b] Includes patients with EM only.

[c] Includes both patients with EM and patients with CM.

[d] Only treatment-emergent AEs are summarized.

Source: Clinical Study Report for HALO LTS.[94]

Immunogenicity testing was performed for all patients in the LTS and for 60 individuals who took part in 1 of the 2 pivotal trials but not the LTS. Samples were taken at different time points, depending on whether the patient had rolled over from the pivotal studies (4 time points), was new to the study (5 time points), or was not participating in the LTS (1 time point).

Overall, 6,238 samples were collected from 1,888 patients. Of these, 114 samples from 52 patients (2.8% of patients tested) were positive for ADAs. Fourteen of the 52 patients were considered negative for treatment-emergent ADA response, since there was no significant increase in titre during the study from pre-dose to post-dose measures. The other 38 were identified as having had a treatment-emergent ADA response either because they showed an increasing titre during the study or because they tested negative pre-dose then positive post-dose. From this group, 21 were labelled as having a transient ADA response, since they later showed a negative ADA result. Eighteen patients had developed neutralizing antibodies, although 16 of these individuals were noted as having transient neutralizing antibodies. Since data are from an interim report, results are incomplete.

### *Critical Appraisal*

#### Internal Validity

Nearly 20% of the overall ITT population discontinued HALO LTS, although the overall withdrawal frequency was similar among active treatment groups. Discontinuation due to AEs was slightly greater in the group of newly randomized patients compared with patients who had rolled over from the pivotal studies, while “withdrawal by subject” was more common in the rollover patients versus those newly randomized. Given the selective patient population (see External Validity), there was potential for survival bias, since any patients who discontinued the pivotal studies due to AEs were excluded. This could result in a greater enrolment of patients who were better able to tolerate fremanezumab and fewer AEs being reported.

#### External Validity

The majority of patients were women and White, and most patients were from North America (48 patients or 3% of the study population was from Canada) which may allow the results to be generalized, with caution, to a broader Canadian population. The exclusion criteria for the LTS were less restricting than the parent studies with regard to previous treatments. About 25% and 23% of patients in the CM and EM groups, respectively, had experience with preventive medication use, either before enrolling in the parent HALO studies or the LTS. Therefore, the results of the HALO LTS do not necessarily reflect what would be expected of a treatment-naive population. Furthermore, the clinical expert suggested that the limitations on BMI and body mass (BMI between 17.5 and 37.5 kg/m$^2$; body mass between 45 and 120 kg) for eligibility may be restrictive, since obesity can be common in patients with CM. The enrolled patient population was also selective because approximately 81% of the patients who had been randomized into HALO CM and 76% of those randomized into HALO EM rolled over from these studies. By the data cut-off date, most patients had been exposed to fremanezumab for approximately 12 months; thus, safety and efficacy results are limited to approximately this time frame of treatment plus the 6.5 months’ follow-up period.

# Discussion

## Summary of Available Evidence

Three multinational double-blind, 1:1:1 randomized, placebo-controlled trials were included in this review. All trials assessed the efficacy and safety of SC injections of fremanezumab quarterly (675 mg/placebo/placebo), fremanezumab monthly (patients with CM: 675 mg/225 mg/225 mg; patients with EM: 675 mg/225 mg/225 mg), and placebo. HALO CM (N = 1,130) was conducted in patients with CM who were using 0 or 1 preventive medication therapies. HALO EM (N = 875) was conducted in patients with EM who were using 0 or 1 preventive migraine therapies. In FOCUS (N = 838), both patients with CM and EM included if they had an inadequate response to 2 to 4 classes of prior preventive migraine therapies. All studies had a 12-week DBTP, while FOCUS had an additional 12-week OLTP. The primary outcome of HALO EM and FOCUS was the change from baseline in MMDs of any severity, while HALO CM assessed the change from baseline in monthly average number of headache days of at least moderate severity as the primary outcome. Secondary efficacy outcomes included the proportion of patients with a 50% reduction in MMDs for all trials, monthly average number of headache days of at least moderate severity, MMDs, monthly average number of days of use of any acute headache medications, and migraine-related disability, as measured using the HIT-6 (HALO CM and FOCUS) and the MIDAS questionnaire (HALO EM). Other patient-reported outcomes, such as WPAI, that reported health-related impairments on work and daily activities, were assessed as exploratory outcomes.

Key critical appraisal issues included the restrictive inclusion and exclusion criteria for the trials. The high selectivity of the study population, based on a stringent list of eligibility criteria of the included studies, may restrict generalizability to the general migraine population. Patients with major cardiovascular and other major comorbid diseases, including psychiatric disorders, were excluded from participation in the studies despite noted prevalence of depression in CM patients, thus limiting full extrapolation of the safety data to the general population. In the FOCUS trial, the presence of EM and CM during the baseline period was evaluated by the use of triptans or ergot derivatives to treat an established headache, and valproic acid was considered a separate class of preventive medication rather than an anticonvulsant. The FOCUS study included an open-label extension phase of up to 46 weeks after the end of the 12-week randomized treatment period, which would more likely bias patients' reporting of headache or migraine, or related subjective outcome measures, such as HIT-6, MIDAS, and MSQoL. Missing data were handled by a prorating method relying on the random missing assumption. If such assumption did not hold, it may have introduced bias; for example, patients with worsened symptoms may have been less likely to complete the daily assessments. Also, efficacy results were confirmed by MMRM, which could have accounted for missing data under the missing-at-random assumption. Overall, the quality of the 3 included trials was considered reasonable.

Two ITCs that compared fremanezumab with other therapies for CM in adults were summarized and critically appraised. One of the ITCs was provided by the sponsor and the other conducted by ICER. The overall results from both ITCs show that fremanezumab has a favourable clinical efficacy profile versus placebo for most of the outcomes analyzed. Throughout the various networks in both ITCs, fremanezumab did not show an effect, either favourable or unfavourable, that would exclude the null versus other active comparators

(including OnaA in a sensitivity analysis). Because of the small size of the networks and the fact that 1 study usually informed the direct evidence between 2 nodes, the ITCs would not provide a statistically robust analysis with sufficient power to determine similarity.

In addition to the main trials reviewed, the HALO LTS, an ongoing, 12-month open-label extension of HALO CM and HALO EM, was summarized (see Other Relevant Evidence). The HALO LTS reported the long-term safety, tolerability, and efficacy of fremanezumab 225 mg and 675 mg for monthly and quarterly doses in patients with CM and EM. HALO LTS patients who rolled over from HALO CM or HALO EM showed a high discontinuation rate, with approximately 79% of patients remaining in the study.

## Interpretation of Results

### Efficacy

Fremanezumab elicited a statistically significant reduction in MMDs of 1 to 3 days from baseline in both the monthly and quarterly treatment groups compared with placebo. Patients with CM and patients who failed 2 to 3 classes of prior preventive migraine therapies reported a slightly greater reduction in MMDs. The clinical expert consulted by CADTH noted that this magnitude of reduction in MMDs may be clinically significant for certain patients and patient groups, highlighting that even a small reduction in MMDs would be meaningful. However, there is no validated MID for this outcome, and it is unclear whether the reduction in MMDs by 1 to 3 days would be perceptible by patients. In addition, the observed effect sizes in MMDs within the HALO EM study were less than the difference the study was powered to detect.

The proportion of patients reaching at least 50% reduction in the MMDs was considered a clinically meaningful outcome by the clinical expert, and a greater proportion with statistical significance was reported in the fremanezumab treatment groups compared with placebo. Studies that included patients with CM reported a statistically significant reduction of 2 to 4 monthly headache days of at least moderate severity from baseline for both the monthly and quarterly treatment groups versus placebo. While the difference was considered clinically meaningful by the clinical expert consulted on this review, there is no validated MID for this outcome. A statistically significant reduction in average use of acute headache medications of 1 to 3 days from baseline was reported in both the monthly and quarterly treatment groups compared with placebo. The reduction in acute medication use was greater in patients with CM and those who failed prior preventive migraine therapies. This reduction was considered clinically meaningful by the clinically expert; however, the difference is difficult to interpret without a validated MID.

Functional improvement was primarily assessed using the HIT-6 and MIDAS scores as secondary outcomes (see Appendix 4 for detailed review of outcomes included in the studies). The reported changes in the HIT-6 were assessed and adjusted for multiplicity only in the HALO CM trial. The ANCOVA-based LSM differences in HIT-6 scores were –2.4 points and –1.9 points in favour of fremanezumab 675 mg/225 mg/225 mg and 675 mg/placebo/placebo versus placebo. However, the assumption of normality was not met, and so the main analysis for this outcome was done using nonparametric tests (Wilcoxon rank sum test). As a result, although the differences between groups were still statistically significant, it is difficult to evaluate the between-group differences relative to the reported between-group MID for the HIT-6 in patients with chronic daily headaches of –2.3 points. Therefore, the clinical relevance of this result is uncertain. Likewise, the change from

baseline in MIDAS score for the fremanezumab treatment groups versus placebo was statistically significant in HALO EM based on the parametric and nonparametric tests, but the clinical significance is uncertain because there is no established MID for the MIDAS score in patients with migraine. The clinical expert consulted for the review indicated the difference was likely important, and patient input indicated that any improvement in daily functioning would be a significant and meaningful. Functioning, as measured by work productivity (WPAI scores), was measured in the studies, as well as health-related quality of life, which were all numerically improved with fremanezumab treatment, but these outcomes were analyzed as exploratory outcomes only, precluding drawing concrete conclusions concerning the results.

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 CADTH for this review, many present tolerability issues for patients. Patient input identified side effects as a major issue with their use of current therapies and a reason for discontinuation. Although fremanezumab appears to be a well-tolerated drug, based on 12-week DBTPs in the included studies, its long-term tolerance and its comparative harms and efficacy versus other comparators are unknown. It is unknown how fremanezumab directly compares with erenumab or OnaA in the more restricted CM population.

In HALO LTS, all outcomes were evaluated through exploratory analyses. In both fremanezumab treatment groups and for both migraine classifications, the mean number of MMDs and MMDs of at least moderate severity decreased from baseline and remained stable for the duration of the study. However, the lack of statistical analyses and a placebo arm do not allow us to interpret the differences in MMDs as clinically meaningful. The use of acute headache medication followed a similar decreasing trend during the LTS but cannot be interpreted. HIT-6 and MIDAS scores, for CM and EM patients, respectively, showed a decrease for both dosage groups over time, indicating that patients experienced reduced migraine-related disability. Quality of life measures (MSQoL and EQ-5D-5L) and patient-reported assessment of clinical change after treatment (PGIC) showed improvements in most patients during the HALO LTS. PHQ-9 scores (for assessing depression in patients) and WPAI scores (how migraine affects work and daily life) both decreased from baseline to end of treatment, suggesting improved patient outcomes during the LTS. Despite the reported differences in outcomes, differences between treatment groups cannot be interpreted due to the lack of statistical analyses and a placebo arm.

The overall results from both ITCs show that fremanezumab has a favourable clinical efficacy profile versus placebo in most of the outcomes. Similarly, and throughout the various networks in both ITCs, fremanezumab did not clearly show a favourable or unfavourable effect that would exclude the null versus other active comparators (including OnaA in a sensitivity analysis). Few favourable effects were demonstrated. In patients with EM who had an inadequate response to 2 or more previous treatments, the fremanezumab treatments groups had significantly better reductions in MMDs at 12 weeks than erenumab, and fremanezumab was significantly better in reducing the days using acute migraine-specific medication at 12 weeks than erenumab. These results should be considered in the light of the fact that the FOCUS trial, included in this network and incorporating both CM and EM patients receiving fremanezumab, biased the result in favour of fremanezumab. In the ICER ITC, the monthly fremanezumab group was significantly better in reducing the MMDs at 12 weeks than topiramate; however, uncertainty in this result stems mainly from clinical heterogeneity in the included studies. In patients with CM who had an inadequate response to less than 2 previous treatments, the monthly and quarterly fremanezumab

were significantly better in terms of the rate of 50% responders at 12 weeks than erenumab. There is uncertainty stemming from the variable definition of responders in the included studies; the sponsor-submitted ITC did not elaborate on how such differences in the outcome definition were handled. Monthly fremanezumab was also significantly better in reducing the days using acute migraine-specific medication at 12 weeks than erenumab. Potential uncertainty in this result stems from the small size of the network (3 studies) and the lack of inconsistency assessment. Despite the limited favourable results from the ITCs, overall, fremanezumab does not demonstrate an effect that would exclude the null when compared with other active comparators. Further studies should evaluate the efficacy of fremanezumab compared with active comparators, especially in populations that have failed prior preventive migraine therapies.

## Harms

Overall, the clinical expert consulted for this review indicated that the incidence of AEs across the studies appeared lower than that for many other preventive treatments for migraine. AEs were reported similarly across treatment arms. AEs were reported in 70% of patients in HALO CM, 60% in HALO EM, and 50% in the FOCUS DBTP. A majority of AEs were due to injection-site reactions. AEs were slightly higher in patients who received at least 1 dose of fremanezumab 675 mg than in patients receiving other fremanezumab doses in FOCUS. One patient in HALO CM died after receiving fremanezumab treatment; the cause of death was chronic obstructive pulmonary disease and was not considered related to the study by the investigator. One patient in HALO EM died 110 days after receiving the first dose of study drug. The cause of death, determined by autopsy, was diphenhydramine overdose (suicide), and the death was assessed as unrelated to the study drug by the investigator. No deaths were reported in the FOCUS study. The occurrence of SAEs and notable harms was reasonable. There were no notable occurrences of the AEs of special interest (e.g., injection-site reactions, anaphylaxis/hypersensitivity reactions, antibody formation, vascular events, constipation, or development of hypertension) identified in the protocol for this review.

Of the 1,888 patients in HALO LTS who received a dose of fremanezumab, 35% had completed the study as of the data cut-off date, while 20% had discontinued. Only 30% of rollover patients completed the study at the data cut-off date compared with 75% of newly enrolled patients, although the overall withdrawal frequency was similar across treatment arms. A significant majority of patients (85%) experienced an AE, and 189 patients (10%) experienced an SAE. Proportionately, AEs and SAEs were slightly higher in the fremanezumab 225 mg monthly group (with loading dose of 675 mg) compared with the 225 mg monthly and 675 mg quarterly groups. Injection-site induration, pain, and erythema were the 3 most common AEs, occurring in 30% of patients. The most common SAEs, occurring in 4 patients each, were status migrainosus and basal cell carcinoma. One death occurred in the fremanezumab 675 mg quarterly group, approximately 300 days after the last dose of the study drug. The patient had a brain aneurysm and multiple strokes. The long-term safety and tolerability of fremanezumab remain unclear, owing to the short time frame of the OLTP, the lack of placebo arm, and lack of blinding. The high proportion of rollover patients who discontinued the study is notable.

### Other Considerations

An ongoing study (ClinicalTrials.gov Identifier: NCT04041284) funded by the sponsor plans to evaluate the efficacy of monthly 225 mg SC injection of fremanezumab in adult patients with migraine and major depressive disorder.[95] Considering the restrictive exclusion criteria of the 3 studies included in this review, the results of the ongoing study may be relevant for assessing the safety and efficacy of fremanezumab in patients with migraine and major depressive disorder, a common disorder in the general patient population.

## Conclusions

Three clinical trials (HALO CM, HALO EM, and FOCUS) with double-blinded treatment periods were included in this review. HALO CM included adult patients with CM, HALO EM included adult patients with EM, and FOCUS included adult patients with either CM or EM. All studies demonstrated that fremanezumab reduced the mean MMDs and average number of headache days of at least moderate severity from baseline compared with placebo, which was considered clinically meaningful by the clinical expert and patient groups. However, the lack of a validated MID for these outcomes limits the interpretation of the clinical significance of fremanezumab compared with placebo on migraine and headache days. HIT-6 scores improved for fremanezumab treatment groups after adjustment for multiplicity, but the clinical significance of the changes for patients with CM are uncertain. Likewise, while MIDAS scores improved for fremanezumab treatment groups, there is no established MID to help determine the clinical significance of the differences versus placebo. Numerical improvements in work and daily life, as well as health-related quality of life, were observed in the fremanezumab treatment groups; however, the outcomes were assessed as exploratory, precluding definitive conclusions. No clear safety issues or tolerability issues emerged from the 3 included studies. Generally, both the sponsor-submitted and ICER ITCs did not identify differences in effects of fremanezumab compared with active comparators with any certainty.

# Appendix 1: Literature Search Strategy

## Clinical Literature Search

| OVERVIEW | |
|---|---|
| **Interface:** | Ovid |
| **Databases:** | MEDLINE All (1946–present)<br>Embase (1974–present)<br>Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid. |
| **Date of Search:** | Oct 06, 2020 |
| **Alerts:** | Weekly search updates until project completion |
| **Study Types:** | None used |
| **Limits:** | Publication date limit: None used<br>Humans<br>Language limit: None used<br>Conference abstracts: excluded |

| SYNTAX GUIDE | |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| MeSH | Medical Subject Heading |
| .fs | Floating subheading |
| exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| # | Truncation symbol for one character |
| ? | Truncation symbol for one or no characters only |
| adj# | Requires terms to be adjacent to each other within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |
| .hw | Heading word; usually includes subject headings and controlled vocabulary |
| .kf | Author keyword heading word (MEDLINE) |
| .kw | Author keyword (Embase); keyword (CDSR) |
| .pt | Publication type |
| .mp | Mapped term |
| .rn | Registry number |
| .yr | Publication year |
| .jw | Journal title word (MEDLINE) |
| .jx | Journal title word (Embase) |
| freq = # | Requires terms to occur # number of times in the specified fields |
| medall | Ovid database code: MEDLINE All, 1946 to present, updated daily |
| oemezd | Ovid database code; Embase, 1974 to present, updated daily |
| cctr | Ovid database code; Cochrane Central Register of Controlled Trials |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **Database(s): Embase 1974 to 2020 October 01, Ovid MEDLINE(R) ALL 1946 to October 01, 2020**<br>**Search Strategy:** | |
| **#** | **Searches** |
| 1 | (Ajovy* or fremanezumab* or PF-04472429 or PF04472429 or PF-4472429 or PF4472429 or RI-307 or RI307 or RN-307 or RN307 or LBR-101 or LBR101 or fremanezumab or TEV48125 or TV-48125 or TV48125 or GTPL9208 or D11055 or PF8K38CG54).ti,ab,hw,kf,rn,nm,ot. |
| 2 | 1 use medall |
| 3 | *fremanezumab/ |
| 4 | (Ajovy* or fremanezumab* or PF-04472429 or PF04472429 or PF-4472429 or PF4472429 or RI-307 or RI307 or RN-307 or RN307 or LBR-101 or LBR101 or fremanezumab or TEV48125 or TV-48125 or TV48125 or GTPL9208 or D11055).ti,ab,kw,dq. |
| 5 | 3 or 4 |
| 6 | conference abstract.pt. |
| 7 | conference review.pt. |
| 8 | 6 or 7 |
| 9 | 5 not 8 |
| 10 | 9 use oemezd |
| 11 | 2 or 10 |
| 12 | remove duplicates from 11 |

| Clinical Trials Registries | | |
|---|---|---|
| **ClinicalTrials.gov** | Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.<br>[Search – Studies with results Ajovy (fremanezumab)] | |
| **WHO ICTRP** | International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.<br>[Search terms – Ajovy (fremanezumab)] | |
| **Health Canada's Clinical Trials Database** | Produced by Health Canada. Targeted search used to capture registered clinical trials.<br>[Search terms – Ajovy (fremanezumab)] | |
| **EU Clinical Trials Register** | European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.<br>[Search terms – Ajovy (fremanezumab)] | |

### Grey Literature

| Search dates: | September 24, 2020– September 29, 2020 |
|---|---|
| **Keywords:** | Ajovy (fremanezumab) |
| **Limits:** | Publication years: None used |

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 Trials Registries
- Databases (free)
- Health Statistics
- Internet Search

# Appendix 2: Excluded Studies

## Table 36: Excluded Studies

| Reference | Reason for exclusion |
|---|---|
| Alex, A., et al. 2020Headache 2020 23(23 | Cohort study |
| Berman, G., et al. 2020 Headache 2020 16(16 | Extension study |
| Bigal, M. E., et al. Cephalalgia 34(12):968-76 | Phase II |
| Bigal, M. E., et al. Cephalalgia 34(7):483-92 | Phase I |
| Bigal, M. E., et al. Lancet Neurology 14(11):1091-100 | Phase II |
| Bigal, M. E., et al. Lancet Neurology 14(11):1081-90 | Phase II |
| Bigal, M. E., et al. Neurology 87(1):41-8 | Phase II |
| Brandes, J. L., et al. Cephalalgia 40(5):470-477 | Subgroup |
| Briceno-Casado, M. D. P., et al. Farmacia Hospitalaria 44(5):212-217 | Review |
| Journal of Headache and Pain 21(1):109 | Extension study, survey |
| Cohen, J. M., et al. Headache 57(9):1375-1384 | Pooled |
| Cohen-Barak, O., et al. Cephalalgia 38(13):1960-1971 | Cohort study |
| Diener, H. C. Arzneimitteltherapie 2016 34(1-2):37 | Phase II |
| Fiedler-Kelly, J., et al. 2020. Headache 2020 23(23 | Pooled |
| Halker Singh, R. B., et al. Cephalalgia 39(1):52-60 | Phase II |
| Lipton, R. B., et al. Neurology 95(7):e878-e888 | Post hoc analysis |
| Senn, S. J., et al. JAMA 321(12):1211-1212 | Review |
| Silberstein, S. D., et al. Headache 59(3):383-393 | phase II |
| Silberstein, S. D., et al. Headache 59(6):880-890 | Pooled |
| Silberstein, S. D., et al. Journal of Headache and Pain 21(1):114 | Subgroup |
| Vanderpluym, J., et al. Neurology 91(12):e1152-e1165 | Extension study, phase II |
| Winner, P. K., et al. Headache 59(10):1743-1752 | Subgroup |
| Pellesi, l. at al. Headache 60(6):1056-1065. 2020 | Review |
| EudraCT Number: 2019-001989-15<br>Sponsor Protocol Number: TV48125-MH-40142 https://www.clinicaltrialsregister.eu/ctr-search/search?query = eudract_number:2019-001989-15 | No data available |

# Appendix 3: Detailed Outcome Data

## Table 37: Subgroup Analyses

| | Subgroup analyses | | |
|---|---|---|---|
| **FOCUS (Study 30068)** | **Fremanezumab 225 mg/225 mg/225 mg or 675 mg/225 mg/225 mg (N = 283)** | **Fremanezumab 675 mg/PB/PB (N = 276)** | **Placebo (N = 278)** |
| **Change in MMD** | | | |
| **Patients who failed 2 to 3 classes of preventive medication and valproic acid for migraine in the past (ANCOVA results) (double-blind mITT analysis set)** | | | |
| LSM estimate (95% CI) | –4.6 (–5.99 to –3.18) | –3.6 (–4.96 to –2.16) | –0.2 (–1.50 to 1.19) |
| Difference in LSM versus placebo (95% CI) [a] | –4.4 (–6.02 to –2.84) P < 0.0001 | –3.4 (0.83) (–5.04 to –1.76) P < 0.0001 | |
| Difference in LSM versus quarterly (95% CI) [a] | –1.0 (–2.70 to 0.65) | | |
| **Responder rate – at least 50% reduction in MMDs at week 12** | | | |
| Odds ratio (95% CI) | 13.23 (2.79 to 62.75) | 14.18 (2.94 to 68.34) | |
| **Migraine classification: CM, n** | 173 | 169 | 167 |
| LSM estimate (95% CI) | –4.5 (–5.39 to –3.61) | –3.9 (–4.79 to –2.99) | –0.7 (–1.64 to 0.20) |
| Difference in LSM versus placebo (95% CI) [a] | –3.8 (–4.76 to –2.80) P < 0.0001 | –3.2 (–4.16 to –2.18) P < 0.0001 | |
| Difference in LSM versus quarterly (95% CI) [a] | –0.6 (0.50) (–1.59 to 0.37) | | |
| **Migraine classification: EM, n** | 110 | 107 | 111 |
| LSM estimate (95% CI) | –3.8 (–4.66 to –2.90) | –3.7 (–4.59 to –2.84) | –0.7 (–1.50 to 0.19) |
| Difference in LSM versus placebo (95% CI) [a] | –3.1 (–4.00 to –2.25) P < 0.0001 | –3.1 (–3.93 to –2.19) P < 0.0001 | |
| Difference in LSM versus quarterly (95% CI) [a] | –0.1 (0.44) (–0.94 to 0.81) | | |
| **Change from baseline in average number of MMDs during the 12-week DBTP by overuse of acute medication (ANCOVA results) (double-blind mITT analysis set)** | | | |
| Overuse of acute medication, n | 146 | 148 | 133 |
| LSM estimate (95% CI) | –4.4 (–5.51 to –3.26) | –3.2 (–4.44 to –1.96) | –0.4 (–1.66 to 0.81) |

| | Subgroup analyses | | |
|---|---|---|---|
| Difference in LSM versus placebo (95% CI) [a] | –4.0<br>(–5.35 to –2.57)<br>P < 0.0001 | –2.8<br>(–4.20 to –1.34)<br>P = 0.0002 | |
| Difference in LSM versus quarterly (95% CI) [a] | –1.2<br>(–2.55 to 0.18)<br>137 | | |

ANCOVA = analysis of covariance. CI = confidence interval; CM = chronic migraine; DBTP = double-blind treatment period; EM = episodic migraine; LSM = least squares mean; MMD = monthly migraine days; mITT = modified intent-to-treat; PB = placebo.

Note: The ANCOVA model includes treatment, gender, region, special group of treatment failure (yes/no) as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates.

Note: Fremanezumab monthly is 675 mg/225 mg/225 mg for patients with CM and 225 mg/225 mg/225 mg for patients with EM. Fremanezumab quarterly is 675 mg/placebo/placebo for patients with both CM and EM.

Note: Subgroup based on migraine classification (as randomized).

[a] P value for the treatment comparison is from an ANOVA with treatment group as a factor.

Source: Clinical Study Reports for FOCUS.[19]

# Appendix 4: Description and Appraisal of Outcome Measures

## Aim

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

- Six-item headache impact test questionnaire (HIT-6)
- Migraine disability assessment score questionnaire (MIDAS)
- Migraine-Specific Quality of Life questionnaire (MSQoL)
- EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L)
- Patients' Global Impression of Change Scale (PGIC)
- Nine-item Patient Health Questionnaire (PHQ-9)
- Work Productivity and Activity Impairment Questionnaire (WPAI)
- Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

## Findings

The HIT-6, MIDAS, MSQoL, EQ-5D-5L, PGIC, PHQ-9, WPAI, and eC-SSRS are briefly summarized in Table 38.

### Table 38: Summary of Outcome Measures and Their Measurement Properties

| Outcome measure | Type | Conclusions about measurement properties | MID |
|---|---|---|---|
| HIT-6 | Questionnaire assessing 6 items: pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress<br><br>Each item rated on a 5-point Likert-type scale<br><br>Total score ranges from 36 to 78, with a higher score indicating a greater impact of headache on daily life (36 to 49: little or no impact, 50 to 55: some impact, 56 to 59: substantial impact, 60 to 78: severe impact) | **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 HDPM<br><br>**Reliability:** Patients with CM and EM: internal consistency (Cronbach alpha = 0.83 to 0.90) and test-retest reliability demonstrated (ICC = 0.77)<br><br>**Responsiveness:** Patients with CM: scores detected changes in disease status based on headache frequency and cumulative hours of headache | Patients with EM:<br>within-group MID = –2.5<br>between-group MID = –1.5<br><br>Patients with chronic daily headaches:<br>between-group MID = –2.3 |
| MIDAS | 5-item questionnaire that evaluates headache-related disability | **Validity:** Concurrent validity among physician-confirmed patients with migraine, demonstrated through correlation with 90-day headache diary | Not identified for migraine |

| Outcome measure | Type | Conclusions about measurement properties | MID |
|---|---|---|---|
| | Score ranges correspond to grades 1 to 4 with a higher grade indicating greater disability due to migraine<br><br>Based on a 3-month recall period | (Pearson r = 0.50 to 0.77, Spearman rho = 0.53 to 0.76)<br>**Reliability:** Acceptable internal consistency (Cronbach alpha = 0.83) and test-retest reliability (item-level, r = 0.52 to 0.82, rho = 0.46 to 0.84; overall score, r = 0.80 to 0.83, rho = 0.77 to 0.78) demonstrated<br><br>**Responsiveness:** Not reported for migraine | |
| MSQoL | Questionnaire consisting of 3 domains and 14 items: MSQoL-RFR (7 items), MSQoL-RFP (4 items), MSQoL-ES (3 items)<br><br>Measures the emotional effects and impact of migraines on normal activities<br><br>Scores are rescaled to range from 0 to 100, with higher scores indicating better HRQoL<br><br>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 HDPM); and discriminant validity by statistically significant differences between groups based on headache frequency, HIT-6, MIDAS, and PHQ-4<br><br>**Reliability:** Patients with CM and EM: acceptable internal consistency demonstrated in the overall population (Cronbach alpha = RFR 0.96, RFP 0.90, ES 0.87) and in the CM and EM populations individually (Cronbach alpha ≥ 0.86 for each of the MSQoL domains). Patients with CM: Cronbach alpha range 0.90 to 0.97 across the 3 domains<br><br>**Responsiveness:** Patients with CM: large effect size for patients with ≥ 50% improvement and moderate effect size for patients with 30% to 50% improvement | Patients with ≤ 15 HDPM: Group-level MIDs (distribution-based)<br>RFR = 3.2<br>RFP = 4.6<br>ES = 7.5<br><br>Individual-level MIDs (anchor-based)<br>RFR = 4.9; 5.0<br>RFP = 5.0; 7.9<br>ES = 8.0; 10.6<br><br>Patients with CM: within-group MIDs (anchor-based)<br>RFR = 10.9 (95% CI = 9.4 to 12.4)<br>RFP = 8.3 (95% CI = 6.7 to 9.9)<br>ES = 12.2 (95% CI = 10.2 to 14.3) |
| EQ-5D-5L | Generic quality-of-life instrument applied to many health conditions<br><br>Part 1: health state rated for 5 domains (mobility, self-care, usual activities, pain/discomfort, and mood) on a scale from 1 to 5, with higher numbers representing more severe problems<br><br>Part 2: a 100 mm VAS with end points labelled 0 (worst imaginable health state) to 100 (best imaginable health state) | **Validity:** Not reported for migraine<br><br>**Reliability:** Not reported for migraine<br><br>**Responsiveness:** Not reported for migraine | Not identified for migraine<br><br>Nonspecific MID estimate = 0.056 (SD = 0.011) for Canadian population |

| Outcome measure | Type | Conclusions about measurement properties | MID |
|---|---|---|---|
| | Score generated with a multi-attribute utility function | | |
| PGIC | Generic, self-reported global assessment of clinical change after treatment<br><br>Answered on a scale from 1 (no improvement or worsening disease) to 7 (great deal better) | **Validity:** Not reported for migraine<br><br>**Reliability:** Not reported for migraine<br>**Responsiveness:** Not reported for migraine | Not identified for migraine |
| PHQ-9 | 9 items for depressive disorders, where items correspond to criteria for diagnosing major depressive disorder from the DSM-IV<br><br>Each item rated on a 4-point scale with each number corresponding to frequency of symptoms (0 = no symptoms to 3 = symptoms nearly every day) | **Validity:** Patients with migraine: moderate correlation with MIDAS (r = 0.38), strong correlation with HIT-6 (r = 0.52), and strong correlation with MSQoL (r = –0.54)<br><br>**Reliability:** Patients with migraine: acceptable internal consistency demonstrated (Cronbach alpha = 0.894)<br><br>**Responsiveness:** Not reported for migraine | Not identified for migraine |
| WPAI | 6 items to measure health-related impairments on work and daily activities | **Validity:** The general form has been validated; however, no evidence found in patients with migraine<br><br>**Reliability:** Not reported for migraine<br><br>**Responsiveness:** Not reported for migraine | Not identified for migraine |
| eC-SSRS | An assessment of a patient's suicidal ideation and behaviour with 4 subscales (ideation severity, ideation intensity, behaviour, and lethality)<br><br>The items on each subscale are rated on 3- to 6-point ordinal scales | **Validity:** Not reported for migraine<br><br>**Reliability:** Not reported for migraine<br><br>**Responsiveness:** Not reported for migraine | Not identified for migraine |

CM = chronic migraine; *DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth edition*; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; EM = episodic migraine; EQ-5D-5L = EuroQol 5-Dimension 5-Levels questionnaire; ES = emotional state; HDPM = headache days per month; HIT-6 = 6-item headache impact test; ICC = intraclass correlation coefficient; MID = minimal important difference; MIDAS = migraine disability assessment score; MSQoL = Migraine-Specific Quality of Life questionnaire; PGIC = Patients' Global Impression of Change; PHQ = Patient Health Questionnaire; RFP = role function–preventive; RFR = role function–restrictive; SD = standard deviation; VAS = visual analogue scale; WPAI = Work Productivity and Activity Impairment questionnaire.

### Six-Item Headache Impact Test Questionnaire (HIT-6)

HIT is a multi-question health assessment that quantifies the impact of headache on a patient's life.[34] The HIT 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.[34] The HIT-6 is a short-form version of HIT, which was developed for practical reasons.[96] Six items (questions) were selected from a pool of 89 questions (54 questions from HIT and 35 questions suggested by clinicians). HIT-6 measures pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress.[97] Each of the 6 items is answered on a 5-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, with a higher score indicating a greater impact of headache on daily life.[35,97] The scores may also be interpreted using 4 groupings: a score of 36 to 49 points indicates little or no impact, 50 to 55 points mean some impact, 56 to 59 points indicate substantial impact, and 60 to 78 points reflect severe impact.[97]

HIT-6 was first tested by conducting an internet-based survey of 1,103 adults who had experienced a headache in the past 4 weeks (that was not due to cold, influenza, head injury, or hangover).[96] A follow-up survey of 540 of the original adults was conducted 14 days after the first survey.

Reliability: The instrument showed good internal consistency (Cronbach alpha = 0.89 and 0.90 for the first and second survey, respectively) and test-retest reliability (ICC = 0.78, n = 540).

Construct validity: Correlation between HIT-6 scores and the Short-Form 8 Health Survey (SF-8) 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).[96,98,99] HIT-6 was weakly correlated 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.

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.[96]

A study by Kawata et al. was conducted in patients with chronic daily headaches (≥ 15 headache days per month).[97] 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 4 months after their baseline assessment. The mean HIT-6 score was 65.6 (SD 7.0), and 87% of patients had a score of 60 or more.

Reliability: The instrument showed good internal consistency (Cronbach alpha = 0.87).

Construct validity: Correlation between HIT-6 scores and Short-Form 36 Health Survey (SF-36) domain scores was 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 SF-36.[97]

Further testing of HIT-6 was completed by Yang et al. in 2,049 patients with EM or CM.[100] Adults who had been participants in 2 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 CM with a mean HIT-6 score of 62.5 (SD = 7.8). Adults with EM represented 42.1% of the population

(mean HIT-6 score = 60.2; SD = 6.8), while the remainder (51.5%) had nonmigraine headaches (mean HIT-6 score = 49.1; SD = 8.7).

Reliability: The instrument showed strong[98] internal consistency (Cronbach 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).

Construct validity: Correlation between HIT-6 scores and other scores (MIDAS, headache pain severity, and number of headache days per month) was 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 number of headache days per month, respectively.

Discriminant validity: HIT-6 scores differed significantly between subgroups of CM (mean = 62.5; SD = 7.8), EM (mean = 60.2; SD = 7.8), and nonmigraine headaches (mean 49.1; SD = 8.7; P < 0.01); however, the sample size of the CM group was much smaller, which may have affected these results. The authors also stated that patients with CM were more likely to have an increased impact severity level than patients with EM and nonmigraine headaches, in that order.[100]

Rendas-Baum et al. validated the HIT-6 in 1,384 patients with CM, pooled from 2 studies investigating OnaA for treatment of migraines, PREEMPT-1 and PREEMPT-2.[36] Validity, reliability, and responsiveness were evaluated. Convergent validity was assessed by correlation of HIT-6 with MSQoL; 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 the 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 279, 280 to 419, and ≥ 420) at week 24. Test-retest reliability was assessed with the ICC among a stable subsample at weeks 8 and 12. Internal consistency was assessed with Cronbach 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).

Validity: HIT-6 correlated moderately to strongly[99] with MSQoL (–0.86 to –0.59) and demonstrated convergent validity.

Reliability: Test-retest reliability was demonstrated with an ICC of 0.76 to 0.80. HIT-6 also demonstrated internal consistency, with Cronbach alpha of 0.75 to 0.92, and average inter-item correlation and item-total correlation above the threshold of 0.40.

Responsiveness: 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.

MID: A MID in HIT-6 score was suggested by Coeytaux et al. from a study involving 71 patients who suffered from chronic daily headaches (≥ 15 headache days per month).[35] Patients were randomly assigned to 10 acupuncture sessions administered over 6 weeks and usual medical care (n = 34) or to usual medical care alone (n = 37). The mean age of the study population was 46 years (range = 19 to 83) and 80% were women. Patients suffered from a mean of 24.2 headaches (SD = 5.8) in the month before study enrolment.

The mean pain severity was 6.4 (SD = 2.0) on an 11-point scale. There were no significant differences in baseline characteristics between the 2 groups.

Before randomization, HIT-6 was administered at baseline and again at 6 weeks. At 6 weeks, the follow-up test included 1 additional question to determine the patient's perceived clinical change to define a meaningful or important clinical change: "Compared with 6 weeks ago, my headache condition is a) much better; b) somewhat better; c) about the same; d) somewhat worse; or e) much worse."[35] The MID was established using an anchor-based approach that compared HIT-6 scores of patients who reported clinical improvement with HIT-6 scores 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 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 2 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.

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 6 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.[35] Similar MID estimates were obtained using different anchors (Table 39). 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 in the study, given that patients had to recall their headache condition 6 weeks earlier.

## Table 39: MIDs for HIT-6 Based on 4 Methods

| Method | Description | MID, 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 = 6-item headache impact test; MID = minimal important difference.

Source: Coeytaux et al. (2006).[35]

Smelt et al. developed within-group and between-group MIDs for HIT-6 in patients with EM.[101] The dataset consisted of patients (N = 490) with migraine in the Netherlands who participated in a randomized trial that compared a proactive approach by general practitioners with usual care. The average age of patients was 48 years, 86% were women, and patients experienced an average of about 6 headache days per month. The diagnosis of migraine, however, was not based on the International Headache Society criteria. Change scores on HIT-6 from baseline to month 3 (N = 368) were compared with 2 anchor questions: "(1) Compared to 3 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 3 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 MID was suggested by a mean change approach, which defines the MID as the mean change in HIT-6 score of the group of patients who reported being "somewhat better." The between-group MID was proposed 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 MID. The within-group MID was estimated to be –2.5 points, based on the mean change approach, and –6 points, based on the receiver operating characteristic curve approach. The between-group MID was estimated to be –1.5 points.

### Migraine Disability Assessment Score Questionnaire (MIDAS)

MIDAS is a 5-item questionnaire that evaluates headache-related disability through 5 questions regarding the number of days lost in 3 domains: paid work or schoolwork; housework or chores; and family, social, or leisure activities.[37] The last 2 questions capture additional days with significant limitations to activity (≥ 50% reduced productivity) in the employment domains and household work domains.[102] The questions are answered based on a 3-month recall interval, which allows the questions to accurately capture self-reported information while also providing enough time to capture the long-term experience with headaches. An overall score for the questionnaire is calculated by summing the lost days recorded in the 5 questions. Two questions are not included in the scoring, which ask about the frequency of headaches and intensity of headache pain. These are used to provide clinicians with additional information for managing treatment decisions. The overall score translates to a 4-point grading scale: grade 1 = scores ranging from 0 to 5; grade 2 = 6 to 10; grade 3 = 11 to 20; grade 4 = 21 or greater. Grade 1 is classified as minimal or infrequent disability, grade 2 as mild or infrequent disability, grade 3 as moderate disability, and grade 4 as severe disability.

MIDAS has been validated in terms of internal consistency and test-retest reliability in 2 studies by Stewart et al. (2001; 1999). Both studies collected data using telephone interviews and a clinically validated computer-assisted telephone interview to interview respondents about their headaches; the data were used to define cases of migraine in combination with International Headache Society criteria.[102,103] Individuals with a diagnosis of migraine headache were invited to participate in the reliability studies. A total of 124 respondents with migraines and 100 nonmigraine headache controls agreed to participate, which involved completing MIDAS twice.[103] Response rates for the second questionnaire were 78% for the group with migraine and 80% for those without migraines. 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 alpha. There was substantial agreement[104] based on a Pearson correlation, ranging from 0.60 to 0.75 for each question, and Spearman correlation, ranging from 0.67 to 0.84, demonstrating test-retest reliability.[103] The overall MIDAS score also demonstrated internal consistency (Cronbach alpha = 0.83).

Similar methods were used to evaluate reliability in the second study by Stewart et al.[102] In this study, 2 completed questionnaires were received from 197 patients living with migraines (97 from the US and 100 from the UK), which were completed a median of 21.5 days apart. Each MIDAS question score was moderately to almost perfectly[104] correlated by Pearson correlation coefficient (r = 0.52 to 0.82) and moderately to substantially correlated[104] by Spearman correlation coefficient (rho = 0.46 to 0.71), demonstrating test-retest reliability.[102] Further, the overall MIDAS score also demonstrated test-retest reliability through a high correlation[104] (Pearson r = 0.80 to 0.83 and Spearman rho = 0.77 to 0.78).[102]

Concurrent validity of MIDAS was also assessed through a correlation between MIDAS score and a 90-day headache diary, both of which were completed by 144 patients with physician-confirmed migraine diagnosis who were trained to use the diary.[102,105] The

individual items and overall MIDAS score demonstrated concurrent validity through a moderate to strong correlation[99] between the questionnaire and daily headache dairy (Pearson r = 0.50 to 0.77, Spearman rho = 0.53 to 0.76).[102,105]

Based on the studies summarized, MIDAS is considered reliable and valid in those experiencing headaches and migraines; however, the proportion of patients with CM versus EM in these studies is unknown. Evidence regarding responsiveness or a MID was not identified.

### Migraine-Specific Quality of Life Questionnaire (MSQoL)

MSQoL is a disease-specific instrument that assesses the impact of migraine on a patient's HRQoL. version 1.0 of MSQoL was a 16-item instrument developed and validated by Jhingran et al.[39] MSQoL v2.1 is a 14-item instrument developed from MSQoL v1.0 with various items reworded for clarification and the items shortened for easier administration. MSQoL v2.1 was used in the studies in this review.

MSQoL assesses HRQoL across 3 domains: role function–restrictive (RFR, 7 items assessing how migraine limits a patient's daily social and work-related activities), role function–preventive (RFP, 4 items assessing how migraine prevents these activities), and emotional state (ES, 3 items assessing the emotions associated with migraine).[38] Participants respond to the 14 items based on a 4-week recall period and using a 6-point Likert-type scale: none of the time, a little bit of the time, some of the time, a good bit of the time, most of the time, and all of the time, which are assigned scores of 1 to 6, respectively. Raw dimension scores are computed as a sum of item responses and are rescaled to a scale of 0 to 100 points, producing an overall score for each domain. A higher score indicates better HRQoL.[38]

A study by Bagley et al. (2012) provided evidence of the validity and reliability of MSQoL v2.1 in patients with EM and CM.[38] The study was a web-based, cross-sectional survey conducted in 8,726 patients with EM (< 15 headache days per month) or CM (≥ 15 headache days per month) from 9 different countries. Of these, 499 (5.7%) patients had CM, with mean MSQoL domain scores of RFR 44.37 (SD = 22.07), RFP 61.37 (SD = 26.10), and ES 48.27 (SD = 28.12). Patients with EM (94.3%) had mean MSQoL domain scores of 56.46 (SD = 24.13) for RFR, 71.68 (SD = 23.96) for RFP, and 67.20 (SD = 26.64) for ES. Reliability was assessed via internal consistency (measured with Cronbach alpha) for the overall sample for RFR, RFP, and ES (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 EM and CM samples as Cronbach alpha was 0.86 or higher for each of the MSQoL domains. Construct validity was assessed using Pearson correlation coefficients of the MSQoL scores and other HRQoL instruments. Based on the overall patient population (both CM and EM), correlations were moderate to strong between the MSQoL and HIT-6 (r = –0.60 to –0.71), weak to moderate for MSQoL and PHQ-4 (r = –0.31 to –0.42), and weak for MSQoL and MIDAS (r = –0.38 to –0.39) and for MSQoL and headache days per month (r = –0.17 to –0.24).[38,99] Overall, this provided some support for convergent and discriminant validity of the MSQoL. Similar results were also obtained for the CM and EM groups alone.[38] Known-groups validity was also demonstrated using the same HRQoL measures, as a statistically significant difference was observed for the mean MSQoL scores across migraine frequency groups.

Rendas-Baum et al. (2013) provided further validation of MSQoL v2.1 in patients with CM undergoing prophylactic treatment.[106] Data were pooled from 2 clinical trials of OnaA, PREEMPT-1 and PREEMPT-2, and included 1,376 patients.

Reliability: Internal consistency at baseline was acceptable, with Cronbach alpha of 0.80 for all 3 scales, varying between 0.80 for ES and 0.93 for RFR. At 24 weeks, Cronbach alpha remained acceptable and ranged from 0.90 to 0.97 across the 3 domains and the 2 studies.

Construct validity: MSQoL and HIT-6 scores were moderately to strongly correlated,[99] Pearson values ranging from r = –0.59 (ES) to r = –0.75 (RFR) at baseline and r = –0.74 (ES and RFP) and r = –0.86 (RFR) at 24 weeks.

Responsiveness: MSQoL change scores indicated large and moderate effect sizes for patients who experienced ≥ 50% improvement and improvement between 30% and 50%, respectively.[106]

The MID in MSQoL v2.1 score was determined from a multi-centre, double-blind, placebo-controlled, randomized trial of 328 patients with CM.[107] CM 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 per day (n = 165) or placebo (n = 163) for 16 weeks. The mean age was 38.2 years (range = 18 to 74), and 85% of the study population were women. The patients had suffered from chronic daily headaches for approximately 9 years and reported 20 headache days per month at baseline. Outcomes measured included MIDAS, MSQoL v2.1, subject global impression of change (SGIC), and PGIC. SGIC and PGIC, completed at the end of the study, used a 7-point scale ranging from 1 = very much improved to 7 = very much worse.[107]

MID was established using an anchor-based approach, with the SGIC as the anchor.[107] The MID was estimated as the change in MSQoL domain score that corresponded to a unit improvement on the SGIC (i.e., the beta coefficient of the regression equation of MSQoL domain with SGIC was the MID). For change from baseline in MSQoL-RFR versus SGIC, there was an improvement in MSQoL-RFR, with a regression-estimated MID of 10.9. For change from baseline in MSQoL-RFP versus SGIC, there was an improvement in MSQoL-RFP, with a regression-estimated MID of 8.3. For change from baseline in MSQoL-ES versus SGIC, there was improvement in MSQoL-ES, with a regression-estimated MID of 12.2 (Table 40).

## Table 40: MID for Each MSQoL Domain — Within-Group Difference in Patients With CM

| MSQoL domain | Regression-estimated MID (95% CI) within-group differences |
|---|---|
| **Role function–restrictive (RFR)** | 10.9 (9.4 to 12.4) |
| **Role function–preventive (RFP)** | 8.3 (6.7 to 9.9) |
| **Emotional state (ES)** | 12.2 (10.2 to 14.3) |

CI = confidence interval; CM = chronic migraine; MID = minimal important difference; MSQoL = Migraine-Specific Quality of Life questionnaire.

Source: Dodick et al. (2007).[107]

Cole et al. identified group-level and individual-level MIDs for the RFR, RFP, and ES domains of the MSQoL v2.1.[108] The analyses were performed on pooled data from 2 clinical trials of topiramate for migraine prophylaxis (N = 916) and the QualityMetric National Headache Survey (N = 1,016). The 2 trials were randomized, double-blind, placebo-controlled and conducted in Canada and the US. Patients were 12 to 65 years of age, had

a minimum 6-month history of migraine, and experienced 3 to 12 migraines per month (but not more than 15 headache days per month during the 28-day baseline period). Patients were randomized to placebo or topiramate 50, 100, or 200 mg/day and continued 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, were able to converse in English, and experienced a headache at least once in the past 4 weeks before the telephone interview. No intervention was administered to patients in the QualityMetric survey.

Group-level MIDs were determined using a distribution-based technique, with Cohen d effect sizes from the pooled topiramate trial data. Table 41 shows the group-level MIDs for RFR, RFP, and ES domains.

## Table 41: Group-Level MIDs for MSQoL in Patients With a Maximum of 15 Headache Days per Month

| MSQoL domain | Distribution-based: MID |
|---|---|
| **Role function–restrictive (RFR)** | 3.2 |
| **Role function–preventive (RFP)** | 4.6 |
| **Emotional state (ES)** | 7.5 |

MID = minimal important difference; MSQoL = Migraine-Specific Quality of Life Questionnaire.

Source: Cole et al. (2009).[108]

Cole et al. also calculated individual-level MIDs with anchor-based versus distribution techniques.[108] In anchor-based techniques, the anchors were average monthly migraine rate (30%, 40%, or 50% reduction), migraine status (yes/no), MIDAS, more or less headaches compared with 3 months ago (yes/no), bothered by headaches more now compared with 3 months ago (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 MIDs suggested by Cole et al. from anchor-based techniques (Table 42) were generally smaller than those reported in Dodick et al. (Table 40). The MIDs were 4.9 and 5.0 for RFR, 5.0 and 7.9 for RFP, and 8.0 and 10.6 for ES. Importantly, the MIDs proposed by Dodick et al. were based on patients with CM, whereas the datasets used by Cole et al. included patients with a maximum of 15 headache days per month (i.e., most patients in the datasets used by Cole et al. would be below the threshold for classification of CM).

In 1 distribution-based technique, the MIDs were calculated from one-half the SD of each MSQoL domain, from the pooled topiramate trial dataset and the QualityMetric dataset separately. In a second distribution-based technique, the MIDs were calculated from the standard error of the mean of the MSQoL domains in the pooled clinical trial dataset. The MIDs from distribution-based techniques ranged from 4.8 to 8.6 (RFR), 7.9 to 9.9 (RFP), and 10.6 to 12.4 (ES). The anchor-based MIDs were similar to the distribution-based MIDs using standard error of the mean; however, they were less than the distribution-based MIDs using one-half SD (Table 42). The estimates based on anchor techniques are preferred to those of distribution techniques.

## Table 42: Individual-Level MIDs for MSQoL in Patients With EM

| MSQoL domain | Anchor-based MID[a] | Distribution-based (0.5 SD) MID[b] | Distribution-based (SEM) MID |
|---|---|---|---|
| **Role function–restrictive (RFR)** | 4.9; 5.0 | 8.3; 8.6 | 4.8 |
| **Role function–preventive (RFP)** | 5.0; 7.9 | 9.9; 8.5 | 7.9 |
| **Emotional state (ES)** | 8.0; 10.6 | 12.4; 11.5 | 10.6 |

EM = episodic migraine; MID = minimal important difference; MSQoL = Migraine-Specific Quality of Life questionnaire; SD = standard deviation; SEM = standard error of mean.

Source: Cole et al. (2009).[108]

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

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

### EuroQol 5-Dimensions 5-Levels Questionnaire (EQ-5D-5L)

The EQ-5D 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.[40] As a generic measure of HRQoL that can capture the net effect of treatment benefits and harms, the EQ-5D provides valuable information from the patient perspective. The original 3-level version, EQ-5D-3L, was introduced in 1990 and was composed of 5 dimensions pertaining to HRQoL.[40] Respondents indicated their health status in terms of 5 HRQoL dimensions based on 3 levels of severity. To improve sensitivity and reduce ceiling effects, the EQ-5D-3L was updated to have 5 levels in 2005, resulting in the EQ-5D-5L, which was used in the studies of this review.

The EQ-5D-5L consists of a descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients respond to each dimension using 5 levels, where level 1 = no problems, level 2 = slight problems, level 3 = moderate problems, level 4 = severe problems, and level 5 = extreme problems or unable to perform.[40] Respondents are asked to choose the level that reflects their health state for each of the 5 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 5 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, are not used to produce an individual dimension score. Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm, taking the local patient and population preferences into account. Therefore, the index score is a country-specific value and a major feature of the instrument.[109] The range of index scores differs 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 health states that society, not the patient, considers to be worse than dead.

The EQ VAS records the respondent's self-rated health on a vertical VAS, on which the end points are 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 point of the VAS that best represents their health on that day. The EQ-5D index and VAS scores can be summarized

and analyzed as continuous data.[40,109] Hence, the EQ-5D produces 3 types of data for each respondent:

- A profile indicating the extent of problems on each of the 5 dimensions represented by a 5-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 EQ 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 6 countries with chronic conditions;[40] however, evidence of validity in patients with migraines was not identified. A Canadian-specific estimate of a MID for the EQ-5D-5L was generated by simulating the effects of single-level transitions in each dimension.[41] The results yielded MIDs with a summarized mean of 0.056 (SD = 0.011), and a summarized median of 0.056 (interquartile range = 0.049 to 0.063).[41]

### Patients' Global Impression of Change Scale

PGIC is a self-administered global assessment of the change of clinical status following treatment.[94] Patients are asked to rate how headaches and migraines have affected their general quality of life and health status since beginning treatment. The scale ranges from 1 to 7, with the steps corresponding to improving condition: 1 = no change or worsening condition; 2 = almost the same or hardly any change at all; 3 = a little better, but no noticeable change; 4 = somewhat better, but the change has not made any real difference; 5 = moderately better with slight but noticeable change; 6 = better with definite improvement that has made a real and worthwhile difference; and 7 = a great deal better, and a considerable improvement that has made all the difference.

Clinical Global Impression (CGI) scales are among the most widely used, rapid, and accessible measures for evaluating psychiatric outcomes in clinical trials. Despite wide acceptance, little psychometric validation of the scales has been performed, especially 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 CGI measures may not lend themselves to the establishment of a clinically important change, as they are too simple to precisely measure treatment effects, especially as new drugs may only offer incremental benefits.[110-112] Evidence of validity or an MID for patients with migraines was not identified.

### Nine-Item Patient Health Questionnaire (PHQ-9)

PHQ-9 is a questionnaire used for screening rather than diagnosing patients and consists of 9 items corresponding to criteria for diagnosing major depressive disorder from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[94,113] Patients score each item for how frequent symptoms occurred during the past 2 weeks (0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day). The total score ranges from 0 to 27 (from best to worst). A score of 0 to 4 = none/minimal depression, 5 to 9 = mild depression, 10 to 14 = moderate depression, 15 to 19 = moderately severe depression, and 20 to 27 = severe depression.[114]

PHQ-2 consists of the first 2 questions from PHQ-9 and is used as a rapid screening tool to identify patients who may have depression.[94] Patients complete PHQ-2, and those with a score of at least 3 complete the remaining 7 questions from the PHQ-9.

The validity and reliability of the PHQ-9 in patients with migraine was assessed by Seo et al.[42] Consecutive patients (N = 132) visiting a hospital headache clinic in Korea were recruited. Patients were diagnosed with migraine based on the International Classification of Headache Disorders-3 and were 16 to 70 years of age. Patients were administered the PHQ-9, as well as the Mini International Neuropsychiatric Interview-Plus Version 5.0.0 (MINI), the Beck Depression Inventory-II (BDI-II), MIDAS, HIT-6, and MSQoL. PHQ-9 was translated into Korean and was deemed to be identical to the English version. Of the 132 patients, 73 (55%) had CM.

Validity: PHQ-9 score correlated strongly with BDI-II (Spearman rho = 0.754, P < 0.001), moderately with MIDAS (0.377, P < 0.001), and strongly with both HIT-6 (0.519, P < 0.001) and MSQoL (–0.538, P < 0.001), demonstrating construct validity.[98] In receiver operating characteristic analyses, at a cut-off score of 7, relative to the MINI, the sensitivity of the PHQ-9 was 79.5%, specificity 81.7%, positive predictive value 64.6%, and negative predictive value 90.5%.

Reliability: Cronbach alpha for PHQ-9 was 0.894, suggesting acceptable internal consistency.

A Canadian study from an outpatient clinic in Alberta screened patients using the PHQ-9 via telephone interview.[43] The study population consisted of 830 adult patients with neurological conditions such migraine, epilepsy, multiple sclerosis, Parkinson disease, and stroke. The overall study population was 61.6% women, 47.6% of whom were 18 to 50 years old, 30.3% between 51 and 64, and 22.2% older than 65. Patients with migraine made up 25% (n = 208) of the study population. Pooled estimate sensitivity and specificity were determined to be 90% (95% CI, 81 to 97) and 85% (95% CI, 79 to 90), respectively, and estimates were found to be reasonably homogeneous ($I^2$ = 43.5%, $tau^2$ = 0.03; and $I^2$ = 2.3%, $tau^2$ = 0.00).

### Work Productivity and Activity Impairment Questionnaire (WPAI)

WPAI is a questionnaire that measures impairments in work productivity and daily activities due to generic or specific health problems.[43] Respondents provide their employment status, after which they answer 3 questions related to work hours missed due to health issues, work hours missed for other reasons, and hours worked. The questionnaire had 2 additional questions asking about how health issues have affected productivity at work and activities outside of work. Each item of the WPAI is rated on an 11-point scale from 0 = no impairment to 10 = complete impairment.

The general form of WPAI was validated on a sample of 106 employed individuals who were affected by a symptom or health problem during the past 7 days of recruitment.[43] No studies were found that validated the instrument in patients with migraine. A MID for the WPAI in patients with migraine was not identified in the literature.

### Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

eC-SSRS is a computer-administered interview-based assessment tool for measuring past and current suicidal ideation and behaviour.[45,94] When administered with the clinician-based C-SSRS, the electronic version showed convergent validity.[45]

C-SSRS was developed to monitor changes in suicidality over time by incorporating assessments of lifetime suicidal ideation and behaviour as well as between-visit changes.[115] The instrument has 4 subscales: severity of ideation (e.g., specificity of suicidal

thoughts or intent with methods or plans), intensity of ideation (e.g., frequency and duration of suicidal thoughts), behaviour (e.g., preparatory actions, suicide attempts, and nonsuicidal injurious behaviour), and lethality (assessment of actual suicide attempts). The items on the ideation and lethality subscales are rated on 3- to 6-point ordinal scales, and the behaviour subscale uses a nominal scale. A higher total score indicates a higher level of suicidality.

The psychometric properties of the C-SSRS were assessed in 3 studies that were presented in 1 publication. Study 1 included adolescents who had previously attempted suicide; study 2 involved adolescents with a diagnosis of major depressive disorder; and study 3 was conducted in adult patients who presented to the emergency department for psychiatric reasons.[115] The intensity of ideation subscale demonstrated moderate to high internal consistency in all 3 studies. In support of convergent validity, the suicidal ideation and behaviour subscales on the C-SSRS correlated moderately to strongly with the corresponding suicide-related items on the Montgomery–Åsberg Depression Rating Scale and BDI, as well as with the Scale for Suicide Ideation and the Columbia-Suicide History Form in studies 1 and 3. Further analysis in studies 1 and 2 showed that the change in the severity and intensity of ideation subscale scores over time significantly corresponded with score changes in the Scale for Suicide Ideation or Suicidal Ideation Questionnaire–Junior. Similarly, the classification of suicidal behaviours on the C-SSRS over time in study 1 demonstrated moderate to full agreement with the classification of the same behaviour using the Columbia-Suicide History Form. The divergent validity of the C-SSRS severity and intensity of ideation subscales were analyzed in study 1, and a weak to moderate correlation between these subscales and somatic depression items on the BDI and the Montgomery–Åsberg Depression Rating Scale was observed; however, this study population did not include adults with major depressive disorder.[115]

An MID was not reported for the C-SSRS, but predictive validity was examined in 2 studies. For each increase in C-SSRS level of lifetime suicide ideation by 1 standard deviation in an adolescent population, the odds of attempting suicide during the 24-week study increased by 45%.[115] A validation study of eC-SSRS evaluated an existing set of assessments extracted from multiple studies in which the majority (91%) of total patients had major depressive disorder and demonstrated that patients who reported severe lifetime suicidal ideation or a history of suicidal behaviour at baseline were up to 9 times more likely to report suicidal behaviour during their study participation.[116]

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