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Ajovy™ (Fremanezumab): A New Preventive Treatment of Migraines in Adults

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Migraine is a disorder characterized by severe headaches that are often associated with debilitating symptoms, including photophobia, phonophobia, nausea, vomiting, vertigo, cutaneous allodynia, and cognitive dysfunction.[1] According to the Global Burden of Disease Study, migraine was ranked as the third most prevalent disorder and the third-highest cause of disability for both males and females under 50 years of age worldwide.[2] In 2015, the U.S. National Center for Health Statistics reported that migraine has negatively affected 14.2% of U.S. adults, specifically 20.2% of adult females and 9.4% of adult males.[3] In other words, 1 out of 7 Americans are currently suffering from this disabling disorder.[3] Typically, migraine can be classified as episodic migraines (EM) or chronic migraines (CM). EM is defined as having headaches on <15 days per month, whereas CM is experiencing headaches on ≥15 days per month for >3 months.[2,4,5] In addition to its negative physical and psychological impact on patients, migraine presents a socio-economic burden to not only the patients, but also the society and the healthcare system. For example, it is estimated that the migraine's annual indirect costs can surpass $11 billion.[6]

Currently, there are several off-label pharmacological therapies available for migraine prophylaxis, including: beta-blockers (i.e. metoprolol, propranolol, and timolol), anti-depressants (i.e. amitriptyline and venlafaxine), anti-convulsants (i.e. topiramate and valproate), triptans, and calcitonin gene-related peptide (CGRP) antagonist (i.e. erenumab and galcanezumab), etc.[7-10] Unfortunately, based on a retrospective analysis, it is estimated that only 17-29% of patients suffering from migraine are adherent to their treatment regimen.[5,11] Thus, the need for a novel migraine therapy that may improve compliance is warranted.

Fremanezumab (Ajovy™) was approved by the FDA on September 14th, 2018 for the preventive treatment of migraine in adults. While there are other CGRP antagonists currently approved for migraine prophylaxis, such as erenumab and galcanezumab, these medications require monthly dosing.[9,10] At present, fremanezumab is the first and only migraine medication that can be dosed either monthly or quarterly (i.e. every 3 months).[12] This article aims to evaluate current clinical evidences on the efficacy and safety of fremanezumab in the prophylactic management of migraine.

Clinical Pharmacology

Fremanezumab is a fully humanized IgG2Δa/kappa monoclonal antibody that binds the CGRP ligand which in turn inhibits activation of the CGRP receptor.[1,12] Generally, CGRP receptor activation causes cerebral vasodilation, neurogenic inflammation and sensitization of the trigeminovascular sensory fibers.[7] Consequently, this cascade leads to nociceptive transmission, and as a result, contributes to migraine development.[7] CGRP activity antagonism with fremanezumab inhibits part of the trigeminal response associated with migraines and reduces patient pain perception.

Fremanezumab pharmacokinetics are not affected by age, race, sex, or weight.[12] Fremanezumab is metabolized by enzymatic proteolysis into small peptides and amino acids.[12] Since fremanezumab is not metabolized by cytochrome P450 (CYP450) enzymes, it is not expected to have drug-drug interactions with medications that are substrates, inducers, or inhibitors of CYP450 enzymes.[12] Furthermore, there was no clinically significant interaction detected with other medications that are commonly used in the preventive treatment and acute management of migraines.12 Impaired renal or hepatic function is not anticipated to affect fremanezumab's pharmacokinetics; however, limited data are available in these patient populations. At the moment, no dose adjustments are required.[12]

Clinical Trials

Fremanezumab was approved by the FDA as a preventive treatment of migraine in adults based primarily on clinical evidences from two phase III trials.[13] These phase III trials aimed to evaluate the efficacy and safety of both fremanezumab monthly and quarterly dosing regimens comparing to placebo in preventing EM and CM. Additionally, two phase IIb trials also provided critical safety and efficacy data supporting the use of fremanezumab in the prophylactic management of migraine.

The following section will discuss the phase IIb clinical trials

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as well as the two pivotal phase III clinical trials on fremanezumab (HALO-EM and HALO-CM). In addition, two post-hoc analyses will also be briefly reviewed below. A summary of results can be seen in **Table 2** and **Table 3**. A summary of adverse events (**Table 4**), from these trials will also be discussed in the safety section of this article.

Phase IIb Trials

Bigal et al. conducted a multicentre, randomized, double-blind, placebo-controlled, phase IIb study to assess the safety and efficacy of fremanezumab as a preventive treatment of EM.[4]

Inclusion criteria were men and women between 18-65 years of age with a diagnosis of EM. Key exclusion criteria were diagnosis of CM, opioids or barbiturate medications for >4 days during the run-in phase, or previously failed ≥3 preventive medications. Baseline characteristics of study participants were mean age of 41 years, 88% female, mean monthly migraine days (MMD) of 11 days, and approximately 29% of enrolled participants used migraine preventive medications at the time of the study.[4]

Participants were randomly assigned in 1:1:1 ratio to receive subcutaneous injections of 225 mg fremanezumab (n = 95), 675 mg fremanezumab (n = 96), or placebo (n = 104) every 28-day treatment cycle for a total of 3 cycles (3 months). The study's primary outcome was change from baseline in migraine days during weeks 9-12 of treatment period and safety and tolerability of fremanezumab. The secondary efficacy outcome was change from baseline in headache-days during weeks 9-12 of treatment phase. These primary and secondary outcomes are also assessed during weeks 1-4 and weeks 5-8, which have shown to be superior to placebo throughout the study.[4]

The primary outcome, change from baseline in MMD, was -3.46 days in the placebo group, -6.27 days in the fremanezumab 225 mg (difference versus placebo = -2.81 days; 95% CI -4.07 to -1.55) and -6.09 days in the 675 mg groups (difference versus placebo = -2.64 days; 95% CI -3.90 to -1.38). During the trial, the most common adverse effects were injection site pain (9% in the fremanezumab 225 mg group, 4% in the fremanezumab 675 mg group, and 6% in the placebo group). Other common adverse effects, including injection-site reactions such as erythema and bruising (6-11% in fremanezumab groups vs 3-4% in placebo group), nausea (1% in fremanezumab groups vs 4% in placebo group), and upper respiratory tract infection (2-4% in fremanezumab groups vs 4% in placebo group), were reported with similar prevalence in both treatment and placebo groups.[4]

Bigal and colleagues also studied the safety and efficacy of fremanezumab as CM prophylaxis in a separate multi-centre, randomized, double-blind, double-dummy, placebo-controlled, phase IIb trial.[14]

Inclusion criteria were men and women between 18-65 years of age with CM. Key exclusion criteria were use of onabotulinumtoxinA within 6 months prior to study entry, used opioids or barbiturate medications for >4 days during the run-in phase, or previously failed ≥3 preventive medications were excluded from the study. Baseline characteristics of study participants included: approximate mean age of 41 years, 86% female, mean MMD of 17 days. Among enrolled participants, 40% in the fremanezumab 675/225 mg group, 38% in the fremanezumab group, and 38% in the placebo group used ≥1 migraine prophylactic therapies, such as topiramate, propranolol, and trans-magnetic stimulation, at the time of the trial.[14]

Participants were randomly assigned in 1:1:1 ratio to receive subcutaneous injections of fremanezumab 675/225 mg (675 mg in the first treatment cycle, and 225 mg in the second and third treatment cycles; n = 88), fremanezumab 900 mg (n = 87), or placebo (n = 89) every 28-day treatment cycle for a total of 3 cycles. The study's primary efficacy outcome was mean change from baseline in number of headache-hours during weeks 9-12 of treatment period. The secondary efficacy outcome was mean change from baseline in number of moderate or severe headache-days during weeks 9-12 of treatment phase. The primary outcome, change from baseline in the reduction of headache-hours, compared to placebo was -22.74 hours in the fremanezumab 675/225 mg group (95% CI, -44.28 to -1.21; p=0.0386) and -30.41 hours in the fremanezumab 900 mg group (95% CI, -51.88 to -8.95; p=0.0057).[14]

Table 1 | Select Fremanezumab Pharmacokinetics[12]

Parameters	Value
Absorption	
T_{max}	5-7 days
Time to steady state	169 days (~6 months)
Distribution	
V_d	~6 L
Metabolism	
Enzymatic proteolysis	Degradation into peptides and amino acids
Elimination	
CL	0.141 L/day
$T_{1/2}$	~31 days

CL = apparent clearance; L = liter; $t^1/_2$ = half-life; T_{max} = median time to maximum concentrations; V_d = volume of distribution

The most common adverse effects were mild injection site pain (7% in the fremanezumab 675/225 mg group, 9% in the fremanezumab 900 mg group, and 3% in the placebo group). Other common adverse effects, including injection-site reactions (erythema, pruritus, etc.), back pain, and urinary tract infection, had no significant difference in overall incidences in both treatment and placebo groups.[14]

Phase III Trials

HALO-EM

HALO-EM was a multi-national, randomized, double-blind, placebo-controlled, parallel-group clinical trial to assess the safety and efficacy of fremanezumab as a preventive treatment of episodic migraine.[1,15] The study comprised of 4 phases: a screening visit, 28-day pre-treatment period, 12-week treatment period, and a final evaluation phase at week 12. During the pre-treatment period, information from patient's daily headache diary was collected to aid in determining their study eligibility as well as randomization to different treatment groups.[1]

Inclusion criteria were age 18-70 years, a history of migraine for ≥12 months prior to study's screening visit, onset of migraine prior to 50 years of age, and EM episodes during the 28-days pre-treatment period. Exclusion criteria were patients who received onabotulinumtoxin A in the 4 months prior to screening visit, interventions such as nerve blocks or transcranial magnetic stimulation in the 2 months prior to screening visit, opioid or barbiturate medications for >4 days during the pre-treatment period, or previously failed to respond to ≥2 preventive medications after ≥3 months of treatment.[1]

Patients were randomly assigned in 1:1:1 ratio to receive a

monthly dose of fremanezumab 225 mg subcutaneously (n = 290) at baseline, week 4, and week 8; a single quarterly dose of fremanezumab 675 mg (n = 291) at baseline, then placebo at week 4, and week 8; or all placebo (n = 294) at baseline, week 4, and week 8 for 12 weeks.[1]

The study's primary outcome was mean change from baseline in MMD during the 12-week period after initiation of treatment.[1] The secondary efficacy outcomes included the proportion of patients achieving at least a 50% reduction in the MMD from baseline to week 12, the mean change in monthly days with acute headache medications use from baseline to week 12, the mean change in MMD from baseline to week 4, the mean change in MMD in patients not receiving concomitant migraine preventive medication from baseline to week 12, and the mean change in the Migraine Disability Assessment (MIDAS) score. The MIDAS questionnaire was utilized to evaluate patient's disability related to headache; its score ranges from 0 to 270, a higher score indicates greater disability.[1]

Baseline characteristics of study participants included a mean age of 42 years, 84% female, MMD of 9 days. Additionally, among enrolled patients, 21.4% in the fremanezumab monthly dosing group, 19.9% in the quarterly dosing group, and 21.1% in the placebo group were also taking other migraine prophylactic drugs. While more participants from the monthly fremanezumab group reported prior topiramate use, those from the quarterly fremanezumab group reported higher MIDAS score among the three study groups.[1]

For the primary outcome, fremanezumab monthly dosing reduced MMD from baseline by -1.5 days compared to placebo (95% CI, -2.01 to -0.93 MMD) and quarterly dosing reduced MMD by -1.3 compared to placebo (95% CI, -1.79 to -0.72 MMD).[1] The difference in MMD was first detected during the 4-week period after the initiation of fremanezumab.[1]

During the trial, higher number of treatment-related adverse effects were reported in fremanezumab groups. The most common adverse effects were injection site pain (30% in the fremanezumab monthly dosing group, 29.6% in the fremanezumab quarterly dosing group, and 25.9% in the placebo group). Other common adverse events included: injection site induration and erythema, upper respiratory tract infection, and nasopharyngitis. Furthermore, while no clinically significant changes in physical exams and laboratory parameters was reported, 4 patients in the fremanezumab monthly dosing group were found to develop anti-drug antibodies against this medication without any concerning adverse reactions.[1] A detailed summary of both primary and secondary endpoints can be seen in **Tables 2** and **3**.

HALO-CM

The HALO-CM trial was a multi-national, randomized, double-blind, placebo-controlled, parallel-group clinical trial to assess the safety and efficacy of fremanezumab as a preventive treatment of CM.[5,15] The study comprised of 4 phases: a screening visit, 28-day pre-intervention phase (as explained above), 12-week intervention phase, and a final evaluation phase at week 12.[5]

Inclusion criteria were age 18-70 years, a history of migraine for ≥12 months, meeting criteria for CM during the 28-days pre-intervention phase. Exclusion criteria were onabotulinumtoxin A in the 4 months prior to the screening visit, nerve blocks and transcranial magnetic stimulation in the prior 2 months, opioid or barbiturate medication for >4 days during the pre-intervention phase, or previously failed to respond to ≥2 preventive medications. Baseline characteristics of study participants included: mean age of 41 years, 88% female, mean monthly migraine days (MMD) of 16 days. Approximately 21% of patients enrolled were also taking a preventive migraine medication for ≥2 months prior to the study's pre-intervention phase.[5]

Patients were randomly assigned in a 1:1:1 ratio to receive a monthly dose regimen of fremanezumab (n = 375), a quarterly dose regimen (n = 375), or a matching placebo regimen (n = 371). All of the studied patients received 3 subcutaneous injections at baseline and 1 injection at weeks 4 and 8. In the fremanezumab-monthly arm, patients received 675 mg fremanezumab (as 3 injections of 225 mg fremanezumab) at baseline, and then, 225 mg of fremanezumab at weeks 4 and 8. In the quarterly dose arm, patients received 675 mg fremanezumab (as 3 injections of 225 mg fremanezumab) at baseline, and placebo at week 4 and 8. In the

Table 2 | Summary of Primary Outcomes from HALO-EM and HALO-CM Clinical Trials[1,5]

Result	Fremanezumab Monthly Dosing	Fremanezumabe Quarterly Dosing	Placebo
HALO-EM			
	n=287	**n=288**	**n=290**
Mean change in MMD (baseline to week 12)	-3.7 (95% CI, -4.15 to -3.18) Difference vs placebo: -1.5 (95% CI, -2.01 to -0.93)	-3.4 (95% CI, -3.94 to -2.96) Difference vs placebo: -1.3 (95% CI, -1.79 to -0.72)	-2.2 (95% CI, -2.68 to -1.71)
HALO-CM			
	n=375	**n=375**	**n=371**
Mean change in MMD (baseline to week 12)	-4.6±0.3 Difference vs placebo: -2.1±0.3 (P<0.001)	4.3±0.3 Difference vs placebo: -1.8±0.3 (P<0.001)	-2.5±0.3

All data is reported as least-squares mean; **MMD** = Monthly migraine days; **95% CI** = 95% confidence interval

Table 3 | Summary of Select Secondary Outcomes from HALO-EM and HALO-CM Clinical Trials[1,5]

Result	Fremanezumab Monthly Dosing	Fremanezumabe Quarterly Dosing	Placebo
HALO-EM			
	n=287	**n=288**	**n=290**
Proportion of patients achieving ≥50% reduction in MMD (baseline to week 12)	n=137 (47.7%) Difference vs placebo: 19.8% (95% CI, 12.0 to 27.6)	n=128 (44.4%) Difference vs placebo: 16.5% (95% CI, 8.9 to 24.1)	n=81 (27.9%)
Mean monthly days with any acute headache medication use (baseline to week 12)	-3.0 (95% CI, -3.41 to -2.56) Difference vs placebo: -1.4 (95% CI, -1.84 to -0.89)	-2.9 (95% CI, -3.34 to -2.48) Difference vs placebo: -1.3 (95% CI, -1.76 to -0.82)	-1.6 (95% CI, -2.04 to -1.20)
MIDAS score	-24.6 (95% CI, -27.68 to -21.45) Difference vs placebo: -7.0 (95% CI, -10.51 to -3.53)	-23.0 (95% CI, -26.10 to -19.82) Difference vs placebo: -5.4 (95% CI, -8.90 to -1.93)	-17.5 (95% CI, -20.62 to -14.47)
HALO-CM			
	n=375	**n=375**	**n=371**
Proportion of patients achieving ≥50% reduction in MMD (baseline to week 12)	n=153 (41%) P < 0.001 vs placebo	n=141 (38%) P < 0.001 vs placebo	n=67 (18%)
Mean monthly days with use of any acute headache medication (baseline to week 12)	-4.2±0.3 Difference vs placebo: -2.3±0.3 (P < 0.001)	-3.7±0.3 Difference vs placebo: -1.8±0.3 (P < 0.001)	-1.9±0.3
HIT-6 score (change from baseline during 4-week period after last treatment dose)	-6.8±0.4 Difference vs placebo: -2.4±0.5 (P < 0.001)	-6.4±0.5 Difference vs placebo: -1.9±0.5 (P < 0.001)	-4.5±0.5

All data is reported as least-squares mean; MMD = Monthly migraine days; 95% CI = 95% confidence interval; MIDAS = Migraine Disability Assessment; HIT-6 score = six-item Headache Impact Test

placebo arm, patients received 3 placebo injections at baseline, and 1 placebo injection at weeks 4 and 8.[5]

The primary outcome was mean MMD change from baseline during the 12-week period after initiation of treatment. The secondary efficacy outcomes included the following: mean MMD (change from baseline), the proportion of patients achieving at least a 50% reduction in MMD, the mean monthly days with acute headache medications use (change from baseline to week 12), the mean monthly headache days (change from baseline to week 4), the mean monthly headache days in patients not receiving concomitant migraine preventive medication (change from baseline to week 12), and the mean change (from baseline) in the six-item Headache Impact Test (HIT-6) score during the 4-week period after last dose of treatment.[5]

The primary outcome of change in MMD was -4.6±0.3 days in the fremanezumab-monthly arm, -4.3±0.3 days in the fremanezumab-quarterly arm, and -2.5±0.3 days in the placebo arm (P<0.001 when comparing both fremanezumab arms to placebo). The proportion of patients achieving at least 50% reduction in MMD was 41% in the fremanezumab-monthly arm, 38% in the fremanezumab-quarterly arm, and 18% in the placebo arm (P<0.001 when comparing both arms to placebo).[5]

During the trial, a statistically higher number of patients from the fremanezumab-monthly arm reported experiencing adverse events, most commonly injection site pain (26% in the fremanezumab-monthly arm, 30% in the fremanezumab-quarterly arm, and 28% in the placebo arm). Abnormal liver function and possible drug-induced liver injury was reported in 5 patients (1%) from the fremanezumab-monthly arm, 5 patients (1%) from the fremanezumab-quarterly arm, and 3 patients (<1%) from the placebo arm; however, this negative effect was determined to be statistically insignificant (P = 0.73). Furthermore, while no anaphylactic reaction was reported during the study, 2 patients in the frema-

nezumab-quarterly group were found to develop antidrug antibodies against this medication, with no clinically meaningful changes in other physical or laboratory parameters.[5] A detailed summary of both primary and secondary endpoints can be seen in Table 2 and Table 3.

Other Published Articles

Bigal et al. conducted a post-hoc analysis for the phase IIb fremanezumab trials for CM.[16] The post-hoc analysis evaluated the onset of fremanezumab's effect by analyzing change in mean headache-hours from baseline. A total of 261 patients were included in this analysis. At baseline, patients experienced on average 162 headache-hours every month, and 22 headache days and 17 migraine days every month.[16]

While the fremanezumab 675/225 mg dose showed statistically significant decrease in headache-hours from placebo on day 7 (P = 0.048), the fremanezumab 900 mg dose significantly reduced headache-hours after 3 days of treatment comparing to placebo (P = 0.0331). This improvement was seen consistently throughout the clinical trial (month 3, P = 0.0386 in 675/225 mg group; P = 0.0057 in 900 mg group). Regarding to change in weekly moderate to severe headache days, both fremanezumab doses were also superior to placebo at week 2 (P = 0.031 in 675/225 mg group; P = 0.005 in 900 mg group).[16]

Adverse Effects and Precautions

Fremanezumab is generally well-tolerated with the most common adverse effect being injection site reactions such as injection site pain, induration, and erythema.[12] A summary of reported adverse events from both HALO-EM and HALO-CM clinical trials can be seen in Table 4. In general, no significant difference was reported in incidence of fatigue, upper respiratory tract infections, nasopharyngitis, urinary tract infections, bronchitis, sinusitis, nausea, or liver function tests.

Clinical Implications

Results from the HALO-EM and HALO-CM clinical trials have shown that both of the fremanezumab dosing regimens (monthly 225 mg and quarterly 675 mg) can lead to a statistically significant reduction in MMD. During the clinical trials, patients with EM experienced a reduction of 1.3-1.5 MMD comparing those receiving a placebo.[1] Likewise, patients suffering from CM reported having 1.8-2.1 fewer headache days per month when compared to placebo group.[5] Furthermore, in the phase IIb trial, the baseline MMD was 11 days and MIDAS score of 45-49, and 29% of patients were taking other preventive therapies for migraine at time of study.[4] In the HALO-EM, the baseline MMD was 9 days and MIDAS score 37-42, and 21% of patients were on other concomitant prophylactic therapies.[1] Evidences seem to suggest that those patients who had more severe EM (higher baseline MMD and MIDAS score) were seeing a larger reduction in MMD.[1,4]

Furthermore, both of the HALO-EM and HALO-CM studies excluded patients who have previously failed to respond to ≥2 preventive migraine medications which may reduce the generalizability in this population.[1,5] These patients would likely have a greater need for a new therapy option.

Regarding fremanezumab's safety profile, the most common side effect being mild injection site pain.[1,5] Even though, a few

Table 4 | Select Adverse Events Reported in the HALO-EM and HALO-CM Clinical Trials[1,5]

Result	Fremanezumab Monthly Dosing	Fremanezumabe Quarterly Dosing	Placebo
HALO-EM			
	n=290	**n=291**	**n=293**
Injection site pain	87 (30%)	86 (29.6%)	76 (25.9%)
Injection site induration	71 (24.5%)	57 (19.6%)	45 (15.4%)
Injection site erythema	52 (17.9%)	55 (18.9%)	41 (14%)
Upper respiratory tract infection	16 (5.5%)	11 (3.8%)	15 (5.1%)
Aspartate aminotransferase or alanine aminotransferase ≥3 ULN	2 (0.7%)	1 (0.3%)	0
HALO-CM			
	n=379	**n=376**	**n=375**
Injection site pain	99 (26%)	114 (30%)	104 (28%)
Injection site induration	90 (24%)	74 (20%)	68 (18%)
Injection site erythema	75 (20%)	80 (21%)	60 (16%)
Upper respiratory tract infection	16 (4%)	18 (5%)	15 (4%)
Possible drug-induced liver injury	5 (1%)	5 (1%)	3 (<1%)
Alanine aminotransferase ≥3 ULN	3 (<1%)	2 (<1%)	1 (<1%)
Aspartate aminotransferase ≥3 ULN	2 (<1%)	3 (<1%)	0

All data is reported as least-squares mean; MMD = Monthly migraine days; 95% CI = 95% confidence interval; MIDAS = Migraine Disability Assessment; HIT-6 score = six-item Headache Impact Test

patients developed antidrug antibodies against fremanezumab, there was no report of any significant change in vital signs, physical, or laboratory parameters.[1,5] Moreover, there is currently no required renal or hepatic dose adjustment for fremanezumab, and it also has no known major drug-drug interaction.[12]

Limitations to treatment with fremanezumab are mainly related to its relatively high cost, uncertainties in long-term efficacy and safety data, and lack of head-to-head clinical trials comparing its efficacy and safety with other prophylactic migraine medications. Further research on long-term efficacy and safety would be beneficial and will come as the drug becomes available on the market.

Dosing and Administration

Fremanezumab is available as a 225 mg/1.5 mL single-dose prefilled syringe that is administered subcutaneously.[12] There are two approved dosing schedule for fremanezumab: 225 mg monthly subcutaneous injection, or 675 mg quarterly (every 3 months) which is given as three consecutive 225 mg subcutaneous injections.[12] No specific recommendation regarding dose or frequency is mentioned in the package insert. The recommended site of injections are abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated.[12] For multiple subcutaneous injections, the same body site may be used, but not the exact location of the previous injection.[12] Fremanezumab should not be administered concomitantly with other injectables drugs such as insulin at the same injection site.[12] Hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, can occur within hours and up to 1 month after the injection.[12] If patients miss a dose of fremanezumab, it is recommended that they take it as soon as possible and adjust their schedule according to the date of the last dose.[12]

Cost and Availability

The current wholesale acquisition cost of fremanezumab is $575 per monthly dose and $1,725 per quarterly dose, which totals $6,900 per year of treatment.[17-19] Teva Pharmaceuticals[a] states that patient copay may vary depending on different prescription insurance plans, and it could be as low as $0 for some commercially insured patients.[17] Nevertheless, fremanezumab still has a much higher price tag comparing to other preventive migraine medications such as beta-blockers or anticonvulsants.

Conclusion

Fremanezumab is a newly FDA-approved medication for the preventive treatment of migraine in adults. Presently, it is the first and only selective CGRP receptor antagonist used for migraine prophylaxis that offers monthly and quarterly (i.e. every 3 months) dosing options. Current evidences from clinical trials suggest that fremanezumab is effective at reducing the mean MMD by 1.3-1.5 days in EM and by approximately 1.8-2.1 days in CM. Additionally, fremanezumab is well-tolerated with the most common adverse effect being injection site reactions. Given the poor adherence rate (17-29%) to current migraine treatments, fremanezumab, with its quarterly dosing, represents a potential new option to this unmet medical need. All things considered, fremanezumab has shown to be a promising prophylactic therapy for migraine, especially in patients who have suboptimal response to other preventive medications.

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Emgality® (Galcanezumab): A New Treatment for Preventing Migraines

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In the 2016 Global Burden of Disease study,1.04 billion people had a diagnosis of migraine was ranked among the top ten causes of life with disability in all 195 counties with 1.04 billion patients.[1] This disease affects more than 30 million American adults and accounts for more than 90% of patients with recurrent headache presenting to primary care offices and emergency departments, with three times more women affected by migraine compared to men.[2] Migraine is a neurological disease typically characterized by recurrent unilateral headaches with pulsating quality and moderate to severe intensity. A typical migraine attack consists of three phases: 1.pre-migraine (≤ 72 hours, fatigue, food craving, repetitive yawning,); 2. migraine (4-72 hours, unilateral pain, pulsating pain, moderate to severe pain,); 3.migraine hangover (≤ 24 hours, new or persisting symptoms after migraine pain has resolved).[3] According to the Medical Expenditures Panel Survey, the total unadjusted cost associated with migraine in the U.S. is estimated to be as high as $56 billion annually, yet migraine remains under-recognized and under-treated.[4]

Migraine medication therapy includes acute and preventative treatments. Acute migraine relief medications such as triptans, ergotamines, as well as nonsteroidal anti-inflammatory drugs are used to abort the migraine attack.[5] However, for patients with frequent migraine attacks and for whom abortive treatments are inadequately effective, preventive therapies are recommended, such as divalproex sodium, gabapentin, lamotrigine, oxcarbazepine, and topiramate. Side effects with these treatments such as weight gain, drowsiness, hair thinning, alopecia, tremor, and gastrointerstinal disturbance may lead to their discontinuation or poor compliance.[6]

Although prevention treatments indicated in 39% of patients with migraine, only 13% received it. In addition, up to 68% of patients who use preventive medications stop doing so within 6 months because of insufficient benefit, dissatisfaction with drug, or poor tolerability. [7] There is a significant need for new treatment options with improved efficacy and tolerability.

Emgality® (galcanezumab-gnlm) is a humanized monoclonal antibody that is approved by FDA for preventive treatment of migraines in adults in September 2018. The purpose of this article is to the efficacy and safety data of galcanezumab from clinical trials in the prevention of migraine.

Pharmacology

Mechanism of Action

Galcanezumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the calcitonin gene-related peptide (CGRP) receptor and antagonizes CGRP receptor function. CGRP is distributed throughout the nervous system and it is concentrated at anatomical sites, such as the trigeminovascular system, which are involved in migraine pathophysiology. CGRP concentrations are elevated during acute migraine attacks and may be chronically elevated in patients with chronic migraine. Blocking CGRP or its receptor might treat an acute migraine attack or prevent migraines from occurring. Galcanezumab is an efficacious, selective, competitive CGRP receptor antagonist that binds the receptor and prevents native CGRP ligand binding.[8]

Pharmacokinetics

Galcanezumab administered subcutaneously exhibits linear pharmacokinetics that C_{max} and the area under the concentration time curve from dosing to infinity ($AUC_{(0\rightarrow\infty)}$) were generally dose proportional over the full single dose range (1, 5, 25, 75, 200 and 600 mg). Four consecutive doses of 150 mg administered with a 14-day dosing interval were as predicted from single-dose administration. A 3.5-fold accumulation of drug concentrations was observed after the fourth dose but had not reached steady state.[9] The apparent Vd of galcanezumab is 7.3 L. Galcanezumab is degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG with a clearance rate of 0.008L/h and the elimination half-life was approximately 27 days. The pharmacokinetics of galcanezumab were not affected by age, sex, race or subtypes of migraine spectrum, based on a population pharmacokinetics analysis. Body weight has no clinically relevant effect on the pharmacokinetics of galcanezumab. Renal and hepatic impairment do not expect to affect the pharmacokinetics of galcanezumab. In the clinical studies, creatinine clearance did not affect the pharmacokinetics of galcanezumab in patients with mild or moderate renal impairment. Patients with severe renal impairment (creatinine clearance < 30 mL/min) were not studied. Based on a population pharmacokinetics analysis, bilirubin concentration did not significantly influence the clearance of galcanezumab.[10]

Clinical Trials

One phase II and three phase III studies established galcanezumab safety and efficacy for preventative treatment of migraines. The following section discusses the clinical trials in detail. A summary of results is available in **TABLE 2** and **TABLE 3**. Safety and adverse events are discussed separately and presented in **TABLE 4.**

In all trails, migraine headache was defined as a headache, with or without aura, of ≥ 30 minutes duration with both of the following required features (A and B): A) ≥ 2 of the following characteristics, unilateral location, pulsatile quality; moderate or severe pain intensity; aggravation by or causing avoidance of routine physical activity; B) During headache ≥ 1 of the following: nausea and/or vomiting; photophobia and phonophobia. Migraine headache day (MHD) was defined as a calendar day on which a migraine headache or probable migraine headache occurred. Migraine, both episodic migraine (EM, a frequency of 4 to 14 MHDs per month) and chronic migraine (CM, ≥15 MHDs per month, of which ≥ 8 were MHDs for > 3 months) are associated with medical and psychiatric comorbidities and disability that greatly impact quality of life. The specific signs and symptoms of

Table 1 | Select Galcanezumab Kinetics[9,10]

Parameters	Value
Absorption	
C_{max}	14,650 ng/mL
AUC_{max}	169 days (~6 months)
Distribution	
V_d	~6 L
Metabolism	
Enzymatic proteolysis	Degradation into peptides and amino acids
Elimination	
CL	0.141 L/day
$T_{1/2}$	~31 days

CL = apparent clearance; L = liter; $t^1/_2$ = half-life; T_{max} = median time to maximum concentrations; V_d = volume of distribution

episodic and chronic migraine were defined by International Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 beta guidelines. According to the American Migraine Prevalence and Prevention Study outlined recommended that migraine prevention should be initiated ≥6 MHDs per month. The mean value was defined as the average of months from mixed model repeated measures (MMRM) model. For the measurement of secondary endpoints, the trails used Migraine-Specific Quality of Life Questionnaire Role-function Restrictive Domain (MSQ RF-R). MSQ RFR is a health status instrument that addresses physical and emotional limitations of specific concern to individuals with migraine, consists of 14 items, 0-100 scale with higher scores indicating a better health status and a positive change in scores reflecting functional improvement.[11-15]

PHASE II TRIAL

Skljarevski et al. conducted a double-blind, placebo-controlled randomized clinical trial to assess whether 1 dose once monthly of galcanezumab was superior to placebo for EM prevention. This was a phase 2b study in patients with EM and comprised 4 study periods (SPs) between July 7, 2014 to August, 2015 including: 1) screening and washout (SP1); 2) a prospective baseline period for determining the frequency of MHDs (SP2); 3) double-blind treatment (SP3, month 1,2,3); and 4) a 3-month post-treatment period (SP4). The patient population consisted of males and females aged 18 to 65 years who had a history of EM. Patients were excluded from the study who had failed to respond to ≥ 2 effective migraine prevention treatments.[11]

Patients were randomly allocated in a 2:1:1:1 ration to receive either monthly subcutaneous placebo (n=137) or galcanezumab at doses of 5 mg (n=68), 50 mg (n=68), 120 mg (n=70), or 300 mg (n=67), respectively. Baseline demographic and clinical characteristics were not significantly different between any group. Interventions were administered during office visits. Patients called into electric patient reported outcome interactive voice response system (ePRO) daily to record their headache information. If a patient discontinued the study early during SP3, that patient immediately entered SP4.[11]

During the study, acute migraine treatments were allowed as needed (opioids or barbiturates were not permitted). Concomitant medications allowed included acetaminophen, nonsteroidal anti-inflammatory drugs, aspirin, triptans, corticosteroids (periodic topical or inhaled but not oral or injected), and ergotamines and their derivatives. Preventive treatments were permitted on an individual basis only during SP4.[11]

For the primary endpoint, the mean change from baseline in the number of MHDs at month 3 was different for both galcanezumab 120 mg (-4.3 MHDs, 95% CI, -4.9 to -3.7 MHDs) and galcanezumab 300 mg (-4.3 MHDs; 95% CI, -4.9 to -3.7 MHDs) with placebo (-3.4 MHDs, 95% CI, -3.8 to -2.9 MHDs). The posterior probability of greater improvement (Bayesian analysis) in MHDs with galcanezumab, 120 mg (99.6%; -4.8 MHDs, 90% BCI, -5.4 to -4.2 MHDs) compared with placebo (90% BCI; -3.7 MHDs, -4.1 to -3.2 MHDs) was greater than the specified threshold (95%) for the mean change from baseline in the number of MHDs at month 3.[11]

For the secondary endpoints, there was a significant greater proportion of patients with 50% reduction of MHDs in the 120 mg galcanezumab group (76.5%, n=69) compared with the placebo group (60.9%, n=134). Furthermore, the 50% reduction of MHDs in other dosing groups were 75.4% (5mg galcanezumab, n=65), 65.5% (50 mg galcanezumab, n=68) and 70.1% (300 mg galcanezumab, n=66), respectively.[11]

Functional impact owing to monthly migraine headaches, assessed by Headache Impact Test-6 (HIT-6, a clinical evaluation of the impact of headache on a patient's quality of life, Little or no impact scores ≤ 49; Some impact scores= 50–55. Substantial impact scores = 56–59. Severe impact scores≥ 60) scales was significantly improved by galcanezumab 120 mg (-10.0 points; 95% CI, -12.2 to -7.7 points; P=0.04) compared with placebo (-7.3 points; 95% CI, -8.8 to -5.7 points).[11]

PHASE III TRIALS

EVOLVE-1

The EVOLVE-1 (Evaluation of LY2951742 in the Prevention of Episodic Migraine 1) trial was a double-blind, randomized, placebo-controlled trial comparing galcanezumab vs placebo. Patients were randomly allocated in 2:1:1 to monthly subcutaneous placebo (n=433), glacanezumab 120 mg (n=213) and glacanezumab 240 mg (n=212).[12]

The study design consisted of 4 SPs: 1) initial screening and washout of all migraine preventive treatments (3-45 days); 2) a prospective lead-in (baseline) period (30-40 days) for determining the frequency of MHDs; 3) a double-blind treatment period (month 1, 2,3,4,5 and 6); 4) a 4-month post treatment period (month 7, 8, 9 and 10). Patients used a handheld diary device daily to record their headache information. Patients continued daily-diary entries and could continue to take acute migraine medications (eg, triptans, ergots, nonsteroidal anti-inflammatory drugs, aspirin, and acetaminophen; opioids and barbiturate-containing medications limited to 3 days monthly; and only 1 corticosteriod injection was allowed during any period). During the posttreatment period, patients received no investigational product (IP; either galcanezumab dose or placebo).[12]

Patients were included in the study who were 18 to 65 years of age, have a diagnosis of EM. Patients' enrollment was required sufficient compliance with ePRO defined as ≥ 80% daily diary entries. Patients were excluded due to participation in any other clinical trial or medical research; current using or prior exposure to any CGRP antibody; hypersensitive to multiple drugs or monoclonal antibodies; failure to respond to ≥ 3 migraine preventive treatments. Preventative migraine treatments were discontinued ≥ 30 days prior to visit 2. Botulinum toxin A and B administered in the head or neck area must had been discontinued at least 4

months prior to SP2. Baseline demorgraphics of sex, age, race/ethnicity, and body mass index were similar across groups.[12]

The primary outcome was the overall mean change from baseline in the number of monthly MHDs during the treatment period (month 1 to 6). Galcanezumab 120 mg reduced MHDs by 4.7 days from baseline, a significant reduction compared with placebo (-2.8 MHDs, difference= -1.9 MHDs; 95% CI, -2.5 to -1.4 MHDs). The primary outcome was also significant for galcanezumab 240 mg compared to placebo (240 mg vs placebo, -4.6 vs -2.8 MHDs, difference=-1.8 MHDs; 95% CI, -2.3 to -1.2 MHDs). No comparison between active groups were reported.[12]

The secondary outcome of ≥50% mean reduction from baseline in MHDs was achieved by 62.3% of patients in the galcanezumab 120 mg group (n= 210) compared to 38.6% in the placebo group (OR: 2.6; 95% CI, 2.0 to 3.4). Also 60.9% of patients with galcanezumab 240 mg (n=208) group achieved that as well compared to 38.6% of patients in the placebo group (OR =2.5; 95% CI, 1.9 to 3.2). Galcanezumab treatment statistically improved MSQ RFR scores compared with placebo during month 4 to month 6 (120 mg vs placebo: 32.4 vs 24.7 points, difference= 7.7 points, 95% CI: 5.2 to 10.3 points; 240 mg vs placebo: 32.1 vs 24.7 points, difference= 7.4 points, 95% CI: 4.8 to 10.0).[12]

EVOLVE-2

The EVOLVE-2 was a Phase 3, multicenter, placebo-controlled, double-blind, randomized clinical trial analyzing the efficacy and safety of two dosing regimens of galcanezumab: 120 mg or 240 mg, compared to placebo. The study was composed of 4 SPs: 1) medical examinations and washout of migraine preventive medications for ≥30 days (4 months for onabotulinumtoxin); 2) SP2 established the baseline number of MHDs; 3) SP3 was a 6 month double-blind treatment phase; 4) SP4 was a 4-month post treatment period. Patients were randomly allocated in a 2:1:1 to monthly subcutaneous placebo (n=461), glacanezumab 120 mg (n=213) and glacanezumab 240 mg (n=212).[13]

Patients were included in the study between 18 and 65 years with a diagnosis of migraine with or without aura at least 1 year prior to enrollment, migraine onset prior to age 50 years, 4-14 MHDs, ≥ 2 migraine attacks during SP2, and an 80% compliance rate in using ePRO, and they had to agree to use an acceptable method of birth control during the study and for ≥ 5 months afterwards. Patients were excluded if they had failed treatment with ≥ 3 migraine prevention drugs from different classes or if they were using opioids or barbiturates ≥ twice per month. Other factors included participation in another clinical trial within the past 30 days, prior exposure to any CGRP antibodies, known hypersensitivity to multiple drugs, or presence of any medical or psychiatric illness that would preclude study participation. The baseline characteristics for each treatment group were similar.[13]

The primary outcome was the overall mean change from baseline in the number of monthly MHDs during the treatment period (month 1 to 6). Galcanezumab 120 mg reduced MHDs by 4.3 days from baseline, a significant reduction compared with placebo (-2.3 MHDs, difference= -2.0 MHDs; 95% CI, -2.6 to -1.5 MHDs). The primary outcome was also significant for galcanezumab 240 mg compared to placebo (240 mg vs placebo, -4.2 vs -2.3 MHDs, difference= -1.9 MHDs; 95% CI, -2.4 to -1.4 MHDs).[13] For the secondary outcomes, galcanezumab 120 mg and 240 mg groups experienced ≥ 50% reduction in MHDs compared to the placebo group (59% and 57% vs 36%, P< 0.001). Also galcanezumab 120 mg and 240 mg resulted in significant (P<0.001) reductions in MHDs with acute migraine medication use compared to the placebo group (-3.7 MHDs and -3.6 MHDs vs -1.9 MHDs, P<0.001). Both galcanezumab 120 mg vs placebo (28.5 vs 19.7 points; difference=8.8 points; 95% CI, 6.3 to 11.3) and 240 mg vs placebo (27.0 vs 19.7 points; difference=7.4 points; 95% CI, 4.9 to 9.9) significantly (P< 0.001) improved the means of the MSQ RF-R score averaged over month 4 to month 6.[13]

REGAIN

REGAIN is a phase 3 study with a 3-month double-blind, placebo-controlled treatment phase and 9-month open-label extension to evaluate the efficacy and safety of galcanezumab in the preventive treatment of CM. Eligible patients were randomized 2:1:1 to receive monthly subcutaneous injections of placebo (n= 558), galcanezumab 120 mg (with a 240-mg loading dose, n=278), or galcanezumab 240 mg (n=277) for the 3-month double-blind period.[14]

Patients were included in the study if they were between 18 to 65 years at screening with a diagnosis of CM and migraine onset before 50 years of age. Patients had to have ≥ 15 headaches days per month, of which ≥ 8 were migraine, for > 3 months before screening and as assessed by the ePRO diary during the 1-month prospective baseline period. Patients also needed ≥ 1 headache-free day per month within 3 months before screening and during baseline. Patients had to be ≥ 80% compliant with ePRO daily diary entries. Patients were excluded with persistent daily headache, cluster headache, head or neck trauma within the past 6 months, possible posttraumatic headache, or primary headache other than CM. Patients could not have previously failed to respond to adequate trials of migraine preventives from ≥ 3 different medication classes. Patients could not take therapeutic antibodies during or within 1 year before the study and could not have serious or unstable medical or psychiatric conditions, history of stroke or substance abuse or dependence in the past year or be at risk for acute cardiovascular events based on history or ECG findings. Demographic and baseline characteristics were generally similar across the groups.[14]

For the primary endpoint, the mean change across month 1 to month 3 of galcanezumab 120 mg demonstrated a significant reduction in MHDs from baseline compared with placebo (-4.8 vs -2.7 MHDs, difference = -2.1 MHDs; 95% CI, -2.9 to -1.3 MHDs); galcanezumab 240 mg vs placebo (-4.6 vs -2.7 MHDs, difference= -1.9 MHDs; 95% CI: -2.7 to -1.1 MHDs) (both P<0.001).[14]

Secondary endpoints included the proportion of patients with 50% reduction from baseline in MHDs. There were greater proportions of patients with 50% reduction in MHD in the galcanezumab 120 mg group (n=273) compared to the placebo group (n=538) across month 1 to 6 (27.6% vs 15.4%, OR =2.1; 95% CI, 1.6 to 2.8) and 240 mg (n=274) vs placebo (27.5% vs 15.4%, OR =2.1; 95% CI, 1.6 to 2.8). Also Galcanezumab treatment statistically improved the mean change from baseline in MSQ RF-R, and the scores compared with placebo during month 1 to 3 (120 mg vs placebo: 21.8 vs 16.8 points, difference= 5.0 points, 95% CI, 2.1 to 8.0 points; and 240 mg vs placebo: 23.1 vs 16.8 points, difference= 6.3 points, 95% CI, 3.0 to 9.6) (both P< 0.001).[14]

Safety

The most common adverse events (AEs, incidence ³ 2% for galcanezumab and at least 2% greater than placebo) reported for galcanezumab were injection site pain, upper respiratory tract

Table 2 | Summary of Galcanezumab Clinical Trial Primary Outcomes

Trial	Intervention	Primary Outcome	Results
Phase 2 Skljarevski et al[12]	Galcanezumab 120 (n=69) subQ monthly Galcanezumab 300 mg (n=66) subQ montly Placebo (n=134) subQ monthly	Mean change in MHDs from baseline during the last 4-weeks of a 12-week trial	**120 mg vs placebo:** -4.8 vs -3.7 MHDs Difference: -1.1 MHDs (95% CI: -2.0 to -0.3) **300 mg vs placebo:** -4.3 vs -3.7 MHDs Difference: -0.6 MHDs (95% CI: -1.5 to 0.2)
EVOLVE-1[13]	Galcanezumab 120 mg subQ monthly (n=210) Galcanezumab 240 mg subQ monthly (n=208) Placebo (n=425) subQ monthly	Mean change in MHDs from baseline in a 6-month trial (month 1 to 6)	**120 mg vs placebo:** -4.7 vs -2.8 MHDs Difference: -1.9 MHDs (95% CI: -2.5 to -1.4) **240 mg vs placebo:** -4.6 vs -2.8 MHDs Difference: -1.8 MHDs (95% CI: -2.3 to -1.2)
EVOLVE-2[14]	Galcanezumab 120 mg subQ monthly (n=226) Galcanezumab 240 mg subQ monthly (n=220) Placebo (n=450) subQ monthly	Mean change in MHDs from baseline in a 6-month trial (month 1 to 6)	**120 mg vs placebo:** -4.3 vs -2.3 MHDs Difference: -2.0 MHDs (95% CI: -2.6 to -1.5) **240 mg vs placebo:** -4.2 vs -2.3 MHDs Difference: -1.9 MHDs (95% CI: -2.4 to -1.4)
REGAIN[15]	Galcanezumab 120 mg subQ monthly (n= 273) Galcanezumab 240 mg subQ monthly (n=274) Placebo (n=538) subQ monthly	Mean change in MHDs from baseline in a 3-month trial (month 1 to 3)	**120 mg vs placebo:** -4.8 vs -2.7 MHDs Difference: -2.1 MHDs (95% CI: -2.9 to -1.3) **240 mg vs placebo:** -4.6 vs -2.7 MHDs Difference: -1.9 MHDs (95% C, -2.7 to -1.1)

95% CI= 95 confidence interval**; mg=** milligram**; MHDs=**migraine headache days**; subQ=**subcutaneous

Table 3 | Summary of Galcanezumab Clinical Trial Secondary Outcomes

Trial	Intervention	Secondary Outcome	Results
Phase 2 Skljarevski et al[12]	Galcanezumab 120 mg subQ monthly (n=62) Placebo (n=126) subQ monthly	Proportion achieving ≥ 50% mean reduction from baseline in MHDs at the last 28-day period of the 12-week trial	**120 mg vs placebo:** 75.8% vs 61.9%
EVOLVE-1[13]	Galcanezumab 120 mg subQ monthly (n=210) Galcanezumab 240 mg subQ monthly (n=208) Placebo (n=425)	Proportion achieving ≥ 50% mean reduction from baseline in MHDs in the 6-month trial (month 1 to 6)	**120 mg vs placebo:** 62.3% vs 38.6% OR: 2.6 (95% CI: 2.0 to 3.4) **240 mg vs placebo:** 60.9% vs 38.6% OR: 2.5 (95% CI: 1.9 to 3.2)
	Galcanezumab 120 mg subQ monthly (n=207) Galcanezumab 240 mg subQ monthly (n=202) Placebo (n=419)	The mean change from baseline in MSQ RF-R score[a] (month 4 to month 6)	**120 mg vs placebo:** 32.4 vs 24.7 points OR: 7.7 (95% CI: 5.2 to 10.3) **240 mg vs placebo:** 32.1 vs 24.7 points OR: 7.4 points (95% CI: 4.8 to 10.0)
EVOLVE-2[14]	Galcanezumab 120 mg subQ monthly (n=226) Galcanezumab 240 mg subQ monthly (n=220) Placebo (n=450)	Proportion achieving ≥ 50% mean reduction from baseline in MHDs in the 6-month trial (month 1 to 6)	**120 mg vs placebo:** 59.3% vs 36% OR: 2.6 (95% CI: 2.0 to 3.3) **240 mg vs placebo:** 56.5% vs 36% OR: 2.3 (95% CI: 1.8 to 3.0)

Table 3 | Summary of Galcanezumab Clinical Trial Secondary Outcomes (Continued)

Trial	Intervention	Secondary Outcome	Results
EVOLVE-2[14]	Galcanezumab 120 mg subQ monthly (n=226) Galcanezumab 240 mg subQ monthly (n=219) Placebo (n=443)	The mean change from baseline in MSQ RF-R score[a] from month 4 to month 6	**120 mg vs placebo:** 28.5 vs 19.7 points Difference: 8.8 points (95% CI: 6.3 to 11.3) **240 mg vs placebo:** 27.0 vs 19.7 points Difference: 7.4 points (95% CI: 4.9 to 9.9)
REGAIN[15]	Galcanezumab 120 mg subQ monthly (n=273) Galcanezumab 240 mg subQ monthly (n=274) Placebo (n=538)	Proportion achieving ≥ 50% mean reduction from baseline in MHDs in the 3-month trial (month 1 to 3)	**120 mg vs placebo:** 27.6% vs 15.4% OR: 2.1 (95% CI: 1.6 to 2.8) **240 mg vs placebo:** 27.5% vs 15.4% OR: 2.1 (95% CI: 1.6 to 2.8)
	Galcanezumab 120 mg subQ monthly (n=252) Galcanezumab 240 mg subQ monthly (n=253) Placebo (n=494)	The mean change from baseline in MSQ RF-R[a] score at month 3 in a 3-month trial	**120 mg vs placebo:** 21.8 vs 16.8 points Difference: 5.1 points (95% CI: 2.1 to 8.0) **240 mg vs placebo:** 23.1 vs 16.8 points Difference: 6.3 points (95% CI: 3.0 to 9.6)

a: **MSQ RF-R** = Migraine-Specific Quality of Life Questionnaire Role-function Restrictive Domain, a health status instrument that addresses physical and emotional limitations of specific concern to individuals with migraine, consists of 14 items, 0-100 scale with higher scores indicating a better health status and a positive change in scores reflecting functional improvement

95% CI=95% confidence interval; **mg**=milligram; **MHDs**=migraine headache days; ; **OR**= odds ration; **subQ**=subcutaneous

infection, nasopharyngitis, nausea, fatigue, back pain and urinary tract infection. In EVOLVE-1, EVOLVE-2 and REGAIN trials, the occurrence of any AEs was similar between placebo and galcanezumab groups (Table 4).[12-14] In the phase 2 trial conducted by Skljarevski et al, injection-site pain was more frequent in galcenezumab dose groups than placebo, but the injection site pain was self-limited, usually resolved during the day of injection and was reported as mild to moderate by all patients.[11] In EVOLVE-1 trail, 11 patients (5 in the placebo group and 6 in the galcanezumab 120 mg group) reported a total of 12 serious AEs. But no patients in the 240 mg dose group reported a serious AEs. The percentage of patients who reported ≥1 TEAE was greater in the galcanezumab dose groups but none was significant (120 mg galcanezumab vs 240 mg galcanezumab vs placebo, 65.5% vs 67.7% vs 60.4%). Injection site pain was the most frequently reported TEAE among groups but there were no significant differences (120 mg galcanezumab vs 240 mg galcanezumab vs placebo, 16% vs 20.5% vs 17.4%).[12] In EVOLVE-2 trial, TEAEs were reported

by 147 (65%) and 163 (71.5%) of the patients receiving galcanezumab 120 and 240 mg, and by 287 (62.3%) placebo patients. The percentage of serious AEs, which were 1.1%, 2.2% and 3.1% for placebo, galcanezumab 120 mg and galcanezumab 240 mg groups, did not differ significantly.[13] In REGAIN trial, incidences of individual treatment-emergent AEs (TEAEs) were low, with the most common being injection-site pain (6-7%, n=17-20 in galcanezumab groups vs 4%, n=24 in placebo group). In REGAIN trail, there were 10 serious AEs with 4 (0.7%) reported in the placebo group, 1(0.4%) in the galcanezumab 120 mg (colon cancer) and 5 (1.8%) in the galcanezumab 240 mg group (hypokalemia, nephrolithiasis, acute pancreatitis, pulmonary embolism and renal colic).[14]

Dosing and Administration

Galcanezumab is a sterile clear to opalescent, colorless to slightly yellow to slightly brown solution available as a 120 mg/mL in a single-dose prefilled pen and a 120 mg/mL in a single-dose prefilled syringe. The recommended dosage of galcanezumab is 240 mg (two consecutive subcutaneous injections of 120 mg each) once as a loading dose, followed by monthly doses of 120 mg injected subcutaneously. If a dose of galcanezumab is missed, administer as soon as possible. Thereafter, galcanezumab can be scheduled monthly from the date of the last dose. For use in specific populations: 1) pregnancy, there are no adequate data on the developmental risk associated with the use of galcanezumab in pregnant women. Administration of galcanezumab to rats and rabbits during the period of organogenesis or to rats throughout pregnancy and lactation at plasma exposures greater than that expected clinically did not result in adverse effects on development; 2) lactation, there are no data on the presence of galcanezumab in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Emgality and any potential adverse effects on the breastfed infant from Emgality or from the underlying maternal condition; 3) pediatric use, safety and effectiveness in pediatric patients have not been established; 4) geriatric use, clinical studies of Emgality did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.[10]

Discussion

The clinical trials for galcanezumab report significant reductions in the mean change from baseline in MHDs by approximately 1 to 2.5 days per month for galcanezumab 120 mg and by about 1.2 to 2.5 days per month for galcanezumab 240 mg compared to placebo. The reduction among patients using galcanezumab during 6 months of treatment can translate to the equivalent of approximately 8 weeks of additional migraine-free days over the course of a year. It was found in the EVOLVE-1, EVOLVE-2 and REGAIN trails, AEs in the galcanezumab 240 mg group were always higher than galcanezumab 120 mg group, respectively (32.73% vs 30.58%, 38.16% vs 34.51% and 14.89% vs 13.55%) with very little additional benefit. The loading dose recommended at first dose was used in the REGAIN trail, which was likely to help patients reach steady state faster and minimize the increased AD seen with the higher doses. Compared to current migraine preventative therapies, the side effect profile ap-

Table 4 | Select Galcanezumab Adverse Events from Clinical Trials

Trial	Intervention	Any AE	Serious AE	Injection Pain
Skljarevski et al[12] Phase 2	Placebo (n=137)	16.8%	0	2.92%
	Galcanezumab 120 mg (n=70)	32.9%	1.4%	14.3%
EVOLVE-1[13]	Placebo (n=432)	29.9%	1.2%	17.4%
	Galcanezumab 120 mg (n=206)	30.6%	2.9%	16.0%
	Galcanezumab 240 mg (n=220)	32.7%	0	20.5%
EVOLVE-2[14]	Placebo (n=461)	32.5%	1.1%	8.5%
	Galcanezumab 120 mg (n=226)	34.5%	2.2%	9.3%
	Galcanezumab 240 mg (n=228)	38.2%	3.1%	8.8%
REGAIN[15]	Placebo (n=558)	9.5%	1.3%	4.3%
	Galcanezumab 120 mg (n=273)	13.6%	1.8%	6.2%
	Galcanezumab 240 mg (n=282)	14.9%	2.8%	7.1%

95% CI= 95 confidence interval; **mg=** milligram; **MHDs=**migraine headache days; **subQ=**subcutaneous

pears to be better with most AE consistent with only injection site reactions.[11-14]

Furthermore, all trails excluded patients with previous failures with two to three FDA approved preventative treatment therapies for migraines. Restrictions in the exclusion criteria may limit the generalizability of the results. Patients may prefer to exhaust all oral forms of therapy before trying injectable medications. Nevertheless, further study is needed to evaluate the benefits and risks of the use of galcanezumab in these patient population.

Although the results of four clinical trials were shown to be significant, the clinicians still need to make individualized decisions for each patient. For example, Nicoles et al. reported that the patients with EM or CM who experienced worsening in the number of MHDs following initial treatment responded with continued treatment, most do not show substantial reduction in MHDs, then overall benefit of therapy should be determined collaboratively between the patient and physician.[15] Considering the cost, Emgality is currently priced in the U.S. at $575 once-monthly, or $6,900 annually. Eli lily provide Emgality (galcanezumab) for up to 12 months free to all eligible patients with commercial insurance.

Conclusion

Galcanezumab is the monoclonal antibody that targets and anatagonizes the CGRP receptor and FDA approved for migraine preventative therapy. Clinical trials have demonstrated that galcanezumab 120 mg subcutaneous monthly significantly reduces MHDs in patients with EM or CM. Galcanezumab is generally well-tolerated by patients but cost will likely be the greatest limitation to clinical use as its efficacy is likely at least as effective as current migraine preventative treatments.

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