1 PRODUCT NAME

Emgality Solution for Injection in Pre-filled Pen 120 mg/ml

Emgality Solution for Injection in Pre-filled Syringe 100 mg/ml

2 INDICATIONS AND USAGE

2.1 Migraine

Emgality Solution for Injection in Pre-filled Pen 120 mg/ml is indicated for the preventive treatment of migraine in adults.

2.2 Episodic Cluster Headache

Emgality Solution for Injection in Pre-filled Syringe 100mg/ml is indicated for the reduction in the frequency of attacks in adults with episodic cluster headache.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dosing for Migraine

The recommended dosage of Emgality is 240mg (two consecutive subcutaneous injections of 120mg each) once as a loading dose, followed by monthly doses of 120mg injected subcutaneously.

If a dose of Emgality is missed, administer as soon as possible. Thereafter, Emgality can be scheduled monthly from the date of the last dose.

3.2 Recommended Dosing for Episodic Cluster Headache

The recommended dosage of Emgality is 300 mg galcanezumab injected once monthly subcutaneously (three consecutive subcutaneous injections of 100 mg each) at the onset of the cluster period.

The treatment benefit should be assessed after the first dose of treatment. Any further decision to continue once monthly treatment during the current cluster period or to initiate treatment for subsequent cluster periods should be based on individual patient basis and clinical judgement *[see 13.2 Clinical Studies]*. If further dosing is warranted, galcanezumab should be administered no more than once monthly during a cluster period, and should not be used after the end of a cluster period.

Patients should be instructed to inject a missed dose as soon as possible and inject the next dose, if required, a month from the date of administering the missed dose. If a patient administers a partial dose (injects only 1 or 2 of the syringes), they should be instructed to inject the missed syringes(s) as soon as possible and then inject the next complete dose, if required, a month from the date of administering the missed syringe(s).

3.3 Important Administration Instructions

Emgality is for subcutaneous use only.

Emgality is intended for patient self-administration. Prior to use, provide proper training to patients and/or caregivers on how to prepare and administer Emgality using the single-dose pre-filled pen or single-dose pre-filled syringe, including aseptic technique *[see How Supplied (14.1)/Storage and Handling (14.3) and Instructions for Use]*:

- Protect Emgality from direct sunlight.
- Prior to subcutaneous administration, allow Emgality to sit at room temperature up to 30°C for 30 minutes. Do not warm by using a heat source such as hot water or a microwave.
- Do not shake the product.
- Inspect Emgality visually for particulate matter and discoloration prior to administration, whenever solution and container permit *[see Dosage Forms and Strengths (4) and How Supplied (14.1)/Storage and Handling (14.3)]*. Do not use Emgality if it is cloudy or there are visible particles.
- Administer Emgality in the abdomen, thigh, back of the upper arm or buttocks subcutaneously. Do not inject into areas where the skin is tender, bruised, red or hard.
- Both the pre-filled pen and pre-filled syringe are single-dose and delivers the entire contents.

4 DOSAGE FORMS AND STRENGTHS

Emgality is a sterile, clear to opalescent, preservative-free, and colorless to slightly yellow to slightly brown solution available as follows:

- Injection: 120 mg/mL in a single-dose prefilled pen
- Injection: 100 mg/mL in a single-dose prefilled syringe

5 CONTRAINDICATIONS

Emgality is contraindicated in patients with serious hypersensitivity to galcanezumab or to any of the excipients *[see Warnings and Precautions (6)]*.

6 WARNINGS AND PRECAUTIONS

6.1 Hypersensitivity Reactions

Hypersensitivity reactions, including dyspnea, urticaria and rash, have been reported with Emgality in clinical studies and the postmarketing setting. Cases of anaphylaxis and angioedema have also been reported in the postmarketing setting. If a serious or severe hypersensitivity reaction occurs, discontinue administration of Emgality and initiate appropriate therapy *[see Contraindications (5), Adverse Reactions (7) and Patient Counseling Information (15)]*. Hypersensitivity reactions can occur days after administration and may be prolonged.

7 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see Contraindications (5) and Warnings and Precautions (6)]*

7.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

Migraine

The safety of Emgality has been evaluated in 2,586 patients with migraine who received at least one dose of Emgality, representing 1,487 patient-years of exposure. Of these, 1,920 patients were exposed to Emgality once monthly for at least 6 months and 526 patients were exposed for 12 months.

In placebo-controlled clinical studies (Studies 1, 2 and 3), 705 patients received at least one dose of Emgality 120mg once monthly and 1451 patients received placebo, during 3 months or 6 months of double-blind treatment *[see Clinical Studies (13.1)]*. Of the Emgality-treated patients, approximately 85% were female, 77% were white and the mean age was 41 years at study entry.

The most common adverse reaction was injection site reactions. In Studies 1, 2 and 3, 1.8% of patients discontinued double-blind treatment because of adverse events. Table 1 summarizes the adverse reactions that occurred within up to 6 months of treatment in the migraine studies.

Table 1: Adverse Reactions Occurring in Adults with Migraine with an Incidence of at least 2% for Emgality and at least 2% Greater than Placebo (up to 6 Months of Treatment) in Studies 1, 2 and 3

Adverse Reaction	Emgality 120mg Monthly (N=705) %	Placebo Monthly (N=1,451) %
Injection site reactions[a]	18	13

[a] Injection site reactions include multiple related adverse event terms, such as injection site pain, injection site reaction, injection site erythema and injection site pruritus.

Adverse reactions that occurred at an incidence of 1 % or less are constipation, pruritus, urticaria and vertigo.

Episodic Cluster Headache

Emgality was studied for up to 2 months in a placebo-controlled trial in patients with episodic cluster headache (Study 4) *[see Clinical Studies (13.2)]*. A total of 106 patients were studied (49 on Emgality and 57 on placebo). Of the Emgality-treated patients, approximately 84% were male, 88% were white, and the mean age was 47 years at study entry. Two Emgality-treated patients discontinued double-blind treatment because of adverse events.

In patients with episodic cluster headache treated with Emgality 300 mg monthly, the most common adverse drug reaction was injection site reactions (16%), and less frequent adverse reactions (≤2%) included constipation and vertigo. Injection site reactions included multiple preferred terms such as injection site pain, injection site swelling, injection site discoloration, injection site erythema, and injection site urticaria.

7.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease.

For these reasons, comparison of the incidence of antibodies to galcanezumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of Emgality has been evaluated using an in vitro immunoassay for the detection of binding anti-galcanezumab antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro ligand-binding immunoassay was performed to detect neutralizing antibodies.

In controlled studies with Emgality up to 6 months (Study 1, Study 2 and Study 3), the incidence of anti-galcanezumab antibody development was 4.8% (33/688) in patients receiving Emgality once monthly (32 out of 33 of whom had *in vitro* neutralizing activity). With 12 months of treatment in an open-label study, up to 12.5% (16/128) of Emgality-treated patients developed anti-galcanezumab antibodies, most of whom tested positive for neutralizing antibodies.

Although anti-galcanezumab antibody development was not found to affect the pharmacokinetics, safety or efficacy of Emgality in these patients, the available data are too limited to make definitive conclusions.

7.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of EMGALITY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to EMGALITY exposure.

Immune System Disorders — Anaphylaxis, angioedema [*see Contraindications (5) and Warnings and Precautions (6.1)]. Skin and Subcutaneous Tissue Disorders* — Rash.

7.4 Overdose

Doses up to 600 mg have been administered subcutaneously to humans without dose-limiting toxicity. In case of an overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

7.5 Effects on the Ability to Drive and Use Machines

There are no known effects on the ability to drive or use machines associated with the use of galcanezumab.

8 INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

No drug interaction studies were conducted. No pharmacokinetic drug interactions are expected based on the characteristics of galcanezumab.

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of Emgality 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 *(see Animal Data)*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively. The estimated rate of major birth defects (2.2% - 2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia during pregnancy.

Data

Animal Data

When galcanezumab was administered to female rats by subcutaneous injection in two studies (0, 30, or 100 mg/kg; 0 or 250 mg/kg) prior to and during mating and continuing throughout organogenesis, no adverse effects on embryofetal development were observed. The highest dose tested (250 mg/kg) was associated with a plasma exposure ($C_{ave, ss}$) 38 or 18 times that in humans at the recommended human dose (RHD) for migraine (120mg) or episodic cluster headache (300mg), respectively. Administration of galcanezumab (0, 30, or 100 mg/kg) by subcutaneous injection to pregnant rabbits throughout the period of organogenesis produced no adverse effects on embryofetal development. The higher dose tested was associated with a plasma $C_{ave, ss}$ 64 or 29 times that in humans at 120mg or 300mg, respectively.

Administration of galcanezumab (0, 30, or 250 mg/kg) by subcutaneous injection to rats throughout pregnancy and lactation produced no adverse effects on pre- and postnatal development. The higher dose tested was associated with a plasma $C_{ave, ss}$ 34 or 16 times that in humans at 120mg or 300mg, respectively.

9.2 Lactation

Risk Summary

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.

9.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

9.4 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 DESCRIPTION

Galcanezumab is a humanized IgG4 monoclonal antibody specific for calcitonin-gene related peptide (CGRP) ligand. Galcanezumab is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. Galcanezumab is composed of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy chains and has an overall molecular weight of approximately 147 kDa.

Emgality is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution available in a single-dose pre-filled pen or pre-filled syringe. Emgality is supplied in a 1ml single-dose pre-filled pen to deliver 120mg of galcanezumab or a 1ml single-dose pre-filled syringe to deliver 100mg of galcanezumab. Each ml of solution contains 100mg or 120mg of galcanezumab; L-histidine (0.5mg), L-histidine hydrochloride monohydrate (1.5mg), polysorbate 80 (0.5mg), sodium chloride (8.8mg); water for injection. The pH range is 5.3 - 6.3.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Galcanezumab is a humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the receptor.

11.2 Pharmacodynamics

Pharmacotherapeutic group: analgesics, other antimigraine preparations, ATC code: N02CX08

There are no relevant data on the pharmacodynamic effects of galcanezumab.

11.3 Pharmacokinetics

Galcanezumab exhibits linear pharmacokinetics and exposure increases proportionally with doses between 1 and 600mg.

A loading dose of 240mg achieved the serum galcanezumab steady-state concentration after the first dose. A dose of 300 mg monthly would achieve steady-state concentration after the fourth dose. The time to maximum concentration is 5 days and the elimination half-life is 27 days.

There was no difference in pharmacokinetic parameters between healthy volunteers, patients with episodic or chronic migraine, and patients with episodic cluster headache.

Absorption

Following a subcutaneous dose of galcanezumab, the time to maximum concentration was about 5 days.

Injection site location did not significantly influence the absorption of galcanezumab.

Distribution

The apparent volume of distribution (V/F) of galcanezumab was 7.3L (34% Inter Individual Variability [IIV]).

Metabolism and Elimination

Galcanezumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

The apparent clearance (CL/F) of galcanezumab was 0.008 L/h and the elimination half-life of galcanezumab was approximately 27 days.

Specific Populations

Age, Sex, Weight, Race, Ethnicity

The pharmacokinetics of galcanezumab were not affected by age, sex, race, subtypes of migraine spectrum (episodic or chronic migraine), or headache diagnosis (migraine vs. episodic cluster headache) based on a

population pharmacokinetics analysis. Body weight has no clinically relevant effect on the pharmacokinetics of galcanezumab.

Patients with Renal or Hepatic Impairment

Renal and hepatic impairment are not expected to affect the pharmacokinetics of galcanezumab. Population pharmacokinetic analysis of integrated data from the galcanezumab clinical studies revealed that 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) have not been studied. Based on a population PK analysis, bilirubin concentration did not significantly influence the CL/F of galcanezumab.

No dedicated clinical studies were conducted to evaluate the effect of hepatic impairment or renal impairment on the pharmacokinetics of galcanezumab.

Drug Interaction Studies

P450 Enzymes

Galcanezumab is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers or inhibitors of cytochrome P450 enzymes are unlikely.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of galcanezumab has not been assessed.

Mutagenesis

Genetic toxicology studies of galcanezumab have not been conducted.

Impairment of Fertility

When galcanezumab (0, 30 or 250 mg/kg) was administered to male rats by subcutaneous injection prior to and during mating, no adverse effects on fertility was observed. The higher dose tested was associated with a plasma exposure ($C_{ave, ss}$) 8 or 4 times that in humans at the recommended human dose (RHD) for migraine (120mg) or episodic cluster headache (300mg), respectively. When galcanezumab was administered to female rats by subcutaneous injection in two studies (0, 30 or 100 mg/kg; 0 or 250 mg/kg) prior to and during mating and

continuing throughout organogenesis, no adverse effects on fertility were observed. The highest dose tested (250 mg/kg) was associated with a plasma $C_{ave,\ ss}$ 38 or 18 times that in humans at 120mg or 300mg, respectively.

13 CLINICAL STUDIES

13.1 Migraine

The efficacy of Emgality was evaluated as a preventive treatment of episodic or chronic migraine in three multicenter, randomized, double-blind, placebo-controlled studies: two 6-month studies in patients with episodic migraine (Studies 1 and 2) and one 3-month study in patients with chronic migraine (Study 3).

Episodic Migraine

Study 1 (NCT02614183) and Study 2 (NCT02614196) included adults with a history of episodic migraine (4 to 14 migraine days per month). All patients were randomized in a 1:1:2 ratio to receive once-monthly subcutaneous injections of Emgality 120mg, Emgality 240mg or placebo. All patients in the 120mg Emgality group received an initial 240mg loading dose. Patients were allowed to use acute headache treatments, including migraine-specific medications (i.e., triptans, ergotamine derivatives), NSAIDs and acetaminophen during the study.

The studies excluded patients on any other migraine preventive treatment, patients with medication overuse headache, patients with ECG abnormalities compatible with an acute cardiovascular event and patients with a history of stroke, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, deep vein thrombosis or pulmonary embolism within 6 months of screening.

The primary efficacy endpoint for Studies 1 and 2 was the mean change from baseline in the number of monthly migraine headache days over the 6-month treatment period. Key secondary endpoints included response rates (the mean percentages of patients reaching at least 50%, 75% and 100% reduction from baseline in the number of monthly migraine headache days over the 6-month treatment period), the mean change from baseline in the number of monthly migraine headache days with use of any acute headache medication during the 6-month treatment period and the impact of migraine on daily activities, as assessed by the mean change from baseline in the average Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) Role Function-Restrictive domain score during the last 3 months of treatment (Months 4 to 6). Scores are scaled from 0 to 100, with higher scores indicating less impact of migraine on daily activities.

In Study 1, a total of 858 patients (718 females, 140 males) ranging in age from 18 to 65 years, were randomized. A total of 703 patients completed the 6-month double-blind phase. In Study 2, a total of 915 patients (781 female, 134 male) ranging in age from 18 to 65 years, were randomized. A total of 785 patients completed the 6-month double-blind phase. In Study 1 and Study 2, the mean migraine frequency at baseline was approximately 9 migraine days per month and was similar across treatment groups.

Emgality 120mg demonstrated statistically significant improvements for efficacy endpoints compared to placebo over the 6-month period, as summarized in Table 2. Emgality treatment with the 240mg once-monthly dose showed no additional benefit over the Emgality 120mg once-monthly dose.

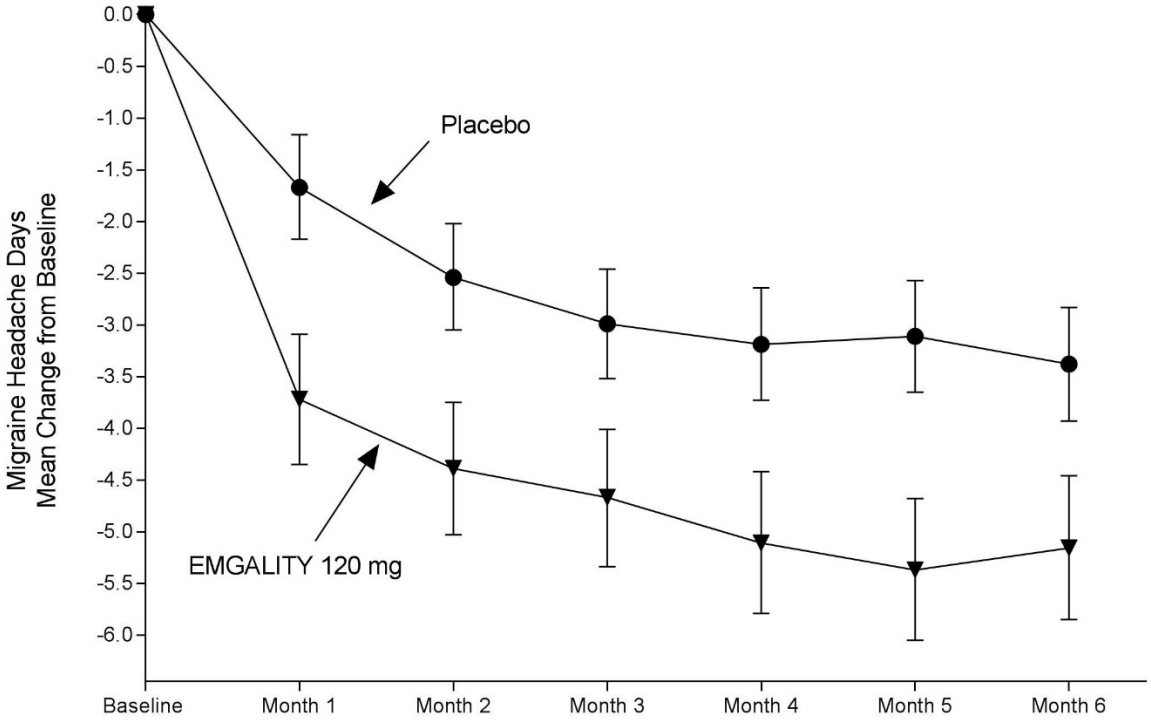
Table 2: Efficacy Endpoints in Studies 1 and 2

	Study 1		Study 2	
	Emgality 120mg N = 210	Placebo N = 425	Emgality 120mg N = 226	Placebo N = 450
Monthly Migraine Headache Days (over Months 1 to 6)				
Baseline migraine headache days	9.2	9.1	9.1	9.2
Mean change from baseline	-4.7	-2.8	-4.3	-2.3
Difference from placebo[a]	-1.9		-2.0	
≥50% Migraine Headache Days Responders (over Months 1 to 6)				
% Responders [a]	62%	39%	59%	36%
≥75% Migraine Headache Days Responders (over Months 1 to 6)				
% Responders [a]	39%	19%	34%	18%
100% Migraine Headache Days Responders (over Months 1 to 6)				
% Responders [a]	16%	6%	12%	6%
Monthly Migraine Headache Days that Acute Medication was Taken (over Months 1 to 6)				
Mean change from baseline (days) [a]	-4.0	-2.2	-3.7	-1.9
MSQ Role Function-Restrictive Domain Score (over Months 4 to 6)				
Baseline	51.4	52.9	52.5	51.4
Mean change from baseline[b]	32.4	24.7	28.5	19.7
Difference from placebo [a]	7.7		8.8	

[a] $p<0.001$

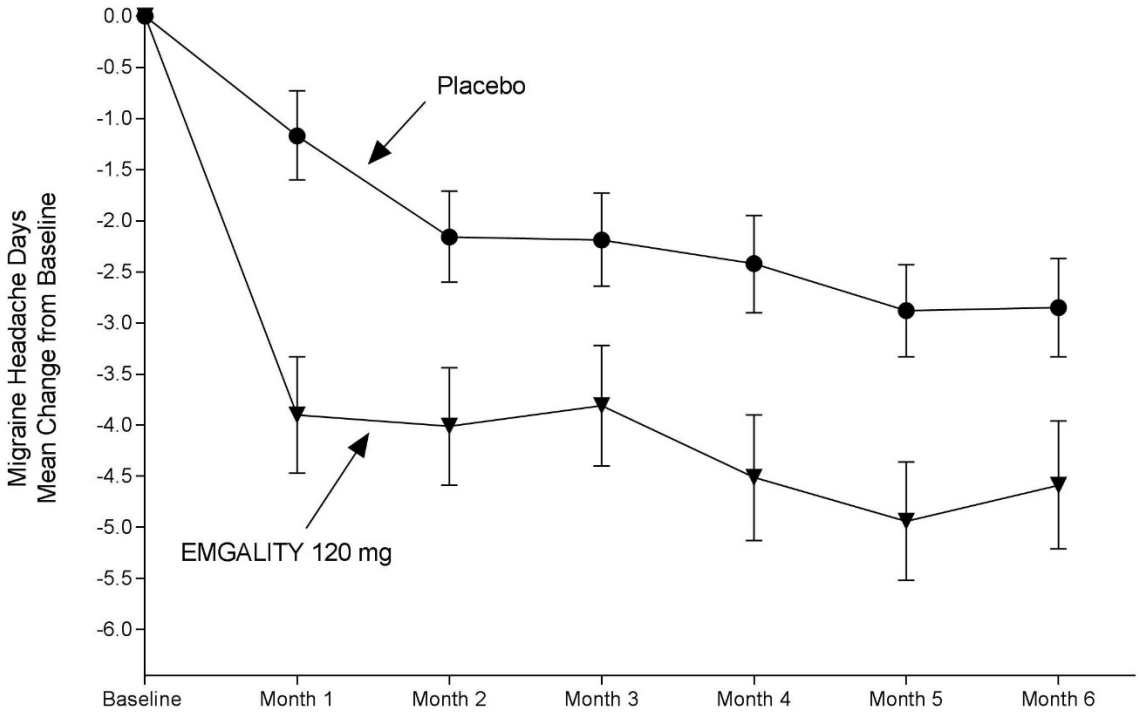
[b] N = 189 for Emgality 120mg and N = 377 for placebo in Study 1; N = 213 for Emgality 120mg and N = 396 for placebo in Study 2.

Figure 1: Change from Baseline in Monthly Migraine Headache Days in Study 1[a]



[a] Least-square means and 95% confidence intervals are presented.

Figure 2: Change from Baseline in Monthly Migraine Headache Days in Study 2[a]



[a] Least-square means and 95% confidence intervals are presented.

Figure 3 shows the distribution of change from baseline in the mean number of monthly migraine headache days in bins of 2 days, by treatment group, in Study 1. A treatment benefit over placebo for Emgality is seen across a range of changes from baseline in monthly migraine headache days.

Figure 3: Distribution of Change from Baseline in Mean Monthly Migraine Headache Days over Months 1 to 6 by Treatment Group in Study 1

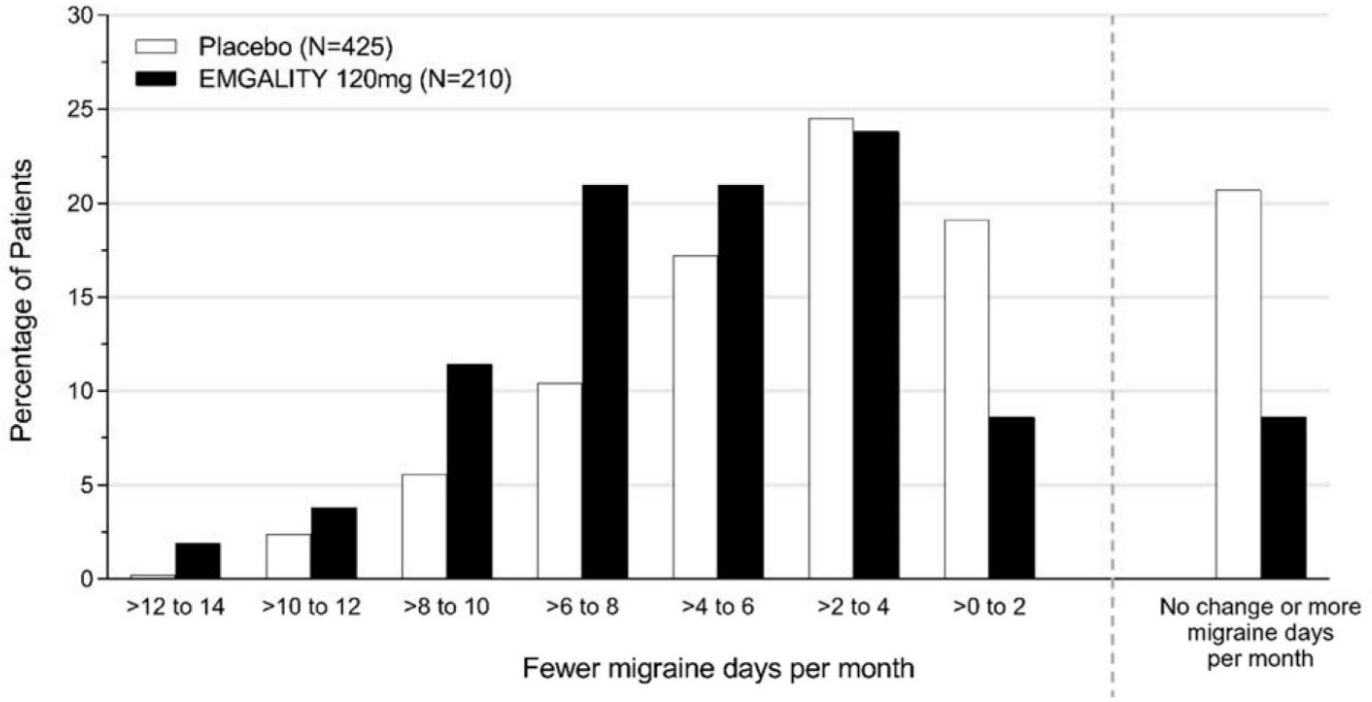
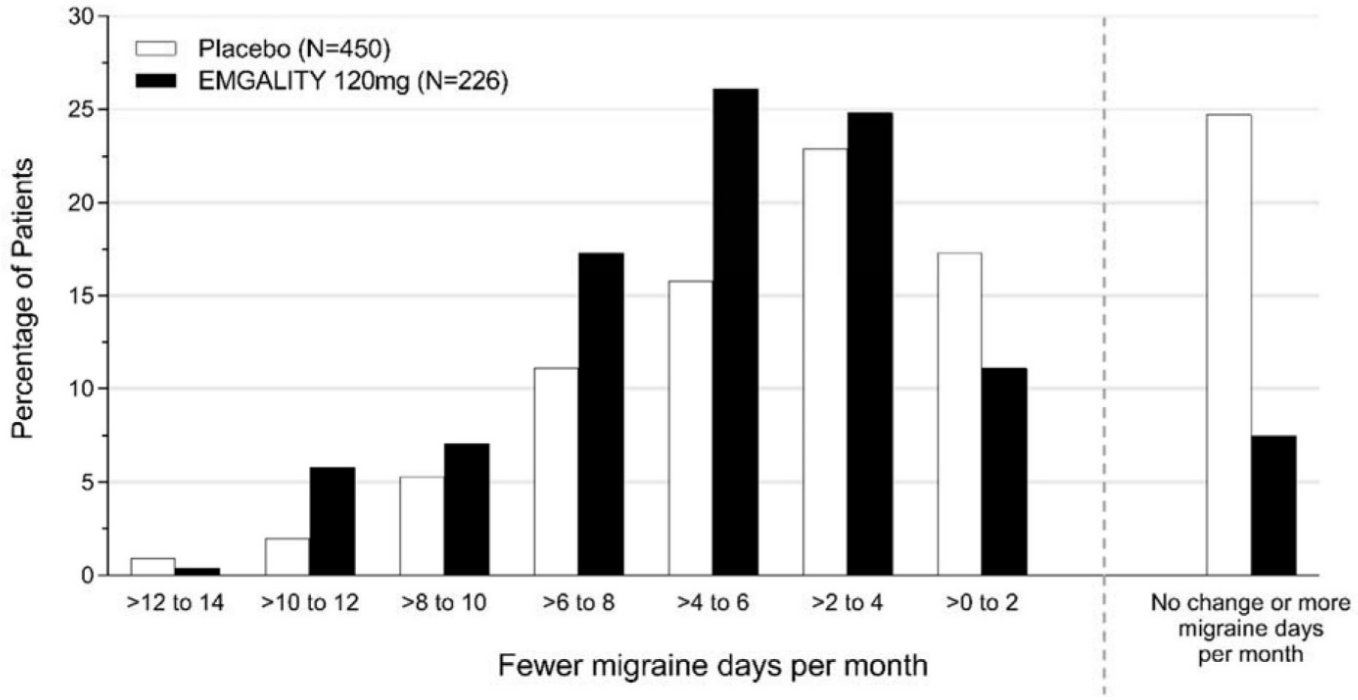


Figure 4 shows the distribution of change from baseline in the mean number of monthly migraine headache days in bins of 2 days, by treatment group, in Study 2. A treatment benefit over placebo for Emgality is seen across a range of changes from baseline in monthly migraine headache days.

Figure 4: Distribution of Change from Baseline in Mean Monthly Migraine Headache Days over Months 1 to 6 by Treatment Group in Study 2



Chronic Migraine

Study 3 (NCT02614261) included adults with a history of chronic migraine (≥15 headache days per month with ≥8 migraine days per month). All patients were randomized in a 1:1:2 ratio to receive once-monthly subcutaneous injections of Emgality 120mg, EMGALITY 240mg or placebo over a 3-month treatment period. All patients in the 120mg Emgality group received an initial 240mg loading dose.

Patients were allowed to use acute headache treatments including migraine-specific medications (i.e., triptans, ergotamine derivatives), NSAIDs and acetaminophen. A subset of patients (15%) was allowed to use one concomitant migraine preventive medication. Patients with medication overuse headache were allowed to enroll.

The study excluded patients with ECG abnormalities compatible with an acute cardiovascular event and patients with a history of stroke, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, deep vein thrombosis or pulmonary embolism within 6 months of screening.

The primary endpoint was the mean change from baseline in the number of monthly migraine headache days over the 3-month treatment period. The secondary endpoints were response rates (the mean percentages of patients reaching at least 50%, 75% and 100% reduction from baseline in the number of monthly migraine headache days over the 3-month treatment period), the mean change from baseline in the number of monthly

migraine headache days with use of any acute headache medication during the 3-month treatment period and the impact of migraine on daily activities as assessed by the mean change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at Month 3. Scores are scaled from 0 to 100, with higher scores indicating less impact of migraine on daily activities.

In Study 3, a total of 1,113 patients (946 female, 167 male) ranging in age from 18 to 65 years, were randomized. A total of 1,037 patients completed the 3-month double-blind phase. The mean number of monthly migraine headache days at baseline was approximately 19.

Emgality 120mg demonstrated statistically significant improvement for the mean change from baseline in the number of monthly migraine headache days over the 3-month treatment period and in the mean percentage of patients reaching at least 50% reduction from baseline in the number of monthly migraine headache days over the 3-month treatment period, as summarized in Table 3. Emgality treatment with the 240mg once-monthly dose showed no additional benefit over the Emgality 120mg once-monthly dose.

Table 3: Efficacy Endpoints in Study 3

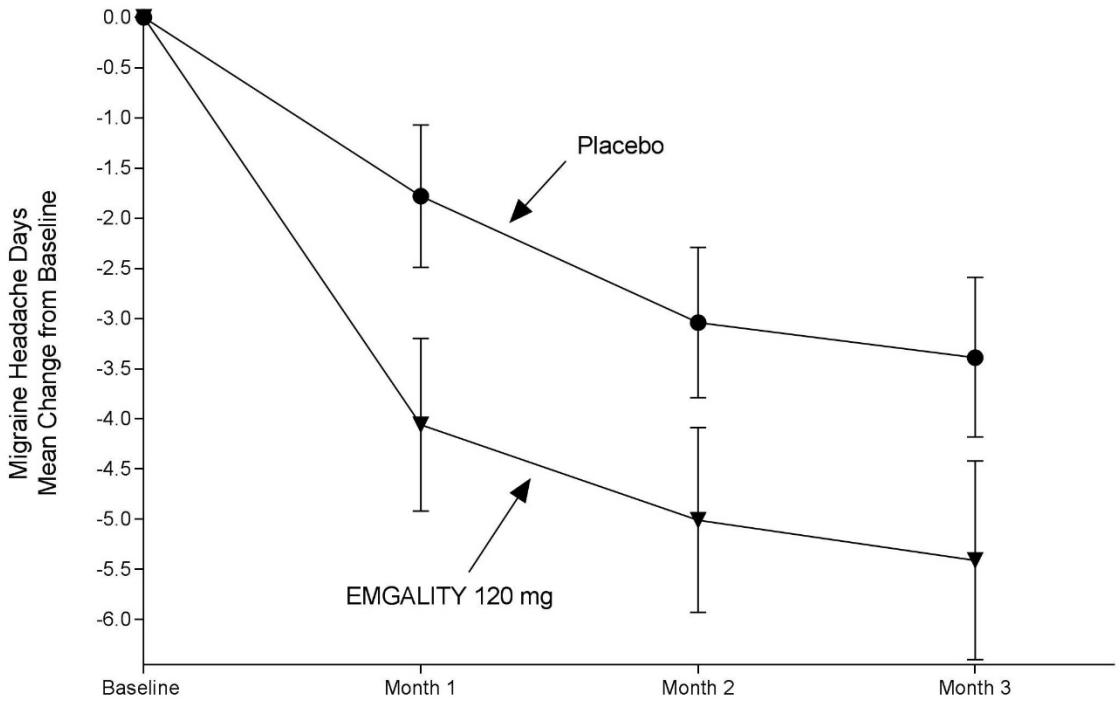
	Emgality 120mg N = 273	**Placebo N =538**
Monthly Migraine Headache Days (over Months 1 to 3)		
Baseline migraine headache days	19.4	19.6
Mean change from baseline	-4.8	-2.7
Difference from placebo[a]	-2.1	
≥50% Migraine Headache Days Responders (over Months 1 to 3)		
% Responders[a]	28%	15%

[a] p<0.001

Study 3 utilized a sequential testing procedure to control the Type-I error rate for the multiple secondary endpoints. Once a secondary endpoint failed to reach the required level for statistical significance, formal hypothesis testing was terminated for subsequent endpoints and p-values were considered nominal only. In Study 3, Emgality 120mg was not significantly better than placebo for the proportion of patients with ≥75% or 100% reduction in migraine headache days. Patients treated with Emgality 120mg showed a nominally greater reduction in the number of monthly migraine headache days that acute medication was taken (-4.7 for Emgality

120mg vs. -2.2 for placebo; nominal p-value <0.001) and the mean change from baseline in the MSQ Role Function-Restrictive Domain score at Month 3 was nominally greater in patients treated with Emgality 120mg than in patients on placebo (21.8 for Emgality 120mg vs. 16.8 for placebo; nominal p-value <0.001).

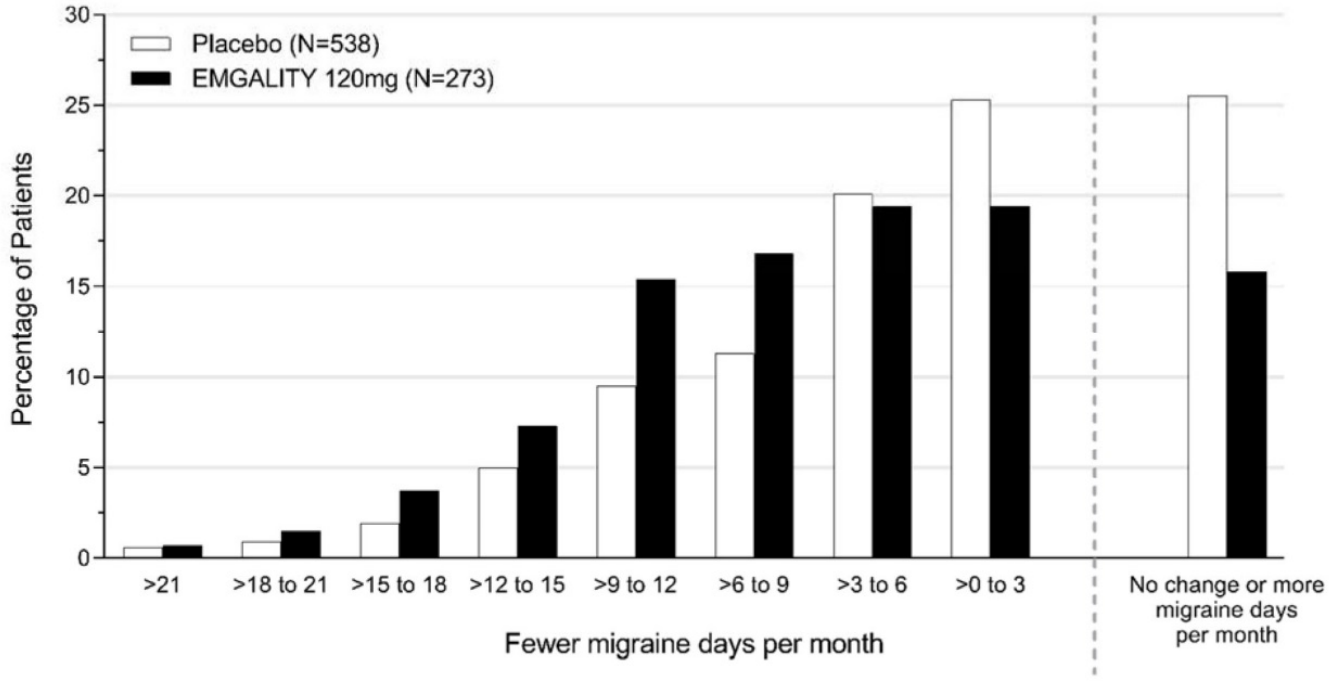
Figure 5: Change from Baseline in Monthly Migraine Headache Days in Study 3[a]



[a] Least-square means and 95% confidence intervals are presented.

Figure 6 shows the distribution of change from baseline in the mean number of monthly migraine headache days for the 3-month study period in bins of 3 days by treatment group. A treatment benefit over placebo for Emgality is seen across a range of changes from baseline in monthly migraine headache days.

Figure 6: Distribution of Change from Baseline in Mean Monthly Migraine Headache Days over Months 1 to 3 by Treatment Group in Study 3



13.2 Episodic Cluster Headache

The efficacy of Emgality was evaluated for the treatment of episodic cluster headache in a randomized, 8-week, double-blind, placebo-controlled study (Study 4).

Study 4 (NCT02397473) included adults who met the International Classification of Headache Disorders 3rd edition (beta version) diagnostic criteria for episodic cluster headache and had a maximum of 8 attacks per day, a minimum of one attack every other day, and at least 4 attacks during the prospective 7-day baseline period. All patients were randomized in a 1:1 ratio to receive once-monthly subcutaneous injections of Emgality 300 mg or placebo. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen, and NSAIDs during the study.

The study excluded patients on other treatments intended to reduce the frequency of cluster headache attacks; patients with medication overuse headache; patients with ECG abnormalities compatible with an acute cardiovascular event or conduction delay; and patients with a history of myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, deep vein thrombosis, or pulmonary embolism within 6 months of screening. In addition, patients with any history of stroke, intracranial or carotid aneurysm, intracranial hemorrhage, or vasospastic angina; clinical evidence of peripheral vascular disease; or diagnosis of Raynaud's disease were excluded.

The primary efficacy endpoint for Study 4 was the mean change from baseline in weekly cluster headache

attack frequency across Weeks 1 to 3. A secondary endpoint was the percentage of patients who achieved a response (defined as a reduction from baseline of 50% or greater in the weekly cluster headache attack frequency) at Week 3.

In Study 4, a total of 106 patients (88 males, 18 females) were randomized and treated. Study participants were male and female patients 18 to 65 years of age (inclusive) with a history of episodic cluster headache who met the International Classification of Headache Disorders 3rd edition (ICHD-3-beta version 2013) and had a prior history of a cluster period lasting 6 weeks or longer. A total of 90 patients completed the 8-week double-blind phase. In the prospective baseline phase, the mean number of weekly cluster headache attacks was 17.5, and was similar across treatment groups.

Table 4 summarizes subgroup analyses of weekly cluster headache attack frequency by the average number of attacks reported during the baseline period.

Table 4: Weekly Cluster Headache Attack Frequency by Baseline Average Attacks (Numbers of Attacks) Repeated Measures Analysis

Baseline Average Number of Attacks	N	Overall Weeks 1-3 LS Mean Change from Baseline (SE)	LS Mean Change Difference (SE)	95% CI	Within-Subgroup P-value
≤4 attacks per day					
PBO	50	-2.46 (1.36)	-4.30 (1.64)	(-7.57, -1.03)	.011
GMB 300 mg	41	-6.76 (1.52)			
>4 attacks per day					
PBO	7	-26.98 (6.08)	11.96 (6.79)	(-5.92, 29.84)	.143
GMB 300 mg	8	-15.02 (5.53)			
≤3 attacks per day					
PBO	43	-1.66 (1.38)	-4.97 (1.72)	(-8.41, -1.53)	.005
GMB 300 mg	35	-6.63 (1.59)			
>3 attacks per day					
PBO	14	-17.38 (5.08)	5.85 (4.81)	(-4.47, 16.18)	.244
GMB 300 mg	14	-11.52 (4.69)			
≤2 attacks per day					
PBO	27	-2.24 (1.04)	-2.80 (1.30)	(-5.43, -0.17)	.037
GMB 300 mg	25	-5.04 (1.10)			
>2 attacks per day					
PBO	30	-6.94 (2.89)	-3.11 (3.13)	(-9.44, 3.21)	.326
GMB 300 mg	24	-10.05 (3.18)			

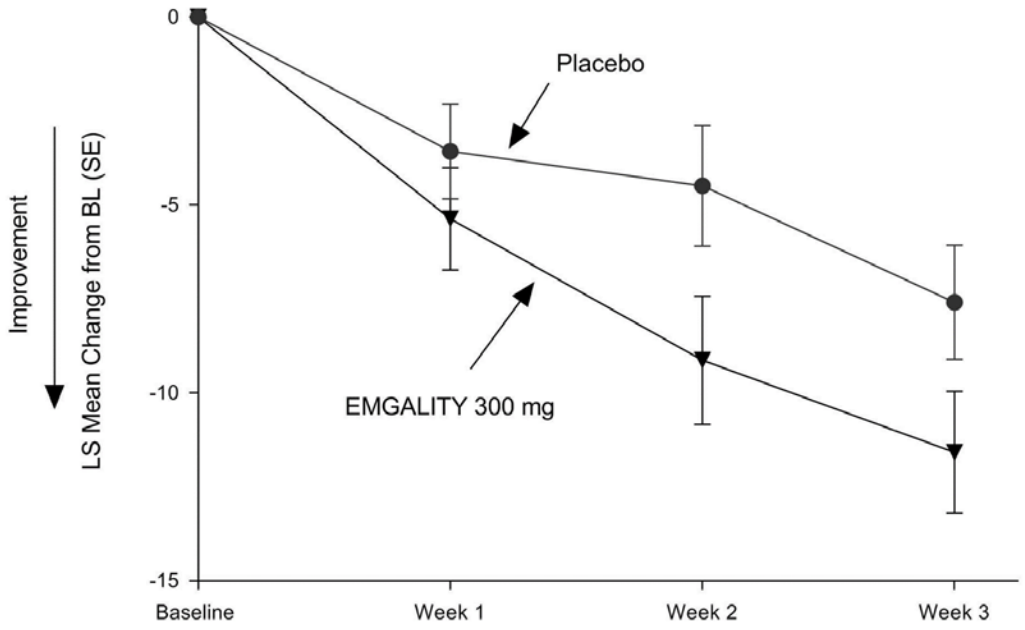
Abbreviations: CI = confidence interval; GMB = galcanezumab; LS = least squares; PBO = placebo; SE = standard error.

Emgality 300 mg demonstrated statistically significant improvements for efficacy endpoints compared to placebo, as summarized in Table 5.

Table 5: Efficacy Endpoints in Study 4

	Emgality 300 mg N = 49	Placebo N = 57
Mean Reduction in Weekly Cluster Headache Attack Frequency (over Weeks 1 to 3)		
Prospective Baseline Cluster Headache Attack Frequency	17.8	17.3
Mean change from baseline	-8.7	-5.2
Difference from placebo	-3.5	
p-value	0.036	
≥50% Weekly Cluster Headache Attack Frequency Responders (at Week 3)		
% Responders	71.4%	52.6%
Difference from placebo	18.8%	
p-value	0.046	

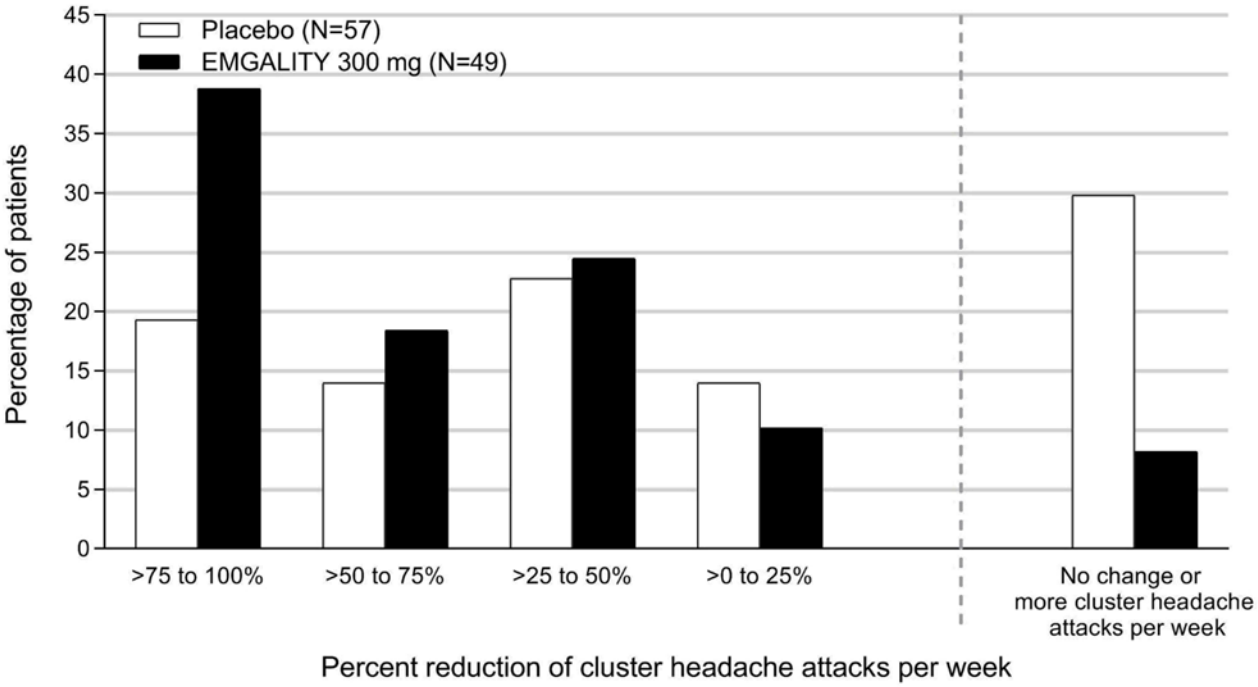
Figure 7: Mean Change in Weekly Cluster Headache Attack Frequency over Weeks 1 to 3 in Study 4[a]



[a] Abbreviations: BL = baseline; LS = least square; SE = standard error.

Figure 8 shows the distribution of the average percent change from baseline in weekly cluster headache attack frequency across Weeks 1 to 3 in bins of 25%, by treatment group, in Study 4.

Figure 8: Distribution of the Average Percent Change from Baseline in Weekly Cluster Headache Attack Frequency over Weeks 1 to 3 in Study 4[a]

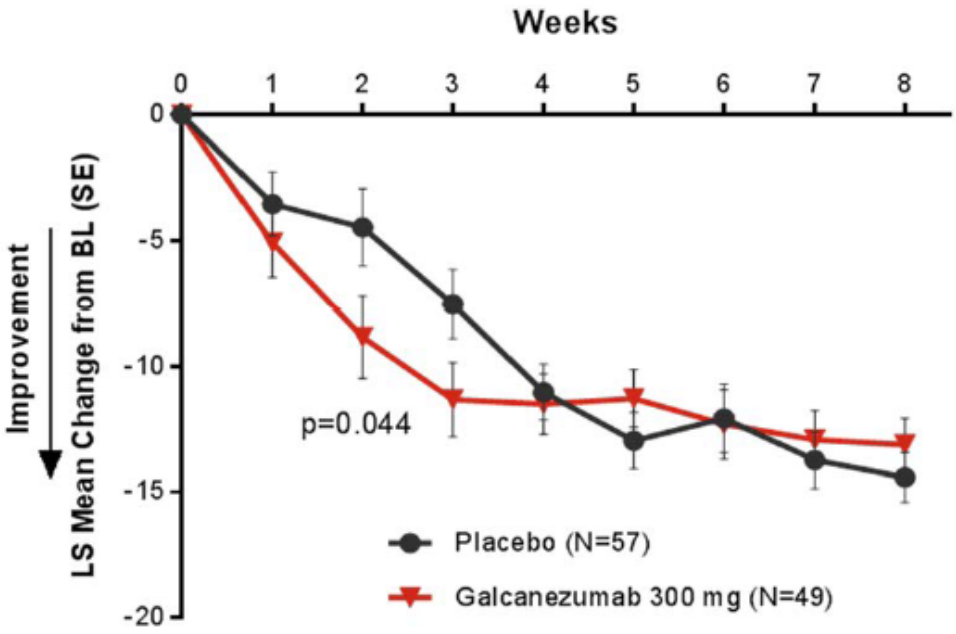


[a] N = number of intent to treat patients with non-missing average percentage change from baseline in weekly cluster headache attack frequency over weeks 1 to 3.

For the primary efficacy endpoint, galcanezumab 300 mg significantly reduced the overall mean weekly cluster headache attack frequency across Weeks 1 to 3 compared with placebo (-8.7 versus -5.2 attacks; p=0.036).

Figure 9 shows mean change in weekly cluster headache attack frequency across Weeks 1 to 8. As observed in the primary analysis, galcanezumab reduced mean weekly attack frequency during Weeks 1 to 3. Beginning at Week 4, the mean reduction in number of weekly cluster headache attacks in both treatment groups overlap, likely reflective of the natural course of spontaneous remission in episodic cluster headache. The benefit of a second monthly dose of galcanezumab compared to placebo was not demonstrated.

Figure 9: Mean change from baseline in weekly cluster headache attack frequency during the 8-week double-blind treatment phase.



Abbreviations: BL = baseline; LSMean = Least Squares Mean; SE = standard error
Note: Repeated measures model included data from all 8 weeks of double-blind treatment phase. P-value is for difference at Visit 2.

14 HOW SUPPLIED/STORAGE AND HANDLING

14.1 How Supplied

1ml solution in a type I clear glass syringe.

EMGALITY is supplied as follows:

	Pack Size
Pre-filled Pen	
120 mg/mL single-dose	Carton of 1
Pre-filled Syringe	
100 mg/mL single-dose	Carton of 3

14.2 Incompatibilities

Not applicable for subcutaneous single-dose product.

14.3 Storage and Handling

- Store refrigerated at 2°C to 8°C in the original carton to protect Emgality from light until use.
- Do not freeze.
- Do not shake.
- Emgality may be stored outside of refrigeration in the original carton at temperatures up to 30°C for up to 7 days. Once stored out of refrigeration, do not place back in the refrigerator.

- If these conditions are exceeded, Emgality must be discarded.
- Discard the Emgality single-dose pre-filled pen or pre-filled syringe in a puncture-resistant container.

15 PATIENT COUNSELING INFORMATION

Advise the patient to read the Instructions for Use.

Instructions on Self-Administration

Provide guidance to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique and how to use the pre-filled pen correctly *[see Instructions for Use]*. Instruct patients and/or caregivers to read and follow the Instructions for Use each time they use Emgality.

Hypersensitivity Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of serious or severe hypersensitivity reactions *[see Warnings and Precautions (6)]*.

16 PRODUCT OWNER

Eli Lilly and Company, Indianapolis, IN 46285, USA

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