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Efficacy and Safety of Galcanezumab as a Preventive Treatment for Episodic Migraine in South Korean Patients: A Post-Hoc Analysis of a Phase 3 Clinical Trial

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Background and Purpose The estimated prevalence of migraines in South Korea is 6.0%, with affected patients having unmet needs. The efficacy, safety, and tolerability of galcanezumab, a humanized monoclonal antibody, for episodic migraine (EM) prevention was evaluated in South Korean patients.

Methods During the double-blind period of the EVOLVE-2 phase 3 trial, patients with EM were randomized into placebo, 120 mg-galcanezumab, and 240-mg galcanezumab treatment groups. The primary endpoint was the overall mean change from baseline in the number of monthly migraine headache days during the 6-month double-blind period. We conducted a post-hoc analysis of the South Korean cohort in EVOLVE-2.

Results Among 98 South Korean patients in the intent-to-treat population, significant changes from baseline were observed in the number of monthly migraine headache days in the 240-mg galcanezumab group compared with the placebo group (-2.64, p=0.013), in the percentage of patients with ≥50% reduction in the number of monthly migraine headache days (120 mg: odds ratio=2.43, p=0.030; 240 mg: odds ratio=2.60, p=0.019), in the number of monthly migraine headache days with acute medication use (120 mg: -2.22, p=0.006; 240 mg: -2.23, p=0.005), and in the Migraine-Specific Quality-of-Life Role Function-Restrictive (120 mg: 8.34, p=0.040). Numerical improvements from baseline were observed relative to the placebo group in at least one galcanezumab group for: the percentage of patients with ≥75% reduction in the number of monthly migraine headache days functional impairment, and disease severity. The most common treatment-emergent adverse event in the combined galcanezumab group was injection site reaction, which led to treatment discontinuation for one patient.

Conclusions Galcanezumab treatment demonstrated efficacy and a favorable safety and tolerability profile in South Korean patients with EM.

Keywords episodic migraine; monoclonal antibody; calcitonin gene-related peptide; galcanezumab; South Korea.

INTRODUCTION

Migraine is a prevalent and burdensome neurological disease that has an estimated global prevalence of 11.6%.[1] The prevalence is approximately 9.1%[2] in the Asia-Pacific region and approximately 6% in South Korea (8%–9% in females, 3% in males).[2-7]

The substantial burden of headache and its accompanying symptoms can impact daily activities and quality of life.[8-11] Preventive treatment could potentially improve the functional ability of patients, reduce headache-related disability, and enhance the response to acute treatments by reducing the frequency and severity of migraine attacks.[12] However, a recent survey of South Korean neurologists found that more than half of the respondents

were not satisfied with the effectiveness of preventive medication.[13]

In South Korea, current clinical practice guidelines for episodic migraine (EM) prevention recommend antiepileptic drugs, beta blockers, calcium-channel blockers, antidepressants, angiotensin-receptor blockers, and angiotensin-converting enzymes.[14] However, these medications were not initially developed as preventive treatments for migraine and some are associated with issues involving efficacy and tolerability.[15-17]

Calcitonin gene-related peptide (CGRP) is a molecular mediator of neurogenic inflammation and is implicated in migraine pathophysiology.[18-20] Several monoclonal antibody and small-molecule treatments for migraine that target CGRP signaling have been developed and approved.[21] Galcanezumab is a humanized IgG4 monoclonal antibody that selectively binds the CGRP ligand and prevents its biological activity without blocking the CGRP receptor. Phase 2 and 3 randomized, double-blind, placebo-controlled studies involving adult patients with EM (EVOLVE-1, EVOLVE-2, and NCT02959177),[22-24] chronic migraine (REGAIN),[25] and episodic or chronic migraine for whom previous migraine preventive medication from two to four categories had failed (CONQUER)[26] found that galcanezumab treatment was effective and safe.[22,23,25,26] Open-label studies have further demonstrated the efficacy, safety, and tolerability of galcanezumab treatment for up to 18 months.[27-30] Galcanezumab has been approved by the Food and Drug Administration for the prevention of migraine in adults, along with approval from the European Medicines Agency for migraine prophylaxis in adults who have at least 4 monthly migraine headache days.[31-33] Galcanezumab was the first CGRP monoclonal antibody treatment approved in South Korea; the Ministry of Food and Drug Safety approved it in September 2019[34] for the preventive treatment of migraine in adults.

The current analysis investigated the efficacy and safety of galcanezumab for the preventive treatment of EM in the subgroup of South Korean patients included in the EVOLVE-2 study.

METHODS

Patients and study design

EVOLVE-2 (NCT02614196) was a phase 3, multicenter, randomized, double-blind, placebo-controlled study comprising the following four periods: 3–45-day screening (study period [SP] I), 30–40-day baseline (SP II), 6-month double-blind treatment (SP III), and 4-month follow-up (SP IV) (Fig. 1). The trial sites of the study were in North America, South America, Europe, and Asia. Patients were 18–65 years

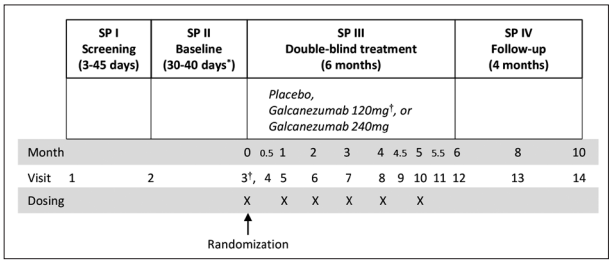

Fig. 1. Study design of EVOLVE-2. *The eligibility period is between a minimum of 30 days and a maximum of 40 days. Investigators may have up to 5 additional days (beyond the 40 days) if needed to schedule the appointment for a third visit of the patient; †Patients randomized to the 120-mg dose will receive a loading dose of 240 mg at the time of the first injection only (at visit 3). SP, study period.

old at the time of screening, had migraine onset prior to 50 years old, and had an EM diagnosis according to the International Classification of Headache Disorders 3rd edition criteria. Patients were excluded if prior treatment with three or more adequately dosed preventive treatments from different specified drug classes had failed, if they had received a therapeutic antibody in the 12 months prior to study inclusion, or if they had any medical or psychiatric illness that would preclude study participation. Key elements of the protocol are available at https://clinicaltrials.gov/ct2/show/NCT02614196.

Following the prospective baseline period, eligible patients were randomized at a 2:1:1 ratio to receive subcutaneous injections of placebo, 120-mg galcanezumab, or 240-mg galcanezumab once each month, respectively, during the double-blind treatment period. Patients who received the 120-mg dose during the double-blind period received a 240-mg loading dose at the time of the first injection only. The double-blind treatment period was followed by a 4-month post-treatment phase during which patients no longer received the study medication.

EVOLVE-2 was designed to allow maximized extended enrollment. This provision enabled patient enrollment to continue in South Korea and Taiwan if the required prespecified number of patients for each of these countries was not reached when the EVOLVE-2 study had reached its planned total sample size (the primary study cohort) for the primary analysis.

As per the study protocol, the concomitant use of acute medications for migraine treatment was permitted during the postbaseline periods, inclusive of the following: acetaminophen, NSAIDs, triptans, ergotamine and its derivatives, isometheptene mucate, dichloralphenazone, and acetaminophen combination (Midrin), or combinations of these. The use of medications containing opioids and barbiturates was restricted to no more than 3 days per month, and a single dose

of injectable steroids was allowed only once during the study in emergency situations.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the appropriate Institutional Review Boards at the different study sites. The clinical trial was conducted according to the Good Clinical Practice and Declaration of Helsinki guidelines. All patients provided written informed consent before participating in the study. The study is registered at ClinicalTrials.gov (NCT02614196).

Outcome measures

The primary endpoint of EVOLVE-2 was the overall mean change from baseline in the number of monthly migraine headache days during the 6-month double-blind treatment period. Key secondary endpoints included the following: proportion of patients with ≥50%, ≥75%, and 100% reductions from baseline in monthly migraine headache days during the 6-month double-blind treatment phase (due to the small sample, the South Korean population was not calculable); mean change from baseline in the Role Function−Restrictive (RF-R) domain score of the Migraine-Specific Quality-of-Life Questionnaire version 2.1 (MSQv2.1) (average of months 4, 5, and 6); overall mean change from baseline in the number of monthly migraine headache days that required medication for the acute treatment of migraine or headache during the 6-month double-blind treatment phase; and mean change from baseline in the Patient Global Impression of Severity (PGI-S) score (average of months 4, 5, and 6). Other secondary endpoints included the mean change from baseline in total score on the migraine disability assessment (MIDAS) (at month 6).

MSQv2.1 assesses quality of life in patients with migraine during the previous 4 weeks across the three unique domains of RF-R, Role Function−Preventive (RF-P), and Emotional Function (EF).[35,36] The assessed items included limitations of patient performance in normal activities (for RF-R), interruptions of patient performance in normal activities (for RF-P), and impact of migraine on patient emotions such as frustration or helplessness (for EF). The item responses range from 1 to 6 (1=none of the time, 2=a little bit of the time, 3=some of the time, 4=a good bit of the time, 5=most of the time, and 6=all of the time). All items are reverse-coded and standardized to a 0−100 scale, with higher scale scores indicating better migraine-related quality of life.[37]

The MIDAS is a self-administered questionnaire designed to measure headache-related disability over the previous 3 months.[38,39] The questionnaire is based on five questions about the number of days missed in school or paid work, household work, and family, social, or leisure activities due to headache as well as the number of additional days with substantial limitations to activity in the domains of employment and household work during the previous 3 months. The MIDAS score is derived from the sum of the lost days/days with activity limitation due to headache recorded from the responses to these questions, with sum-score categories of little or none (0−5, grade I), mild (6−10, grade II), moderate (11−20, grade III), and severe (≥21, grade IV). Two additional questions not scored on the MIDAS questionnaire collected information on headache frequency and the level of headache pain on a scale from 0 to 10.

The PGI-S is a one-item questionnaire on patient-reported severity of a specific condition, with possible responses ranging from 1 ("normal, not at all ill") to 7 ("extremely ill").

Safety, tolerability, and immunogenicity

Assessments of safety and tolerability included evaluating medication discontinuation, treatment-emergent adverse events (TEAEs) including potential hypersensitivity events, and serious adverse events (SAEs). Immunogenicity was evaluated using treatment-emergent antidrug antibodies (TE-ADAs).

Statistical analysis

The key efficacy and safety outcomes obtained in the current analysis of the subpopulation of South Korean patients in EVOLVE-2 are presented herein. Results for the South Korean subpopulation are presented alongside the all-patients population (inclusive of South Korean patients) for reference only, since the regulatory submission was based on this population. All efficacy analyses were conducted on the intent-to-treat population, which consisted of patients who were randomly selected to receive at least one dose of placebo or galcanezumab. Analyses were conducted according to the treatment group to which the patients were randomized. For continuous measures of changes from baseline, the mixed models for repeated measures (MMRM) approach was used with terms for treatment, months, treatment-by-month, baseline, baseline-by-month, and baseline monthly migraine headache days with the exception of the all-patients population, for which a term for pooled region/country was also included in the model. Unstructured covariance was used to model within-patient errors for the primary efficacy measure. For repeated binary efficacy measures, a categorical, pseudo-likelihood-based repeated-measures model for binary outcomes was used with terms for treatment, months, treatment-by-month, and baseline monthly migraine headache days with the exception of the all-patients population, for which a term for pooled region/country was also includ-

ed in the model.

Safety and exposure analyses were conducted on the safety population, which consisted of data from all randomized patients (including South Korean ones) who received at least one dose of placebo or galcanezumab. The analyses were based on the modal treatment that the patients received during the double-blind treatment phase. MMRM models were used to estimate the treatment effect compared to placebo and presented using mean-differences and standard errors (SEs), whereas those for binary outcomes were presented using odds ratios and 95% confidence intervals. Treatment effects were evaluated based on a two-sided significance cutoff of 0.05. Only summary statistics were generated for the safety analyses. All statistical analyses were performed using SAS Enterprise Guide software (version 7.1, SAS Institute, Cary, NC, USA).

Availability of data and materials

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the respective study has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at https://vivli.org/.

RESULTS

Patient disposition

The study initially included 1,696 patients who were screened

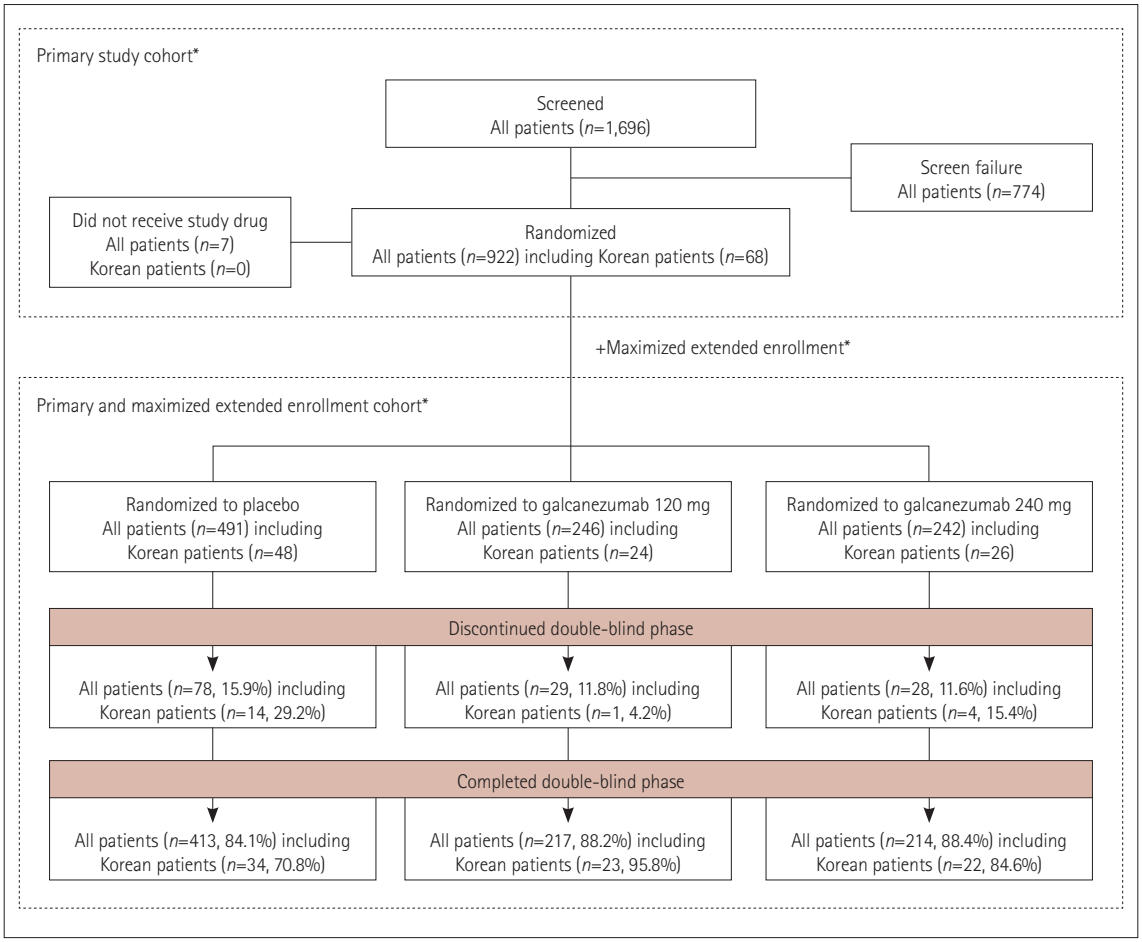

Fig. 2. Flowchart of patient inclusion throughout EVOLVE-2. The all-patients population includes South Korean patients. *EVOLVE-2 was designed to allow maximized extended enrollment. This provision enabled patient enrollment to continue in South Korea and Taiwan if the required prespecified number of patients for each of these countries was not reached when EVOLVE-2 had reached its planned total sample size (the primary study cohort) for the primary analysis. *n*, number of patients.

and 922 who were randomized, including 68 South Korean patients (Fig. 2). This population represented the primary study cohort.[23] A further 30 South Korean patients were randomized at a later stage through the maximized extended enrollment provision (see Methods section for more information). The intent-to-treat population therefore included 98 South Korean patients in the primary and maximized extended enrollment cohorts. Hereafter, the entire primary and maximized extended enrollment cohort is referred to as the all-patients population. More than 70% of the entire population in each treatment group completed the double-blind treatment period (Fig. 2).

Baseline demographics and disease characteristics

Baseline demographics and disease characteristics for the subgroup of South Korean patients in EVOLVE-2 are presented in Table 1, with corresponding data for the all-patients population included for reference. Within the South Korean population, demographic, clinical, quality of life, and disability measures were generally similar across treatment groups, while there were notable differences between treatment groups in measures related to prior preventive treatment (Table 1). Lower body mass index, shorter migraine disease duration, milder headache pain score, fewer monthly migraine headache days with acute medication use and lower MIDAS total score were observed in South Korean patients, as were higher rates of prior preventive treatment and failure with ≥1 or ≥2 prior preventive treatment classes, and higher MSQ RF-R and PGI-S scores (Table 1).

Efficacy

Monthly migraine headache days

In the South Korean cohort, treatment with 240-mg galcanezumab resulted in a significantly larger reduction from baseline in the overall mean number of monthly migraine headache days compared with placebo (-2.64, p=0.013) (Fig. 3A). The corresponding result in the 120-mg galcanezumab group

Table 1. Baseline demographics and disease characteristics for EVOLVE-2

	South Korean patients			All patients*		
	Placebo	Galcanezumab 120 mg	Galcanezumab 240 mg	Placebo	Galcanezumab 120 mg	Galcanezumab 240 mg
Number of patients*	48	24	26	491	246	242
Age, years	44.6±10.3	41.1±11.4	41.9±11.6	42.5±11.3	40.8±11.2	42.0±10.8
Sex, female *n* (%)	38 (79.2)	19 (79.2)	22 (84.6)	415 (84.5)	210 (85.4)	205 (84.7)
Body mass index, kg/m^2	22.5±2.3	23.0±2.4	23.7±3.5	26.5±5.3	26.6±5.2	26.9±5.5
Duration of migraine disease, years	13.0±9.5	13.5±10.0	13.3±10.4	20.6±12.7	19.5±11.8	19.5±12.1
Days with migraine headache per month	8.5±2.7	8.4±2.8	8.1±2.8	9.2±3.0	9.1±2.9	9.0±2.9
Headache pain score	5.4±1.8	6.0±1.7	6.0±1.7	6.5±1.8	6.4±1.7	6.6±1.7
Migraine attacks per month	5.6±1.7	5.4±1.6	4.9±1.3	5.6±1.8	5.5±1.8	5.6±1.8
Days with migraine headache of category ≥8 per month	30 (62.5)	15 (62.5)	16 (61.5)	329 (67.0)	165 (67.1)	162 (66.9)
Days with migraine headache with acute medication use per month	5.5±3.0	5.7±3.0	5.5±3.4	7.5±3.4	7.4±3.4	7.4±3.3
Prior preventive treatment	41 (85.4)	23 (95.8)	24 (92.3)	326 (66.4)	167 (67.9)	159 (65.7)
Failed ≥1 prior preventive treatment classes	20 (41.7)	15 (62.5)	10 (38.5)	150 (30.6)	91 (37.0)	78 (32.2)
Failed ≥2 prior preventive treatment classes	13 (27.1)	10 (41.7)	8 (30.8)	69 (14.1)	37 (15.0)	38 (15.7)
Number of patients	48	24	26	486	246	241
MSQ RF-R score†	58.0±17.7	54.5±12.9	55.6±13.4	51.6±16.0	52.9±14.7	51.7±16.1
MIDAS total score‡	21.2±19.5	27.1±27.0	19.9±20.5	34.0±30.7	30.6±27.6	32.2±28.4
Number of patients	48	24	26	487	246	241
PGI-S score	4.8±1.0	5.0±0.9	5.0±0.8	4.3±1.2	4.1±1.2	4.2±1.2

Data are mean±SD, *n* (%), or *n* values.
*The number of patients for the all-patients population is slightly larger in the table than in the primary publication[35] due to the EVOLVE-2 study being designed to allow maximized extended enrollment. This provision enabled patient enrollment to continue in South Korea and Taiwan if the required prespecified number of patients for each of these countries was not reached when EVOLVE-2 had reached its planned total sample size for the primary analysis; †Higher MSQ RF-R scores indicate better migraine-related quality of life; ‡Higher MIDAS total scores indicates greater headache-related disability.
MIDAS, migraine disability assessment; MSQ, migraine-specific quality-of-life questionnaire; *n*, number of patients in the intent-to-treat population; PGI-S, patient global impression of severity; RF-R, role function-restrictive; SD, standard deviation.

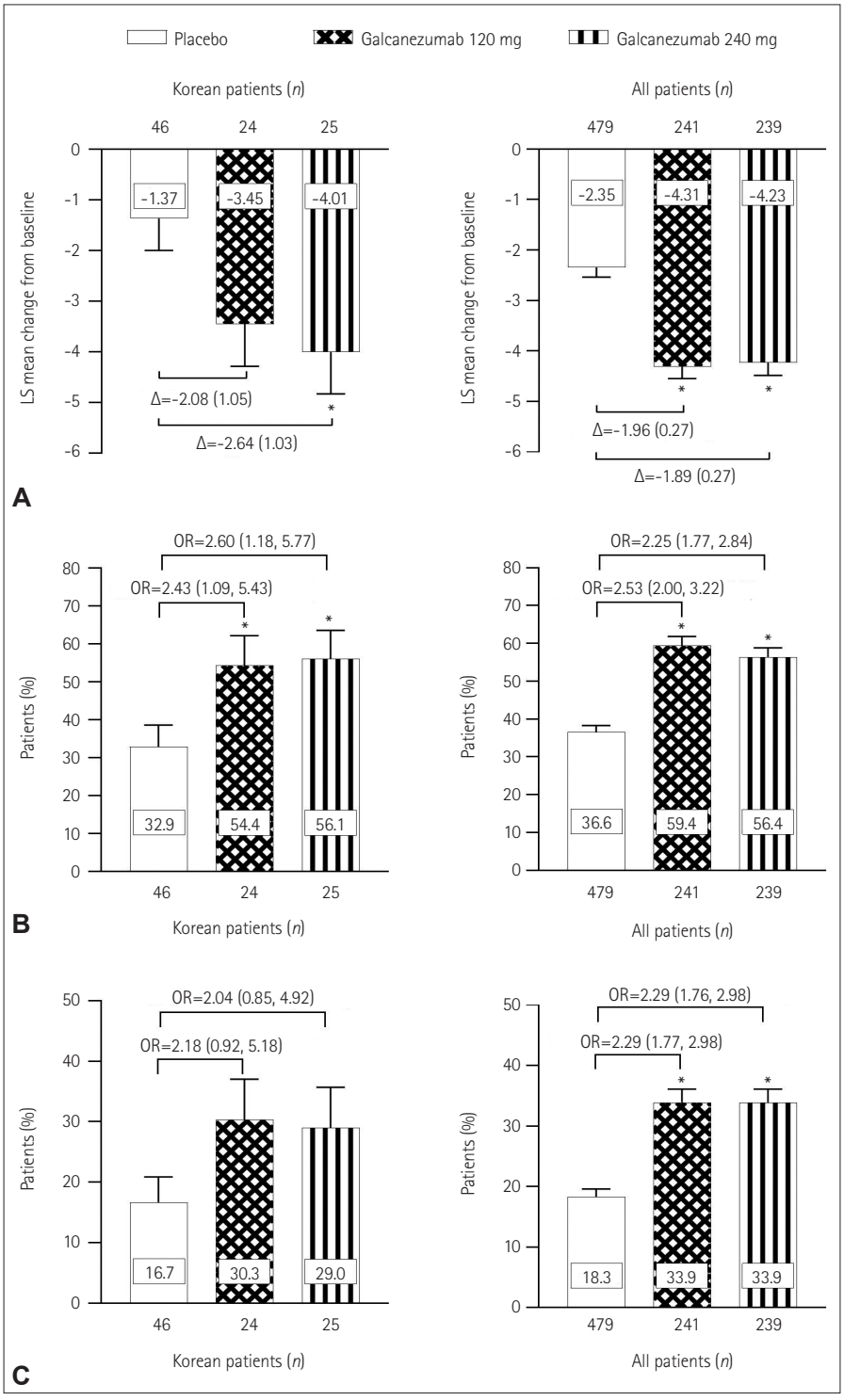

Fig. 3. Overall mean change from baseline in the number of days with migraine headache per month and the proportions of patients with ≥50% and ≥75% reduction in the number of monthly migraine headache days, for South Korean patients and all-patients in EVOLVE-2. A: Overall mean change from baseline in the number of days with migraine headache per month during the double-blind period (months 1–6). Differences between group means (standard error) are expressed as Δ. B: Overall mean proportion of patients with ≥50% reduction from baseline in the number of days with migraine headache per month during the double-blind period (months 1–6). ORs with 95% confidence intervals for between-groups comparisons are presented. C: Overall mean proportion of patients with ≥75% reduction from baseline in the number of days with migraine headache per month during the double-blind period (months 1–6). ORs and 95% confidence intervals for between-groups comparisons are presented. *p<0.05. LS, least squares; *n*, number of intent-to-treat patients who had nonmissing baseline and at least one postbaseline value; OR, odds ratio.

was not significantly different from placebo (-2.08, p=0.052). In the all-patients population, significantly larger reductions from baseline in the overall mean number of monthly migraine headache days were observed in both galcanezumab dose groups compared with placebo (Fig. 3A, p<0.001).

Reductions of ≥50% and ≥75% in the number of monthly migraine headache days

Galcanezumab treatment at both 120 mg and 240 mg resulted in a significantly larger proportion of South Korean patients with ≥50% reduction from baseline in the number of monthly migraine headache days compared with placebo (Fig. 3B, p<0.05). The corresponding result for a ≥75% reduction from baseline was not significantly different from placebo (Fig. 3C). In the all-patients population, significantly larger proportions of patients with ≥50% or ≥75% reduction from baseline were observed in both galcanezumab dose groups compared with placebo (Fig. 3B and C; p<0.001).

Monthly migraine headache days with acute medication use

In the South Korean cohort, galcanezumab treatment at either 120 mg or 240 mg resulted in a significantly larger reduction from baseline in the overall mean number of monthly migraine headache days with acute medication use compared with placebo (Fig. 4, p<0.01). In the all-patients population, significantly larger reductions from baseline were observed in both galcanezumab dose groups compared with placebo (Fig. 4, p<0.001).

Patient-reported outcomes

In the South Korean cohort, galcanezumab treatment at 120 mg resulted in a significantly larger increase from baseline in the mean MSQ RF-R score compared with placebo (Table 2, p=0.040). The corresponding result for the 240-mg galcanezumab group was not significantly, different from placebo. In the all-patients population, significantly larger increases from baseline were observed in both galcanezumab dose groups compared with placebo (Table 2, p<0.001).

In the South Korean cohort, galcanezumab treatment at either dose resulted in no significant difference from baseline in the mean MIDAS total score compared with placebo (Table 2). In the all-patients population, significantly larger decreases from baseline were observed in both galcanezumab dose groups compared with placebo (Table 2, p<0.001).

In the South Korean cohort, galcanezumab treatment at either dose resulted in no significant difference from baseline in the mean PGI-S score compared with placebo (Table 2). For the all-patients population, significantly larger decreases from baseline in the mean PGI-S score were observed in both galcanezumab dose groups compared with placebo (120 mg, p=0.002; 240 mg, p=0.009; Table 2).

Safety, tolerability, and immunogenicity

The adverse events (AEs) during the double-blind period, including TEAEs reported by ≥5% of South Korean patients in the combined galcanezumab group, are summarized in Table 3, with corresponding data for the all-patients population presented for reference. No deaths were reported in either population, and no SAEs were reported in either galcanezumab dose group in the South Korean population. One South Korean patient in the 240-mg galcanezumab group discontinued treatment due to an injection site reaction. The

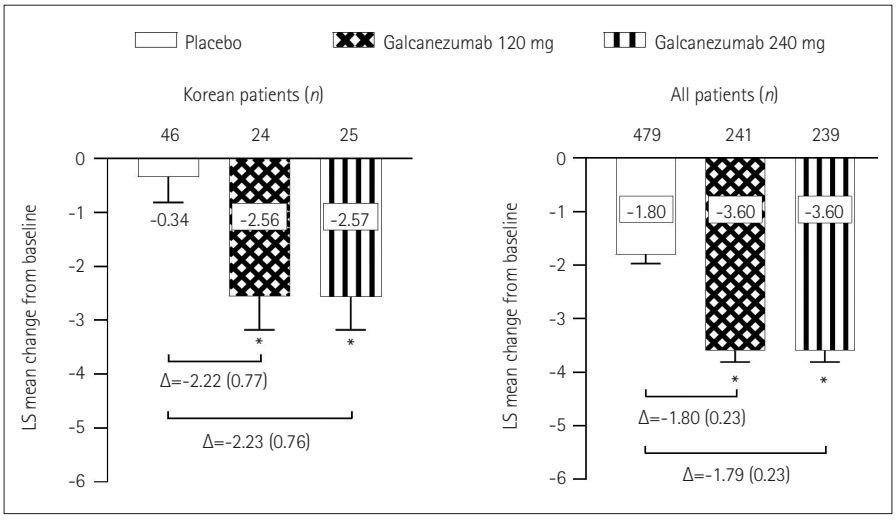

Fig. 4. Overall mean change from baseline in the number of days with migraine headache per month with acute medication use for South Korean patients and all-patients in EVOLVE-2. Overall mean change from baseline in the number of days with migraine headache per month with acute medication use during the double-blind period (months 1–6). Data are mean and standard error values. Differences between group means are expressed as Δ. *p<0.05. LS, least squares; n, number of intent-to-treat patients who had a nonmissing baseline and at least one postbaseline value.

Table 2. Mean change from baseline in MSQ RF-R, MIDAS total, and PGI-S scores for South Korean patients and all patients in EVOLVE-2

	South Korean patients			All patients		
	Placebo	Galcanezumab 120 mg	Galcanezumab 240 mg	Placebo	Galcanezumab 120 mg	Galcanezumab 240 mg
MSQ RF-R†						
Number of patients	35	23	25	422	227	229
Change from baseline	14.64±2.51	22.98±3.12	20.97±2.99	19.81±0.87	28.42±1.10	27.02±1.11
Change from baseline vs. placebo		8.34±3.99	6.34±3.88		8.61±1.22	7.21±1.22
p value		0.040*	0.107		<0.001*	<0.001*
MIDAS total‡						
Number of patients	34	23	22	401	216	213
Change from baseline	-7.18±4.16	-8.80±5.11	-3.59±5.10	-12.59±1.24	-21.12±1.55	-19.96±1.56
Change from baseline vs. placebo		-1.62±6.56	3.59±6.54		-8.52±1.74	-7.37±1.74
p value		0.806	0.584		<0.001*	<0.001*
PGI-S						
Number of patients	35	23	25	422	227	229
Change from baseline	-0.99±0.20	-1.17±0.25	-1.37±0.24	-0.95±0.06	-1.23±0.08	-1.18±0.08
Change from baseline vs. placebo		-0.18±0.32	-0.38±0.31		-0.28±0.09	-0.23±0.09
p value		0.560	0.219		0.002*	0.009*

Data are mean±SE, *n* (%), or *n* values. Mean changes from baseline in MSQ RF-R and PGI-S scores during the double-blind period (average of months 4–6). Mean changes from baseline in MIDAS total score at month 6 of the double-blind period.
*$p<0.05$; †Higher MSQ RF-R scores indicate better migraine-related quality of life; ‡Higher MIDAS total scores indicate greater headache-related disability.
MIDAS, migraine disability assessment; MSQ, migraine-specific quality-of-life questionnaire; *n*, number of intent-to-treat patients who had a non-missing baseline and at least one postbaseline value; PGI-S, patient global impression of severity; RF-R, role function-restrictive; SE, standard error.

TEAE frequencies in both galcanezumab dose groups were similar in South Korean patients and in both galcanezumab dose groups of the all-patients population, while that in the placebo group was numerically lower for South Korean patients (47.9%) than the all-patients population (62.3%).

The most common TEAEs (occurred in ≥5% of patients in the combined galcanezumab group) in the South Korean population were injection site reaction nasopharyngitis, upper respiratory tract infection, and rhinitis (Table 3).

TE-ADA incidence rates are also listed in Table 3, with corresponding data for the all-patients population presented for reference. Among patients evaluable for TE-ADAs in the South Korean population (44 in the placebo and 49 in the combined galcanezumab groups), 15.9% in the placebo group presented with ADAs at baseline, with 11.4% having neutralizing ADAs. In the combined galcanezumab group, 16.3% (8/49) of patients presented with ADAs at baseline, with 8.2% (4/49) having neutralizing ADAs. Within the South Korean population, there were no patients in the placebo group with TE-ADA or neutralizing TE-ADA during the postbaseline period. In the combined galcanezumab group, 10.2% (5/49) had TE-ADA and neutralizing TE-ADA during the postbaseline period (Table 3).

DISCUSSION

This post-hoc analysis of the EVOLVE-2 South Korean cohort revealed that patients with EM treated using galcanezumab had a favorable efficacy profile with fewer monthly migraine headache days compared with placebo. Overall, galcanezumab had a favorable safety profile in the subpopulation of South Korean patients compared with the all-patients cohort of the EVOLVE-2 study.

The primary study cohort and all-patients population exhibited similar baseline demographics and disease characteristics.[23] Larger proportions of South Korean patients than all-patients reported prior preventive treatment and failure with treatment of ≥1 or ≥2 prior preventive drug classes. These findings could be due to South Korean patients having easier access to hospitals, including tertiary ones, and therefore a higher probability of receiving preventive treatment. This might result in patients who are naïve to treatment preferring to seek formal treatment rather than applying for participation in a clinical trial. However, patients with experience of prior preventive treatments and of preventive treatment failure might be more eager to participate in clinical trials.

Fewer monthly migraine headache days with acute medication use, lower MIDAS total scores, and higher MSQ RF-R

Table 3. Summary of safety, tolerability, and immunogenicity data

	South Korean patients			All patients		
	Placebo	Galcanezumab 120 mg	Galcanezumab 240 mg	Placebo	Galcanezumab 120 mg	Galcanezumab 240 mg
Number of patients	48	23	27	491	240	248
Deaths	0	0	0	0	0	0
SAE	2 (4.2)	0 (0)	0 (0)	6 (1.2)	5 (2.1)	7 (2.8)
Discontinued treatment due to AE	0 (0)	0 (0)	1 (3.7)	8 (1.6)	5 (2.1)	9 (3.6)
TEAE	23 (47.9)	17 (73.9)	20 (74.1)	306 (62.3)	156 (65.0)	175 (70.6)
TEAEs reported by ≥5% of South Korean patients in the combined galcanezumab group						
Reaction at the injection site	0 (0)	3 (13.0)	7 (25.9)	0 (0)	8 (3.3)	21 (8.5)
Nasopharyngitis	3 (6.3)	5 (21.7)	4 (14.8)	42 (8.6)	21 (8.8)	18 (7.3)
Upper respiratory tract infection	2 (4.2)	5 (21.7)	3 (11.1)	18 (3.7)	16 (6.7)	13 (5.2)
Rhinitis	0 (0)	2 (8.7)	1 (3.7)	4 (0.8)	3 (1.3)	1 (0.4)
TE-ADAs						
Subjects evaluable for TE-ADAs*	44	23	26	472	237	234
TE-ADAs present at baseline†	7 (15.9)	2 (8.7)	6 (23.1)	42 (8.9)	19 (8.0)	29 (12.4)
Neutralizing TE-ADAs at baseline†	5 (11.4)	0 (0)	4 (15.4)	22 (4.7)	11 (4.6)	16 (6.8)
TE-ADA present during the postbaseline period†‡	0 (0)	2 (8.7)	3 (11.5)	3 (0.6)	22 (9.3)	14 (6.0)
Neutralizing TE-ADA present during the postbaseline period†‡§	0 (0)	2 (8.7)	3 (11.5)	1 (0.2)	22 (9.3)	12 (5.1)

Data are *n* (%) or *n* values. Overview of AEs and TEAEs reported by ≥5% of South Korean patients in the combined galcanezumab group during the double-blind treatment period of EVOLVE-2, with corresponding safety data for the all-patients population presented for comparison.
*A subject is TE-ADA evaluable if there is at least one nonmissing test result for ADA for both the baseline and postbaseline periods; †Percentages were calculated using TE-ADA-evaluable subjects as the denominator; ‡A TE-ADA evaluable subject was considered to have TE-ADA if the subject had at least one postbaseline titer with a fourfold or larger increase from the baseline measurement (treatment-boosted). If the baseline result was without ADA, then the subject had TE-ADA if there was at least one postbaseline result of ADA with a titer ≥1:20 (treatment-induced); §Neutralizing antibodies were present among subjects with TE-ADA.
AE, adverse event; *n*, number of patients in safety population; SAE, serious adverse event; TE-ADAs, treatment-emergent antidrug antibodies; TEAE, treatment-emergent adverse event.

scores in the South Korean patients than in the all-patients population could be due to South Korean patients experiencing milder-intensity headaches. Indeed, the South Korean population in EVOLVE-2 reported lower headache pain scores at baseline than did the all-patients population. Cultural and social differences could also contribute to the lower MIDAS total score and higher MSQ RF-R score in South Korean patients compared with in all patients.

Galcanezumab treatment resulted in a larger reduction from baseline in the mean number of monthly migraine headache days among South Korean patients compared with placebo. For the 120-mg galcanezumab group, the reduction from baseline in the mean number of monthly migraine headache days was not significantly different from placebo. The lack of significance among South Korean patients may be due to the smaller sample. In fact, the relative effect in South Korean patients was larger than in the all-patients cohort; however, the SE of South Korean patients was larger than that of all-patients. Galcanezumab treatment also resulted in larger proportions of South Korean patients with ≥50% and ≥75% reductions in the number of monthly migraine headache days, larger reductions in acute medication use, positive impacts on quality of life, and reduced functional impairment (except for in the 240-mg galcanezumab group) and disease severity from baseline compared with the placebo group. These findings suggest that galcanezumab treatment exhibits a clinically meaningful level of efficacy in preventing EM among South Korean patients. These results were especially encouraging considering that South Korean patients who had tried but not responded to preventive treatments from up to two different classes were included in the analysis. In addition, regarding the reduction in the mean number of monthly migraine headache days with acute medication use, this is an important consideration since such medication overuse may lead to the development of headache.[40]

Efficacy results for the South Korean population were largely consistent with those for the all-patients population, except for the change in MIDAS total score. Considerably smaller responses were generally observed in South Korean patients compared with all-patients, and the galcanezumab treatment groups did not differ significantly from the place-

bo group. This could be due to the larger proportions of South Korean patients with prior preventive treatment failure, which could have driven a lower expectation for positive results.

Overall, the safety data suggest that galcanezumab is safe and well-tolerated among South Korean patients. AE frequency in both galcanezumab dose groups was generally similar in the South Korean and all-patients populations. Within the South Korean population, the most common TEAE in the combined galcanezumab group was an injection site reaction, which was the third most common TEAE in that group for the all-patients population, after injection site pain and nasopharyngitis.

The results of these analyses suggest that galcanezumab is a viable preventive treatment option to address the existing unmet needs for South Korean patients with EM. In fact, in a survey conducted in 2008 across eight Asian countries including South Korea, physicians reported that 71% of their patients with migraine were not receiving preventive treatment at the time of completing the survey, and recommended that 68% of them needed such treatment.[41] A more recent survey conducted in 2019 among patients who reported having EM in specialized headache clinics in South Korea confirmed the inadequate use of preventive medication prior to visiting their current hospital, with approximately one-quarter having used preventive medication regularly.[42] It is particularly noteworthy that among the respondents in the most-severe disability category (MIDAS grade IV), only one-third had regularly taken preventive medication in the past. In addition, less than half of the respondents with prior experiences of preventive medication were satisfied overall with such treatment.[42]

Some limitations of the present study should be noted. The inclusion and exclusion criteria and small sample may limit the generalizability of the results to the broader South Korean population. For example, patients were excluded if prior treatment with three or more adequately dosed preventive treatments from different specified drug classes had failed, or if they had electrocardiograms that revealed abnormalities compatible with acute cardiovascular events and/or serious cardiovascular risk. Although the data were gathered prospectively, this was a post-hoc analysis of a subset of South Korean patients with no adjustments made for multiplicity or multiple comparisons. Due to the small sample of the South Korean population, there was also insufficient statistical power for detecting between-treatment-group differences. Although the South Korean population sample was small, importantly, the direction of the results were largely consistent with those from the all-patients population.

In conclusion, this study found that galcanezumab treatment demonstrated efficacy and a favorable safety and tolerability profile in South Korean patients with EM.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due the reasons are explained in our data sharing statement in the 'Availability of data and materials' section on page 4 but are available on reasonable request.

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Conflicts of Interest

Byung-Kun Kim and Min Kyung Chu, contributing editors of the Journal of Clinical Neurology, were not involved in the editorial evaluation or decision to publish this article.

BKK was a principal investigator for a multicenter trial sponsored by Otsuka Japan, Novartis International AG, Ildong Pharm, Lundbeck, Abbvie and Eli Lilly. BKK worked as an advisory member for Lundbeck Korea and received lecture honoraria from GSK Korea, SK Chemicals, Teva Korea, Abbvie Korea and Yuyu Pharmaceutical Company in the past 24 months. SJC was a site investigator of a multicenter trial sponsored by Allergan, Abbvie Inc., Ildong Pharmaceutical Co., LTD, Novartis International AG, Eli Lilly and Company, Hyundaipharm. Co. Ltd, Biohaven Asia Pacific Ltd, and H. Lundbeck A/S (Lundbeck), and received lecture honoraria from Allergan Korea, WhanIn Pharm Co., LTD, Boryung Pharmaceutical Co.,Ltd., Shinpoong Pharma. Co., Ltd, Yuyu Pharmaceutical Company, and SK chemicals in the past 24 months. JHH is a full-time employee of Eli Lilly and Company. GDA is a full-time employee and a minor stockholder of Eli Lilly and Company. TP is a full-time employee of Eli Lilly and Company.

MK was a site investigator sponsored by Otsuka Korea, Novartis International AG, and Eli Lilly and Company. KO was a site investigator for a multicenter trial sponsored by Otsuka Korea, Novartis International AG, Eli Lilly and Company, Ildong Pharmaceutical, Jeil Pharmaceutical, Korean Drug Co., Samjin Pharmaceutical, and Shin Poong Pharmaceutical. HSM was a principal investigator for a multicenter trial sponsored by Otsuka Korea, Novartis International AG, Ildong Pharm and Eli Lilly and Company. HSM received lecture honoraria from GSK Korea, SK Chemicals, Allergan Korea and Yuyu Pharmaceutical Company in the past 24 months. MKC was a site investigator for a multi-center trial sponsored by Allergan Korea, Biohaven pharmaceuticals, and Lundbeck-Korea. He has received lecture honoraria from Allergan Korea, Handok-Teva, Eli Lilly and Company and Yuyu Pharmaceutical Company in the past 24 months. He received grants from Yonsei University College of Medicine (2018-32-0037) and National Research Foundation of Korea (2019R1F1A1053841).

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