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Long-term safety and efficacy of onabotulinumtoxinA for the prevention of chronic migraine in a South Korean population: COMPEL study

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Abstract

The international, multicenter Chronic Migraine OnabotulinumtoxinA Prolonged Efficacy Open Label (COMPEL) study evaluated long-term safety and efficacy of onabotulinumtoxinA in individuals with chronic migraine (CM). This post hoc analysis evaluates the safety and efficacy of onabotulinumtoxinA in South Korean patients for up to 108 weeks of treatment. OnabotulinumtoxinA 155 U was administered every 12 weeks for 9 treatment cycles (108 weeks). The primary efficacy measure was change from baseline in headache-day frequency for the 28-day period ending at week 108. Additional outcome measures included change in 6-item Headache Impact Test (HIT-6) scores and measures of migraine-related disability and quality of life. Safety and tolerability were assessed from the frequency of adverse events (AEs). Of 716 patients in the United States, South Korea, and Australia, 80 were from South Korean study sites; 58 (72.5%) South Koreans and 315 (49.5%) non-Koreans completed the study. Within-group improvements in all efficacy measures from baseline to week 108 were statistically significant ($P<0.05$). Mean change in headache-day frequency (SD) at week 108 was similar for South Koreans and non-Koreans (–11.8 [7.8] vs –10.6 [6.2]; $P=0.115$). However, at week 108, the South Korean subgroup showed significantly greater reductions in moderate to severe headache days (–10.8 [7.0] vs –9.3 [5.9]; $P=0.040$) and in HIT-6 scores (–9.8 [8.6] vs –6.7 [7.0]; $P<0.001$). Treatment-related AEs occurred less frequently in South Koreans than non-Koreans (7.5% vs 19.7%). In the COMPEL study, onabotulinumtoxinA was an effective and well-tolerated preventive treatment for South Koreans with CM.

Keywords: Chronic migraine; COMPEL; efficacy; Korean; onabotulinumtoxinA; tolerability

INTRODUCTION

Chronic migraine (CM) is characterized by headaches that occur on 15 or more days per month, with migraine attacks on at least 8 of those days, for a period of at least 3 months.[1] CM has a worldwide prevalence of 1.4% to 2.2% in adults[2] and is associated with increased disability, quality of life impairments, medical and psychiatric comorbidities, and greater health care utilization.[3,4] In Asia, the reported prevalence of CM is 1.0% to 1.7%.[2] However, migraine treatment response data in Asian populations are limited, with a particular need for additional study in Koreans.[5,6] The Korean Headache Survey, a nationwide, cross-sectional, population-based survey, estimated 1-year prevalence of migraine (based on number of cases per 100 individuals) to be 17.5% and determined CM to be the predominant form of chronic daily headache in South Korea.[5,7] In a small South Korean population sample, severe migraine-related disability affected approximately 40% of adults with CM, as assessed by the 6-item Headache Impact Test (HIT-6).[7] CM in South Korea also has been associated with an increased risk of anxiety and depression[8] and suicidal ideation.[9] Nevertheless, based on Korean Headache Survey data, fewer than 50% of South Koreans may seek a medical consultation for chronic daily headache.[7,10] In addition, a large nationwide survey on traditional Korean medicine

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for chronic diseases suggests that up to 20% of South Koreans with migraine may be using traditional medicine for treatment.[11]

The Phase 3 Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials were the first large double-blind trials to demonstrate the favorable efficacy and safety profile of onabotulinumtoxinA (Botox®, Allergan plc, Dublin, Ireland) as preventive treatment for CM.[12] Smaller studies have demonstrated that onabotulinumtoxinA has favorable efficacy profiles in South Korean[13] and Taiwanese[14] patients. However, lateral eyebrow elevation appears to be a more common adverse event (AE) in those from Asia[13,14] than in predominantly white populations.[12]

The Chronic Migraine OnabotulinumtoxinA Prolonged Efficacy Open Label (COMPEL) study evaluated the long-term (108-week) efficacy and safety of onabotulinumtoxinA in adult patients with CM in study centers located in Australia, South Korea, and the United States.[15] The results supported the efficacy and safety of onabotulinumtoxinA for the prevention of headaches in adults with CM for up to 108 weeks.[16] A post hoc analysis was conducted to evaluate the efficacy and safety of onabotulinumtoxinA in the South Korean subgroup of the COMPEL study population.

METHODS

Study design and treatment

COMPEL (ClinicalTrials.gov identifier NCT01516892) was an international, multicenter, open-label, long-term, prospective study conducted in adults with CM. Study design and methodology have been published previously.[15] Briefly, the study included 24 US, 6 South Korean, and 5 Australian study sites, and patients received injections of onabotulinumtoxinA 155 U for CM, with or without concomitant stable oral preventive treatment, at 31 fixed sites across 7 head and neck muscle areas every 12 weeks for 9 treatment cycles (108 weeks), according to the recommended injection paradigm.[17]

Study patients

Adults aged ≥18 years with a diagnosis of CM (≥15 headache days/month) were eligible for inclusion if they had not previously received onabotulinumtoxinA for any reason. Other key inclusion criteria included a stable medical condition, a negative urine pregnancy test at screening, and the ability to follow instructions and attend follow-up visits. Individuals were excluded if they had a clinically significant medical condition (aside from CM) or a condition that might put the patient at increased risk with exposure to onabotulinumtoxinA. Individuals were also excluded due to a diagnosis of chronic tension-type headache, cluster headache, hypnic headache, hemicrania continua, or headache attributed to another disorder, severe major depressive disorder, suicidal ideation, or nursing, planning a pregnancy during the study, or not using a reliable form of contraception (for females of childbearing potential).[16] This study was approved by the Quorum Review Institutional Review Board (Seattle, WA, USA) and was conducted in compliance with Good Clinical Practice. Written informed consent was obtained from each patient prior to enrollment in the study.[15] Patients were withdrawn from the study for safety reasons if they became pregnant or showed any signs of suicidal ideation.

For the present analysis, the South Korean subgroup consisted of all patients enrolled at South Korean study sites, and the non-Korean subgroup comprised all patients enrolled at US and Australian study sites.

Assessments

The primary efficacy measure was the change from baseline in headache-day frequency for the 28-day period ending at week 108 (after 9 treatment cycles). Secondary efficacy measures included headache-day frequency in the 28-day period ending at week 60 (after 5 treatment cycles) and change from baseline in HIT-6 at weeks 60 and 108. Exploratory efficacy measures included changes from baseline in moderate to severe headache days and in measures of migraine-related disability on the Migraine Disability Assessment (MIDAS) questionnaire and quality of life on the Migraine-Specific Quality of Life (MSQ) questionnaire. In addition, the relationship between onabotulinumtoxinA and changes in depressive symptoms, as assessed by the 9-item Patient Health Questionnaire (PHQ-9), and in symptoms of anxiety, as assessed by the 7-item Generalized Anxiety Disorder (GAD-7) questionnaire, was explored. Safety and tolerability were assessed at each visit for patients who received at least 1 onabotulinumtoxinA treatment. Outcomes for the above assessments were compared between the South Korean and non-Korean subgroups.

Statistical analyses

A 2-sided paired *t*-test was used to compare efficacy outcomes with baseline measures. The *t*-test was also used to assess the difference in the change from baseline between the South Korean and non-Korean subgroups.

An intention-to-treat (ITT) analysis was undertaken on all patients with 1 or more efficacy assessments for the primary efficacy analysis. Modified last observation carried forward methodology was used to impute missing headache day data and missing post-baseline HIT-6 scores, including data for those who withdrew from the study. The approach and rationale have been described previously.[16] Observed data were used for exploratory outcome measures.

RESULTS

Patient disposition and demographics

A total of 716 adults were enrolled in the COMPEL study across all 35 study sites. The South Korean subgroup consisted of 80 study patients. The ITT population comprised 715 patients, inclusive of all South Koreans; 25 patients with fewer than 15 headache days per month at baseline were also included in the ITT population. All South Korean patients, however, had 15 or more headache days/month.

A greater percentage of South Korean patients (n=58, 72.5%) than non-Korean patients (n=315, 49.5%) completed the study. The key reasons for study discontinuation among South Korean patients were withdrawal of consent, loss to follow-up, or protocol violation (Table 1). Only 1 South Korean patient withdrew from the study because of an AE. South Korean patients had a similar mean age as non-Koreans, but a lower mean body mass index. South Korean patients also were found to have an older mean age at onset of CM, shorter time since CM onset, and reduced likelihood of a family history of migraine. South Koreans were less likely than non-Korean patients to have taken either acute (90% vs 99.8%) or preventive treatment (56.2% vs 84.0%) for migraine (Table 1).

Efficacy outcomes

South Korean and non-Korean study patients exhibited similar mean (SD) headache days at baseline: 21.9 (4.4) and 22.0 (4.9), respectively (Supplementary Figure 1A). The mean (SD) change from baseline in headache-day frequency for the 28-day period ending at week 108 (the primary endpoint) was significant in both the South Korean and non-Korean subgroups (–11.8 [7.8] and –10.6 [6.2], respectively; both $P<0.001$ vs baseline). There were no significant differences between subgroups (Figure 1A).

Both subgroups also experienced significant mean changes from baseline in headache-day frequency for the 28-day period ending at week 60 (secondary endpoint) as well as at week 24 (both $P<0.001$). Again, there were no significant between-group differences. After 24 weeks, 43.9% of the South Korean population and 39.1% of the non-Korean population had experienced a 50% or greater reduction in headache days from baseline (mean difference between populations of 4.8% [95% CI: –7.9%, 17.6%]). This proportion further improved to 54.7% and 53.9%, respectively, at week 60 (mean difference: 0.8% [95% CI: –12.4%, 14.1%]) and 64.3% and 61.4%, respectively, at week 108 (mean difference: 2.8% [95% CI: –11.1%, 16.8%]).

The frequency of moderate to severe headache days at baseline was also similar across subgroups, with mean (SD) moderate to severe headache days of 17.6 (6.1) in South Korean and 18.0 (5.6) in non-Korean patients (Supplementary Figure 1B). Both the South Korean and non-Korean subgroups experienced significant mean changes from baseline in moderate to severe headache days per 28 days at weeks 24, 60, and 108 (all $P<0.001$ vs baseline; Figure 1B). The reduction in moderate to severe headache days was significantly greater in the South Korean population at week 108 than in the non-Korean population ($P=0.040$).

The mean (SD) change from baseline in HIT-6 total scores following treatment with onabotulinumtoxinA (secondary endpoint) was significant in both the South Korean and non-Korean populations at weeks 24, 60, and 108 (all $P<0.001$ vs baseline; Figure 2A). The reduction in HIT-6 scores was significantly greater in the South Korean population at week 108 than in the non-Korean population ($P<0.001$). After 24 weeks, 61.3% of the South Korean population and 53.4% of the non-Korean population had a 5 point or greater change in HIT-6 scores (mean difference between populations of 7.9% [95% CI: –3.5%, 19.2%]); this further improved in the South Korean population to 63.8% after 60 weeks (non-Korean population: 59.4%; mean difference between populations of 4.4% [95% CI: –6.9%, 15.6%]) and to 70.0% after 108 weeks (non-Korean population: 56.9%; mean difference between populations of 13.1% [95% CI: 2.4%, 23.9%]).

Table 1: Patient disposition and demographics and baseline clinical characteristics of the South Korean and non-Korean subgroups

Variable	South Korean population (n=80)	Non-Korean population (n=636)
Withdrew from study, n(%)	**22 (27.5)**	**321 (50.5)***
Patient withdrew consent	12 (15.0)	80 (12.6)
Lost to follow-up	6 (7.5)	76 (11.9)
Protocol violation	3 (3.8)	57 (9.0)
Other	0 (0.0)	43 (6.8)
Lack of efficacy	0 (0.0)	35 (5.5)
Adverse event	1 (1.3)	24 (3.8)
Pregnancy	0 (0.0)	5 (0.8)
Age, years, mean (SD)	46.2 (11.0)	42.6 (11.3)
Female, n (%)	55 (68.8)	552 (86.8)
Race, n (%)		
Asian	80 (100.0)	9 (1.4)
White	0 (0.0)	582 (91.5)
Body mass index, kg/m^2, mean (SD)	23.3 (3.2)	27.9 (6.6)
PHQ-9 total score, mean (SD)	8.5 (4.8)	9.3 (5.6)
GAD-7 total score, mean (SD)	7.8 (5.5)	6.1 (5.3)
Age of onset of CM, years, mean (SD)	41.7 (11.6)	31.3 (13.5)
Time since onset of CM, years, mean (SD)	4.7 (6.1)	11.3 (11.3)
Family history of migraine, yes, n (%)	30 (37.5)	419 (65.9)
Medication use, n (%)		
Previously taken acute medications	72 (90.0)	635 (99.8)
Previously taken preventive medications	45 (56.2)	534 (84.0)
Severity of pain during headache, n (%)		
Mild	1 (1.3)	2 (0.3)
Moderate	29 (36.3)	267 (42.0)
Severe	50 (62.5)	367 (57.7)

CM, chronic migraine; GAD-7, 7-item Generalized Anxiety Disorder questionnaire; PHQ-9, 9-item Patient Health Questionnaire; SD, standard deviation.
*Primary reason for discontinuation missing for 1 patient.

OnabotulinumtoxinA was also associated with a significant change in MIDAS total scores from baseline for the South Korean and non-Korean populations at weeks 24, 60, and 108 (all P<0.001 vs baseline; Figure 2B). There was no significant difference between the South Korean and non-Korean populations at any time point. Similarly, onabotulinumtoxinA was associated with a significant change in all MSQ subscale scores from baseline at week 108 in both the South Korean and non-Korean patients (Figure 3). For both subgroups, changes from baseline in the mean MSQ-Role Function Preventive score, MSQ-Role Function Restrictive score, and MSQ-Emotional Function score at weeks 24, 60, and 108 were significant (all P<0.001). The change in MSQ subscale scores from baseline was numerically lower in the South Korean population at week 108 for MSQ-Role Function Preventive and MSQ-Role Function Restrictive, and significantly lower at all time points for MSQ-Emotional Function. OnabotulinumtoxinA was also associated with significant changes from baseline in mean PHQ-9 scores and GAD-7 scores at weeks 24, 60, and 108 (all P<0.001 vs baseline; Figure 4). There was no significant difference between populations

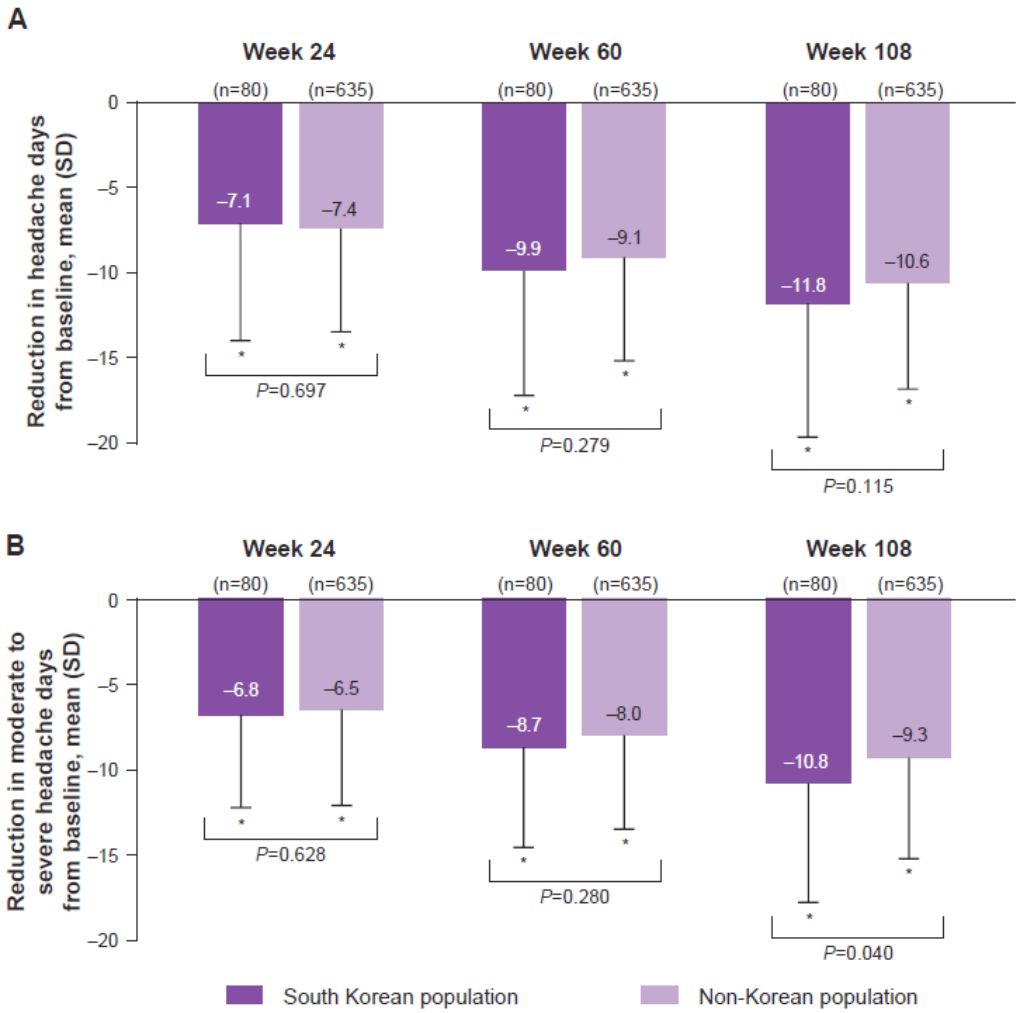


Figure 1. Effect of onabotulinumtoxinA on change in (A) headache days and (B) moderate to severe headache days from baseline in the South Korean and non-Korean populations.
*Indicates $P<0.001$ for within-group change from baseline; missing data imputed using modified last observation carried forward.
P values on the figure indicate between-group comparisons.

Table 2: Summary of AEs in Korean and non-Korean populations

AE, n (%)	South Korean population (n=80)	Non-Korean population (n=636)
TEAE		
≥1 TEAE	43 (53.8)	393 (61.8)
Serious TEAE	10 (12.5)	65 (10.2)
TEAE in those who discontinued therapy	1 (1.3)	31 (4.9)
TRAE		
≥1 TRAE	6 (7.5)	125 (19.7)
Serious TRAE	0 (0.0)	1 (0.2)
TRAE in those who discontinued therapy	0 (0.0)	13 (2.0)

AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

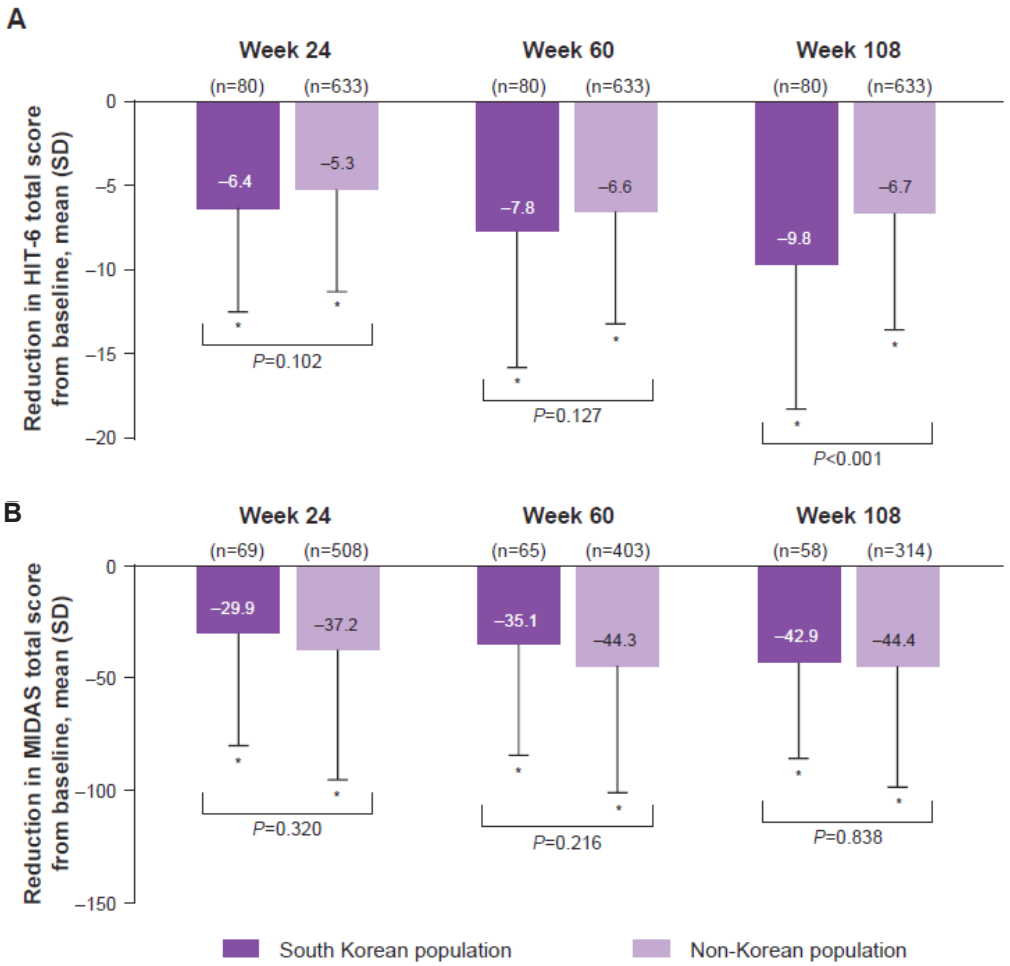


Figure 2. Effect of onabotulinumtoxinA on the change in (A) HIT-6 and (B) MIDAS scores from baseline in the South Korean and non-Korean populations.
HIT-6, 6-item Headache Impact Test; MIDAS, Migraine Disability Assessment questionnaire.
*Indicates $P<0.001$ for within-group change from baseline; missing data imputed using modified last observation carried forward for HIT-6; observed data used for MIDAS scores.
P values on the figure indicate between-group comparisons.

for PHQ-9 or GAD-7 scores at any time.

Safety and tolerability

OnabotulinumtoxinA was well tolerated in the overall study population, including the South Korean and non-Korean subgroups. Treatment-emergent AEs were reported in 43 (53.8%) South Korean patients and 393 (61.8%) non-Korean patients (Table 2). Serious treatment-emergent AEs were reported in a similar percentage of South Korean (12.5%) and non-Korean patients (10.2%). A slightly lower percentage of South Koreans (1.3%) discontinued treatment due to a treatment-emergent AE than was observed for non-Koreans (4.9%). Treatment-related AEs occurred substantially less frequently in the South Korean population (7.5%) than in the non-Korean population (19.7%). No South Korean patient experienced a serious treatment-related AE compared to 1 (0.2%) non-Korean patient. No South Korean patients discontinued treatment due to a treatment-related AE compared to 2.0% of non-Korean patients.

No new or unexpected treatment-related AEs occurred in the South Korean population (skin tightness, n=3, 3.8%; facial paresis, n=2, 2.5%; eyelid edema and eyelid ptosis, both n=1, 1.3%). Treatment-related AEs occurring in more than 1% of the non-Korean population included neck pain (n=29, 4.6%), musculoskeletal stiffness (n=17, 2.7%), eyelid ptosis (n=17, 2.7%), injection site pain (n=14, 2.2%), headache (n=12, 1.9%),

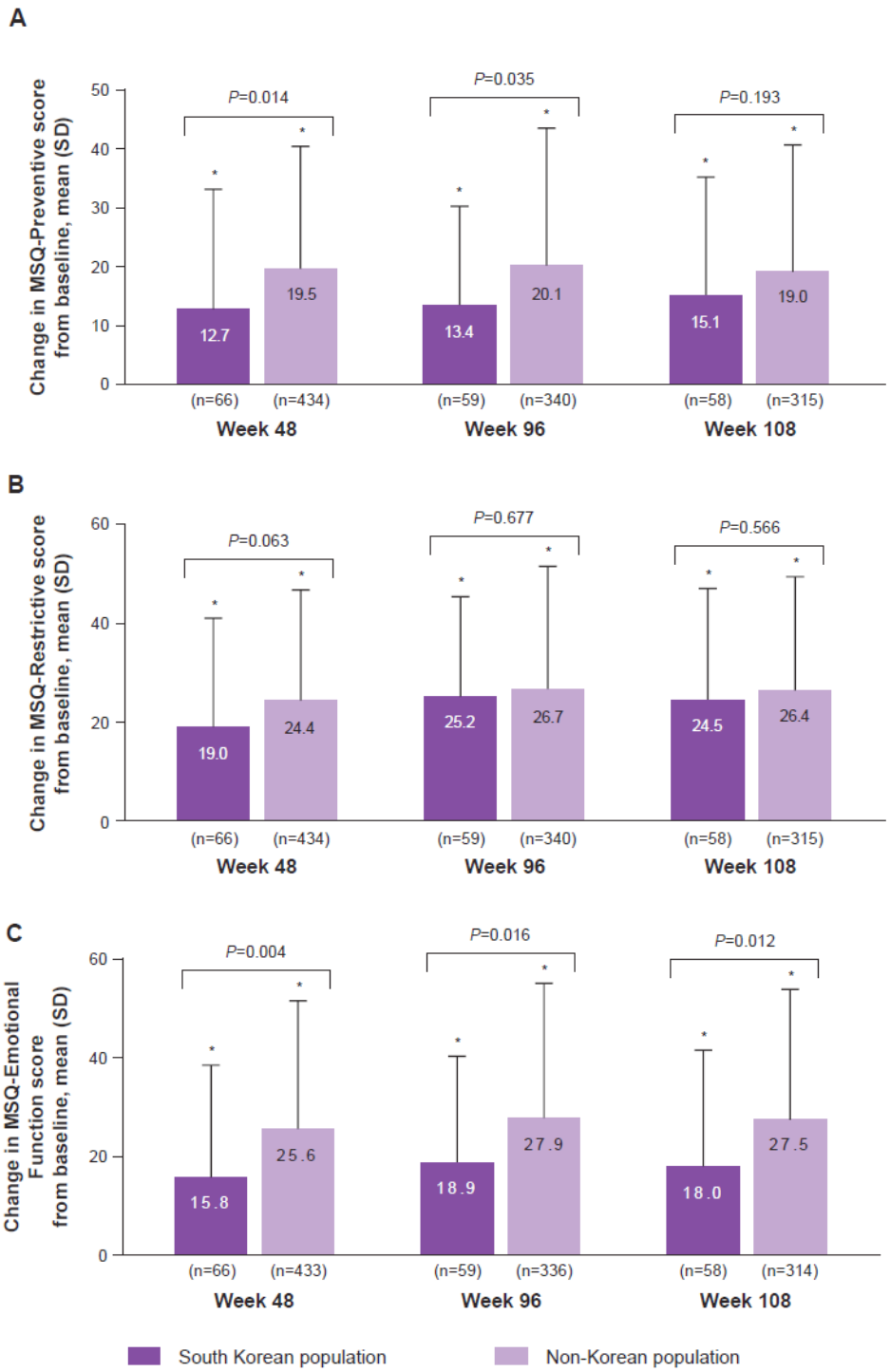


Figure 3. Effect of onabotulinumtoxinA on the change in MSQ (A) Role Function-Preventive, (B) Role Function-Restrictive, and (C) Emotional Function scores in the South Korean and non-Korean populations.
MSQ, Migraine-Specific Quality of Life questionnaire.
*Indicates $P<0.001$ for within-group change from baseline; observed data used.
P values on the figure indicate between-group comparisons.

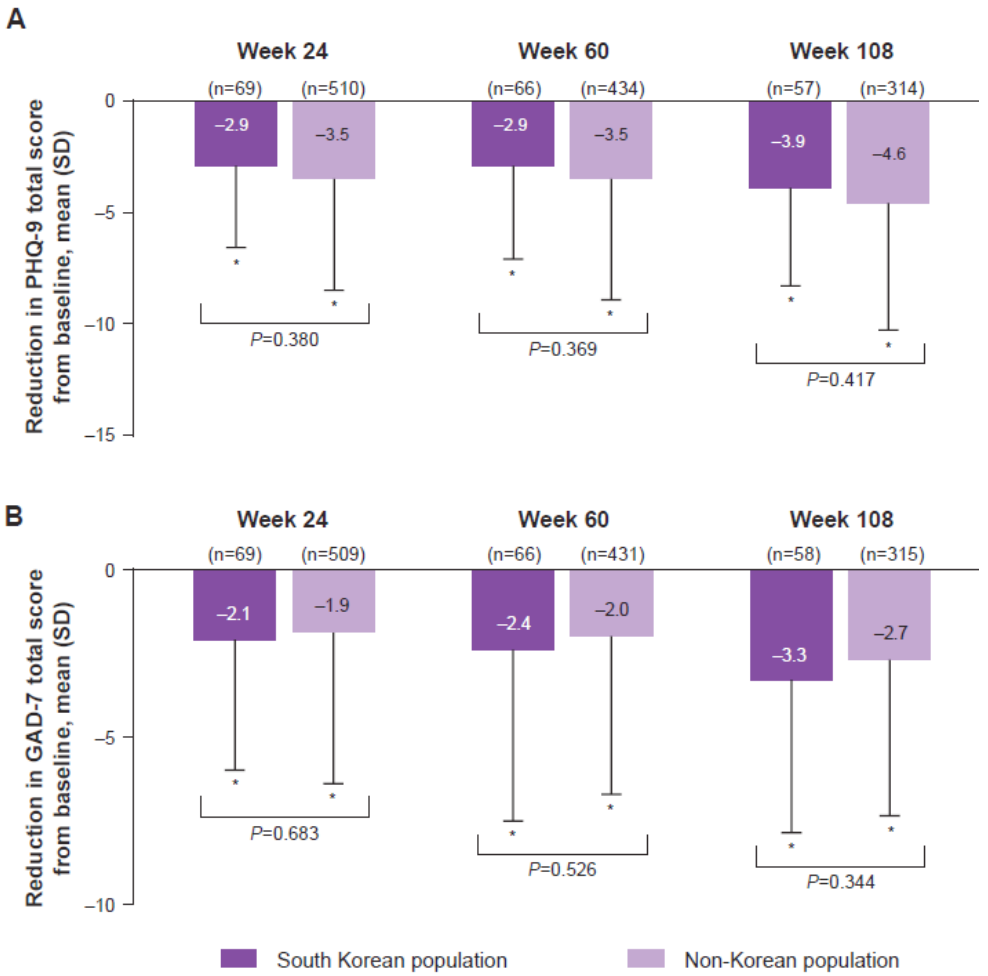


Figure 4. Effect of onabotulinumtoxinA on change from baseline for (A) PHQ-9 scores and (B) GAD-7 scores in the South Korean and non-Korean populations.
*Indicates $P<0.001$ for within-group change from baseline; observed data used.
GAD-7, 7-item Generalized Anxiety Disorder questionnaire; PHQ-9, 9-item Patient Health Questionnaire.

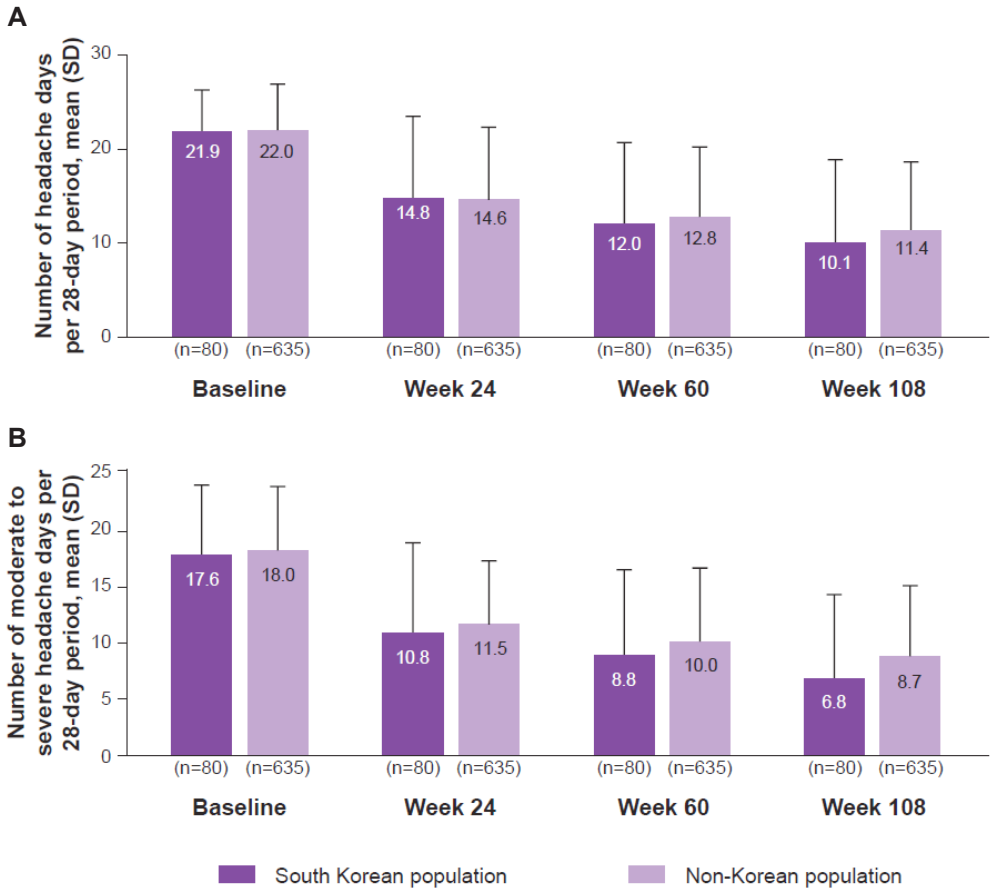
muscular weakness (n=10, 1.6%), facial paresis (n=7, 1.1%), and migraine (n=7, 1.1%).

DISCUSSION

The COMPEL study provides additional evidence for the long-term efficacy of onabotulinumtoxinA for the prevention of headache in CM and the consistency of effect over 9 treatment cycles (108 weeks).[16] In this subanalysis of the COMPEL data in South Korean study patients, onabotulinumtoxinA treatment was associated with a reduction in mean headache day frequency compared with baseline over 9 treatment cycles (108 weeks), improved HIT-6 scores, and reduced moderate or severe headache days.

Existing data pertaining to the efficacy and safety of onabotulinumtoxinA in South Koreans with CM are limited. A retrospective analysis of subjective improvements in headache after a single treatment cycle with onabotulinumtoxinA demonstrated that 83.9% of the 62 individuals followed up at 3 months had a moderate response (ie, there was improvement, but migraine attacks continued) to good response (ie, there were no migraine attacks after treatment).[13] Using more objective criteria (ie, headache diaries), a retrospective review of 94 Taiwanese patients with refractory CM reported that 39.4% of patients experienced a 30% or greater reduction in headache day frequency, corresponding to an average decrease of 6.5 headache days per 28-day period at week 12 after a single treatment cycle.[14]

The data presented in this study complement and reinforce these results, demonstrating a similar



Supplementary Figure 1. Effect of onabotulinumtoxinA on (A) headache frequency and (B) moderate to severe headache frequency in the Korean and non-Korean populations.

reduction in headache days after 2 treatment cycles (–7.1 headache days) with further improvement at 9 treatment cycles (–11.8 headache days). Furthermore, the results from the COMPEL study show that onabotulinumtoxinA treatment is associated with a beneficial effect across a range of efficacy measures in the South Korean population. Across the majority of primary and secondary efficacy measures, onabotulinumtoxinA was associated with efficacy in the South Korean subgroup equivalent to or greater than their non-Korean counterparts. Moderate to severe headache days and HIT-6 scores showed a significantly greater reduction from baseline in South Korean patients compared with non-Korean patients at week 108. Mean reduction in headache days showed a numerically greater change in South Korean patients compared with non-Korean patients at week 108; however, this difference was not significant (P=0.115). Regarding exploratory measures, there was little difference between South Koreans and non-Koreans except for the MSQ-Emotional Function subscale scores, where the change from baseline was significantly lower in the South Korean population at all reported times.

Overall, South Korean patients experienced fewer AEs and treatment-related AEs than non-Korean patients. This reduction in AEs may have contributed to the higher percentage of patients who completed the study in the South Korean compared with the non-Korean population (58/80, 72.5% vs 315/636, 49.5%). Other studies have reported that onabotulinumtoxinA is associated with a greater prevalence of appearance-related AEs in Asian people with migraine, including upward deviation of the lateral eyebrow.[14] It has been suggested that, to avoid lateral eyebrow elevation, broader spacing of forehead injections may be required in the Asian population.[13] In the COMPEL study, we found a slightly higher incidence of facial paresis (2.5% vs 1.3%) and skin tightness (3.8% vs 0.6%) in South Koreans compared with non-Korean patients. The

incidence of eyelid ptosis was slightly lower in the South Korean than the non-Korean population (1.3% vs 2.7%). Neck pain and eyelid ptosis were less common in the South Korean population in our study compared with a study from Taiwan[14] (neck pain: 0.0% vs 5.3%, respectively; eyelid ptosis: 1.3% vs 4.3%, respectively).

The reason for these favorable efficacy and safety outcomes in the subgroup of South Korean study patients is unclear, although differences in patient demographics, baseline characteristics, and injection technique may contribute. South Korean patients exhibited a lower mean BMI compared with non-Koreans (23.3 vs 27.9 kg/m^2, respectively), suggesting that low BMI was not a risk factor for AEs. South Korean patients also exhibited less refractory disease, as suggested by a lower proportion of Korean patients having previously received preventive treatment (56.2% vs 84%). Furthermore, insights into the practice and placement of onabotulinumtoxinA injections gained as a result of the earlier PREEMPT trials[18] were used in training modules for this study. It is likely that these insights led to a reduced incidence of appearance-related AEs in our population overall,[16] including treatments by Korean physicians in particular.

The strengths and limitations of the COMPEL study have been discussed previously in detail.[16] Given that the efficacy and safety of onabotulinumtoxinA have been established in placebo-controlled randomized clinical trials,[12] an open-label study is appropriate to further assess long-term efficacy and safety. Nonetheless, unintentional bias, low persistency rates, and changes in concomitant medication may complicate the interpretation of results.[16] Persistence rates were substantially higher for South Korean patients compared with non-Korean patients, further increasing the generalizability of our results in the South Korean population.

In conclusion, the results of this international, multicenter, open-label, long-term prospective study support the efficacy and safety of onabotulinumtoxinA for the prevention of headaches in adult South Korean study patients with CM for up to 108 weeks (9 treatment cycles). OnabotulinumtoxinA was effective in Korean patients with CM and was associated with a significantly greater reduction in moderate to severe headache days and headache-related impact of migraine at week 108 compared with non-Korean study patients. Furthermore, long-term onabotulinumtoxinA treatment was well tolerated in the South Korean population with no new safety concerns identified. Overall, these results support the efficacy and safety of onabotulinumtoxinA for up to 108 weeks (9 treatment cycles) in South Korean people with CM.

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RESEARCH DATA FOR THIS ARTICLE

Data reported in this manuscript are available within the article and its supplementary materials. Additional data from the COMPEL study (ClinicalTrials.gov identifier NCT01516892) may be requested at http://www.allerganclinicaltrials.com/PatientDataRequest.htm.

DISCLOSURE

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Conflict of interest: Byung-Kun Kim has received honoraria for lecture fees from Allergan, Pfizer, Sandoz, Abbott, and YuYu Pharma. Min Kyung Chu in the past 12 months has received honoraria from Allergan Korea and YuYu Pharma. Aubrey Manack Adams is an employee of Allergan plc and holds stock in the company. Andrew M. Blumenfeld within the past 12 months has served on advisory boards for Allergan, Amgen, Alder, Teva, Supernus, Promius, Eaglet, and Eli Lilly; he has received funding for speaking from Allergan, Amgen, Pernix, Supernus, Depomed, Avanir, Eli Lilly, Teva, and Promius; and he holds patents for onabotulinumtoxinA in migraine that Allergan owns.

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