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# OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program

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*Objective* – Chronic migraine (CM) is a prevalent and disabling neurological disorder. Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program assessed efficacy and safety of onabotulinumtoxinA (BOTOX®) for prophylaxis of headaches in adults with CM. This secondary analysis assessed patients who received all five treatment cycles and completed the study. *Materials and methods* – PREEMPT (two phase III studies: 24-week double-blind, placebo-controlled [DBPC], parallel-group phase, followed by 32-week open-label [OL] phase) evaluated the efficacy and safety of onabotulinumtoxinA in CM (≥15 days/month with headache lasting ≥4 h a day). Patients were randomized (1:1) to onabotulinumtoxinA or placebo every 12 weeks for two cycles, followed by onabotulinumtoxinA for three cycles. Multiple headache symptom measures were evaluated. Results for the completer (five cycles) subgroup of patients are reported. *Results* – Of 1384 total PREEMPT patients, 1005 received all five treatment cycles (513 received onabotulinumtoxinA only [onabotulinumtoxinA/onabotulinumtoxinA (O/O)] and 492 received two cycles of placebo then three cycles of onabotulinumtoxinA [placebo/onabotulinumtoxinA (P/O)]). Demographics were similar between treatment groups. At Week 56, after all patients were treated with onabotulinumtoxinA, there continued to be significant between-group differences favoring the O/O vs P/O group for the following headache symptom measures: LS mean change from baseline in frequencies of headache days (−12.0 O/O, −11.1 P/O; $P = 0.035$), migraine days (−11.6 O/O, −10.7 P/O; $P = 0.038$), and moderate/severe headache days (−11.0 O/O, −10.1 P/O; $P = 0.042$). For other measures (cumulative hours of headache on headache days, frequency of headache episodes, and percentage with severe Headache Impact Test (HIT)-6 score, and total HIT-6 and Migraine-Specific Quality of Life Questionnaire scores), there were also large mean improvements from baseline. The percent of patients with a ≥50% reduction from baseline in frequency of headache days was significantly greater for the onabotulinumtoxinA-only group at Week 56 (69.6% O/O, 62.8% P/O; $P = 0.023$). The treatment-related adverse event rate was 28.5% for onabotulinumtoxinA vs 12.4% for placebo in the DBPC phase and 34.8% for patients treated with onabotulinumtoxinA for all five cycles throughout the 56-week trials. *Conclusions* – This subgroup analysis demonstrated improvements

**S. K. Aurora[1], D. W. Dodick[2], H.-C. Diener[3], R. E. DeGryse[4], C. C. Turkel[4], R. B. Lipton[5], S. D. Silberstein[6]**

[1]Stanford University, Stanford, CA, USA; [2]Mayo Clinic Arizona, Phoenix, AZ, USA; [3]University of Essen, Essen, Germany; [4]Allergan, Inc., Irvine, CA, USA; [5]Albert Einstein College of Medicine, Bronx, NY, USA; [6]Thomas Jefferson University, Philadelphia, PA, USA



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S. K. Aurora, Department of Neurology & Neurological Sciences, Stanford University, 300 Pasteur Drive, Stanford, CA 94305, USA
Tel.: (650) 723-5184
Fax: (212) 614-5010
e-mail: saurora@stanford.edu

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with onabotulinumtoxinA treatment (five cycles) vs placebo (two cycles)/onabotulinumtoxinA (three cycles) for multiple headache symptom measures and suggests that at Week 56, patients treated earlier with onabotulinumtoxinA had better outcomes. These findings demonstrate the continued need and cumulative benefit over time with continued prophylaxis, an important and clinically pragmatic observation for clinicians and patients.

## Introduction

Chronic migraine (CM) is a disabling, underdiagnosed, and undertreated neurological disorder affecting approximately 2% of the population (1, 2). Currently, CM is defined as headache on ≥15 days per month for >3 months, with ≥8 days meeting criteria for migraine without aura or demonstrating response to migraine-specific treatment (3, 4).

Persons with CM have a poor health-related quality of life (HRQoL), which correlates with headache frequency and severity of disability (5). These patients may spend at least half their days suffering from debilitating pain and associated symptoms (5). More than 50% of patients with migraine have reported that their headaches result in severe disability or require bed rest (6). However, even though in comparison with episodic migraine (EM, <15 headache days per month) CM is associated with a significantly higher burden of illness (7), there are far fewer approved therapies for CM than for EM.

Although most individuals (~88%) with CM seek medical care, the majority of patients are underdiagnosed: only 20% of those with CM receive a diagnosis of CM, chronic daily headache, or transformed migraine (2). Additionally, in part due to the dearth of approved treatments for CM, it remains largely undertreated. Although most patients with CM meet Headache Consortium Guidelines for Prevention, a recent study demonstrated that just 33.3% of these patients were currently using preventive medications (2). This is despite the fact that preventive treatment has been shown to reduce the frequency of migraine headache days, as well as their severity and associated disability (8).

Considering the prevalence of CM around the globe, it is surprising that few clinical trials have investigated preventive medications over the long term or specifically for patients with CM (8). These patients have typically been excluded from clinical trials of prophylactic medications, despite the fact that recent epidemiological studies have demonstrated the substantial burden of this disease on the global population (9–11). One prophylactic option has been studied—onabotulinumtoxinA, or BOTOX® (Allergan, Inc., Irvine, CA, USA)—and it is thus far the only such therapy approved specifically for use within this patient population.

The recent Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program combined the two largest clinical trials conducted to date within this patient population. The results from this well-designed, placebo-controlled trial demonstrated that onabotulinumtoxinA was effective, safe, and well tolerated in the treatment of headaches in CM patients (12–14). Each arm of the PREEMPT studies included a 24-week double-blind phase and a 32-week open-label extension, making these studies the longest trials to date to examine headache prophylaxis within this population. The results from the entire 56-week trial demonstrated that patients treated with onabotulinumtoxinA had better outcomes than those treated with placebo (12). The following analysis examines the effects of onabotulinumtoxinA on the subset of CM patients in the PREEMPT clinical program who received all five treatment cycles of onabotulinumtoxinA.

## Materials and methods

### Study design

Full details of the PREEMPT study design and methodology have been previously described (12, 13). In brief, the PREEMPT clinical program consisted of two multicenter trials: PREEMPT 1 (NCT00156910) (15), conducted across 56 sites in North America, and PREEMPT 2 (NCT00168428) (14), conducted at 66 sites across North America and Europe. As described in Fig. 1, each phase III trial consisted of a 28-day baseline screening period and a 24-week double-blind, placebo-controlled phase (DBPC) with two injection cycles, followed by a 32-week open-label (OL) phase with three injection cycles. Patients used an interactive voice response system daily telephone diary to record their headache symptoms and acute headache medications, and study visits occurred every 4 weeks.

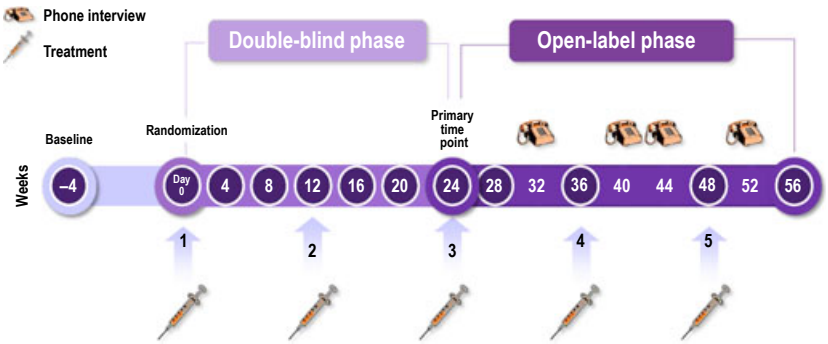


**Figure 1.** PREEMPT study design.

For the DBPC phase, patients were randomized (1:1) to onabotulinumtoxinA (155 U) or placebo. Patients were stratified by whether or not they overused acute headache medication during the 28-day baseline (with medication overuse defined as intake during baseline of simple analgesics on ≥15 days, or other medication types or combinations of types for ≥10 days, with intake on ≥2 days/week from the category of overuse). Study medications were administered as 31 fixed-site, fixed-dose, intramuscular injections across seven specific head/neck muscle areas every 12 weeks for 24 weeks (two cycles). If needed, an additional 40 U of onabotulinumtoxinA or placebo could be administered among three muscle groups (occipitalis, temporalis, or trapezius; a total of eight sites) using a protocol-defined, follow-the-pain strategy. The maximum total dose of onabotulinumtoxinA per cycle was 195 U in 39 sites. In the OL phase, all patients who completed the DBPC phase were eligible to receive onabotulinumtoxinA treatment at Weeks 24, 36, and 48.

Each investigator obtained approval from an Independent Ethics Committee or a local Institutional Review Board prior to study initiation.

### Study participants

Details on study participants and eligibility criteria have been described elsewhere (14, 15). Briefly, eligible patients were aged 18–65 years with a history of migraine as defined in the International Classification of Headache Disorders (ICHD)-II Section 1, Migraine, with the exception of 'complicated migraine' (4). During baseline, participants had to have headache occurring on ≥15 days/4 weeks, with each day consisting of ≥4 h of continuous headache, and ≥50% of headache days being migraine or probable migraine days (referred to as migraine days). They also had to experience ≥4 distinct headache episodes, each lasting ≥4 h during this period. No use of any headache prophylactic medication within 4 weeks prior to the start of baseline was allowed, although protocol-defined overuse of acute medications during the 28-day baseline period was not a criterion for exclusion. All patients were naïve to prior botulinum toxin of any serotype.

### Statistical analyses

PREEMPT data were pooled for integrated analysis of efficacy and safety; the complete statistical methodology has been published elsewhere (12, 13). The subanalyses presented here include only the patients who completed all five treatment cycles. The primary comparison between groups was by covariate analysis of variance (ANCOVA), with baseline count as covariate. Responder incidences and other binomial responses were compared using Pearson's chi-squared tests, except that logistic regression with baseline covariate was used for variables that had an imbalance at baseline. Missing data were imputed using a prespecified modified last-observation-carried-forward methodology, except for total Headache Impact Test (HIT)-6 (16) and Migraine-Specific Quality of Life Questionnaire (MSQv2.1) scores (17, 18) (observed data without imputation). Statistical comparisons in the OL phase were evaluated as mean change from baseline for all patients receiving onabotulinumtoxinA. Additional statistical comparisons in the OL phase were based on the patients' DB phase randomization to onabotulinumtoxinA or placebo. Treatment groups are referred to as onabotulinumtoxinA only (onabotulinumtoxinA/onabotulinumtoxinA [O/O]) or placebo then onabotulinumtoxinA treatment (placebo/onabotulinumtoxinA [P/O]).

### Efficacy and safety outcome measures

*Efficacy* – All efficacy analyses on the subgroup of patients who completed all five treatment

cycles were based on changes from the PREEMPT 28-day baseline (Week 0) to each 28-day period ending at Weeks 4, 8, 12, 16, 20, and 24 (DB phase) and Weeks 28, 32, 36, 40, 44, 48, 52, and 56 (OL phase). Specific endpoint definitions have been previously described (14, 15). The primary endpoint for the pooled analysis was mean change from baseline in the frequency of headache days at 24 weeks. The secondary endpoints included the change from baseline in the frequencies of migraine days, moderate/severe headache days, headache episodes, migraine episodes, and acute headache medication intakes, as well as the change from baseline in total cumulative hours of headache on headache days and the percent of patients with severe (≥60) HIT-6 score. The proportions of patients who experienced ≥50% reduction from baseline in frequencies of headache days, migraine days, moderate/severe headache days, headache episodes, migraine episodes, and total cumulative hours of headache on headache days were also determined. Headache impact on functioning, vitality, and psychological distress was measured by change from baseline in HIT-6 score and the proportion of patients with a ≥5-point change from baseline in individual HIT-6 score (according to the HIT-6 user guide, a ≥5-point decrease in HIT-6 score for an individual patient is considered clinically meaningful) (19). A between-group minimally important difference (MID) of ≥2.3 has been established for total HIT-6 score, as well (20). Health-related quality of life was measured by change from baseline in mean MSQv2.1 score across three domains: role function restrictive (RF), role function preventive (RP), and emotional functioning (EF). MIDs for all domains of the MSQv2.1 have also been established for between-group differences (3.2, 4.6, and 7.5 for RR, RP, and EF, respectively) and within-group changes (+10.9, +8.3, and +12.2 for RR, RP, and EF, respectively) (21, 22).

*Safety* – Safety and tolerability analyses were performed on all patients who completed the five cycles and received at least three doses of study medication.

## Results

### Baseline patient demographics

Of the 1384 total patients randomized in PREEMPT, 1005 received all five treatment cycles. Of these, 513 received onabotulinumtoxinA only (the O/O group), and 492 were randomized to two cycles of placebo and then three cycles of onabotulinumtoxinA (the P/O group). Of the 492, two patients received onabotulinumtoxinA for cycle one and are summarized with the P/O group for efficacy (as randomized) and with the O/O group for safety (as treated).

Demographics were similar between the treatment groups for most outcome measures (Table 1). The only observed significant baseline imbalances were in total cumulative hours of headache on headache days and in frequency of migraine and headache episodes (Table 1). This is consistent with the PREEMPT intent-to-treat population baseline demographics previously described (12, 13).

**Table 1** Pooled patient baseline demographics and characteristics

| | Patients who completed all five treatment cycles | | |
|---|---|---|---|
| | OnabotA/OnabotA ($n$ = 513) | Placebo/OnabotA ($n$ = 492) | $P$ value |
| Mean age, years (SD) | 41.4 (10.2) | 42.3 (10.7) | 0.243 |
| Female,% | 87.7 | 86.4 | 0.528 |
| Caucasian,% | 89.7 | 91.7 | 0.277 |
| Time since onset of CM, years (SD) | 19.6 (12.4) | 19.3 (12.6) | 0.584 |
| Mean frequency of headache days (SD) | 19.9 (3.7) | 19.8 (3.7) | 0.616 |
| Mean frequency of migraine days (SD) | 19.1 (4.0) | 19.0 (4.0) | 0.618 |
| Mean frequency of moderate/severe headache days (SD) | 18.1 (4.2) | 18.0 (4.2) | 0.928 |
| Mean frequency of cumulative hours of headache occurring on headache days (SD) | 292.8 (118.1) | 277.7 (117.4) | 0.043 |
| % Patients with severe (≥60) HIT-6 score* | 93.8 (24.2) | 92.9 (25.7) | 0.578 |
| Mean frequency of headache episodes (SD) | 12.4 (5.3) | 13.2 (5.6) | 0.017 |
| Mean frequency of migraine episodes (SD) | 11.6 (5.1) | 12.4 (5.5) | 0.011 |
| % Patients overusing acute headache medication† | 64.9 | 68.5 | 0.228 |
| Mean frequency of acute headache medication intakes | 26.6 (19.5) | 28.2 (21.2) | 0.224 |
| Mean HIT-6 score* (SD) | 65.4 (4.0) | 65.4 (4.3) | 0.702 |
| Mean MSQ score‡ | | | |
| Role restrictive | 39.0 (16.3) | 38.8 (17.3) | 0.613 |
| Role preventive | 56.7 (21.1) | 56.1 (21.5) | 0.682 |
| Emotional functioning | 43.3 (23.8) | 43.3 (25.1) | 0.972 |

CM, chronic migraine; HIT-6, Headache Impact Test-6; HRQoL, health-related quality of life; MSQ, Migraine-Specific Quality of Life Questionnaire; OnabotA, onabotulinumtoxinA; SD, standard deviation.

*HIT-6: scores of 36–49 indicate little or no impact; 50–55, some impact; 56–59, substantial impact; and 60–78, severe impact.

†Patients must have taken acute headache medication at least twice per week in each baseline week with ≥5 diary days and on ≥10–15 days (depending on medication category) during the baseline period.

‡MSQ: scores range from 0 (poor HRQoL) to 100 (good HRQoL).

Efficacy results: patients who completed all five treatment cycles

*Primary efficacy variable: frequency of headache days* – OnabotulinumtoxinA was significantly favored over placebo for the primary efficacy variable, mean change from baseline in frequency of headache days at all time points in the DBPC phase (Fig. 2). After all patients were treated with onabotulinumtoxinA in the OL phase, there continued to be significant between-group differences at all time points favoring those patients treated with onabotulinumtoxinA for five treatment cycles compared with those treated with placebo followed by onabotulinumtoxinA (Week 56: [−12.0 O/O vs −11.1 P/O; $P = 0.035$]; Table 2, Fig. 2).

*Secondary efficacy variables* – For all secondary efficacy variables evaluated, except acute headache medication intakes, there were statistically significant between-group differences favoring onabotulinumtoxinA over placebo at Week 24 (Table 2). There were also statistically significant decreases from baseline at Week 24 and Week 56, as indicated by the 95% confidence intervals (CIs; Table 2) for all of these measures. In addition, at Week 56, after all patients were treated with onabotulinumtoxinA, there were significant between-group differences favoring the early onabotulinumtoxinA-treated group vs the later onabotulinumtoxinA-treated group for mean change from baseline in frequency of migraine days (−11.6 O/O, −10.7 P/O; $P = 0.038$) and moderate/severe headache days (−11.0 O/O, −10.1 P/O; $P = 0.042$; Table 2).

*Fifty percent responder analysis* – By the end of the OL phase, approximately 70% of the early onabotulinumtoxinA-treated patients had a ≥50% reduction from baseline in frequency of headache days, and approximately 69% of the early onabotulinumtoxinA-treated patients had a ≥50%

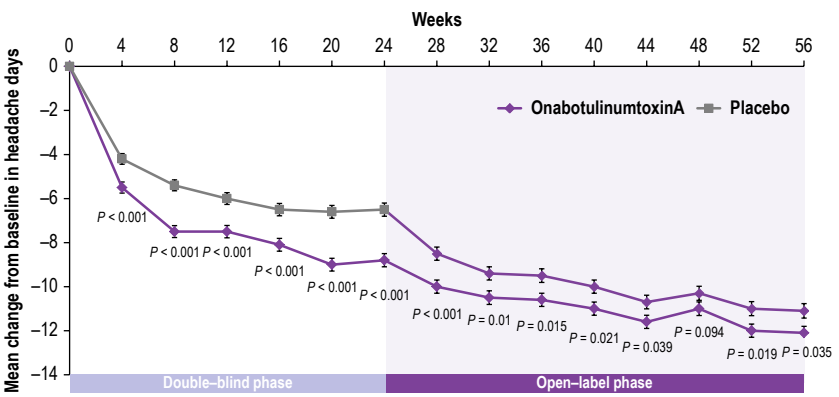


**Figure 2.** Mean change from baseline in frequency of headache days in patients who completed all five treatment cycles. Mean ± SE.

**Table 2** Efficacy at weeks 24 and 56 in patients who completed all five treatment cycles

| | Week 24 | | | Week 56 | | |
|---|---|---|---|---|---|---|
| LS mean change from baseline (95% CIs) | OnabotA ($n = 513$) | Placebo ($n = 492$) | *P* value* | OnabotA/OnabotA ($n = 513$) | Placebo/OnabotA ($n = 492$) | *P* value* |
| Frequency of HA days | −8.8 (−9.4, −8.2) | −6.5 (−7.1, −5.9) | <0.001 | −12.0 (−12.6, −11.5) | −11.1 (−11.8, −10.5) | 0.035 |
| Frequency of migraine days | −8.6 (−9.2, −8.0) | −6.2 (−6.7, −5.5) | <0.001 | −11.6 (−12.2, −11.0) | −10.7 (−11.3, −10.0) | 0.038 |
| Frequency of moderate/severe HA days | −8.2 (−8.7, −7.6) | −5.8 (−6.4, −5.2) | <0.001 | −11.0 (−11.5, −10.4) | −10.1 (−10.7, −9.5) | 0.042 |
| Total cumulative HA hours on HA days | −121.8 (−135.9, −112.2) | −82.0 (−91.9, −67.3) | <0.001 | −166.8 (−182.7, −158.2) | −151.2 (−160.5, −134.3) | 0.063 |
| Frequency of HA episodes | −5.9 (−6.1, −5.2) | −4.8 (−5.4, −4.4) | <0.001 | −8.1 (−8.3, −7.4) | −7.5 (−8.3, −7.3) | 0.057 |
| Frequency of migraine episodes | −5.5 (−5.8, −4.9) | −4.4 (−5.0, −4.1) | <0.001 | −7.5 (−7.7, −6.8) | −7.0 (−7.8, −6.8) | 0.088 |
| Frequency of acute HA medication intakes | −10.4 (−11.8, −8.7) | −9.3 (−11.0, −8.0) | 0.263 | −16.1 (−17.4, −14.1) | −16.1 (−18.2, −14.8) | 0.939 |
| Frequency of triptan intakes | −3.4 (−3.8, −2.8) | −2.1 (−2.8, −1.6) | <0.001 | −4.6 (−5.1, −3.9) | −4.2 (−5.0, −3.7) | 0.166 |

CI, confidence interval; HA, headache; OnabotA, onabotulinumtoxinA.
**P* values are adjusted for baseline.

reduction in frequency of migraine days. These results were significantly better than those found in the group of patients treated with placebo followed by three cycles of onabotulinumtoxinA (63%, $P = 0.023$ for frequency of headache days and 61%, $P = 0.006$ for frequency of migraine days; Fig. 3).

*Headache impact on disability, functioning, and health-related quality of life* – At Week 24, onabotulinumtoxinA treatment significantly improved headache impact compared with placebo as measured by the proportion of patients who had a severe (≥60) HIT-6 score (63% onabotulinumtoxinA vs 79% placebo; $P < 0.001$). Compared with placebo, onabotulinumtoxinA treatment significantly improved both total HIT-6 score ($P < 0.001$) and the proportion of patients who had a ≥5-point individual decrease in HIT-6 score at Week 24 ($P < 0.001$; Table 3). Additionally, for all role function domains of the MSQ, onabotulinumtoxinA treatment was significantly favored compared with placebo at Week 24 (Table 3). At Week 56, after all patients were treated with onabotulinumtoxinA, there continued to be significant improvements relative to baseline across all HIT-6 and MSQ measures (Table 3). However, at Week 56, there were no longer statistically significant differences in HRQoL measures between the group that received five treatment cycles and those that received three.

### Safety and tolerability results: patients who completed all five treatment cycles

The treatment-related adverse event (AE) rate was 28.5% for onabotulinumtoxinA vs 12.4% for placebo in the DB phase; it was 34.8% for patients treated only with onabotulinumtoxinA for all five cycles throughout the 56-week trials (Table 4). The most frequently reported treatment-related adverse events in patients who received all five treatment cycles of onabotulinumtoxinA were neck pain (4.3%), muscular weakness (1.6%), injection site pain (2.1%), and eyelid ptosis (1.9%).

These AEs are consistent with the known tolerability profile of onabotulinumtoxinA from the 24-week double-blind and 56-week analyses, and no new safety or tolerability issues emerged. Safety and tolerability results for the subgroup of

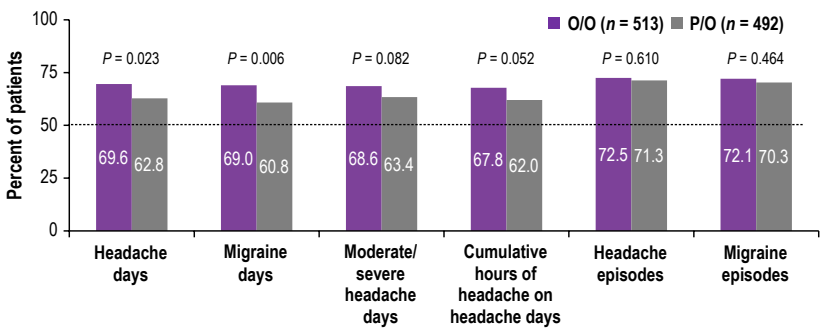


**Figure 3.** Percent of patients who completed all five treatment cycles and were classified as ≥50% responders at week 56.

**Table 3** Headache impact and HRQoL at weeks 24 and 56 in patients who completed all five treatment cycles

| | Week 24 | | | Week 56 | | |
|---|---|---|---|---|---|---|
| Mean (95% CIs) | OnabotA ($n = 513$) | Placebo ($n = 492$) | *P* value | OnabotA/OnabotA ($n = 513$) | Placebo/OnabotA ($n = 492$) | *P* value |
| % Patients with severe (≥60) HIT-6 score* | 62.6 (58.4, 66.8) | 78.5 (74.8, 82.1) | <0.001 | 47.8 (43.4, 52.1) | 49.4 (45.0, 53.8) | 0.605 |
| Mean change from baseline in HIT-6 score* | −5.5 (−6.1, −4.8) | −2.3 (−2.8, −1.8) | <0.001 | −8.1 (−8.9, −7.4) | −7.5 (−8.2, −6.7) | 0.157 |
| % Patients with ≥5-point reduction in HIT-6 score*† | 44.1 (39.8, 48.4) | 25.4 (21.6, 29.3) | <0.001 | 59.1 (54.8, 63.3) | 57.7 (53.4, 62.1) | 0.666 |
| Mean change from baseline in MSQ score‡ | | | | | | |
| Role restrictive | 18.3 (16.4, 20.3) | 8.5 (6.8,10.3) | <0.001 | 26.5 (24.3, 28.7) | 24.5 (22.3, 26.8) | 0.267 |
| Role preventive | 14.4 (12.5, 16.3) | 6.7 (−5.0, 8.4) | <0.001 | 20.3 (18.2, 22.4) | 19.7 (17.5, 21.9) | 0.675 |
| Emotional functioning | 19.6 (17.2, 22.0) | 9.7 (7.5, 11.8) | <0.001 | 26.2 (23.7, 28.8) | 24.6 (21.9, 27.3) | 0.210 |

CI, confidence interval; HIT-6, Headache Impact Test-6; HRQoL, health-related quality of life; MSQ, Migraine-Specific Quality of Life Questionnaire; OnabotA, onabotulinumtoxinA.

*HIT-6: scores of 36–49 indicate little or no impact; 50–55, some impact; 56–59, substantial impact; and 60–78, severe impact.

†A ≥5-point reduction is considered a clinically meaningful individual response.

‡MSQ: scores range from 0 (poor HRQoL) to 100 (good HRQoL).

**Table 4** Summary of adverse events in patients who completed all five treatment cycles

| | DB phase (24 weeks) | | OL phase (32 weeks) | Entire 56-week trial | |
|---|---|---|---|---|---|
| | OnabotA ($n$ = 515) $N$ (%) | Placebo ($n$ = 490) $N$ (%) | Any OnabotA ($n$ = 1005) $N$ (%) | Five cycles of OnabotA (O/O) ($n$ = 515) $N$ (%) | Three cycles of OnabotA (O/P) ($n$ = 490) $N$ (%) |
| All adverse events* (AEs) | 320 (62.1) | 260 (53.1) | 589 (58.6) | 403 (78.3) | 372 (75.9) |
| Treatment-related AEs† | 147 (28.5) | 61 (12.4) | 182 (18.1) | 179 (34.8) | 153 (31.2) |
| Serious AEs | 18 (3.5) | 11 (2.2) | 37 (3.7) | 38 (7.4) | 24 (4.9) |
| Treatment-related serious AEs | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.2) | 0 (0.0) |
| Deaths | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

515 patients include two patients who received placebo at cycle two and onabotulinumtoxinA at the other four cycles, these patients are not included in the efficacy analysis of randomized patients.

DB, double-blind; OL, open-label; OnabotA, onabotulinumtoxinA.

*All adverse events include all reported events, regardless of relationship to treatment.

†Treatment-related adverse events are those that in the investigator's opinion may have been caused by the study medication with reasonable possibility.

patients who completed all five treatment cycles were similar to the overall PREEMPT intent-to-treat population (12–14).

As shown in Table 5, the rate of treatment-related AEs progressively decreased with subsequent onabotulinumtoxinA injections, further supporting onabotulinumtoxinA as a safe and tolerable treatment.

## Discussion

Despite the availability of data demonstrating that CM is associated with significant disability and reduced HRQoL (2, 23), there are limited options presently available to effectively treat the CM population (24, 25). Although there are migraine-specific oral prophylactic medications available, none is approved for use in CM, leaving these patients with few treatment options; onabotulinumtoxinA is the only agent specifically approved for use as CM prophylaxis therapy.

PREEMPT is the largest clinical program to investigate the use of onabotulinumtoxinA as a prophylactic treatment for CM according to a defined set of diagnostic criteria and defined clinically relevant outcome measures. Results of the PREEMPT study have been previously published and have demonstrated onabotulinumtoxinA to be efficacious, safe, and tolerable in a CM population (12, 13, 15).

The present analysis of the 56-week PREEMPT clinical program extends earlier findings in support of onabotulinumtoxinA as a safe and effective long-term prophylactic treatment for CM, as it demonstrates statistically significant and clinically meaningful improvements with onabotulinumtoxinA treatment (five cycles) vs placebo (two cycles)/onabotulinumtoxinA (three cycles) for multiple headache symptom measures. The differences between the O/O and P/O groups at 56 weeks are small; also, many differences are not statistically significant because all study participants had been treated with onabotulinumtoxinA for at least three cycles by the end of trial, and therefore, we would not expect a big difference between treatment groups at 56 weeks. However, the analysis shows that patients continue to improve on onabotulinumtoxinA treatment. Patients who began treatment with onabotulinumtoxinA later in the trial had positive responses as well, but those treated earlier with onabotulinumtoxinA had better outcomes. Patients who received five treatment cycles did better at 56 weeks and continued to improve from baseline. This suggests that the longer a patient is treated with onabotulinumtoxinA, the more he or she will benefit—with continuing improvements seen at five treatment cycles.

Specifically, repeated treatment with onabotulinumtoxinA significantly reduced headache-related disability and improved functioning and overall HRQoL over the 56-week period. Patients who continued with treatment had a statistically significantly greater improvement in the frequencies of headache days (the primary outcome measure), migraine days, and moderate/severe headache days. Furthermore, more patients in the O/O group had a ≥50% reduction from baseline in frequency of headache days and migraine days than seen in patients in the P/O group, who started onabotulinumtoxinA later in the OL phase and therefore had only three treatment

**Table 5** Adverse events by treatment cycle for patients who received all five treatments of onabotulinumtoxinA

| Adverse event | Treatment cycle 1 ($N$ = 513) | Treatment cycle 2 ($N$ = 513) | Treatment cycle 3 ($N$ = 513) | Treatment cycle 4 ($N$ = 513) | Treatment cycle 5 ($N$ = 513) |
|---|---|---|---|---|---|
| Overall | 248 (48.3%) | 191 (37.2%) | 194 (37.8%) | 135 (26.3%) | 98 (19.1%) |

cycles of onabotulinumtoxinA. Additionally, patients who continued to receive onabotulinumtoxinA after the 24-week DBPC period continued to demonstrate ongoing improvement in other measures of efficacy, such as total cumulative headache hours on headache days (−121.8 after two treatments; −166.8 after five treatments), frequency of headache episodes (−5.9 after two treatments; −8.1 after five treatments), frequency of migraine episodes (−5.5 after two treatments; −7.5 after five treatments), frequency of acute headache medication intakes (−10.4 after two treatments; −16.1 after five treatments), and frequency of triptan intakes (−3.4 after two treatments; −4.6 after five treatments). The results after five treatment cycles of onabotulinumtoxinA were not compared statistically with the results after two treatment cycles, but we think the additional improvement is clinically significant.

There were no statistically significant differences in HRQoL measures between the participants who received five treatment cycles and those who received three. It is possible that patients who will respond to onabotulinumtoxinA feel an improvement in their HRQoL soon after beginning treatment and that that level is maintained. The HIT-6 score demonstrated better HRQoL, which was felt quickly with onabotulinumtoxinA treatment, and there was continued improvement with additional treatments as reflected by continued decrease in HIT-6 score with additional treatment cycles. Specifically, at Week 24, 44% of patients treated with two cycles of onabotulinumtoxinA had a ≥5-point reduction in HIT-6 score [a reduction of five points is considered a clinically meaningful individual response (19)]. At Week 56, after three more injections of onabotulinumtoxinA, the proportion of patients with a ≥5-point reduction in HIT-6 score increased to 59%.

In addition to these efficacy findings, onabotulinumtoxinA has been demonstrated to be a safe and well-tolerated treatment for the prophylaxis of headache in adults with CM (12, 14, 15). This is corroborated by the high proportion of patients who completed the 56-week study (72.6%), indicating a favorable tolerability profile for onabotulinumtoxinA. Additionally, there was no difference in baseline characteristics between the group that received five treatment cycles compared with subjects who did not complete all five treatment cycles ($N = 379$). Age, gender, race, BMI, and time since onset of migraine as well as acute and prophylactic medication use were all similar. Demographics were similar between subjects who completed all five treatments and the group that did not complete. In general, the incidence rates for total AEs were lower in the later treatment cycles. One possible explanation for the decrease in AEs is that patients are better able to tolerate onabotulinumtoxinA with continued exposure.

Most CM patients will require long-term management, but clinical trials assessing the effectiveness of longer term treatment for CM (≥1 year) are few in number. The advantages of the present analysis are the well-designed PREEMPT clinical trials, the length of study, and the large number of patients who completed the five treatment cycles, which allowed for meaningful results. A major limitation of this analysis is the bias introduced by patients who decided to drop out due to lack of efficacy (2.7%) or because of side effects (4.6%).

This subgroup analysis of the PREEMPT clinical program demonstrated statistically significant and clinically meaningful long-term improvements with onabotulinumtoxinA treatment (five cycles) vs placebo (two cycles)/onabotulinumtoxinA (three cycles) for multiple headache symptom measures in patients with CM. This analysis suggests that, at Week 56, CM patients treated earlier with onabotulinumtoxinA had better outcomes with repeated treatments. Continuing prophylaxis therapy with onabotulinumtoxinA significantly reduced headache-related disability and improved functioning and overall quality of life over the 56-week period. These observations are important to clinical practice, as many patients need to continue to receive treatment over the long term to manage this chronic condition, and according to this analysis, when they continue treatment, they will continue to receive benefit and the benefit continues to accrue, at least up to 56 weeks. No apparent efficacy plateau effect was reached after five treatment cycles. And no cumulative toxicity was observed. Additional studies would be needed to see when a plateau might be reached or if continued improvement could be expected for longer periods of time. The results of the present secondary analysis helped form the basis of an ongoing evaluation of the efficacy and tolerability of onabotulinumtoxinA for the prophylaxis of headaches in CM over a longer term period—beyond five treatments (26). Additionally, these data provide valuable information to clinicians who are currently treating CM.

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David W Dodick serves on advisory boards and has consulted for Allergan, Amgen, Alder, Arteaus, Pfizer, Merck, Coherex, Ferring, Neurocore, Neuralieve, Neuraxon, NuPathe, MAP, SmithKline Beecham, Boston Scientific, Medtronic, Inc., Nautilus, Eli Lilly & Company, Novartis, Colucid, GlaxoSmithKline, Autonomic Technologies, MAP Pharmaceuticals, Inc., Zogenix, Inc., Impax Laboratories, Inc., and Bristol Myers Squibb. Dr. Dodick has received funding for travel, speaking, or editorial activities from the following: CogniMed, Scientiae, IntraMed, SAGE Publishing, Lippincott Williams & Wilkins, Oxford University Press, Cambridge University Press, Miller Medical, and Annenberg for Health Sciences; he serves as Editor-in-Chief and on the editorial boards of *The Neurologist, Lancet Neurology*, and *Postgraduate Medicine* and has served as Editor-in-Chief of *Headache Currents* and as an Associate Editor of *Headache*. He receives publishing royalties for *Wolff's Headache,* 8th edition (Oxford University Press, 2009) and *Handbook of Headache* (Cambridge University Press, 2010).

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