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Research Submissions

OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Results From the Double-Blind, Randomized, Placebo-Controlled Phases of the PREEMPT Clinical Program

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Objective.—To assess the efficacy, safety, and tolerability of onabotulinumtoxinA (BOTOX®) as headache prophylaxis in adults with chronic migraine.

Background.—Chronic migraine is a prevalent, disabling, and undertreated neurological disorder. Few preventive treatments have been investigated and none is specifically indicated for chronic migraine.

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Conflict of Interest: D.W.D. has received honoraria from Allergan, Merck, Neuralieve, Coherex, Kowa, Minster, NeurAxon, H Lundbeck, Endo, Pfizer, Nupathe, and MAP Pharmaceuticals, in addition to being a consultant to and on the advisory board of these pharmaceutical companies. He has also received funding from Advanced Neurostimulation Systems, St. Jude Medical Center, and Medtronic. S.K.A. received, within the last 2 years, grants and research support from Advanced Bionics, Alexza, Allergan, Capnia, GlaxoSmithKline, MAP Pharmaceuticals, Merck and Co., Ortho-McNeil, Neuralieve, NuPathe, and Takeda. She is a consultant for Ortho-McNeil, Merck and Co., GlaxoSmithKline, Allergan, Neuralieve, NuPathe, and MAP Pharmaceuticals. She has also received honoraria from Merck and Co., GlaxoSmithKline, Kowa, NuPathe, and Ortho-McNeil. C.C.T., R.E.D., and M.F.B. are employees of Allergan, Inc., and own stock in the company. S.D.S. and R.B.L. have received honoraria and research funding from Allergan, Inc., in addition to being consultants to and on the advisory board of Allergan. H.C.D. received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Addex Pharma, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, CoLucid, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Grunenthal, Janssen-Cilag, Lilly, La Roche, 3M Medica, Minster, MSD, Novartis, Johnson & Johnson, Pierre Fabre, Pfizer, Schaper and Brummer, Sanofi-Aventis, Weber & Weber. He also received financial support for research projects from Allergan, Almirall, AstraZeneca, Bayer, GlaxoSmithKline, Janssen-Cilag, and Pfizer. Headache research at the Department of Neurology in Essen, where H.C.D. is Professor, is supported by the German Research Council (DFG), the German Ministry of Education and Research (BMBF), and the European Union.

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Methods.—The 2 multicenter, pivotal trials in the PREEMPT: Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy clinical program each included a 24-week randomized, double-blind phase followed by a 32-week open-label phase (ClinicalTrials.gov identifiers NCT00156910, NCT00168428). Qualified patients were randomized (1:1) to onabotulinumtoxinA (155-195 U) or placebo injections every 12 weeks. Study visits occurred every 4 weeks. These studies were identical in design (eg, inclusion/exclusion criteria, randomization, visits, double-blind phase, open-label phase, safety assessments, treatment), with the only exception being the designation of the primary and secondary endpoints. Therefore, the predefined pooling of the results was justified and performed to provide a complete overview of between-group differences in efficacy, safety, and tolerability that may not have been evident in individual studies. The primary endpoint for the pooled analysis was mean change from baseline in frequency of headache days at 24 weeks. Secondary endpoints were mean change from baseline to week 24 in frequency of migraine/probable migraine days, frequency of moderate/severe headache days, total cumulative hours of headache on headache days, frequency of headache episodes, frequency of migraine/probable migraine episodes, frequency of acute headache pain medication intakes, and the proportion of patients with severe (≥60) Headache Impact Test-6 score at week 24. Results of the pooled analyses of the 2 PREEMPT double-blind phases are presented.

Results.—A total of 1384 adults were randomized to onabotulinumtoxinA (n = 688) or placebo (n = 696). Pooled analyses demonstrated a large mean decrease from baseline in frequency of headache days, with statistically significant between-group differences favoring onabotulinumtoxinA over placebo at week 24 (–8.4 vs –6.6; $P < .001$) and at all other time points. Significant differences favoring onabotulinumtoxinA were also observed for all secondary efficacy variables at all time points, with the exception of frequency of acute headache pain medication intakes. Adverse events occurred in 62.4% of onabotulinumtoxinA patients and 51.7% of placebo patients. Most patients reported adverse events that were mild to moderate in severity and few discontinued (onabotulinumtoxinA, 3.8%; placebo, 1.2%) due to adverse events. No unexpected treatment-related adverse events were identified.

Conclusions.—The pooled PREEMPT results demonstrate that onabotulinumtoxinA is an effective prophylactic treatment for chronic migraine. OnabotulinumtoxinA resulted in significant improvements compared with placebo in multiple headache symptom measures, and significantly reduced headache-related disability and improved functioning, vitality, and overall health-related quality of life. Repeat treatments with onabotulinumtoxinA were safe and well tolerated.

Key words: botulinum toxin A, chronic migraine, prophylaxis

Abbreviations: AE adverse event, CDH chronic daily headache, CM chronic migraine, CTTH chronic tension-type headache, EM episodic migraine, HIT Headache Impact Test, HRQoL health-related quality of life, ICHD-II International Classification of Headache Disorders, second edition, IHS International Headache Society, ITT intent-to-treat, IVRS interactive voice response system, mLOCF modified last-observation carried forward, MPA mouse protection bioassay, MSQ Migraine-Specific Quality of Life Questionnaire, PREEMPT Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy, TNA toxin neutralizing antibodies

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Chronic migraine (CM) is a complex, progressive headache disorder affecting approximately 1.3-2.4% of the general adult population.[1-3] According to the second edition of the International Classification of Headache Disorders (ICHD-II) and subsequent revised ICHD criteria, CM is recognized as a complication of migraine that is distinguished from episodic migraine (EM) by the frequency of headache.[4,5] CM is characterized by headache on ≥15 days per month, of which at least 8 headache days per month meet criteria for migraine without aura or respond to migraine-specific treatment.[5] CM is associated with significant disability, reduced health-related quality of life (HRQoL), and considerable healthcare cost.[6,7] Patients with CM are less likely to attend social functions and perform household work compared with those with EM, and 1 in 5 CM sufferers is occupationally disabled, thereby affecting their ability to lead productive lives.[8,9] Few preventative treatments for CM have been investigated, and none is currently approved for CM prophylaxis.[10-13] The effectiveness of both acute migraine treatments and prophylactic medications may be further complicated by frequent overuse of acute headache pain medication (eg, simple analgesics, triptans, opioids, ergots) by this patient population.[14-16]

OnabotulinumtoxinA (BOTOX®; Allergan, Inc., Irvine, CA, USA) has shown efficacy in relieving pain associated with a variety of conditions, including migraine headache.[10,11,17-27] Previous exploratory trials

evaluating the efficacy and safety of onabotulinumtoxinA in headache prophylaxis have yielded mixed results.[10,11,28-30] In 2 large, randomized, placebo-controlled exploratory studies of EM, no significant between-group difference was observed in frequency of headache episodes.[28,29] The baseline mean number of headache days in these studies was approximately 8-10 per month. A study of chronic tension-type headache (CTTH) did not observe a significant difference favoring onabotulinumtoxinA in the number of headache-free days per month.[30] These trials have not established the efficacy of onabotulinumtoxinA in either EM or CTTH. However, it is possible that the study designs, including patient selection criteria, dosage, and injection paradigms, might not have been optimal in these exploratory studies.[10,11,28-30] Results from exploratory studies in patients with chronic daily headache (CDH) suggested efficacy with onabotulinumtoxinA within the CM patient population subset, warranting confirmation and further investigation.[10,11,31] Therefore, we designed and conducted 2 large, phase 3 studies to evaluate the efficacy, safety, and tolerability of onabotulinumtoxinA in adults with CM. A pooled analysis of these 2 Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) studies was performed to examine the durability and precision of the individual study efficacy and tolerability results and, potentially, to provide additional clinically relevant insights. We report herein the pooled results of the randomized, placebo-controlled, double-blind phases of these phase 3 studies.

METHODS

Study Design.—The PREEMPT studies were conducted from January 23, 2006 to July 16, 2008, at 56 North American sites in PREEMPT 1 and from February 7, 2006 to August 11, 2008, at 66 global sites (50 North American and 16 European) in PREEMPT 2. Predefined pooling of PREEMPT 1 and 2 studies was performed to confirm the efficacy, safety, and tolerability of onabotulinumtoxinA for prophylaxis of headaches in adults with CM and to provide additional statistical power to identify efficacy, safety, and tolerability results that could be missed if each study were reported only separately. Each study had a 28-day baseline screening phase (hereafter referred to as baseline) and a 24-week, double-blind phase with 2 injection cycles, followed by a 32-week, open-label phase with 3 injection cycles (Fig. 1). Patients used an interactive voice response system (IVRS) daily telephone diary to record their headache symptoms and acute treatments.

Both studies were conducted in accordance with the Declaration of Helsinki ethical principles, Good Clinical Practices, principles of informed consent, and requirements of public registration of clinical trials (ClinicalTrials.gov Identifiers NCT00156910 and

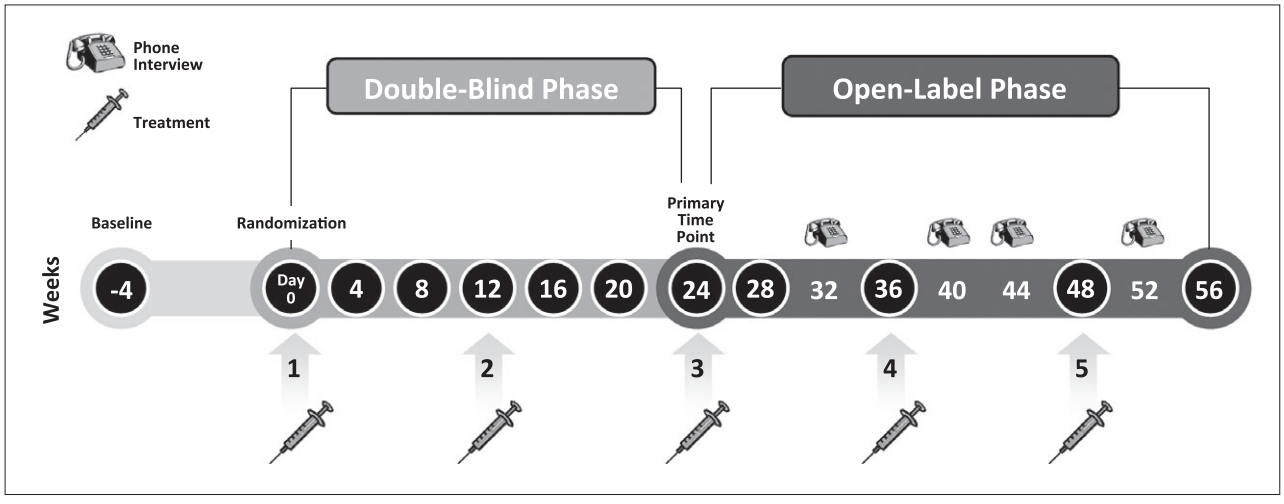


Fig 1.—Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) study design.

NCT00168428). Each investigator obtained approval from an Independent Ethics Committee or a local Institutional Review Board prior to study initiation. Written informed consent was obtained from each randomized patient.

Study Patients.—Inclusion and exclusion criteria of the individual PREEMPT studies were the same and are described elsewhere.[32,33] Briefly, eligible patients were men or women aged 18-65 years with a history of migraine meeting the diagnostic criteria listed in ICHD-II (2004) Section 1, Migraine,[4] with "complicated migraine" excepted. All patients were required during the 28-day baseline to provide diary data on ≥20 days and to have had ≥15 headache days (defined as a calendar day consisting of ≥4 hours of continuous headache), of which ≥50% were migraine or probable migraine days (referred to hereafter as migraine days), and to have had ≥4 distinct headache episodes each lasting ≥4 hours. Thus, patients with continuous headache were excluded. Patients were also excluded if they had used any headache prophylactic medication within 4 weeks prior to start of baseline, or had previous exposure to any botulinum toxin serotype or a positive urine pregnancy test.

Randomization, Stratification, and Study Treatment.—The recruitment period was between January 2006 and July 2007, with a 56-week follow-up period after the last patient was enrolled. Eligible patients were randomized (1:1) in double-blind fashion to onabotulinumtoxinA or placebo. Randomization, which has been previously described,[32,33] was stratified in blocks of 4 for each investigator site and by whether or not patients were overusing acute headache pain medication (yes/no) during the 28-day baseline according to protocol-defined frequency of use. Investigators were trained not to enroll patients who frequently used opioids as their acute headache pain medication.

OnabotulinumtoxinA 155 U or placebo was administered as 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas. At the investigator's discretion, an additional 40 U could be administered using a "follow-the-pain" strategy. The maximum dose was 195 U across 39 sites. Dosing and results of this study are specific to the formulation of onabotulinumtoxinA manufactured by Allergan, Inc.

Efficacy and Safety Measures.—For the pooled analyses, the primary efficacy endpoint was mean change from baseline in frequency of headache days for the 28-day period ending with week 24. Secondary efficacy variables evaluated in the pooled analyses included: frequency of migraine days, frequency of moderate/severe headache days, number of cumulative hours of headache on headache days, proportion of patients with severe (≥60 points) Headache Impact Test (HIT)-6 score,[34] frequency of headache episodes, frequency of migraine episodes, and frequency of acute headache pain medication intakes (all categories; referred to hereafter as acute pain medication intakes). Other efficacy analyses included the incidence of patients with a 50% or more decrease from baseline in the frequency of headache days and, separately, headache episodes. Additional assessments of disability, functioning, and HRQoL (eg, mean changes in total HIT-6; Migraine-Specific Quality of Life questionnaire [MSQ v2.1][35,36] evaluations) are also reported. All efficacy analyses primarily examined the mean change from baseline for the 28-day period ending with week 24. All efficacy analyses were also analyzed for the medication overuse stratum. These results will be reported elsewhere.

Statistical Analysis.—The pooled population sample provided >90% power to detect ≥1.75 between-group difference in mean change from baseline of the primary endpoint (headache days), using a 2-sided alpha = 0.05. The pooled population also had greater power than the individual studies[32,33] to identify any safety and tolerability findings.

All efficacy analyses used the intent-to-treat (ITT) population, which included all randomized patients. For each primary and secondary variable, comparisons between treatment groups were made by analysis of covariance of change from baseline, with the same variable's baseline value as a covariate, with main effects of treatment group and acute pain medication overuse strata. The baseline covariate adjustment was prespecified as the primary analysis. Missing data were imputed using a prespecified modified last-observation carried forward methodology (mLOCF) previously described.[32,33] For binomial variables, the between-group comparisons were performed with Pearson's chi-square or Fisher's exact

Table 1.—Baseline Demographics and Characteristics

	OnabotulinumtoxinA (n = 688)	Placebo (n = 696)	*P* value
Mean age, years	41.1	41.5	.579
Female, %	87.6	85.2	.185
Caucasian, %	89.7	90.5	.602
Mean headache days (SD)	19.9 (3.68)	19.8 (3.68)	.498
Mean migraine days (SD)†	19.1 (3.99)	18.9 (4.05)	.328
Mean moderate/severe headache days (SD)	18.1 (4.12)	18.0 (4.25)	.705
Mean cumulative hours of headache occurring on headache days (SD)	295.93 (116.88)	281.22 (114.74)	.021
Percent with severe (≥60) HIT-6 score‡	93.5	92.7	.565
Mean headache episodes (SD)	12.2 (5.25)	13.0 (5.5)	.004
Mean migraine episodes (SD)†	11.4 (5.02)	12.2 (5.42)	.004
Mean HIT-6 score‡	65.5	65.4	.638
Percent overusing acute headache pain medication§	64.8	66.1	.450

†ICHD-II 1.1 (migraine without aura), 1.2 (migraine with aura), 1.6 (probable migraine).[4]
‡Scores of 36-49 indicate little or no impact; 50-55, some impact; 56-59, substantial impact; ≥60, severe impact.
§Patients must have taken acute headache pain medication at least twice per week in any week with ≥5 diary days and ≥10-15 days (depending on medication category) during the baseline period.
HIT = Headache Impact Test.

tests, except that logistic regression with baseline covariate was used for variables with baseline imbalance. This a priori planned analysis corrected for the baseline imbalance. A 2-sided test with $P \leq .05$ was considered to be statistically significant.

Safety analyses were performed on all randomized patients who received at least 1 dose of study medication at day 0.

Contributors.—All authors formed the core writing team for the manuscript and contributed to study conception, design, data analysis, and interpretation. C.C.T., R.E.D., and M.F.B. also provided administrative support and were involved in the collection and/or assembly of data for the PREEMPT trials. S.K.A., S.D.S., R.B.L., and H.C.D. provided patients for the PREEMPT trials. All authors contributed to and commented on the manuscript draft and gave their final approval to submit for publication.

RESULTS

Demographic and Baseline Headache Characteristics.—A total of 3333 patients were screened for the PREEMPT studies, with 1384 patients randomized and thus included in the pooled analyses (n = 688 onabotulinumtoxinA; n = 696 placebo). At baseline, there were no notable differences between the pooled treatment groups for most of the important demographic characteristics (Table 1). However, at baseline the onabotulinumtoxinA group compared with the placebo group on average had significantly fewer headache episodes (12.2 vs 13.0; $P = .004$) and migraine episodes (11.4 vs 12.2; $P = .004$), and significantly more total cumulative hours of headache occurring on headache days (295.9 vs 281.2; $P = .021$) (Table 1). Most patients overused acute pain medications during the 28-day baseline; however, very few (1.7%) had opioid overuse.

The rate of patient compliance in reporting diary data was high both at baseline (>99%) and throughout the 24-week double-blind phases (>93%). There was no difference in diary compliance between treatment groups.

Efficacy Results.—*Primary Variable: Frequency of Headache Days.*—There was a large mean reduction from baseline in the frequency of headache days in both treatment groups. However, onabotulinumtoxinA was statistically significantly more effective than placebo in reducing the mean frequency of headache days at every visit in the double-blind phase

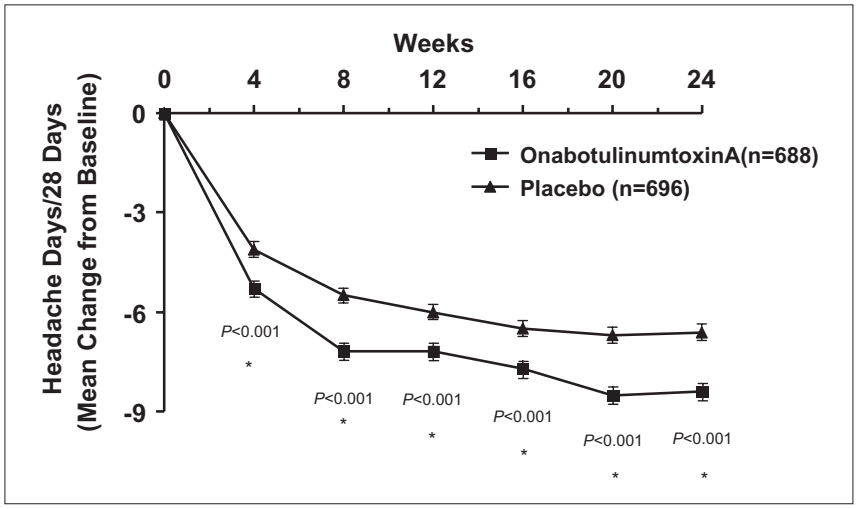


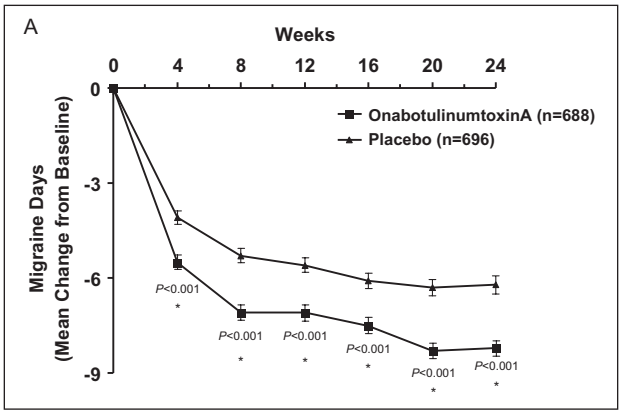
Fig 2.—Primary variable: mean change from baseline in frequency of headache days. Headache days at baseline: 19.9 ± 0.1 onabotulinumtoxinA group versus 19.8 ± 0.1 placebo group, *P* = .498. All data are presented as mean ± standard error.

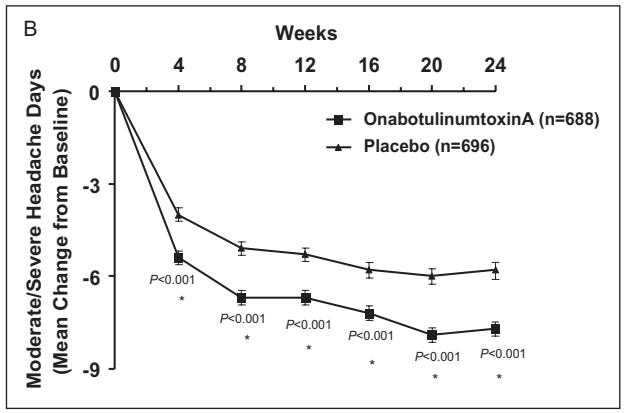
starting at the first post-treatment study visit (week 4) and including the week 24 primary endpoint (–8.4 onabotulinumtoxinA vs –6.6 placebo; $P < .001$; 95% CI [–2.52, –1.13]) (Fig. 2).

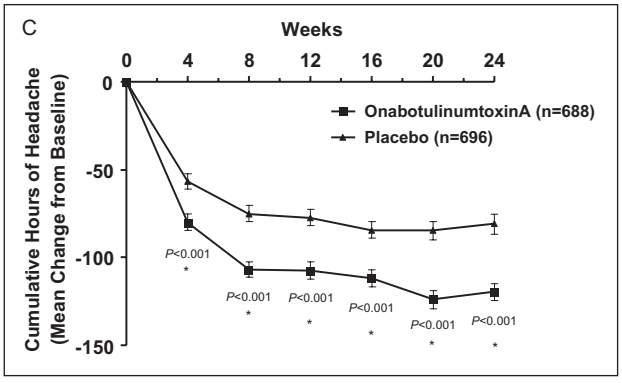
Secondary Efficacy Variables.—Significant differences for onabotulinumtoxinA versus placebo were observed at all time points, starting at the first post-treatment study visit (week 4) and including week 24, for the following secondary efficacy variables: mean change from baseline in frequencies of migraine days ($P < .001$); moderate or severe headache days ($P < .001$); cumulative hours of headache on headache days ($P < .001$); headache episodes ($P = .009$); migraine episodes ($P = .004$); and the proportion of patients with severe (≥60) HIT-6 score ($P < .001$) (Fig. 3A-F). Both treatment arms showed an overall mean reduction in acute pain medication intakes, although no between-group difference was observed ($P = .247$) (Fig. 3G). In a post-hoc analysis, there was statistically significant less use of triptans as acute pain medication at week 24 in the onabotulinumtoxinA group than in the placebo group ($P < .001$) (Table 2).

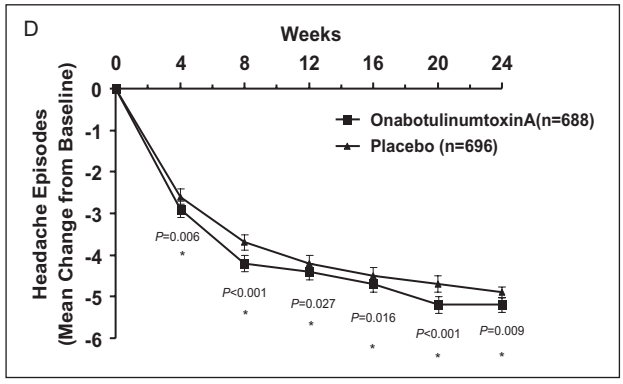
50% Responder Analyses.—A significantly greater percentage of onabotulinumtoxinA-treated than placebo-treated patients had at least a 50% decrease from baseline in the frequency of headache days at all time points, starting at the first post-treatment study visit (week 4) and including week 24 (onabotulinumtoxinA 47.1% vs placebo 35.1%; $P < .001$) (Fig. 4). Although a greater percentage of onabotulinumtoxinA-treated versus placebo-treated patients had at least a 50% decrease from baseline in the frequency of headache episodes at all time points,

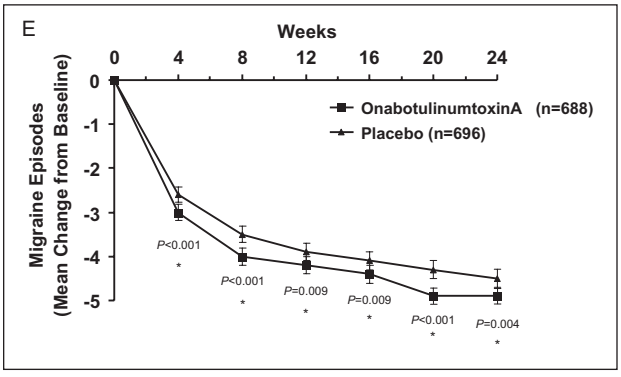
Fig 3.—Secondary efficacy variables per 28 days. (A) Mean change from baseline in frequency of migraine days. Migraine days at baseline: 19.1 ± 0.2 onabotulinumtoxinA group versus 18.9 ± 0.2 placebo group, *P* = .328. (B) Mean change from baseline in frequency of moderate/severe headache days. Moderate/severe headache days at baseline: 18.1 ± 0.2 onabotulinumtoxinA group versus 18.0 ± 0.2 placebo group, *P* = .705. (C) Mean change from baseline in cumulative hours of headache on headache days. Cumulative hours of headache at baseline: 295.9 ± 4.5 onabotulinumtoxinA group versus 281.2 ± 4.4 placebo group, *P* = .021. (D) Mean change from baseline in frequency of headache episodes. Headache episodes at baseline: 12.2 ± 0.2 onabotulinumtoxinA group versus 13.0 ± 0.2 placebo group, *P* = .004. (E) Mean change from baseline in frequency of migraine episodes. Migraine episodes at baseline: 11.4 ± 0.2 onabotulinumtoxinA group versus 12.2 ± 0.2 placebo group, *P* = .004. (F) Percent of patients with severe impact (Headache Impact Test-6 score ≥ 60). Percent patients with severe impact at baseline: 93.5% onabotulinumtoxinA group versus 92.7% placebo group, *P* = .565. (G) Mean change from baseline in acute headache pain medication intakes. Acute headache pain medication intakes at baseline: 26.9 ± 0.7 onabotulinumtoxinA group versus 27.8 ± 0.8 placebo group, *P* = .450. All data are presented as mean ± standard error.

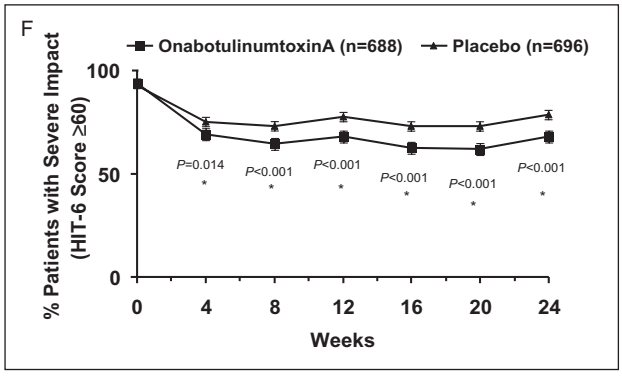

A
Weeks
0 4 8 12 16 20 24
Migraine Days (Mean Change from Baseline)
0 -3 -6 -9
OnabotulinumtoxinA (n=688)
Placebo (n=696)
P<0.001 * P<0.001 * P<0.001 * P<0.001 * P<0.001 * P<0.001 *


B
Weeks
0 4 8 12 16 20 24
Moderate/Severe Headache Days (Mean Change from Baseline)
0 -3 -6 -9
OnabotulinumtoxinA (n=688)
Placebo (n=696)
P<0.001 * P<0.001 * P<0.001 * P<0.001 * P<0.001 * P<0.001 *


C
Weeks
0 4 8 12 16 20 24
Cumulative Hours of Headache (Mean Change from Baseline)
0 -50 -100 -150
OnabotulinumtoxinA (n=688)
Placebo (n=696)
P<0.001 * P<0.001 * P<0.001 * P<0.001 * P<0.001 * P<0.001 *


D
Weeks
0 4 8 12 16 20 24
Headache Episodes (Mean Change from Baseline)
0 -1 -2 -3 -4 -5 -6
OnabotulinumtoxinA(n=688)
Placebo (n=696)
P=0.006 * P<0.001 * P=0.027 * P=0.016 * P<0.001 * P=0.009 *


E
Weeks
0 4 8 12 16 20 24
Migraine Episodes (Mean Change from Baseline)
0 -1 -2 -3 -4 -5
OnabotulinumtoxinA (n=688)
Placebo (n=696)
P<0.001 * P<0.001 * P=0.009 * P=0.009 * P<0.001 * P=0.004 *


F
OnabotulinumtoxinA (n=688)
Placebo (n=696)
% Patients with Severe Impact (HIT-6 Score ≥60)
100 50 0
P=0.014 * P<0.001 * P<0.001 * P<0.001 * P<0.001 * P<0.001 *
0 4 8 12 16 20 24
Weeks

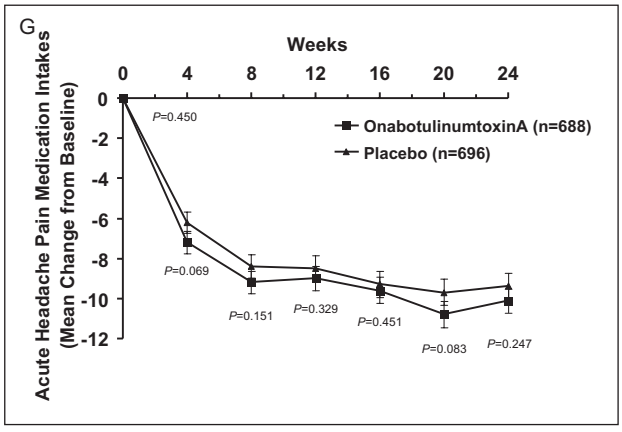

G
Weeks
0 4 8 12 16 20 24
Acute Headache Pain Medication Intakes (Mean Change from Baseline)
0 -2 -4 -6 -8 -10 -12
OnabotulinumtoxinA (n=688)
Placebo (n=696)
P=0.450 P=0.069 * P=0.151 * P=0.329 * P=0.451 * P=0.083 * P=0.247

Table 2.—Efficacy of OnabotulinumtoxinA at Week 24

Variable	OnabotulinumtoxinA (n = 688)	Placebo (n = 696)	Mean intergroup difference†	*P* value†
Change from baseline in frequency of headache days‡§	–8.4	–6.6	–1.8 (–2.52, –1.13)	<.001
Change from baseline in frequency of migraine days§¶	–8.2	–6.2	–2.0 (–2.67, –1.27)	<.001
Change from baseline in frequency of moderate/severe headache days§	–7.7	–5.8	–1.9 (–2.62, –1.26)	<.001
Change from baseline in cumulative total headache hours on headache days§	–119.7	–80.5	–39.2 (–48.40, –21.04)	<.001
Percent of patients with severe (≥60) HIT-6 score§††	67.6%	78.2%	–10.6% (–15.2%, –5.9%)	<.001
Change from baseline in frequency of headache episodes§	–5.2	–4.9	–0.3 (–1.17, –0.17)	.009
Change from baseline in frequency of migraine episodes§¶	–4.9	–4.5	–0.4 (–1.20, –0.23)	.004
Change from baseline in frequency of acute headache pain medication intakes (all categories)	–10.1	–9.4	–0.7 (–2.68, 0.69)	.247
Change from baseline in frequency of triptan intake	–3.2	–2.1	–1.1 (–1.74, –0.61)	<.001
Change from baseline in total HIT-6 scores§††	–4.8	–2.4	–2.4 (–3.11, –1.72)	<.001
Change from baseline in MSQ score				
Role function-restrictive§	17.0	8.6	8.4 (10.76, 6.01)	<.001
Role function-preventative§	13.1	6.4	6.7 (9.01, 4.35)	<.001
Emotional function§	17.9	9.5	8.4 (11.37, 5.56)	<.001

†The 95% confidence intervals and *P* values are adjusted for baseline and for medication overuse stratification.
‡Primary efficacy endpoint.
§Significant between-group differences favoring onabotulinumtoxinA.
¶ICHD-II 1.1 (migraine without aura), 1.2 (migraine with aura), 1.6 (probable migraine).[4]
††Scores of 36-49 indicate little or no impact; 50-55, some impact; 56-59, substantial impact; ≥60, severe impact.
HIT = Headache Impact Test; MSQ = Migraine-Specific Quality of Life questionnaire.

a significant difference between treatment groups was observed only at week 8 ($P = .001$) (Fig. 4).

Headache Impact on Disability, Functioning, and HRQoL.—A statistically significant and clinically meaningful difference for onabotulinumtoxinA versus placebo at all time points starting at the first post-treatment study visit (week 4) and including week 24 was observed in mean change from baseline in total HIT-6 score ($P < .001$) (Table 2). OnabotulinumtoxinA treatment also statistically significantly improved HRQoL ($P < .001$) as measured by changes from baseline in all 3 MSQ role function domains (restrictive, preventive, and emotional) at all time points evaluated (weeks 12 and 24) (Table 2).

Safety and Tolerability.—The nature and frequency of adverse events (AEs) were similar for both groups in this pooled analysis. There was one treatment-related serious AE in the group receiving onabotulinumtoxinA (hospitalization due to migraine). No new safety or tolerability events emerged from the pooled safety results from these phase 3 double-blind study phases, confirming that treatment with 155 U to 195 U of onabotulinumtoxinA every 12 weeks over 24 weeks (2 cycles) was well tolerated.

The onabotulinumtoxinA-treated patients had a greater number of AEs (Table 3) than did placebo-treated patients. The only AEs reported with an incidence ≥5% were neck pain (8.7%) and muscular weakness (5.5%) in the onabotulinumtoxinA group and upper respiratory tract infection (5.3%) in the placebo group. Most AEs were mild or moderate in severity and resolved without sequelae. Serious AEs were reported for 4.8% of patients in the onabotulinumtoxinA group and 2.3% of patients in the placebo group.

Treatment-related AEs of neck pain, muscular weakness, and eyelid ptosis were reported by a higher number of patients in the onabotulinumtoxinA group than in the placebo group (Table 4). Similarly to what

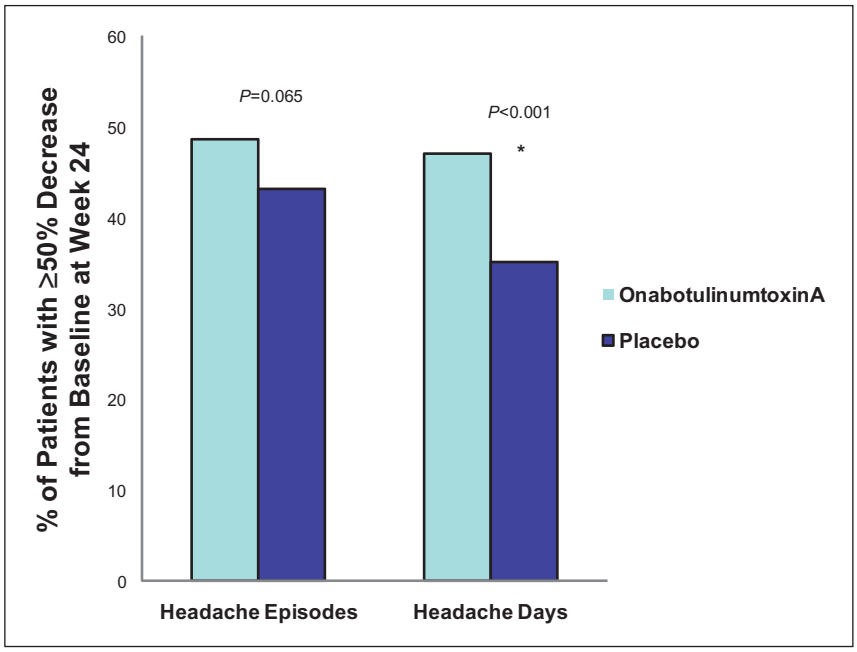


Fig 4.—Percent of patients with a 50% decrease from baseline in frequencies of headache days and headache episodes.

was found in each individual study,[32,33] in the pooled analysis the only treatment-related AE reported with an incidence ≥5% was neck pain (6.7% in the onabotulinumtoxinA group vs 2.2% in the placebo group). The incidence rates for individual treatment-related AEs were consistent with the known pharmacology and established safety of onabotulinumtoxinA when injected into head and neck muscles. No unexpected treatment-related AEs were identified.

In this pooled analysis of the 24-week double-blind PREEMPT phases, 3.8% of patients in the onabotulinumtoxinA group and 1.2% of patients in the placebo group discontinued due to AEs (Table 3). The most frequently reported AEs leading to discontinuation in the onabotulinumtoxinA group were neck pain (0.6%), muscular weakness (0.4%), headache (0.4%), and migraine (0.4%). No death was reported in the studies.

DISCUSSION

Historically, patients with CM have been excluded from migraine prophylaxis trials because they were considered to be too highly disabled and treatment resistant. However, the high prevalence

Table 3.—Summary of Overall Adverse Events Reported in the 24-Week, Double-Blind Phase

	OnabotulinumtoxinA (n = 687) n (%)	Placebo (n = 692) n (%)
All adverse events	429 (62.4)	358 (51.7)
Treatment-related adverse events	202 (29.4)	88 (12.7)
Serious adverse events	33 (4.8)	16 (2.3)
Treatment-related, serious adverse events	1 (0.1)	0 (0.0)
Discontinuations related to adverse events†	26 (3.8)	8 (1.2)
Death	0 (0.0)	0 (0.0)

†Discontinuations during double-blind or open-label phases due to adverse events that onset during the double-blind phase.

Table 4.—Treatment-Related Adverse Events Reported by ≥2% of Patients in the Double-Blind Phase

	OnabotulinumtoxinA (n = 687) n (%)	Placebo (n = 692) n (%)
Total treatment-related adverse events	202 (29.4)	88 (12.7)
Neck pain	46 (6.7)	15 (2.2)
Muscular weakness	38 (5.5)	2 (0.3)
Eyelid ptosis	23 (3.3)	2 (0.3)
Musculoskeletal pain	15 (2.2)	5 (0.7)
Injection-site pain	22 (3.2)	14 (2.0)
Headache	20 (2.9)	11 (1.6)
Myalgia	18 (2.6)	2 (0.3)
Musculoskeletal stiffness	16 (2.3)	5 (0.7)

and great burden of illness suffered by those with CM calls for the development and evaluation of efficacious, safe, and well-tolerated headache prophylaxis therapies.

The individual PREEMPT studies were conducted simultaneously with essentially identical designs, allowing the results to be pooled to determine the precision of and variability around the results for the primary and all secondary endpoints. The results of this pooled analysis demonstrate highly significant differences favoring onabotulinumtoxinA over placebo across multiple headache symptom measures, including the primary endpoint of headache day frequency and all secondary efficacy endpoints, with the exception of acute pain medication intakes. However, in the pooled analysis, as seen in both PREEMPT 1 and 2 studies, there were significant differences favoring onabotulinumtoxinA over placebo for the change from baseline in frequency of triptan intakes. Furthermore, despite a baseline imbalance in the pooled analysis for the frequency of headache episodes and, separately, frequency of migraine episodes, the power of the pooled analysis demonstrated highly significant differences ($P \leq .004$) favoring onabotulinumtoxinA over placebo for the change from baseline in frequencies of headache episodes and migraine episodes, which had been observed in PREEMPT 2 but not in PREEMPT 1. And, as was observed for each of the individual studies, at no time in this pooled analysis was placebo significantly favored over onabotulinumtoxinA for any endpoint.

The multiple headache symptom measures evaluated in PREEMPT are consistent with the recently published recommendation by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for interpreting the clinical importance of group differences in chronic pain clinical studies.[37] These recommendations suggest that additional information about the primary efficacy endpoint that should be considered to adequately understand therapeutic benefit should include not only the magnitude of treatment effect but other aspects as well, including, but not limited to, proportion of treatment responders, onset and durability of treatment benefit, and treatment benefit relative to other treatments. Further, the primary efficacy endpoint alone cannot adequately describe the potential benefits of a treatment without additional consideration of secondary outcomes, safety, and tolerability, and other factors, such as convenience, patient adherence, uniqueness of the mechanism of action, limitations of existing treatments, and cost effectiveness.[37] In this analysis, in addition to the report of the primary efficacy endpoint, a significantly greater percentage of onabotulinumtoxinA-treated than placebo-treated patients had at least a 50% decrease from baseline in the frequency of headache days at all time points, demonstrating a responder rate that is clinically meaningful. OnabotulinumtoxinA versus placebo treatment resulted in highly significant improvements from baseline in HRQoL, which indicates that the benefits of treatment were clinically meaningful to the patients. Furthermore,

onabotulinumtoxinA was superior to placebo in reducing headache-related disability (HIT-6) with between-group differences that were clinically meaningful and exceeded the minimally important difference.[38] The treatment was durable over a 6-month period and convenience is arguably superior compared with the need to consume a medication every day or sometimes twice or 3 times per day. Compliance with migraine prophylactic migraine medications is a major issue. In one study, more than 50% of migraine patients terminated treatment with prophylactic medication within 3 months of initiating the medication.[39] Compliance is far less of an issue with onabotulinumtoxinA because it is injected. Finally, the mechanism of action, while not completely elucidated, is undoubtedly different from that of other prophylactic migraine drugs, and the side-effect and safety profile compare very favorably with other prophylactic migraine medications currently approved or frequently used in clinical practice.

The headache-related burden and disability in individual patients with CM is multifaceted, encompassing headache frequency, duration, and severity. At week 24, the onabotulinumtoxinA group experienced statistically significant improvements over placebo-treated patients across multiple headache symptom dimensions, including frequencies of headache days, headache episodes, migraine days, migraine episodes, moderate/severe headache days, and total cumulative hours of headache. Pooled analyses also showed that at all time points significantly more onabotulinumtoxinA-treated than placebo-treated patients achieved a 50% or greater decrease from baseline in the frequency of headache days.

Analyses from PREEMPT 1[32] were considered along with other factors when it was decided, prior to the unmasking of PREEMPT 2,[33] to amend the PREEMPT 2 primary and secondary endpoints and the individual study analysis plan (discussed below). The pooled analysis plan was also amended at that time to designate headache days as the primary variable for the pooled efficacy analyses. No control for type-1 error was prespecified in the pooled analysis plan. Therefore, to better control the type-1 error for the pooled analyses, a highly conservative Bonferroni adjustment was examined at the week 24 primary time point, which modified the critical level from 0.05 to 0.00625 to account for the primary and 7 secondary efficacy variables (ie, 0.05 divided by 8 = 0.00625). The week 24 efficacy results for the primary variable (headache days) and for all of the secondary efficacy variables (except acute medication intakes [$P = .247$] and headache episodes [$P = .009$]) remained significant for onabotulinumtoxinA versus placebo when evaluating this very conservative multiplicity adjustment.

Statistically significant reductions for onabotulinumtoxinA versus placebo were also seen in headache-related disability, resulting in significantly improved functioning, vitality, and overall HRQoL. The difference between onabotulinumtoxinA- and placebo-treated patients in mean change from baseline in total HIT-6 disability scores at week 24 (2.4) exceeded the established clinically meaningful between-group minimum difference of 2.3.[38]

There was no significant between-group difference in change from baseline in overall use of acute pain medication at week 24, despite within-group reductions from baseline. The apparent discrepancy of a significant reduction in frequency of headache days among onabotulinumtoxinA-treated patients compared with placebo-treated patients, without an accompanying significant difference in frequency of acute pain medication intakes, may be due to the continued or new use by onabotulinumtoxinA-treated patients of acute pain medications for low-grade headaches (ie, headaches that according to the study protocol, did not persist for at least 4 hours and therefore were not counted as a headache day or episode). Post hoc analysis established that patients in the onabotulinumtoxinA group had statistically significantly fewer intakes of triptans at week 24 than did the placebo group.

Analysis of approximately 85 possible predictors of response to change from baseline in frequency of headache days such as age, gender, and body mass index did not reveal any consistent correlation between these characteristics and response to onabotulinumtoxinA treatment in the PREEMPT patient population.

Treatment-related AEs were consistent with the known tolerability profile of onabotulinumtoxinA

when injected into the head and neck muscles, and no newly emerged safety findings were observed. There were significantly more treatment-related AEs in the onabotulinumtoxinA group than in the placebo group. Individual AEs occurred in fewer than 10% of patients, were mild to moderate in severity, and were generally transient.

Although the precise mechanism of onabotulinumtoxinA as headache prophylaxis in CM is not fully elucidated, human and animal studies have shown that onabotulinumtoxinA blocks release of neurotransmitters associated with the genesis of pain.[40-43] The presumed mechanism for headache prophylaxis is that, by blocking release of neurotransmitters, such as substance P, calcitonin gene-related peptide, and glutamate, from the peripheral termini of primary afferents,[40,41,44] onabotulinumtoxinA inhibits peripheral signals to the central nervous system and thus indirectly inhibits central sensitization. Central sensitization results from ongoing input from C-fiber nociceptors. Central sensitization may lead to cutaneous allodynia, which manifests as pain after ordinary nonnociceptive stimulation of skin. Bigal et al[45] reported that in a population-based study, persons with migraine who experienced headache on ≥15 days per month reported significantly higher prevalence as well as significantly more severe cutaneous allodynia during headache attacks than did persons with migraine who experienced headache on <15 days per month. These results suggest that persons with higher migraine headache day frequency are more susceptible to the adverse consequences of central sensitization and that a treatment directed at blocking this aspect of disease manifestation may be helpful.

Immunogenicity manifested as antibody formation has been reported as an uncommon occurrence with chronic use of onabotulinumtoxinA in other therapeutic indications; such toxin neutralizing antibodies (TNA) can specifically inhibit the clinical effectiveness of treatment.[46-48] Long-term management of CM may involve the administration of onabotulinumtoxinA injections to patients repeatedly over several months or years. Samples collected in phase 2 studies that evaluated up to 3 repeated treatments (every 12 weeks) of onabotulinumtoxinA doses as high as 260 U[10,11,28] were evaluated for TNA using the validated mouse protection bioassay (MPA). The MPA is the gold standard for detection of TNA to onabotulinumtoxinA.[49,50] The TNA analysis included 505 onabotulinumtoxinA-treated patients, of whom 496 had analyzable samples. There were no positive TNA, and 1 patient of 496 (0.2%) had inconclusive results. Recognizing that sufficient data were available indicating that there is no heightened risk for immunogenicity in the CM population, and to limit unnecessary animal testing, the principal investigators, study sponsor, and regulatory agencies agreed that additional TNA samples were not required for the PREEMPT studies.

There are several potential limitations in the 2 PREEMPT studies and therefore in this pooled analysis. The PREEMPT clinical program did not include an active comparator, although currently there are no approved prophylactic treatments for CM. Direct comparison of the efficacy and safety of onabotulinumtoxinA treatment with other headache prophylactic treatments in the CM population will require head-to-head comparator trials. Recently, a pilot study reported comparable efficacy results for onabotulinumtoxinA (2 injections of 100-200 U intramuscularly every 12 weeks) and topiramate (100-200 mg/day), with significant reductions from baseline in frequency of headache and frequency of migraine days and improved quality of life with each treatment.[51] However, fewer treatment-related AEs were reported among patients who received onabotulinumtoxinA than among those treated with topiramate. A greater number of topiramate patients (24.1%) than onabotulinumtoxinA patients (2.7%) discontinued the study due to AEs.

Another possible limitation is the notable placebo response in these studies. Clinical studies of the prophylactic treatment of EM have indicated a high variability in rates of placebo response[52] compared with acute migraine treatment studies. This may reflect differences in primary trial endpoints as well as an inherent likelihood for discrepancies between responses measured over a period of months compared with those measured over only a period of hours.[53] In migraine prophylaxis, placebo response rates have also been found to be higher in parallel-

group studies than in crossover trials.[52] Clinical trials of parenteral pain treatments consistently report higher placebo rates than those seen in trials using oral medication. Heightened expectation for results from an injection may elevate the placebo response rates.[53] Other possible explanations of the high placebo response rate are regression to the mean and spontaneous improvement. In these studies, there was a risk that patients and/or investigators may have been unblinded to the study treatment because of the physical changes that may have occurred due to muscle relaxation in the forehead of patients treated with onabotulinumtoxinA. Although this could have contributed to an enhanced active response, it is at odds with a high placebo response and the absence of a parallel nocebo effect. If placebo patients had "seen" the absence of physical changes in foreheads, then they would have been equally unblinded to placebo treatment. Thus, a low placebo response would have been expected. Furthermore, AEs that are known to occur after treatment with onabotulinumtoxinA due to the pharmacologic effects, such as local muscle weakness manifested as ptosis, were reported in patients who were treated with placebo. Indeed, the presence of the placebo response suggests that the blind was maintained.

Prior to study completion and treatment unmasking, the protocol and statistical analysis plan for PREEMPT 2 was amended to change the primary and secondary variables, making frequency of headache days the primary variable.[33] This change was made based on several factors: availability of PREEMPT 1 data, guidance provided in newly issued International Headache Society (IHS) clinical trial guidelines for evaluating headache prophylaxis in CM,[54] and an earlier expressed preference of the US FDA, all of which supported using headache day frequency as a primary outcome measure for CM. Additionally, the variability in duration of headache episodes among migraine sufferers is well known, as illustrated in these trials, highlighting the need for a more standardized and sensitive endpoint such as headache days in future migraine trials. As shown by these trials in this complex and disabled population, multiple outcome measures are useful to fully characterize the multifaceted aspects that contribute to the significant disease burden, disability, and poor quality of life suffered by these patients.

The PREEMPT study population was highly disabled, had suffered with CM for more than 2 decades, and experienced an average of 20 headache days per month. Patients were currently inadequately treated by available medical therapies, and approximately two-thirds had previously failed to respond to headache prophylactic medications that they found to be ineffective and/or intolerable. Two-thirds were overusing acute pain medication at baseline. Population-based epidemiology data provide evidence that the PREEMPT study population is representative of the typical patient with CM seen in clinical practice;[55] therefore, the results from these studies are expected to be relevant to clinical practice for healthcare professionals who treat patients with CM.

Despite this significant disease burden and history of treatment refractoriness, the PREEMPT studies demonstrate that prophylactic treatment with onabotulinumtoxinA compared with placebo led to sustained, significant improvements from baseline across multiple headache symptom measures. The PREEMPT phase 3 CM studies are the largest well-designed, controlled studies conducted to date in this severely disabled population. The results demonstrate that onabotulinumtoxinA is an effective prophylactic treatment for patients with CM, including those who overuse acute pain medications. The PREEMPT studies confirm an effective dose and treatment paradigm. Multiple treatments of 155 U up to 195 U of onabotulinumtoxinA per treatment cycle administered every 12 weeks (2 cycles) were safe and well tolerated.

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