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Research Submissions

OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Analyses of the 56-Week PREEMPT Clinical Program

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

Background.—Chronic migraine is a prevalent, disabling, and undertreated neurological disorder. OnabotulinumtoxinA is the only approved prophylactic therapy in this highly disabled patient population.

Design and Methods.—Two phase III, 24-week, double-blind, parallel-group, placebo-controlled studies, followed by a 32-week, open-label, single-treatment, onabotulinumtoxinA phase, were conducted (January 23, 2006 to August 11, 2008). Qualified subjects were randomized (1:1) to injections of onabotulinumtoxinA (155-195 U) or placebo every 12 weeks for 5 cycles (double-blind: 2, open-label: 3). The pooled primary variable was mean change from baseline in frequency of headache days. Secondary variables included proportion of patients with severe Headache Impact Test-6 score (≥60) and mean changes from baseline in frequencies of migraine days, moderate/severe headache days, and migraine episodes; cumulative hours of headache on headache days; and acute headache medication intakes. The primary time point was week 24. Assessments for the open-label phase (all patients treated with onabotulinumtoxinA) compared double-blind treatment groups

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(onabotulinumtoxinA/onabotulinumtoxinA vs placebo/onabotulinumtoxinA) and are summarized to give a descriptive view of consistent study results, with inferences regarding statistical significance only examined for week 56.

Results.—A total of 1384 patients were randomized to onabotulinumtoxinA (n = 688) or placebo (n = 696) in the double-blind phase; 607 (88.2%) onabotulinumtoxinA/onabotulinumtoxinA and 629 (90.4%) placebo/onabotulinumtoxinA patients continued into the open-label phase. OnabotulinumtoxinA/onabotulinumtoxinA treatment statistically significantly reduced headache-day frequency vs placebo/onabotulinumtoxinA in patients with chronic migraine at week 56 (–11.7 onabotulinumtoxinA/onabotulinumtoxinA, –10.8 placebo/onabotulinumtoxinA; *P* = .019). Statistically significant reductions also favored onabotulinumtoxinA/onabotulinumtoxinA for several secondary efficacy variables at week 56, including frequencies of migraine days (–11.2 onabotulinumtoxinA/onabotulinumtoxinA, –10.3 placebo/onabotulinumtoxinA; *P* = .018) and moderate/severe headache days (–10.7 onabotulinumtoxinA/onabotulinumtoxinA, –9.9 placebo/onabotulinumtoxinA; *P* = .027) and cumulative headache hours on headache days (–169.1 onabotulinumtoxinA/onabotulinumtoxinA, –145.7 placebo/onabotulinumtoxinA; *P* = .018). After the open-label phase (all treated with onabotulinumtoxinA), statistically significant within-group changes from baseline were observed for all efficacy variables. Most patients (72.6%) completed the open-label phase; few discontinued because of adverse events. No new safety or tolerability issues emerged.

Conclusions.—Repeated treatment with ≤5 cycles of onabotulinumtoxinA was effective, safe, and well tolerated in adults with chronic migraine.

Key words: botulinum toxin A, chronic migraine, prophylaxis

Abbreviations: AE adverse event, CI confidence interval, CM chronic migraine, DB double-blind, HIT-6 Headache Impact Test-6, HRQoL health-related quality of life, ICHD-II International Classification of Headache Disorders, IMMPACT Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, MID minimally important difference, MSQ Migraine-Specific Quality-of-Life Questionnaire, OL open-label, O/O onabotulinumtoxinA/onabotulinumtoxinA, P/O placebo/onabotulinumtoxinA, PREEMPT Phase III REsearch Evaluating Migraine Prophylaxis Therapy

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Chronic migraine (CM) is a complex neurological disorder associated with substantial disability[1] that has been estimated to affect approximately 2% of the general population.[2] CM is currently defined as headache on ≥15 days per month for ≥3 months, of which ≥8 days meets criteria for migraine without aura or responds to migraine-specific treatment.[3,4] Patients with CM have lower health-related quality of life (HRQoL), are more likely to suffer from severe disability, and use more healthcare resources than those with episodic migraine (defined as migraine and <15 headache days per month).[3,5-7]

Although there are prophylactic medications available for episodic migraine, their efficacy and safety have not been established in patients suffering from CM.[4,8] In addition, there are few small, double-blind (DB), controlled trials that have investigated the efficacy of an oral prophylactic treatment in chronic daily headache or CM.[9-15] Given the disability associated with CM, the human and economic costs of inadequate treatment,[7] and the tolerability profile of existing migraine preventive medications, it is clear that better treatments are needed for prophylaxis of all migraine types.

OnabotulinumtoxinA has been reported to relieve pain associated with a variety of conditions, including migraine.[16-28] The Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program evaluated the safety and efficacy of onabotulinumtoxinA in adult patients suffering from CM. As previously reported, the pooled results from the DB phases of PREEMPT demonstrated that onabotulinumtoxinA statistically significantly reduced the mean frequency of headache days compared with placebo.[29] Similar statistically and clinically significant mean improvements were observed for pooled secondary efficacy variables, including patient functioning and quality of life. The pooled safety and efficacy results from the entire 56-week PREEMPT clinical program are reported here.

METHODS

Study Design.—The 2 parallel PREEMPT clinical trials were conducted from January 23, 2006 to August 11, 2008, at 122 sites across 6 different countries (Canada: 11 sites, Croatia: 3 sites, Germany: 8 sites, Switzerland: 2 sites, UK: 3 sites, and USA: 95 sites).

Each trial included a 28-day baseline screening period, a 24-week DB phase with 2 injection cycles, and a 32-week open-label (OL) phase with 3 injection cycles. To establish baseline data, patients used a daily interactive telephone diary to record their headache symptoms and use of acute headache medications.

Both studies were conducted in accordance with the Declaration of Helsinki Code of Federal Regulations and Good Clinical Practices; they were publicly registered as required (ClinicalTrials.gov Identifiers NCT00156910 and NCT00168428). Each investigator obtained approval from an Independent Ethics Committee (IEC) or a local Institutional Review Board (IRB) prior to study initiation. These trials were not overseen by an independent data safety monitoring board. However, there were Medical Monitors for each study who performed a safety review to assess the overall safety profile of the study drug on an ongoing basis to ensure that safety issues were addressed in a timely and appropriate manner. Additionally, as specified in the protocol, all adverse events (AEs) that were drug-related and unexpected (ie, not listed as treatment-related in the Investigator's Brochure) were to be reported to the governing IRB/IEC, as required by the IRB/IEC, local regulations, and the governing health authorities. Written informed consent was obtained from each randomized patient. All authors had access to the data for this paper.

Study Participants.—Eligible participants included men and women aged 18 to 65 years with a history of migraine meeting the diagnostic criteria listed in the second edition of the International Classification of Headache Disorders (ICHD-II) (2004) Section 1, Migraine—with the exception of "complicated migraine" (ie, hemiplegic migraine, basilar-type migraine, ophthalmoplegic migraine, migrainous infarction)—and with headache occurring ≥15 days/month.[3,4] During baseline, randomized subjects must have had headache occurring on ≥15 days for 4 weeks, with each day consisting of ≥4 hours of continuous headache, and ≥50% of baseline headache days being migraine or probable migraine days (hereafter referred to as migraine days). Principal exclusion criteria included any medical condition that might put patients at increased risk if they were exposed to onabotulinumtoxinA; diagnosis of other primary or secondary headache disorders; use of any headache prophylactic medication within 28 days of day 1 of the baseline; Beck Depression Inventory score >24; or previous exposure to any botulinum toxin serotype. Details on study participants and their diary reporting procedures have been described elsewhere.[29]

Patient Randomization, Stratification, and Study Treatment.—Subjects in the DB phase were randomized in a blinded fashion (1:1 in blocks of 4) to onabotulinumtoxinA (155 U) or placebo. Patients were stratified by whether or not they overused acute headache medication (yes/no) during the 28-day baseline. Medication overuse was defined as intake during baseline of simple analgesics on ≥15 days, or other medication types or combination of types for ≥10 days, with intake ≥2 days/week from the category of overuse. Patients who completed the 24-week DB phase were eligible for the OL phase, in which all patients received onabotulinumtoxinA. OnabotulinumtoxinA was administered as 31 fixed-site, fixed-dose (5 U), i.m. injections across 7 specific head/neck muscle areas every 12 weeks (weeks 0, 12, 24, 36, and 48). At the investigator's discretion, up to 40 U of additional onabotulinumtoxinA could have been administered among 3 muscle groups (occipitalis, temporalis, or trapezius) using a protocol-defined paradigm.[29,30] Hence the maximum dose per treatment cycle was 195 U over 39 sites.

Efficacy and Safety.—The PREEMPT 1 and 2 studies were pooled for evaluation of the integrated summary of efficacy, safety, and tolerability. All efficacy analyses 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, and 56 (OL phase). The primary endpoint for the pooled analysis was change from baseline in frequency of headache days at 24 weeks. Several secondary efficacy variables were evaluated, as well, including the proportion of patients with severe Headache Impact Test (HIT)-6 score (≥60) and mean changes from baseline in: frequency of migraine days (headache meeting ICHD-II criteria for migraine 1.1, 1.2, or 1.6),[4] frequency of moderate/severe headache days, total cumulative

hours of headache on headache days, frequency of headache episodes (defined as patient-reported headache with a start and stop time indicating that the pain lasted ≥4 continuous hours), frequency of migraine episodes (defined as patient-reported migraine headache with a start and stop time indicating that the pain lasted ≥4 continuous hours), and frequency of acute headache medication intakes. The changes from baseline were also used to determine the proportion of patients who experienced decreases from baseline of ≥50% in frequency of headache days, migraine days, moderate/severe headache days, headache episodes, and migraine episodes, as well as the total cumulative hours of headache on headache days. Disease impact on disability in functioning, vitality, psychological distress, and HRQoL was assessed by mean change from baseline in total HIT-6 score and in the Migraine-Specific Quality-of-Life Questionnaire (MSQ) assessments in 3 functional domains: restrictive, preventive, and emotional.[29] Pooled safety analyses were performed on all patients who received at least 1 dose of study medication at day 0.

Statistical Analysis.—Details of the statistical analyses used throughout the PREEMPT clinical program have been described previously.[29] The monthly observation periods through week 56 were prespecified for each study. Week 24 was prespecified as primary and the other time points were secondary. Efficacy analyses were based on the intent-to-treat population. Results for statistical comparisons in the OL phase are reported for patients based on their initial DB-phase randomization to onabotulinumtoxinA or placebo; thus, the 2 treatment groups reflected patients whose treatment sequence began and ended with onabotulinumtoxinA (O/O) or patients who were given placebo first, followed by onabotulinumtoxinA (P/O). Comparisons between treatment groups for primary and secondary variables were conducted by analysis of covariance of the change from baseline, with the same variable's baseline value as a covariate, with main effects of treatment group and 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, previously defined.[31,32] The measure of proportion of patients with ≥50% response used observed data. For binomial variables, the between-group comparisons were performed with Pearson's chi-square or Fisher's exact test. However, when there was a statistically significant baseline difference between treatment groups, logistic regression was used instead, with the variable's baseline value as covariate. All hypothesis tests were 2-sided, as prespecified in the statistical plans for each study. For the pooled analysis, no method was prespecified to control the type-1 error rate for secondary variables and secondary measurement times, such as those in the OL phase. Instead, *P* values for comparisons of secondary variables and measurement times are declared statistically significant if they were ≤.05, in order to give an overview of consistent results. For example, the method that was prespecified for PREEMPT 2[32] was a fixed-sequence, gate-keeping approach that was applied to the primary and first 5 secondary variables, which are displayed in rank order in Tables 1 and 2. Applying such an algorithm herein, if the *P* value of a primary or secondary variable was >.05 at either week 24 or week 56, the tests of any lower ranked secondary variables would not be considered statistically significant at week 56, regardless of individual *P* values for those variables. All analyses were completed using SAS v9.1 and v9.2 (Statistical Analysis System from SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Disposition and Demographics.—A total of 1384 patients were randomized to onabotulinumtoxinA (n = 688) or placebo (n = 696) in the PREEMPT DB phase; 607 (88.2%) O/O and 629 (90.4%) P/O patients continued into the OL phase (Fig. 1). As reported previously, there were no statistically significant differences between the treatment groups at baseline for most of the important demographic characteristics (Table 1). However, a statistically significant baseline imbalance was observed for a few efficacy variables for the pooled population, with the O/O group having, on average, fewer headache and migraine episodes, and a larger total number of cumulative headache hours on headache days than the placebo group.[29]

Table 1.—Pooled PREEMPT Baseline Patient Demographics and Characteristics

	OnabotulinumtoxinA (n = 688)	Placebo (n = 696)	*P* Value
Mean age, years (SD)	41.1 (10.4)	41.5 (10.7)	.579
Female, %	87.6	85.2	.185
Caucasian, %	89.7	90.5	.602
Mean frequency of headache days (SD)	19.9 (3.7)	19.8 (3.7)	.498
Mean frequency of migraine days† (SD)	19.1 (4.0)	18.9 (4.1)	.328
Mean frequency of moderate/severe headache days (SD)	18.1 (4.1)	18.0 (4.3)	.705
Mean frequency of total cumulative hours of headache occurring on headache days (SD)	295.9 (118.9)	281.2 (114.7)	.021
% Patients with severe (≥60) HIT-6 score	93.5	92.7	.565
Mean frequency of headache episodes (SD)	12.2 (5.3)	13.0 (5.5)	.004
Mean frequency of migraine episodes† (SD)	11.4 (5.0)	12.2 (5.4)	.004
% Patients overusing acute headache medication	64.8	66.1	.620
Mean frequency of acute headache medication intakes (SD)	26.9 (19.1)	27.8 (20.7)	.450
Mean frequency of acute headache medication days (SD)	14.6 (6.4)	14.9 (6.4)	.397
Mean HIT-6 score (SD)	65.5 (4.1)	65.4 (4.3)	.638
Mean MSQ score (SD)			
Role restrictive	38.5 (16.6)	38.7 (17.3)	.974
Role preventive	56.0 (21.2)	56.1 (21.7)	.825
Emotional functioning	42.1 (24.1)	42.4 (25.0)	.806

†International Classification of Headache Disorders (ICHD-II) 1.1 (migraine without aura), 1.2 (migraine with aura), and 1.6 (probable migraine).[3]
HIT-6 = Headache Impact Test-6; MSQ = Migraine-Specific Quality-of-Life Questionnaire.

Interactive telephone diary data reporting compliance was high throughout the 56-week study. Mean patient diary-day compliance was >99% at baseline[29] and remained high (>88%) throughout the study, with no observed differences between pooled treatment groups.

Efficacy Results.—*Primary Efficacy Variable—Frequency of Headache Days.*—Pooled PREEMPT analyses found statistically significant differences in headache-day frequency at week 56, favoring those patients who received onabotulinumtoxinA in the DB and OL phases (O/O-treated patients) over patients who received placebo in the DB phase and did not receive onabotulinumtoxinA until the OL phase (P/O) (Fig. 2). Also, at week 56, there were statistically significant within-group improvements from baseline in the frequency of headache days for patients treated with onabotulinumtoxinA, as indicated by within-treatment 95% confidence intervals (CIs) (Fig. 2; Table 2).

Secondary Efficacy Variables.—In the DB phase, both patient groups experienced large reductions from baseline in all secondary variables evaluated (Fig. 3). Mean reductions from baseline were statistically significantly greater in the O/O group than in the P/O group at week 24 for all secondary variables except for frequency of acute headache medication intakes. However, statistically significant differences in the reduction in frequency of triptan intakes favoring the O/O group compared with the P/O group were observed for the week 24 primary time point ($P < .001$) (Table 2). Additionally, onabotulinumtoxinA treatment (the O/O group) statistically significantly reduced the frequency of acute headache medication days compared with placebo (the P/O group) at week 24 ($P = .016$) (Table 2).

During the OL phase, when all patients were treated with onabotulinumtoxinA, the 95% CIs for all efficacy variables evaluated indicated that there were statistically significant within-group improvements from baseline at week 56 for both the O/O and P/O treatment groups (Table 2). Of note, the changes from baseline increased throughout the OL phase, demonstrating continued improvements after each

Table 2.—Efficacy of OnabotulinumtoxinA at Week 24 and Week 56

Variable	Week 24				Week 56			
	OnabotA† (n = 688)	Placebo† (n = 696)	Mean Intergroup Difference†	*P* Value†	OnabotA/OnabotA† (n = 688)	Placebo/OnabotA† (n = 696)	Mean Intergroup Difference†	*P* Value†
Change from baseline in mean frequency of headache days‡§	−8.4 (−8.90, −7.92)	−6.6 (−7.07, −6.08)	−1.8 (−2.52, −1.13)	<.001	−11.7 (−12.17, −11.20)	−10.8 (−11.32, −10.31)	−0.9 (−1.53, −0.14)	.019
Change from baseline in mean frequency of migraine days§¶	−8.2 (−8.69, −7.70)	−6.2 (−6.69, −5.68)	−2.0 (−2.67, −1.27)	<.001	−11.2 (−11.71, −10.74)	−10.3 (−10.82, −9.80)	−0.9 (−1.52, −0.14)	.018
Change from baseline in mean frequency of moderate/severe headache days§	−7.7 (−8.22, −7.27)	−5.8 (−6.28, −5.30)	−1.9 (−2.62, −1.26)	<.001	−10.7 (−11.18, −10.25)	−9.9 (−10.43, −9.44)	−0.8 (−1.41, −0.09)	.027
Change from baseline in cumulative total headache hours on headache days§	−119.7 (−129.58, −109.76)	−80.5 (−90.56, −70.42)	−39.2 (−48.40, −21.04)	<.001	−169.1 (−179.30, −158.81)	−145.7 (−155.94, −135.36)	−23.4 (−29.15, −2.78)	.018
Percent of patients with severe (≥60) HIT-6 score§††	67.6% (64.1%, 71.1%)	78.2% (75.1%, 81.2%)	−10.6% (−15.2%, −5.9%)	<.001	50.6% (46.9%, 54.3%)	51.9% (48.2%, 55.6%)	−1.3 (−6.6%, 4.0%)	.632
Change from baseline in mean frequency of headache episodes§	−5.2 (−5.61, −4.84)	−4.9 (−5.32, −4.53)	−0.3 (−1.17, −0.17)	.009	−7.4 (−7.79, −6.97)	−7.5 (−7.91, −7.09)	0.1 (−0.87, −0.04)	.075
Change from baseline in mean frequency of migraine episodes§¶	−4.9 (−5.25, −4.50)	−4.5 (−4.90, −4.12)	−0.4 (−1.20, −0.23)	.004	−6.8 (−7.21, −6.43)	−7.0 (−7.37, −6.58)	0.2 (−0.80, −0.09)	.117
Change from baseline in mean frequency of acute headache medication intakes (all categories)	−10.1 (−11.37, −8.81)	−9.4 (−10.62, −8.13)	−0.7 (−2.68, 0.69)	.247	−15.4 (−16.74, −14.05)	−15.7 (−17.05, −14.33)	0.3 (−1.76, −1.29)	.760
Change from baseline in mean frequency of triptan intakes§	−3.2 (−3.63, −2.71)	−2.1 (−2.57, −1.58)	−1.1 (−1.74, −0.61)	<.001	−4.2 (−4.69, −3.67)	−3.8 (−4.35, −3.27)	−0.4 (−1.02, −0.06)	.080
Change from baseline in mean frequency of acute headache medication days	−6.1 (−6.58, −5.54)	−5.3 (−5.77, −4.75)	−0.8 (−1.53, −0.15)	.016	−8.4 (−9.08, −7.79)	−8.5 (−9.16, −7.82)	0.1 (−1.19, 0.46)	.387
Change from baseline in total HIT-6 scores§††	−4.8 (−5.34, −4.29)	−2.4 (−2.85, −1.95)	−2.4 (−3.11, −1.72)	<.001	−7.7 (−8.24, −7.06)	−7.0 (−7.62, −6.40)	−0.6 (−1.49, 0.20)	.069
Change from baseline in MSQ score								
Role restrictive§	17.0 (18.74, 15.21)	8.6 (10.18, 7.00)	8.4 (10.76, 6.01)	<.001	25.2 (27.27, 23.08)	21.8 (23.93, 19.63)	3.4 (6.41, 0.39)	.043
Role preventive§	13.1 (14.83, 11.37)	6.4 (7.98, 4.85)	6.7 (9.01, 4.35)	<.001	19.0 (21.06, 17.01)	17.3 (19.40, 15.26)	1.7 (4.60, 1.20)	.293
Emotional function§	17.9 (20.09, 15.79)	9.5 (11.43, 7.53)	8.4 (11.37, 5.56)	<.001	25.0 (27.41, 22.60)	22.1 (24.66, 19.62)	2.9 (6.36, −0.62)	.051

†The 95% confidence intervals and *P* values are adjusted for baseline and for medication overuse stratification, except for HIT-6 and MSQ scores.
‡Primary efficacy endpoint.
§Statistically significant between-group differences favoring onabotulinumtoxinA at week 24.
¶International Classification of Headache Disorders (ICHD-II) 1.1 (migraine without aura), 1.2 (migraine with aura), and 1.6 (probable migraine).[3]
††Scores of 36-49 indicate little or no impact; 50-55, some impact; 56-59, substantial impact; 60-78, severe impact.
HIT-6 = Headache Impact Test-6; MSQ = Migraine-Specific Quality-of-Life Questionnaire; OnabotA = OnabotulinumtoxinA.

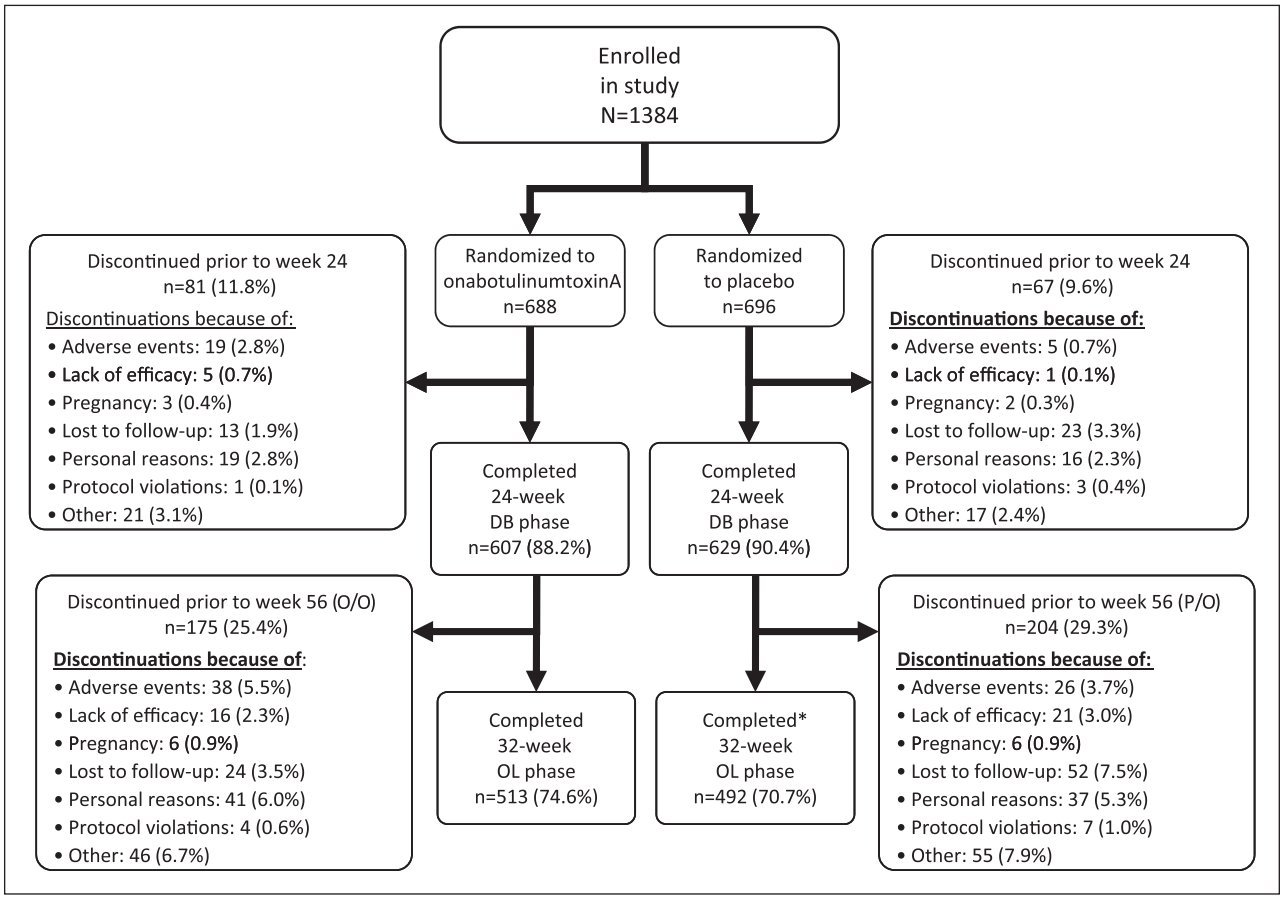

Fig 1.—Patient disposition. DB = double-blind; OL = open-label; O/O = onabotulinumtoxinA/onabotulinumtoxinA; P/O = placebo/onabotulinumtoxinA. *Patients on placebo crossed over to receive onabotulinumtoxinA injections, as described in the *Methods*.

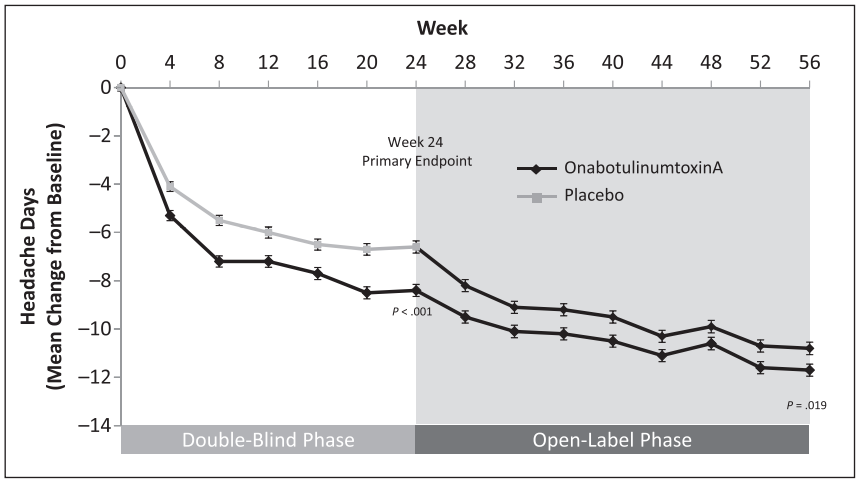

Fig 2.—PREEMPT pooled analysis (primary): mean change from baseline in frequency of headache days. Headache days at baseline: 19.9 ± 0.1 onabotulinumtoxinA group vs 19.8 ± 0.1 placebo group, *P* = .498. 95% confidence intervals at: week 24: O/O −8.90, −7.92; P/O −7.07, −6.08; week 56: O/O −12.17, −11.20; P/O −11.32, −10.31. Data are presented as mean ± standard error. O/O = onabotulinumtoxinA/onabotulinumtoxinA; P/O = placebo/onabotulinumtoxinA.

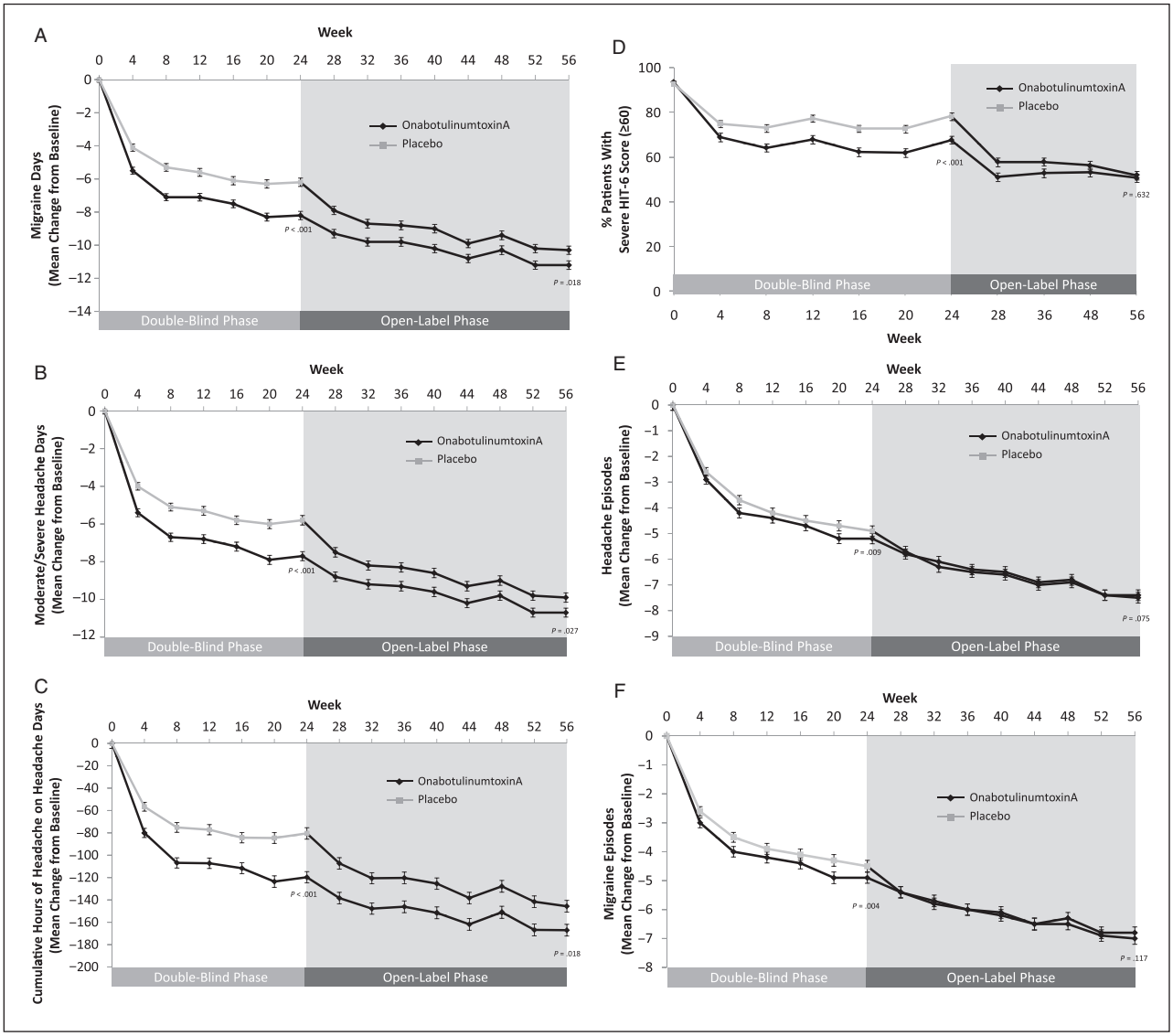

Fig 3.—PREEMPT pooled analysis: Data are presented as mean ± standard error. (A) Frequency of migraine days. Migraine days at baseline: 19.1 ± 0.2 onabotulinumtoxinA group vs 18.9 ± 0.2 placebo group, *P* = .328. 95% confidence intervals (CIs) at: week 24: O/O –8.69, –7.70; P/O –6.69, –5.68; week 56: O/O –11.71, –10.74; P/O –10.82, –9.80. (B) Frequency of moderate/severe headache days. Moderate/severe headache days at baseline: 18.1 ± 0.2 onabotulinumtoxinA group vs 18.0 ± 0.2 placebo group, *P* = .705. 95% CIs at: week 24: O/O –8.22, –7.27; P/O –6.28, –5.30; week 56: O/O –11.18, –10.25; P/O –10.43, –9.44. (C) Total cumulative headache hours on headache days. Cumulative hours of headache at baseline: 295.9 ± 4.5 onabotulinumtoxinA group vs 281.2 ± 4.4 placebo group, *P* = .021. 95% CIs at: week 24: O/O –129.58, –109.76; P/O –90.56, –70.42; week 56: O/O –179.30, –158.81; P/O –155.94, –135.36. (D) Proportion of patients with severe Headache Impact Test (HIT)-6 score. Percent patients with severe impact (HIT-6 score ≥60) at baseline: 93.5% onabotulinumtoxinA group vs 92.7% placebo group, *P* = .565. (E) Frequency of headache episodes. Headache episodes at baseline: 12.2 ± 0.2 onabotulinumtoxinA group vs 13.0 ± 0.2 placebo group, *P* = .004. 95% CIs at: week 24: O/O –5.61, –4.84; P/O –5.32, –4.53; week 56: O/O –7.79, –6.97; P/O –7.91, –7.09. (F) Frequency of migraine episodes. Migraine episodes at baseline: 11.4 ± 0.2 onabotulinumtoxinA group vs 12.2 ± 0.2 placebo group, *P* = .004. 95% CIs at: week 24: O/O –5.25, –4.50; P/O –4.90, –4.12; week 56: O/O –7.21, –6.43; P/O –7.37, –6.58.

treatment cycle (Fig. 3). There were also statistically significant between-group differences at week 56 favoring early over late onabotulinumtoxinA treatment (O/O vs P/O) for frequencies of migraine days and moderate/severe headache days as well as total cumulative hours of headache on headache days (Fig. 3A-C).

Fifty Percent Responder Analyses.—The proportion of patients who demonstrated ≥50% decrease

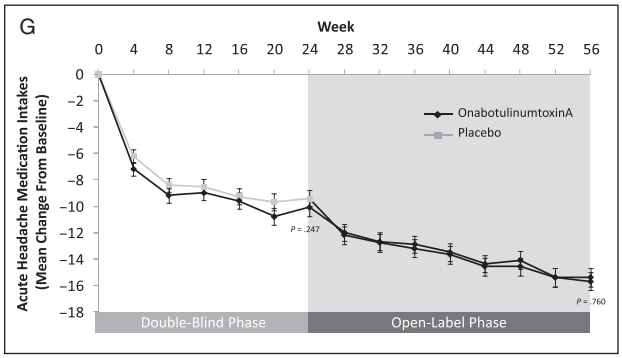

Fig 3.—(G) Frequency of acute headache medication intakes (all categories). Acute headache medication intakes at baseline: 26.9 onabotulinumtoxinA group vs 27.8 placebo group, *P* = .450. 95% CIs at: week 24: O/O −11.37, −8.81; P/O −10.62, −8.13; week 56: O/O −16.74, −14.05; P/O −17.05, −14.33. All data are presented as mean change from baseline ± standard error, except proportion of patients with severe HIT-6 score. O/O = onabotulinumtoxinA/onabotulinumtoxinA; P/O = placebo/onabotulinumtoxinA.

from baseline in frequencies of headache days, migraine days, moderate/severe headache days, and total cumulative hours of headache on headache days statistically and clinically significantly favored onabotulinumtoxinA treatment over placebo at week 24 (Fig. 4A). After all patients were treated with onabotulinumtoxinA, clinically significant improvements were observed in the O/O and P/O groups for frequencies of headache and migraine days, with almost 70% of patients treated with onabotulinumtoxinA throughout the entire study exhibiting ≥50% decrease from baseline in migraine and headache days at the week 56 visit (Fig. 4B).

Headache Impact on Disability, Functioning, and HRQoL.—At week 24, treatment with onabotulinumtoxinA (O/O group) statistically significantly reduced mean total HIT-6 score more than the P/O group. There continued to be between-group differences throughout the OL phase, but this did not reach statistical significance at week 56 (*P* = .069). However, there were statistically significant within-group reductions from baseline for mean total HIT-6 score at week 56 (Table 2). A clinically meaningful between-group difference for onabotulinumtoxinA vs placebo was observed at week 24 in mean change from baseline in total HIT-6 score (2.4; *P* < .001) (Table 2).

OnabotulinumtoxinA treatment statistically significantly improved overall HRQoL vs placebo at week 24 for all 3 MSQ role function domains: emotional, restrictive, and preventive (*P* < .001).[29] Both O/O and P/O groups also experienced statistically significant within-group improvements from baseline in HRQoL at week 56 (Table 2).

Safety and Tolerability Results.—The proportion of patients from the pooled PREEMPT cohorts that completed both phases of the 56-week PREEMPT trials was high (74.6% O/O, 70.7% P/O) (Fig. 1). Throughout the entire 56-week PREEMPT program, only 4.6% of patients discontinued the study because of an AE. The proportion of patients who experienced a serious AE during the DB phase (onabotulinumtoxinA 4.8%, placebo 2.3%) or OL phase (3.8%) was low (Table 3). 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. The only individual treatment-related AEs occurring at a rate ≥5% during the DB phase were neck pain in the onabotulinumtoxinA group (6.7%) and muscular weakness (5.5%, with facial paresis [2.2%] comprising nearly half of these reports) (Table 4). In the OL phase, when all patients were exposed to onabotulinumtoxinA, there were no individual treatment-related AEs occurring at a rate ≥5% (Table 4). During the OL exposure, the most frequently reported treatment-related AEs were: neck pain (4.6%), muscular weakness (3.9%, including facial paresis 1.2%), eyelid ptosis (2.5%), muscle tightness (2.2%), and injection-site pain (2.0%). The majority of all reports of neck pain, the most commonly reported AE in both the DB and OL phases, was rated as mild or moderate in severity, and none were reported as serious AEs. Neck pain did not occur consistently with repeated onabotulinumtoxinA treatment, as incidence rates declined with subsequent treatment cycles. Over the entire 56-week PREEMPT clinical program, the overall AE rate progressively decreased with subsequent onabotulinumtoxinA treatments, indicating that sustained treatments with i.m. injections of 155 to 195 U of onabotulinumtoxinA every 12 weeks were safe and well tolerated.

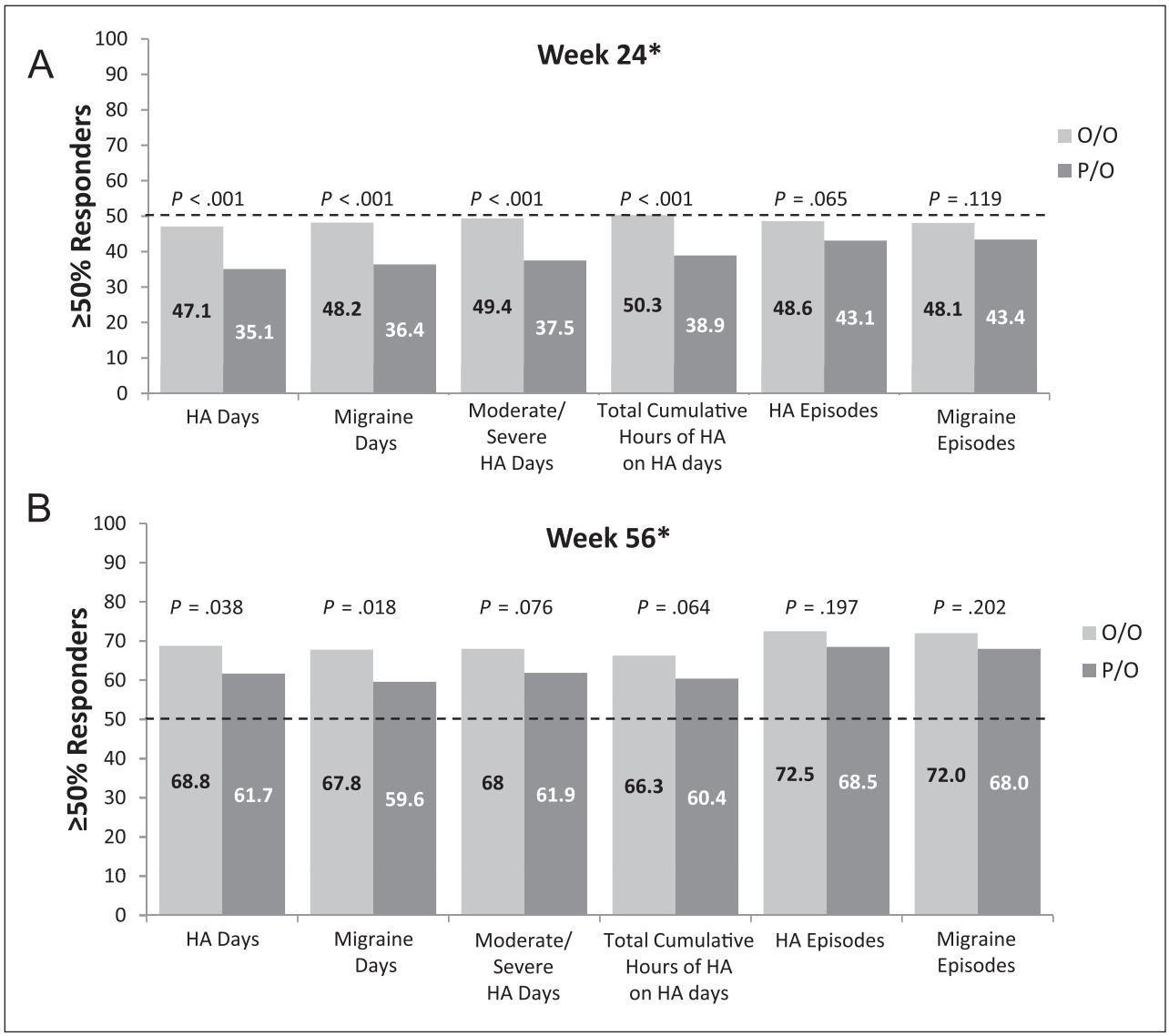

Fig 4.—Decrease from baseline in ≥50% responders for multiple headache (HA) symptom measures at week 24 and week 56. *The data used are "observed data" (without imputation for missing values). O/O = onabotulinumtoxinA/onabotulinumtoxinA; P/O = placebo/onabotulinumtoxinA.

DISCUSSION

There are limited options presently available to effectively treat the CM population,[8,33] and only 33% of patients report taking prophylactic medications.[34] Although there are migraine-specific prophylactic medications, only onabotulinumtoxinA is approved for use in CM. This is largely due to the systematic exclusion of CM patients from controlled trials because of the lack of operational diagnostic criteria and because these patients are generally thought to be treatment-refractory.[8,14] There are a few previous placebo-controlled studies that have investigated prophylactic medication for the treatment of CM; however, these studies are limited by their sample size and diagnostic and eligibility criteria, and do not account for current prophylactic or acute medication use.[9-15]

PREEMPT is the largest clinical program to investigate the use of onabotulinumtoxinA as a prophylactic treatment for CM by using a defined set of diagnostic criteria and defined clinically relevant outcome measures. The pooled analyses of the

Table 3.—Summary of Overall Adverse Events Reported in the DB and OL Phases

	DB Phase (24 Weeks)		OL Phase (32 Weeks)
	OnabotulinumtoxinA (n = 687) n (%)	Placebo (n = 692) n (%)	Total (n = 1205) n (%)
All adverse events†	429 (62.4)	358 (51.7)	703 (58.3)
Treatment-related adverse events‡	202 (29.4)	88 (12.7)	245 (20.3)
Serious adverse events	33 (4.8)	16 (2.3)	46 (3.8)
Treatment-related, serious adverse events	1 (0.1)	0 (0.0)	1 (0.1)
Discontinuations related to adverse events	26 (3.8)	8 (1.2)	31 (2.6)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)

†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.
DB = double-blind; OL = open-label.

entire 56-week PREEMPT clinical program support onabotulinumtoxinA as a safe and effective long-term prophylactic treatment for CM. Statistically significant reductions favoring onabotulinumtoxinA over placebo in the DB phase were observed for the primary variable of headache-day frequency at week 56, with differences observed throughout the OL phase. Statistically significant differences favoring early onabotulinumtoxinA treatment over later use were also observed at week 56 for change from baseline in mean migraine days, moderate/severe headache days, and total cumulative hours of headache on headache days. At the end of the OL phase, after all patients were treated with onabotulinumtoxinA, statistically significant within-group changes from baseline differences were observed for all efficacy variables.

Although there were no statistically significant between-group differences in the frequency of overall acute headache medication intakes in either the DB or OL phases, there were statistically significant within-group reductions. Also, there were significant

Table 4.—Treatment-Related Adverse Events Reported by ≥2% of Patients in the DB and OL Phases

	DB Phase (24 Weeks)		OL Phase (32 Weeks)
	OnabotulinumtoxinA (n = 687) n (%)	Placebo (n = 692) n (%)	Total (n = 1205) n (%)
Total treatment-related adverse events	202 (29.4)	88 (12.7)	245 (20.3)
Neck pain	46 (6.7)	15 (2.2)	55 (4.6)
Muscular weakness	38 (5.5)	2 (0.3)	47 (3.9)
Eyelid ptosis	23 (3.3)	2 (0.3)	30 (2.5)
Musculoskeletal pain	15 (2.2)	5 (0.7)	13 (1.1)
Injection-site pain	22 (3.2)	14 (2.0)	24 (2.0)
Headache	20 (2.9)	11 (1.6)	17 (1.4)
Myalgia	18 (2.6)	2 (0.3)	15 (1.2)
Musculoskeletal stiffness	16 (2.3)	5 (0.7)	20 (1.7)
Muscle tightness	9 (1.3)	1 (0.1)	26 (2.2)

DB = double-blind; OL = open-label.

reductions in the frequency of acute headache medication days favoring onabotulinumtoxinA treatment at week 24. After all patients were treated with onabotulinumtoxinA, there were statistically significant reductions from baseline in frequency of acute headache medication days at week 56. Of note, there were statistically significant reductions in the frequency of triptan intakes favoring onabotulinumtoxinA treatment at week 24 and statistically significant improvement from baseline at week 56. This observation suggests that because patients treated with onabotulinumtoxinA had reduced headache symptoms (such as fewer headache days and episodes), their need to take acute headache medications, specifically triptans, every day was also reduced. A failure to detect differences in acute headache medication intakes may have been confounded by the data collection methodology for this information. Acute headache medications were those reported in the patient diary as being taken for headache. An intake of acute headache medication was defined as the time that a patient reported he or she took medication, regardless of the dose or number of types of medication taken at the same time. For example, 6 aspirin tablets taken at the same time was recorded as 1 intake; similarly, 1 aspirin tablet and 1 sumatriptan tablet taken at the same time was defined as 1 intake. Therefore, there could have been multiple intakes within a given day for each patient.

Unlike onabotulinumtoxinA's function at the neuromuscular junction, the mechanism of onabotulinumtoxinA in antinociception has not been fully elucidated. Several animal and human studies have demonstrated that onabotulinumtoxinA inhibits the release of nociceptive inflammatory mediators such as calcitonin gene-related peptide, glutamate, and substance P from the peripheral termini of nociceptors.[35-42] Inhibition of these neurotransmitters prevents neurogenic inflammation and subsequent peripheral sensitization; as a result, peripheral pain signals to the central nervous system are reduced. Thus, onabotulinumtoxinA may indirectly block central sensitization in migraine and other pain conditions.[35,36,39,42]

Chronic migraine is a common, complex neurological disorder with enormous burden and disability. Patients with CM suffer from frequent debilitating headaches that affect their ability to function and their HRQoL, and the multifaceted nature of the disease makes CM difficult to treat. According to the recently published recommendation by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for interpreting clinical meaningfulness, treatments should take into account not only the primary endpoint, but also secondary outcomes, safety, and tolerability.[43] Indeed, the PREEMPT clinical program assesses many aspects of these guidelines, such as proportion of treatment responders, onset and durability of treatment benefit over 56 weeks, and multiple efficacy measures, including improvements in physical and/or emotional functioning. Treatment with onabotulinumtoxinA significantly reduced multiple CM symptom measures that negatively impact a patient's ability to function (headache days, migraine days, number of hours of headache per month, moderate/severe headache days, headache episodes, and migraine episodes). Additionally, the proportion of patients treated with onabotulinumtoxinA early in the study who had a ≥50% response in reduction of frequency of headache days, migraine days, and moderate/severe headache days at the end of the 56-week program was statistically significantly greater compared to patients treated with onabotulinumtoxinA only later in the OL phase, demonstrating a responder rate that is clinically meaningful. OnabotulinumtoxinA treatment reduced headache-related disability and improved functioning, vitality, and psychological distress as measured by HIT-6. By the end of the DB phase, the mean change from baseline in HIT-6 scores exceeded the established clinically meaningful between-group minimally important difference (MID) of 2.3 at week 24.[44] In the OL phase, during which all patients were treated with onabotulinumtoxinA, continued improvements in the percent of patients with severe HIT-6 scores favoring patients treated early in the study were observed. Clinically significant improvements in HRQoL were observed at week 24 for all 3 role function MSQ domains, where onabotulinumtoxinA treatment (role restrictive [RR] 8.4, role preventive [RP] 6.7, and emotional functioning [EF] 8.4) far exceeded the previously established between-group MIDs (RR 3.2, RP

4.6, and EF 7.5)[45] compared to placebo at the end of the DB phase (week 24). Additionally, the established within-group MIDs (RR 10.9, RP 8.3, and EF 12.2)[46] were also exceeded for onabotulinumtoxinA treatment but not for placebo at week 24 (Table 2). In the OL phase, after all patients were treated with onabotulinumtoxinA, continued improvements from baseline in HRQoL, as assessed by all 3 role function domains of the MSQ, were observed for all patients. The multiple variables assessed in PREEMPT and the statistically significant results are in alignment with the IMMPACT paradigm and demonstrate clinically meaningful benefit of treatment with onabotulinumtoxinA in adults with CM.

The proportion of patients that completed the 56-week study was high (72.6%), indicating a favorable tolerability profile for onabotulinumtoxinA. Although there were more treatment-related AEs in the DB phase for onabotulinumtoxinA-treated patients, these were mild to moderate in severity and short-lived. Only 2.5% of all patients in the DB phase and 2.6% in the OL phase discontinued the study because of AEs. The most frequently reported AEs are not unexpected; neck pain is a known side effect of onabotulinumtoxinA when administered as i.m. injections to the neck muscles[47] and muscular weakness reflects the local pharmacological effects of onabotulinumtoxinA. These AEs are consistent with the known safety and tolerability profile of onabotulinumtoxinA, and no new safety or tolerability issues were reported.

There are several strengths of the PREEMPT clinical program. These trials were well designed, are placebo-controlled, and are the largest studies to date conducted in this severely disabled patient population. The electronic diary, chosen because it is more reliable than paper diaries, provided excellent patient compliance and captured data that did not depend on a long recall time period for patients (>88%). We recognize that there are some limitations to this study. There is no active comparator for efficacy in PREEMPT because at the time these studies were conducted there were no approved agents for the preventative treatment of CM.[48] The placebo response in this trial is consistent with the placebo effect observed in other headache studies.[48,49] Placebo response rates are known to be significantly higher in parallel-group studies than in crossover studies,[49] and parenteral pain treatments have higher placebo rates than placebo pills.[50,51] The placebo response could also be explained by regression to the mean and/or spontaneous improvement. Despite the high placebo response in the PREEMPT clinical program, however, onabotulinumtoxinA treatment benefit was evident across a variety of headache symptom measures. Even using the best blinding practices, physical changes that may have occurred in the forehead of patients treated with onabotulinumtoxinA could have caused unblinding, which might have contributed to the active response. Conversely, one would then have expected a nocebo effect, where patients could have become unblinded to the placebo based on *lack* of physical change, contributing to a lower response in the placebo group, but that was not seen. Additionally, the locations of the onabotulinumtoxinA injections differ from those sites indicated for cosmetic purposes, and the PREEMPT dose used in the glabellar region was lower than the dose approved for temporary improvement in the appearance of moderate to severe glabellar lines.[52] Based on the low AE rates reported in the onabotulinumtoxinA group compared to other migraine treatments that have poor tolerability profiles, it would be difficult for patients to correctly determine which treatment they were given in this trial. Together, these data suggest that the blind was maintained.

When all patients are treated with onabotulinumtoxinA, a statistically significant within-group reduction from baseline was observed for all efficacy variables at week 56. Although all patients in the OL phase were treated with onabotulinumtoxinA, our results show that patients treated earlier in the DB phase (O/O) had greater improvement in multiple headache symptom measures than those who were treated with onabotulinumtoxinA later (O/P) in this study. A precedent has been set for early treatment for other disease states, as the benefits of early treatment intervention have also been observed in OL extensions of clinical trials in multiple sclerosis, Parkinson's disease, and episodic migraine.[53-55]

CONCLUSION

As previously reported, the DB phase of the PREEMPT clinical program demonstrated the efficacy, safety, and tolerability of onabotulinumtoxinA in CM. The 32-week, OL phase of PREEMPT provides further evidence and confirms onabotulinumtoxinA as a safe, well tolerated, and effective long-term prophylactic treatment for CM.

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