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OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline

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ABSTRACT

Acute headache medication overuse (MO) is common in patients with chronic migraine (CM). We evaluated safety and efficacy of onabotulinumtoxinA as preventive treatment of headache in CM patients with baseline MO (CM + MO) in a planned secondary analysis from two similarly designed, randomized, placebo-controlled, parallel, Phase III trials. Patients were randomized to treatment groups (155–195 U of onabotulinumtoxinA or placebo) using MO (patient-reported and diary-captured frequency of intake) as a stratifying variable. Of 1384 patients, 65.3% (n = 904) met MO criteria (onabotulinumtoxinA: n = 445, placebo: n = 459). For the CM + MO subgroup at Week 24, statistically significant between-treatment group mean changes from baseline favoring onabotulinumtoxinA versus placebo were observed for headache days (primary endpoint: −8.2 vs. −6.2; $p < 0.001$) and other secondary endpoints: frequencies of migraine days ($p < 0.001$), moderate/severe headache days ($p < 0.001$), cumulative headache hours on headache days ($p < 0.001$), headache episodes ($p = 0.028$), and migraine episodes ($p = 0.018$) and the percentage of patients with severe Headache Impact Test-6 category ($p < 0.001$). At Week 24, change from baseline in frequency of acute headache medication intakes (secondary endpoint) was not statistically significant ($p = 0.210$) between groups, except for triptan intakes ($p < 0.001$), where the onabotulinumtoxinA-treated group was favored. OnabotulinumtoxinA was effective and well tolerated as headache prophylaxis in CM + MO patients.

1. Introduction

Chronic migraine (CM) is a prevalent and highly disabling primary headache disorder [1,2] afflicting approximately 2.0% of the global population [3]. Patients suffering from CM (≥15 headache days per month for ≥3 months, of which ≥8 headache days per month are migraine and/or are treated and relieved by triptan/ergot) [4] report lower health-related quality of life (HRQoL), use a greater amount of direct and indirect medical/healthcare resources, and incur greater losses of productivity than patients suffering from episodic migraine (<15 headache days per month) [1,5,6]. Treatment of CM generally involves preventive medications, taken on a daily basis whether or not headache is present, and acute treatments, taken when attacks occur to relieve pain and restore function [7]. In addition, identifying and eliminating exacerbating factors, including the overuse of acute medications, is the conventional approach to treatment [7–9].

The frequent intake of analgesics and other acute headache medications may lead to the development of a secondary headache disorder classified as medication overuse headache (MOH), or, conversely, increasing headache frequency may lead to increased intake of acute headache medications. Improvement of headache symptoms upon withdrawal of drug therapy is the major criterion that distinguishes between these two possibilities [8]. Most CM patients seeking treatment in tertiary headache clinics overuse acute headache medications [10]. One study found that as many as 73% of CM patients overuse acute headache medications [7], including simple and combination analgesics, triptans, and opioids. The role of acute medication

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overuse in CM remains unclear: it may be unrelated to progression and consumption simply reflects a more aggressive disease biology, or it may contribute to the transformation from episodic to CM [7,11,12].

Although not always successful [13–15], and although there are no randomized, placebo-controlled trials demonstrating the effectiveness of drug withdrawal alone, termination of acute headache medication overuse is recommended. However, cessation of acute medications is often not a pragmatic treatment solution for many patients, and preventive medication in addition to rescue therapy is necessary to ensure compliance and successful outcomes. In the absence of evidence, textbooks and treatment guidelines have suggested that preventive migraine medications will have limited or no effectiveness in the presence of medication overuse [7,8,10,11,16]. Contrary to these assertions, data presented in this paper, as well as in one other report [17], suggest that certain headache prophylaxis treatments are effective in the preventive treatment of CM, even in the presence of acute medication overuse [18].

Until recently, no global regulatory body had approved any acute or preventive treatment specifically for the severely affected CM population. OnabotulinumtoxinA (BOTOX®, Allergan, Inc., Irvine, CA) is the first headache preventive treatment to receive such approval. Prior to this approval, there have been little controlled data on preventive treatments in CM [17,19,20] and very limited evidence-based data available to help physicians care for these patients [4]. A comprehensive Phase III program, the PREEMPT (Phase III REsearch Evaluating Migraine Prophylaxis Therapy) clinical program (PREEMPT 1 and 2), demonstrated that onabotulinumtoxinA treatment is safe, tolerable, and efficacious as long-term (up to 56 weeks) headache prophylaxis in adults with CM [19,21]. These studies provide an excellent opportunity to test the hypothesis that headache preventive treatment in adults with CM may have benefits even in the face of acute headache medication overuse.

Recent guidelines published by the International Headache Society (IHS) clinical trials subcommittee recognize the high prevalence of medication overuse in CM patients and recommend stratification of these patients in clinical trials [22]. To ensure that the study population reflected the population of patients seen in clinical practice, the PREEMPT clinical program included and stratified CM patients with and without evidence of acute headache medication overuse during the 28-day baseline [19], which is in accordance with the IHS guidelines [22]. Patients with CM enrolled into either PREEMPT study were stratified using a predefined algorithm, based on their frequency of acute headache medication intakes during the 28-day baseline screening period, as "medication overuse-yes" (CM + MO) or "medication overuse-no" (CM − MO) [23,24] and not based on a diagnosis of MOH, which is a secondary headache disorder. The PREEMPT 1 and 2 pooled efficacy, safety, and tolerability results for the CM + MO patient subgroup are the focus of this report.

2. Methods

2.1. Study design

The details of the PREEMPT study design have been previously described elsewhere [19]. The PREEMPT 1 and 2 clinical trials consisted of a 28-day screening period (baseline), a 24-week double-blind (DB) phase with 2 injection cycles, and a 32-week open-label phase with 3 injection cycles. Study visits occurred at every 4 weeks. During baseline, and throughout the trials, patients used an interactive voice response system daily telephone diary to record their headache symptoms and acute headache medication intakes.

Both studies were conducted in accordance with the Declaration of Helsinki ethical principles, Good Clinical Practices, and principles of informed consent. 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 [23,24].

2.2. Study participants

Inclusion and exclusion criteria for the PREEMPT 24-week DB phase have been previously described elsewhere [19,23,24]. Men or women aged 18 to 65 years with a history of migraine as defined in the second edition of the International Classification of Headache Disorders (ICHD-II) Section 1, Migraine [1], with the exception of "complicated migraine," were included. Eligible patients were recruited from 6 countries (United States, Canada, Germany, United Kingdom, Switzerland, and Croatia) and were required to have headache occurring on ≥15 days in 4 weeks, with each day consisting of ≥4 h of continuous headache, and ≥50% of baseline headache days being migraine or probable migraine days (referred to as migraine days) and ≥4 distinct headache episodes lasting ≥4 h each month. Patients diagnosed with another primary or secondary headache disorder (i.e., MOH) were not enrolled. Due to the high prevalence of acute headache medication overuse in patients with CM, these patients were enrolled into the PREEMPT program and were stratified. The investigators for these studies were headache experts and, per protocol, they were instructed to recruit patients who had a primary migraine headache diagnosis and to exclude patients with secondary headache disorders. Patients were 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. Patients were also excluded if they were not in the baseline phase for at least 28 days or they did not record a minimum of 20 days' worth of diary data during the baseline.

2.3. Acute headache medication overuse

Investigators were trained to carefully evaluate potential trial participants, and although opioid intake was not a specific protocol exclusion criterion, patients who were frequently using opioids were an example of participants who should be carefully screened in view of the year-long trial duration. Once enrolled, patients could take acute headache medications as prescribed. Per protocol, investigators did not provide any further instructions or counsel to patients with regard to changing their usual type and pattern of acute headache medication intake.

To be categorized as CM with acute headache medication overuse (CM + MO) during the 28-day baseline, the following criteria had to be met: (1) patients reported the intake of simple analgesics (e.g., acetaminophen) on ≥15 days or (2) patients reported the intake of other medication types or combination of types for ≥10 days, and (3) intakes, overall and in the case of each of the subtypes, had to occur on ≥2 days/week in each week that had at least 5 diary days. Counts were standardized to 28-day equivalents (by prorating) if only 20–27 days of diary data were reported. Also, unless there were diary data for ≥5 days for a given week, intakes on fewer than 2 days/week were insufficient to exclude that patient from the CM + MO subgroup (e.g., a patient reporting medication intake every day for 3 weeks and not reporting any diary data for the remaining week would still be considered to be CM + MO).

2.4. Randomization, stratification, and study treatment

Patients' baseline acute headache medication overuse status was determined using data from the 28-day baseline diaries. Randomization was stratified based on patients' acute headache medication overuse status at the end of the 28-day baseline period, with treatments balanced in blocks of 4 within each acute headache medication overuse stratum for each investigator site.

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All qualified patients were randomized (1:1) to onabotulinumtoxinA (155 U) or placebo, which was to be administered as 31 fixed-site, fixed-dose, intramuscular injections across 7 specific head/neck muscle areas every 12 weeks over 24 weeks (2 cycles). An additional 40 U of onabotulinumtoxinA (maximum dose 195 U) or placebo could have been injected among 3 muscle groups (occipitalis, temporalis, or trapezius), using a protocol-defined, follow-the-pain paradigm [19,25].

2.5. Efficacy and safety

The primary efficacy variable for all subgroup analyses, including CM + MO, was the same as the primary efficacy variable for the intent-to-treat (ITT) primary analyses of the pooled PREEMPT studies [19], as defined in the PREEMPT integrated summary of efficacy analysis plan [i.e., analysis of covariance (ANCOVA) of change from baseline in the frequency of headache days at the end of the DB phase]. Secondary efficacy variables evaluated for the CM + MO subgroup included mean change from baseline for frequencies of migraine days, moderate/severe headache days, total number of cumulative headache hours on headache days, headache episodes, migraine episodes, and acute headache medication intakes. The percentage of patients (not a change from baseline) with a severe (≥60) Headache Impact Test (HIT)-6 score was also evaluated as a secondary endpoint [26]. Additional analysis variables included mean change from baseline in the frequency of acute headache medication days and in the proportion of patients with ≥50% response in headache days, migraine days, moderate/severe headache days, total cumulative hours of headache on headache days, and headache episodes. Lastly, the change from baseline in the proportion of patients who achieved 3- and 6-month persistent shifts from acute headache medication overuse to no acute headache medication overuse as defined in these protocols was determined. Safety analyses were performed on all randomized patients within the CM + MO subgroup who received at least 1 dose of study medication at Day 0.

Other headache impact measures analyzed for the CM + MO subgroup included mean change from baseline in total HIT-6 score and the proportion of patients with a ≥5-point reduction in total HIT-6 score. For total HIT-6 scores, a between-treatment group minimally important difference (MID) has been established as ≥2.3 [27]. Additionally, a clinically meaningful change for an individual patient has been defined as a ≥5-point decrease in total HIT-6 score [28].

HRQoL was measured by the Migraine Specific Quality of Life questionnaire (MSQ v2.1) [29,30] at baseline and at every 12 weeks. A positive change in MSQ scores reflects improvement. For all MSQ domains, between-treatment group MIDs [3.2, 4.6, and 7.5 for role function-restrictive (RR), role function-preventive (RP), and emotional function (EF), respectively] [31] and within-treatment group MIDs (+10.9, +8.3, and +12.2 for RR, RP, and EF, respectively) have been established [32].

2.6. Statistical analysis

The data from the ITT PREEMPT 1 and 2 populations were pooled, as previously described elsewhere [19], and subjected to further analysis. All analyses to determine acute headache medication overuse and country-specific acute headache medication overuse were based on the ITT population, which included all randomized patients. All efficacy analyses in the CM + MO subgroup were based on changes from the PREEMPT 28-day baseline (Week 0) to each 28-day period ending with Weeks 4, 8, 12, 16, 20, and 24 (DB phase). Evaluations of efficacy variables were based on patients' daily diary entries. For each primary and secondary variable, comparisons between treatment groups were made by ANCOVA of change from baseline, with the same variable's baseline value as a covariate, with main effect of treatment group as done previously for the full ITT population [19]. The baseline covariate adjustment was prespecified as the primary analysis. Missing data were imputed using a prespecified modified last observation carried forward methodology previously described elsewhere [23,24]. MSQ v2.1 and the measures of proportion of patients with ≥50% response used observed data (without imputation). For binomial variables, the between-treatment group comparisons were performed with Pearson's chi-square or Fisher's exact tests, except that logistic regression with baseline covariate was used for variables with baseline imbalance. The ordinal and continuous variables for HIT-6 and MSQ v2.1 were analyzed by the Wilcoxon rank–sum test.

3. Results

3.1. Baseline acute headache medication overuse, baseline demographics, and patient disposition

Acute headache medication overuse at baseline occurred in 65.5% [CM + MO subgroup; n = 906 (n = 445 onabotulinumtoxinA; n = 459 placebo)] of the pooled patients in the ITT population (n = 1384) (Fig. 1; Table 1). The largest number of patients in this subgroup overused some combination of ≥2 drug categories (e.g., triptan and simple analgesic, and thus would be deemed as overusers of a combination of acute medications) (total = 45.7%). The next largest proportions of patients overused triptans (23.6%), followed by overuse of combination analgesics (e.g., hydrocodone + acetaminophen taken as a pre-made tablet) (22.3%) (Table 1).

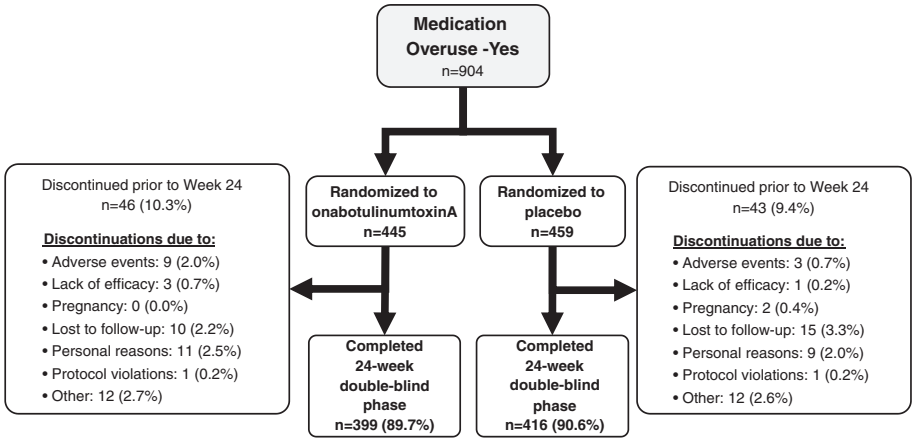

Fig. 1. PREEMPT pooled patient disposition, chronic migraine with acute headache medication overuse subgroup.

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Table 1
Acute headache medication overuse for PREEMPT pooled ITT population: baseline characteristics.

	Baseline acute headache medication overuse, %			
	OnabotulinumtoxinA (n = 688)	Placebo (n = 696)	Total (n = 1384)	*p* value
Total overuse[a]	64.8	66.1	65.5	0.620
Simple analgesics (≥15 days)	13.8	12.5	13.2	0.472
Ergotamines (≥10 days)	0.6	0.3	0.4	0.450
Triptans (≥10 days)	23.4	23.9	23.6	0.844
Opioids (≥10 days)	1.5	2.0	1.7	0.427
Combination analgesics (≥10 days)	20.6	24.0	22.3	0.134
Combination of any drug category (≥10 days)[b]	44.8	46.6	45.7	0.505

ITT = intent-to-treat; PREEMPT = Phase III REsearch Evaluating Migraine Prophylaxis Therapy.
[a] To qualify for acute headache medication overuse, a patient had to take a type of medication at least as many days as indicated in the relevant row for types of medications summarized in this study, including ≥2 times a week in each week with ≥5 diary days, during the baseline period. Two patients were randomized into the no-overuse stratum even though they met criteria for overusing acute headache medication. Thus, while n = 906 reported overuse, n = 904 were in the CM + MO stratum.
[b] Intake combined across at least two drug categories among ergotamines, triptans, analgesics (including simple and combination analgesics as one category), and opioids.

At baseline, there were few significant demographic differences between treatment groups within the CM + MO subgroup (Table 2), and these results were similar to the overall ITT population [19]. In the CM + MO subgroup, onabotulinumtoxinA-treated patients, on average, had significantly fewer headache episodes ($p = 0.006$) and migraine episodes ($p = 0.003$), and significantly more cumulative hours of headache occurring on headache days ($p = 0.007$) than placebo-treated patients. The imbalance within this subgroup is consistent with that previously reported for the entire pooled ITT population [19].

3.2. Efficacy

3.2.1. Efficacy variables related to days and hours of headache

There were significant differences favoring onabotulinumtoxinA-treated patients over placebo-treated patients in the CM + MO subgroup for the mean change from baseline in frequency of headache days. Differences were significant at the Week 24, primary outcome (−8.2 onabotulinumtoxinA vs. −6.2 placebo; $p < 0.001$) and at other time points (Weeks 4, 8, 12, 16, and 20: $p \leq 0.001$; Fig. 2). Within the CM + MO subgroup, onabotulinumtoxinA treatment was also statistically superior to placebo at the Week 24 primary time point for 6 of 7 secondary efficacy endpoints: migraine days ($p < 0.001$), moderate/severe headache days ($p < 0.001$), cumulative hours of headache on headache days ($p < 0.001$), percentage with severe HIT-6 category ($p < 0.001$), headache episodes ($p = 0.028$), and migraine episodes ($p = 0.018$) (Table 3).

3.2.2. Headache impact and HRQoL within the CM + MO subgroup

For the CM + MO subgroup, the mean reduction from baseline in total HIT-6 score significantly favored onabotulinumtoxinA treatment over placebo at all weeks throughout the DB phase (Fig. 3). The between-treatment group difference for change in HIT-6 score at Week 24 was 2.5 ($p < 0.001$) (Fig. 3; Table 3). At Week 24, the percentage of patients with a clinically meaningful individual response (≥5-point reduction in HIT-6 score) [26,28] was significantly greater ($p < 0.001$) for onabotulinumtoxinA treatment compared to placebo treatment (Table 3). At baseline, the majority of patients in the CM + MO subgroup had a total HIT-6 score of ≥60 (94.8% onabotulinumtoxinA; 94.6% placebo), indicating severe impact (Table 2). At Week 24, the proportion of patients with severe headache impact was significantly

Table 2
Baseline demographics and characteristics in the chronic migraine with acute headache medication overuse subgroup.

	CM + MO			
	OnabotulinumtoxinA (n = 445)	Placebo (n = 459)	Total (n = 904)	*p* value
Mean age, years	43.2	43.3	43.3	0.875
Mean years since onset of chronic migraine	21.2	20.3	20.8	0.230
Female, %	87.2	85.6	86.4	0.491
Caucasian, %	91.2	91.3	91.3	0.979
BMI, kg/m^2	26.6	27.0	26.8	0.264
% Patients previously on headache prophylaxis	67.4	70.2	68.8	0.375
Mean headache days (SE)	20.1 (0.18)	19.8 (0.17)	20.0 (0.12)	0.278
Mean migraine[a] days (SE)	19.3 (0.19)	19.1 (0.18)	19.2 (0.13)	0.440
Mean moderate/severe headache days (SE)	18.5 (0.19)	18.0 (0.19)	18.4 (0.14)	0.691
Mean cumulative hours of headache on headache days (SE)	291.3 (5.78)	270.5 (5.18)	280.73 (3.89)	0.007
Mean total HIT-6 score[b]	65.9	65.8	65.8	0.693
% Patients with severe (≥60) HIT-6 score[b]	94.8	94.6	94.7	0.852
Mean headache episodes (SE)	12.8 (0.25)	13.8 (0.26)	13.4 (0.18)	0.006
Mean migraine[a] episodes (SE)	12.1 (0.24)	13.1 (0.25)	12.6 (0.18)	0.003
AHM intakes[c] (SE)	34.6 (0.86)	35.8 (0.96)	35.2 (0.64)	0.331
MSQ[d] score: Role function-restrictive	36.7	37.7	37.2	0.404
MSQ[d] score: Role function-preventive	54.1	54.9	54.5	0.508
MSQ[d] score: Emotional functioning	40.2	40.5	40.3	0.828

AHM = acute headache medication, BMI = body mass index, HIT = Headache Impact Test, HRQoL = health-related quality of life, ICHD = International Classification of Headache Disorders, MSQ = Migraine-Specific Quality of Life questionnaire.
[a] ICHD-II 1.1 (migraine without aura), 1.2 (migraine with aura), 1.6 (probable migraine) [1].
[b] HIT-6 scores: 36–49 = little or no impact; 50–55 = moderate impact; 56–59 = substantial impact; 60–78 = severe impact.
[c] Intakes denote the number of times that a patient self-treated with an acute medication, not the amount of medication(s) taken. An intake occurred each time a patient sought relief, regardless of the number of medications or doses taken at the same time.
[d] MSQ scores range from 0 (poor HRQoL) to 100 (high HRQoL).

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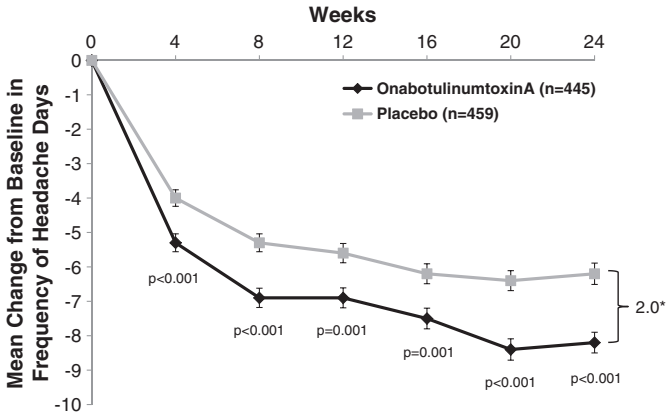

Fig. 2. Mean (SE) change in headache days from baseline in the chronic migraine with acute headache medication overuse subgroup. $p \leq 0.05$ is statistically significant. *Exceeds 1.0, the established minimally important between-group difference [36].

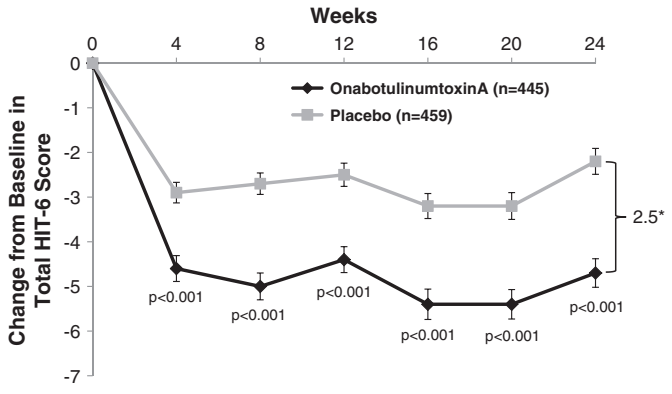

Fig. 3. Change in mean total HIT-6 score from baseline for chronic migraine with acute headache medication overuse subgroup. $p \leq 0.05$ is statistically significant. *Exceeds 2.3, the established minimally important between-group difference [27]. HIT = Headache Impact Test.

lower for onabotulinumtoxinA-treated patients compared to placebo-treated patients (71.0% vs. 81.9%; $p < 0.001$) (Table 3).

HRQoL was measured by the change in MSQ v2.1 [29,30] scores from baseline in the CM + MO subgroup. At Week 24, there was a statistically significant ($p < 0.001$) between-treatment group difference favoring onabotulinumtoxinA over placebo for change from baseline in each MSQ domain score (Table 3). The between-treatment group differences for the three MSQ domain scores (RR, RP, and EF) were 9.3, 8.1, and 9.6, respectively, which exceeded MIDs (3.2, 4.6, and 7.5 for RR, RP, and EF, respectively) [31] (Table 3).

3.2.3. 50% Responder analysis within the CM + MO subgroup

For the CM + MO subgroup at Week 24, significantly more patients treated with onabotulinumtoxinA compared with those who received placebo had a ≥50% reduction from baseline in frequency of headache days (45.8% onabotulinumtoxinA vs. 32.1% placebo; $p < 0.001$), frequency of migraine days ($p < 0.001$), frequency of moderate/severe headache days ($p < 0.001$), total cumulative hours of headache on headache days ($p < 0.001$), and frequency of headache episodes ($p = 0.038$) (Table 4). At no time point was placebo favored (data not shown).

3.2.4. Acute headache medication intake

Within the CM + MO subgroup there was a large mean decrease from baseline for both treatment groups, but no between-treatment group difference in the frequency of acute headache medication intakes at Week 24 (Table 5). The exception was triptans, for which intake frequency was significantly reduced from baseline among onabotulinumtoxinA-treated patients compared to placebo-treated patients at Week 24 (−4.3 onabotulinumtoxinA vs. −2.9 placebo; $p < 0.001$) (Table 5) and at all other time points except Week 12 in the DB phase in the CM + MO subgroup (data not shown). There was an overall reduction from baseline in the mean frequency of multiple analgesic intakes at Week 24 in both treatment groups (−10.2 onabotulinumtoxinA vs. −9.2 placebo; $p = 0.151$) (Table 5) but no between-treatment group difference. However, statistically significant between-treatment group differences in multiple analgesic intakes favoring onabotulinumtoxinA were observed at Weeks 4, 8, 12, and 20 ($p \leq 0.05$; data not shown).

Table 3
Change from baseline in headache characteristics, impact and health-related quality of life at Week 24 in the chronic migraine with acute headache medication overuse subgroup.

Mean change from baseline, variable	CM + MO		
	OnabotulinumtoxinA (n = 445)	Placebo (n = 459)	*p* value[a]
Frequency of headache days (SE)	−8.2 (0.30)	−6.2 (0.31)	<0.001
Frequency of migraine[b] days (SE)	−8.1 (0.30)	−6.0 (0.31)	<0.001
Frequency of moderate/severe headache days (SE)	−7.7 (0.29)	−5.7 (0.31)	<0.001
Total cumulative hours of headache on headache days (SE)	−114.5 (5.77)	−70.8 (6.08)	<0.001
% patients with severe (≥60) HIT-6 score[c,d]	71.0	81.9	<0.001
Frequency of headache episodes (SE)	−5.4 (0.26)	−5.1 (0.25)	0.028
Frequency of migraine[b] episodes (SE)	−5.1 (0.25)	−4.8 (0.25)	0.018
Frequency of AHM intakes[e]	−13.1 (0.90)	−11.8 (0.89)	0.210
Total HIT-6 score[c]	−4.7[f]	−2.2[f]	<0.001
% patients achieving ≥5-point reduction in HIT-6 score[c,d]	38.7	23.3	<0.001
MSQ score[g]: Role function-restrictive	16.9[h]	7.6[h]	<0.001
MSQ score[g]: Role function-preventive	13.9[h]	5.8[h]	<0.001
MSQ score[g]: Emotional functioning	18.3[h]	8.7[h]	<0.001

AHM = acute headache medication, HIT = Headache Impact Test, HRQoL = health-related quality of life, ICHD = International Classification of Headache Disorders, MSQ = Migraine-Specific Quality of Life questionnaire.

[a] $p \leq 0.05$ is statistically significant. The *p* values are adjusted for baseline.

[b] ICHD-II 1.1 (migraine without aura), 1.2 (migraine with aura), 1.6 (probable migraine) [1].

[c] HIT-6: scores 36–49 = little or no impact; 50–55 = moderate impact; 56–59 = substantial impact; 60–78 = severe impact.

[d] Statistics are raw score, not change from baseline.

[e] Intakes denote the number of times that a patient self-treated with an acute medication, not the amount of medication(s) taken. An intake occurred each time a patient sought relief, regardless of the number of medications or doses taken at the same time.

[f] Difference between the groups exceeds the established minimally important between-group difference [27].

[g] MSQ scores range from 0 (poor HRQoL) to 100 (good HRQoL).

[h] Difference between groups exceeds minimally important differences for each MSQ domain [31].

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Table 4
Decrease from baseline in headache outcome measures at Week 24: ≥50% responders in the chronic migraine with acute headache medication overuse subgroup.

Decrease from baseline ≥50% responders, variable	CM + MO		
	OnabotulinumtoxinA (n = 445)	Placebo (n = 459)	*p* value[a]
Frequency of headache days	45.8%	32.1%	<0.001
Frequency of migraine[b] days	47.2%	33.7%	<0.001
Frequency of moderate/severe headache days	48.6%	35.9%	<0.001
Total cumulative hours of headache on headache days	49.2%	36.7%	<0.001
Frequency of headache episodes	46.9%	39.4%	0.038

[a] $p \leq 0.05$ is statistically significant.
[b] ICHD-II 1.1 (migraine without aura), 1.2 (migraine with aura), 1.6 (probable migraine) [1].

The frequency of acute headache medication days was significantly reduced among patients treated with onabotulinumtoxinA compared with placebo at the Week 24 primary time point (Table 5). Statistically significant reductions from baseline favoring onabotulinumtoxinA were also observed for triptan medication days at Week 24 and at all other time points except Week 12 in the DB phase. Although no significant between-treatment group differences in medication days were observed at Week 24 for any other medication category, significant between-treatment group reductions from baseline favoring onabotulinumtoxinA were observed for mean number of multiple analgesic days at Weeks 4, 12, 16, and 20 ($p \leq 0.05$) during the DB phase (data not shown).

3.2.5. Acute headache medication overuse shift

At Weeks 4, 16, and 20 and at the primary endpoint, Week 24, the proportion of patients who had shifted to no medication overuse that would persist for at least 3 months from that time forward significantly favored onabotulinumtoxinA-treated versus placebo-treated patients (Week 24: 53.2% vs. 41.7%; $p = 0.002$; Fig. 4 and data not shown). At every time point in the DB phase, starting with Week 4, the proportion of patients who had shifted to no medication overuse that persisted for at least 6 months significantly favored onabotulinumtoxinA-treated versus placebo-treated patients (data not shown). Also, starting at the primary end point (Week 24), a significantly higher proportion (43.4%) of onabotulinumtoxinA-treated patients (vs. 31.8% placebo; $p = 0.002$) had shifted to no medication overuse that persisted for at least 6 months (Fig. 4).

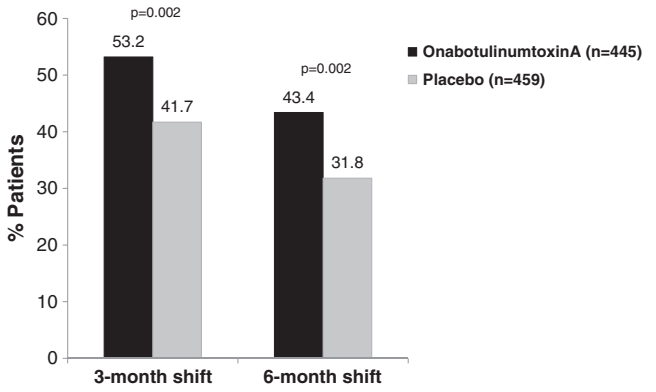

Fig. 4. Percentage of patients with a sustained "shift"* from acute headache medication overuse (CM + MO) to no acute headache medication overuse (CM − MO) for consecutive 3- and 6-month periods. *Patients who no longer reported the intake of simple analgesics on ≥15 days, or other medication types or combination of types for ≥10 days, with intake ≥2 days/week from the category of overuse, in each week with at least 5 diary days, for consecutive 3- or 6-month periods, starting from the month ending with Week 24, going forward.

3.3. Safety and tolerability

The safety profile and adverse event (AE) frequency in the pooled ITT PREEMPT population has been previously reported elsewhere [19]. OnabotulinumtoxinA treatment was shown to be safe and well tolerated [19,23,24]. The frequency of AEs within the CM + MO subgroup was consistent with that reported for the entire ITT population; 62.2% of CM + MO onabotulinumtoxinA-treated patients experienced AEs compared with 50.3% of CM + MO placebo patients (Table 6). Individual AEs within the CM + MO subgroup occurring at a rate of ≥5% were neck pain (8.5%) for onabotulinumtoxinA-treated patients and upper respiratory tract infections (5.5%) for placebo-treated patients. Most AEs reported by patients within the entire PREEMPT population, including the CM + MO subgroup, were mild or moderate in severity and were resolved without sequelae. Treatment-related AEs across the PREEMPT population, including the CM + MO subgroup, were consistent with the known tolerability profile of onabotulinumtoxinA, and no

Table 5
Frequency of acute headache medication intake at baseline and Week 24 in the chronic migraine with acute headache medication overuse subgroup.

Acute headache medication intake, mean	Baseline			Week 24		
	OnabotulinumtoxinA (n = 445)	Placebo (n = 459)	*p* value[a]	OnabotulinumtoxinA (n = 445)	Placebo (n = 459)	*p* value[a]
Total AHM intakes[b]	34.6	35.8	0.331	−13.1	−11.8	0.210
Ergotamine intakes	0.5	0.3	0.416	−0.2	−0.1	0.827
Triptan intakes	10.3	10.5	0.763	−4.3	−2.9	**<0.001**
Simple analgesic intakes	10.9	9.8	0.227	−4.9	−4.0	0.481
Opioid intakes	1.2	1.3	0.795	−0.1	−0.1	0.796
Combination analgesic intakes	11.8	13.9	0.056	−3.5	−4.8	0.453
Multiple analgesic intakes[b]	24.2	25.8	0.294	−10.2	−9.2	0.151
Total AHM days	18.0	18.3	0.349	−7.3	−6.5	**0.033**
Ergotamine days	0.3	0.2	0.663	−0.1	−0.1	0.777
Triptan days	8.3	8.4	0.822	−3.3	−2.4	**<0.001**
Simple analgesic days	7.4	6.8	0.228	−3.4	−2.9	0.561
Opioid days	0.8	0.8	0.815	−0.1	−0.1	0.935
Combination analgesic days	7.2	8.2	0.052	−2.6	−3.0	0.777
Multiple analgesic days	12.3	12.8	0.379	−5.6	−5.2	0.102

AHM = acute headache medication.
[a] $p \leq 0.05$ is statistically significant (indicated by boldface). The *p* values are adjusted for baseline.
[b] Intakes denote the number of times that a patient self-treated with an acute medication, not the amount of medication(s) taken. An intake occurred each time a patient sought relief, regardless of the number of medications or doses taken at the same time.

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Table 6
Summary of overall adverse events in the double-blind phase in the chronic migraine with acute headache medication overuse subgroup.

	CM + MO	
	OnabotulinumtoxinA (n = 444) n (%)	Placebo (n = 457) n (%)
All AEs[a]	276 (62.2)	230 (50.3)
Treatment-related AEs[b]	124 (27.9)	58 (12.7)
Serious AEs	20 (4.5)	9 (2.0)
Treatment-related, serious AEs[b]	1 (0.2)[c]	0 (0)
Discontinuations related to AEs	13 (2.9)	3 (0.7)
Deaths	0 (0)	0 (0)

AE = adverse event.
[a] All adverse events include all reported events, regardless of relationship to treatment.
[b] Treatment-related adverse events are those that in the investigator's opinion may have been caused by the study medication with reasonable possibility.
[c] Migraine requiring hospitalization.

newly emerged safety findings were observed over the 24 weeks of the DB study phase.

4. Discussion

CM patients who overuse acute headache medications are often difficult to treat. The Initiative on Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) recommends that the outcomes of measures for efficacy, safety, and HRQoL; treatment effect size; and safety and tolerability compared with other existing therapies be evaluated to determine clinical meaningfulness of clinical trial results, and to facilitate a complete understanding of the therapeutic benefit of treatments for chronic conditions [33]. The multiple headache symptom measures evaluated in the PREEMPT ITT population and in the CM + MO subgroup are in agreement with these recommendations and demonstrate the efficacy, safety, and tolerability of onabotulinumtoxinA treatment in the CM population, including those who had acute headache medication overuse at baseline. Furthermore, the AEs in the CM + MO subgroup mirrored the demonstrated safety and tolerability profile of onabotulinumtoxinA in the total PREEMPT population and were consistent with the well-established tolerability profile of onabotulinumtoxinA when injected into head/neck muscles [19,23,24].

Frequent use of acute headache medications, and sometime overuse, occurs in patients with CM. Therefore, to be more representative of patients within the clinic, PREEMPT inclusion criteria did not restrict enrollment based on frequency of acute headache medication intakes at baseline. We recognize that including patients with possible medication overuse may not be in agreement with the ICHD-II or ICHD-IIR criteria for CM; however, these criteria continue to be the subject of debate within the headache community [34]. Moreover, randomized controlled trials of preventive medications in this patient population must evaluate the patient population with the greatest unmet treatment need and especially those encountered commonly in clinical practice. The medication overuse stratification for this study was based on a single, 28-day diary in which frequency counts of acute headache medication intake were recorded. The decision to include CM patients with possible medication overuse agrees with the IHS clinical trial guidelines that recommend stratification by medication overuse status. In PREEMPT, a priori stratification afforded the opportunity to further evaluate headache prophylaxis using onabotulinumtoxinA treatment in the CM subpopulation with possible acute headache medication overuse at baseline. It is important to note that the PREEMPT investigators were headache experts and, per protocol, they were instructed to recruit patients who had a primary headache disorder and to exclude patients with secondary headache disorders (e.g., MOH). Patients with excessive intake of acute headache medication were allowed to be enrolled, but this terminology should not be equated with a confirmed secondary headache diagnosis of MOH. For a diagnosis of MOH, the overuse of medication (e.g., use of frequent analgesics for a non-headache related pain condition) must occur during the period of increasing headache frequency. If this cannot be confirmed historically, the diagnosis of MOH cannot be applied, even in the setting of MO. Therefore, we define this subpopulation as "chronic migraine with medication overuse." Our terms within the PREEMPT clinical program are meticulously defined and we interpret our findings, mindful of the confusion in the field about the above diagnostic issues and ongoing evolution of diagnostic criteria.

More than 65% of the entire pooled PREEMPT population (904 of 1384 total patients) had acute headache medication overuse (CM + MO subgroup) during the baseline period. This proportion is similar to a clinic-based study that reported that 73% of all chronic daily headache patients were overusing acute medications [7] and to an earlier CM trial where the majority of patients enrolled (78%) had overuse of acute medication (without a confirmatory diagnosis of MOH) [17]. Additionally, a post hoc analysis of subjects enrolled in a clinical trial evaluating the efficacy of topiramate for the treatment of CM whereby patients without acute medication overuse were to be excluded revealed that 37% of CM patients had acute medication overuse at baseline [35].

In the CM + MO subgroup, the efficacy results were similar to the overall ITT population [19], whereby statistically significant between-treatment group reductions from baseline favoring onabotulinumtoxinA treatment over placebo were demonstrated for the frequency of headache days and other headache symptom measures at the Week 24 primary time point (Table 3). The between-treatment group difference for headache days (2.0) exceeded the between-treatment group MID [36] (Fig. 2) established by Silberstein et al. In that study, 1 additional day of headache was associated with significant reductions in HRQoL [36]. The reductions in headache-day frequency observed in both the PREEMPT ITT population [19] and the CM + MO subgroup reported herein confirm the clinical meaningfulness of the efficacy findings.

A clinically meaningful treatment responder rate has not been established for CM treatment, but the IHS clinical studies subcommittee has suggested a rate of ≥30% represents a clinically meaningful improvement [22]. This is lower than the ≥50% rate of improvement that has traditionally been considered clinically meaningful in studies of episodic migraine [37] and reflects the greater severity and treatment complexity of chronic compared with episodic migraine. For the CM + MO subgroup, the proportions of onabotulinumtoxinA-treated patients showing a ≥50% reduction from baseline were significantly greater than the proportions of placebo patients at the Week 24 primary time point for headache days, headache episodes, moderate/severe headache days, migraine days, and total cumulative hours of headache on headache days (Table 4), and are consistent with the observations in the PREEMPT ITT population [19,21].

Although large mean decreases from baseline were observed for the frequency of acute headache medication intakes, this was the only secondary efficacy variable that did not demonstrate a statistically significant between-treatment group difference at Week 24 in the CM + MO subgroup. The reductions from baseline in both treatment groups may suggest that the process of reporting each intake through the headache diary could itself be considered an intervention and reduce medication intake. These results are consistent with those observed in a DB, randomized trial of topiramate prophylaxis in adults with CM that included patients with acute medication overuse, where reductions from baseline in acute headache medication intakes were observed without a statistically significant difference between treatment groups [17]. The method of recording acute headache medication intakes in the PREEMPT studies may have contributed to the discrepancy of response for the intakes end point: acute headache medication intake was recorded in patient diaries. An acute headache medication intake was defined as the time that a patient reported they took medication (i.e., the unique time a patient "reached" for relief), regardless of the dose or number of types of medication taken at

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the same time. For example, 1 aspirin tablet or 6 aspirin tablets taken at the same time was recorded as 1 intake. Similarly, one sumatriptan (triptan) tablet and one ibuprofen (a simple analgesic) taken at the same time was defined as 1 intake. There also could have been multiple intakes within a given day for each patient (e.g., similar reportings as above reported at different times during the day). Intakes by drug category (i.e., ergotamine, triptan, analgesic, opioid, combination analgesic, and combinations of analgesics) were also evaluated, and it was determined that in the CM + MO subgroup, triptan intakes by onabotulinumtoxinA-treated patients were significantly reduced compared with placebo-treated patients at Week 24. Additionally, within the CM + MO subgroup, reductions in total acute headache medication days and triptan days were significantly greater at Week 24 for the onabotulinumtoxinA-treated patients than for the placebo patients.

Another important responder analysis to evaluate is whether there was a change in the proportion of patients who no longer met criteria for acute headache medication overuse as a result of adding headache prophylactic treatment. Analyses of a 3- and 6-month persistent shift in the CM + MO subgroup from acute headache medication overuse to no acute headache medication overuse indicate that, starting as early as 4 weeks after treatment, significantly more onabotulinumtoxinA-treated than placebo-treated patients had reduced acute headache medication intake to the point that they no longer met criteria for acute headache medication overuse (Fig. 4). Patients with frequent headache may use acute headache medications to treat the pain [11]; therefore, when headache days are reduced, the need to take acute headache medication is also reduced.

Measurements of headache impact and HRQoL demonstrated statistically and clinically meaningful improvements with onabotulinumtoxinA treatment compared with placebo treatment (Table 3). The between-treatment group differences exceeded the established MID for both total HIT-6 scores [27] and the three domains of the MSQ [31]. In addition, onabotulinumtoxinA treatment, but not placebo, exceeded the established within-treatment group MID [32], which also demonstrates onabotulinumtoxinA-treatment as clinically meaningful.

OnabotulinumtoxinA was safe and well tolerated within the CM + MO subgroup. Most AEs were mild or moderate in severity, were resolved without sequelae, and were consistent with the known tolerability profile of onabotulinumtoxinA.

The results of this subgroup analysis are in agreement with the topiramate CM trial [17]. Within the medication overuse subgroup of patients, topiramate significantly reduced the mean number of monthly migraine days from baseline compared with placebo ($p = 0.03$) [17]. The results of the topiramate trial [17] and the results of this current PREEMPT analysis challenge the previous notion that acute headache medication overuse can complicate or limit effectiveness of headache preventive medications [7,8,10,16] Together, these results from well-controlled trials have direct implications for clinical practice by suggesting that patients with chronic migraine with acute headache medication overuse can be effectively treated with onabotulinumtoxinA and topiramate.

4.1. Note

The potency units of BOTOX® are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX® cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

Conflict of interest

As lead author, I take full responsibility for the data, the analyses and interpretation, and the conduct of the research; I had full access to all of the data; and I had the right to publish any and all data, separate and apart from the attitudes of the sponsor.

All authors concur with the submission and the manuscript has been approved by the responsible authorities where the work was carried out.

Disclosures

Stephen D. Silberstein is on the advisory panel of and receives honoraria from Allergan, Amgen, Capnia, Coherex, GlaxoSmithKline, Iroko Pharmaceuticals, Lilly, MAP, Medtronic, Merck, Neuralieve, NINDS, NuPathe, Pfizer, and St. Jude Medical; and serves as a Consultant for and receives honoraria from Amgen, MAP, Nautilus, Opti-Nose, and Zogenix. His employer received research support from Allergan, BMS, Cumberland, ElectroCore, Lilly, Merck, Opti-Nose, St. Jude Medical, and Troy Healthcare.

Andrew M. Blumenfeld has served as an advisory board member for MAP Pharmaceuticals and has received research grants from, been a consultant for, and been on the speaker bureau for Allergan, Inc.

Roger K. Cady has served as an advisory board member for MAP Pharmaceuticals and has received research grants from, been a consultant and advisory board member for, and been on the speaker bureau for Allergan, Inc.

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Mai Sirimanne was an employee of Allergan at the time the study was conducted and the analysis performed, and she continues as a consultant to Allergan.

Ronald E. DeGryse and Catherine C. Turkel are employees of Allergan, Inc.

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David W. Dodick serves on advisory boards and has consulted for Allergan, Inc., Alder, Pfizer, Merck, and Ferring.

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