OnabotulinumtoxinA for Treatment of Chronic Migraine: Analysis of the 56-Week PREEMPT 2 Trial

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PREEMPT
PHASE III RESEARCH EVALUATION MIGRAINE PROPHYLAXIS THERAPY WITH BOTULINUM TOXIN TYPE A

INTRODUCTION

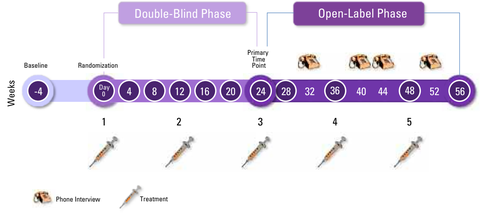
- Chronic migraine (CM) is a neurological disorder that affects up to 2.4% of the general population and is associated with significant disability and impaired health-related quality of life (HRQoL).[1-6]
- Few preventive treatments have been evaluated in CM, and currently none is labeled specifically for headache prophylaxis in patients with CM.
- Based on the results of previous phase 2 trials of onabotulinumtoxinA,[7-9] the PREEMPT (Phase III REsearch Evaluating Migraine Prophylaxis Therapy) clinical program (PREEMPT 1 and 2) was conducted to investigate the safety and efficacy of onabotulinumtoxinA in adults with CM (ICHD-II migraine and ≥15 headache days/month[1,10]).
- Results are reported for the entire 56 weeks of the PREEMPT 2 trial. Results from the 24-week, double-blind phase have already been reported.[11]

METHODS

Study Design

- PREEMPT 2 was conducted from 2006 to 2008 at 66 global sites (50 North American, 16 European).
- This phase 3 trial consisted of a 28-day baseline screening period (hereafter referred to as baseline), a 24-week, double-blind (DB), placebo-controlled phase (2 injection cycles), and a 32-week, open-label (OL) phase (3 treatment cycles) (Figure 1).
- Study visits occurred every 4 weeks.
- Subjects used an interactive voice response system (IVRS) daily telephone diary to record their headache symptoms and acute pain medications.

Figure 1. Study design.



Study Participants

- Men or women aged 18 to 65 years, with a history of migraine as in ICHD-II (2004) Section 1, Migraine,[1] with the exception of "complicated migraine," were eligible.
- During baseline, randomized subjects must have had headache occurring ≥15 days for 4 weeks,[10] with each day consisting of ≥4 hours of continuous headache and ≥50% of baseline headache days being migraine or probable migraine days (referred to as migraine days).
- Randomized subjects must have also had ≥4 distinct headache episodes during baseline, with each headache episode consisting of ≥4 hours of continuous headache.
- No use of any headache prophylactic medication within 4 weeks prior to start of baseline was allowed.
- Investigators were trained not to enroll patients who frequently used opioids as their acute headache pain medication.
- No previous exposure to any botulinum toxin serotype was allowed.

Randomization, Stratification, and Study Treatment

- For the DB phase, qualified subjects were randomized (1:1) to onabotulinumtoxinA (155 U) or placebo, administered as 31 fixed-site, fixed-dose, IM injections across 7 specific head/neck muscle areas every 12 weeks for 24 weeks (2 cycles). An additional 40 U of onabotulinumtoxinA or placebo could have been administered among 3 muscle groups (occipitalis, temporalis, or trapezius; total of 8 sites) using a protocol-defined, follow-the-pain strategy. The maximum total dose was 195 U at 39 sites.
- Randomization was stratified based on the frequency of acute head pain medication intake during the baseline period (designated as "medication overuse–yes" or "medication overuse–no"), with study treatments balanced in blocks of 4 within each medication overuse stratum for each investigator site.
- During the OL phase, all subjects received onabotulinumtoxinA treatment at Weeks 24, 36, and 48.

Efficacy and Safety Measures

- Efficacy analyses were based on change from baseline in each of the 28-day periods ending at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 56.
- The primary efficacy variable was frequency of headache days.
- Secondary efficacy variables included:
  - Frequency of migraine/probable migraine (referred to as migraine) days, frequency of moderate/severe headache days, cumulative hours of headache on headache days, proportion of patients with severe (≥60) Headache Impact Test (HIT)-6 score, and frequency of headache episodes.
- The impact of CM on disability in functioning, vitality, psychological distress, and HRQoL was evaluated by the mean change from baseline in total HIT-6 score and by the Migraine-Specific Quality of Life Questionnaire (MSQ) assessments in 3 functional domains: restrictive, preventive, and emotional.

Statistical Analysis

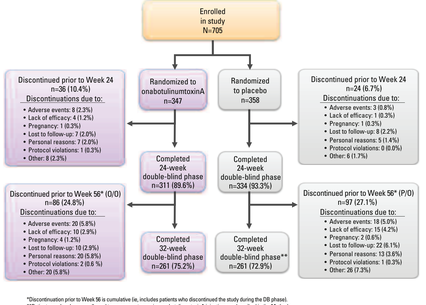
- All efficacy analyses used the intent-to-treat population and included all randomized patients.
- P value ≤0.05 was considered significant.
- Primary and secondary comparisons between groups was by ANCOVA, with baseline count as covariate with treatment and medication overuse stratum as main effects.
- Missing data were imputed using a prespecified modified last-observation carried forward methodology (mLOCF).
- To control the type 1 error rate for multiple secondary endpoints, a fixed-sequence gatekeeping approach was used for the 5 ranked secondary variables at the Week 24 primary visit.
- Statistical comparisons during the OL phase were evaluated as change from baseline. Additional statistical comparisons during this phase were based on the patients' DB-phase randomization to onabotulinumtoxinA (onabotulinumtoxinA/onabotulinumtoxinA [O/O] treatment group) or placebo (placebo/onabotulinumtoxinA [P/O] treatment group).
- Safety analyses were performed on all randomized subjects who received at least 1 dose of study medication at Day 0.

RESULTS

Demographic and Baseline Headache Characteristics

- Overall, 705 patients were randomized to onabotulinumtoxinA (n = 347) or placebo (n = 358) in the PREEMPT 2 DB phase (Table 1; Figure 2).
- Baseline patient demographics and headache characteristics were similar between the onabotulinumtoxinA and placebo groups (Table 1).
- Most patients (n = 444) overused acute pain medications during the 28-day baseline. Few patients (n = 44) used opioids during baseline; only 7 (1.0%) met opioid-overuse criteria.
- The mean patient diary-day compliance rate was >99% at baseline and remained high (>88%) across treatment groups over the course of the 56-week study.

Figure 2. Patient disposition.



*Discontinuation prior to Week 56 is cumulative (ie, includes patients who discontinued the study during the DB phase).
**Patients on placebo were allowed to cross over to receive onabotulinumtoxinA injections as described in the Methods.

Table 1. Baseline Patient Demographics and Characteristics

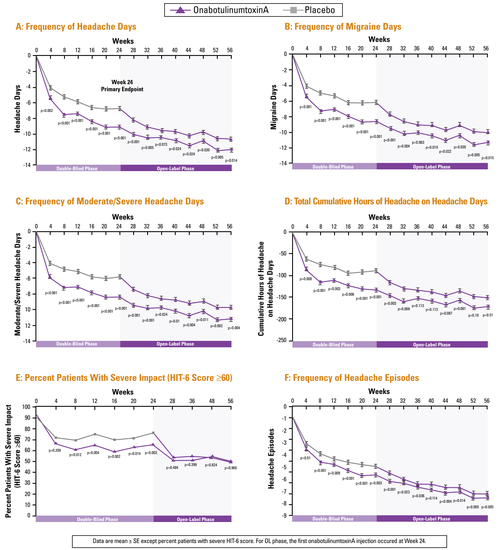
	OnabotulinumtoxinA (n=347)	Placebo (n=358)	p Value
Mean age, years	41.0	40.9	0.849
Mean years since onset of chronic migraine	18.5	17.6	0.279
Female, %	86.2	84.6	0.565
Caucasian, %	89.9	89.7	0.913
Mean BMI, kg/m²	26.7	27.1	0.305
Mean headache days during the 28-day baseline (SD)	19.9 (3.6)	19.7 (3.7)	0.682
Mean migraine days during the 28-day baseline (SD)*	19.2 (3.9)	18.7 (4.1)	0.156
Mean moderate/severe headache days during the 28-day baseline (SD)	18.1 (4.0)	17.7 (4.3)	0.333
Mean cumulative hours of headache occurring on headache days during the 28-day baseline (SD)	296.2 (121.0)	287.2 (118.1)	0.311
% Patients with severe (≥60) HIT-6 score during the 28-day baseline†	92.5	90.8	0.408
Mean headache episodes during the 28-day baseline (SD)	12.0 (5.3)	12.7 (5.3)	0.067
% Patients who had previously used 1 or more headache prophylaxis medications	64.0	66.2	0.536
% Patients overusing acute headache pain medication during the 28-day baseline	63.4	62.6	0.819
Mean HIT-6 score during the 28-day baseline*	65.6	65.0	0.106

BMI = body mass index; HIT = Headache Impact Test.
*ICHD-II 1.1 (migraine without aura), 1.2 (migraine with aura), 1.6 (probable migraine).[1]
†Scores of 36-49 indicate little or no impact; 50-55, some impact; 56-59, substantial impact; ≥60, severe impact.

Efficacy Results

- OnabotulinumtoxinA-treated patients showed statistically significant improvement versus placebo-treated patients for the primary endpoint and all secondary endpoints (Week 24; Figure 3A-F).
- At Week 56, O/O patients showed statistically significant improvement versus P/O patients for the primary variable and multiple secondary variables (Figure 3A-F).
- OnabotulinumtoxinA treatment significantly reduced disability and improved functioning, vitality, and psychological distress during the DB phase compared with placebo, as measured by a significantly greater mean change in total HIT-6 score (Week 24: -4.9 O/O, -2.4 O/P; p < 0.001) and by the lower percentage of patients with a HIT-6 score of severe (≥60; Figure 3E). This between-group difference of 2.5 exceeds established minimal between-group differences,[12] thus supporting the clinical relevance of the significant reductions in multiple headache symptom measures and improved HRQoL.
- By Week 56, when all patients had received onabotulinumtoxinA treatment, nearly half (49.9%) of patients had achieved a mean HIT-6 score in the less-than-severe (<60) category (Figure 3E).
- OnabotulinumtoxinA treatment significantly improved HRQoL as measured by each of the 3 MSQ role function domains, restrictive, preventive, and emotional (p < 0.001), at Weeks 12 and 24 compared to placebo. Treatment with onabotulinumtoxinA far exceeds the between-group minimally important differences (MIDs).[13]
- Also, the MSQ scale scores for the onabotulinumtoxinA group all exceeded the established within-group MIDs,[14] whereas none of the placebo group scores met these MIDs at Week 24. Significant within-group improvements in HRQoL were also observed at Week 56.

Figure 3. Mean changes from baseline in PREEMPT efficacy endpoints.



Data are mean ± SE except percent patients with severe HIT-6 score. For OL phase, the first onabotulinumtoxinA injection occured at Week 24.

Safety and Tolerability

Table 2. Summary of Overall Adverse Events Reported in DB and OL Phases

	DB Phase (24 Weeks)		OL Phase (32 Weeks)
	OnabotulinumtoxinA (n=347), n (%)	Placebo (n=358), n (%)	Total (n=634), n (%)
All AEs*	226 (65.1)	202 (56.4)	383 (60.4)
Treatment-related† AEs	116 (33.4)	49 (13.7)	138 (21.8)
Serious AEs	15 (4.3)	8 (2.2)	18 (2.8)
Treatment-related,† serious AEs	1 (0.3)	0 (0.0)	0 (0.0)
Discontinuations related to AEs	12 (3.5)	5 (1.4)	22 (3.5)
Death	0 (0.0)	0 (0.0)	0 (0.0)

AE = adverse event.
*All AEs include all reported events, regardless of relationship to treatment.
†Treatment-related AEs are those that in the investigator's opinion may have been caused by the study medication with reasonable possibility.

- Few discontinuations resulted from AEs (total 5.4%; O/O 5.8%, P/O 5.0%) over the course of the entire study.
- The only individual AEs occurring at a rate ≥5% during the DB phase were neck pain (9.8%) and muscle weakness (5.2%) in the onabotulinumtoxinA group. In the OL phase, during which all patients received onabotulinumtoxinA, the only individual AEs occurring at a rate ≥5% were neck pain (5.5%) and nasopharyngitis (5.5%).
- Treatment-related AEs throughout the 56-week study were consistent with the known tolerability profile of onabotulinumtoxinA, and no newly emerged safety findings were observed.
- There was 1 serious AE reported by the investigator as treatment-related for onabotulinumtoxinA in the DB phase (intractable migraine requiring hospitalization).
- Most AEs were mild or moderate in severity and resolved without sequelae.
- Throughout the 56-week study period, the overall rate of AEs progressively declined with subsequent onabotulinumtoxinA treatments (data not shown).

CONCLUSIONS

- OnabotulinumtoxinA was significantly more effective than placebo in reducing the frequency of headache days (primary variable) in patients with CM at all time points in the DB phase including Week 24. Significance continued at all time points during the OL phase up to and including Week 56.
- OnabotulinumtoxinA significantly improved multiple headache symptom measures over placebo for all secondary endpoints evaluated at Week 24. Placebo was never significantly favored over onabotulinumtoxinA in the DB phase.
- Statistically significant differences were observed for multiple headache symptom measures in the OL phase for patients who received onabotulinumtoxinA early in this study (ie, in the DB phase; O/O) compared to those patients who received active treatment later in this study (onabotulinumtoxinA for 3 cycles in the OL phase; P/O).
- Subjects who received onabotulinumtoxinA later (P/O) had significant within-group improvements from baseline, but had significantly less improvement compared to those subjects who had received the active treatment early (O/O).
- Significant improvements from baseline for all patients treated with onabotulinumtoxinA were sustained over multiple treatment cycles and across multiple headache symptom measures.
- OnabotulinumtoxinA patients achieved statistical and clinical significant improvements versus placebo-treated patients in functioning, vitality, psychological distress, and overall HRQoL in the DB phase.
- Repeated IM treatment with up to 5 cycles of onabotulinumtoxinA (155 U to 195 U) every 12 weeks over 56 weeks was safe and well tolerated.
- OnabotulinumtoxinA is an effective, safe, and well-tolerated long-term treatment as headache prophylaxis for adults with CM.

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DISCLOSURE

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.

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