

## Research Submissions

# Method of Injection of OnabotulinumtoxinA for Chronic Migraine: A Safe, Well-Tolerated, and Effective Treatment Paradigm Based on the PREEMPT Clinical Program

Andrew Blumenfeld, MD; Stephen D. Silberstein, MD, FACP; David W. Dodick, MD;  
Sheena K. Aurora, MD; Catherine C. Turkel, PharmD, PhD; William J. Binder, MD, FACS

Chronic migraine (CM) is a prevalent and disabling neurological disorder. Few prophylactic treatments for CM have been investigated. OnabotulinumtoxinA, which inhibits the release of nociceptive mediators, such as glutamate, substance P, and calcitonin gene-related peptide, has been evaluated in randomized, placebo-controlled studies for the preventive treatment of a variety of headache disorders, including CM. These studies have yielded insight into appropriate patient selection, injection sites, dosages, and technique. Initial approaches used a set of fixed sites for the pericranial injections. However, the treatment approach evolved to include other sites that corresponded to the location of pain and tenderness in the individual patient in addition to the fixed sites. The Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) injection paradigm uses both fixed and follow-the-pain sites, with additional specific follow-the-pain sites considered depending on individual symptoms. The PREEMPT paradigm for injecting onabotulinumtoxinA has been shown to be safe, well-tolerated, and effective in well-designed, controlled clinical trials and is the evidence-based approach recommended to optimize clinical outcomes for patients with CM.

**Key words:** chronic migraine, onabotulinumtoxinA, prophylaxis, prevention

**Abbreviations:** CDH chronic daily headache, CM chronic migraine, FSFD fixed-site, fixed-dose, FTP follow-the-pain, IM intramuscular, PREEMPT Phase III REsearch Evaluating Migraine Prophylaxis Therapy

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From the Headache Center of Southern California, San Diego, CA, USA (A. Blumenfeld); Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, USA (S.D. Silberstein); Mayo Clinic Arizona, Scottsdale, AZ, USA (D.W. Dodick); Department of Neurology, University of Washington, Swedish Headache and Pain Center, Seattle, WA, USA (S.K. Aurora); Allergan, Inc., Irvine, CA, USA (C.C. Turkel); Department of Head & Neck Surgery, UCLA School of Medicine, Los Angeles, CA, USA (W.J. Binder).

Address all correspondence to A. Blumenfeld, Headache Center, The Headache Center of Southern CA, 320 Santa Fe Drive, Encinitas, CA 92024, USA.

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Chronic migraine (CM) is a disabling neurologic disorder that affects 1.4-2.2% of the general population.<sup>1,2</sup> Patients with CM experience headache  $\geq 15$  days per month for  $\geq 3$  months, with headaches occurring on  $\geq 8$  days being classified as migraine headaches or headaches that respond to migraine-specific medications.<sup>3</sup> CM is the most common type of primary chronic daily headache (CDH) seen in headache specialty centers in the USA.<sup>i,3-5</sup>

The overuse of acute headache medications can be a problem for patients with chronic headache disorders. Most CM patients who seek treatment in tertiary headache clinics overuse acute headache medications.<sup>6</sup> An effective, safe, and well-tolerated prophylactic headache medication will improve the patient's clinical condition and should reduce acute headache medication consumption.<sup>1,7</sup> Only 33.3% of CM patients use prophylactic headache medication.<sup>1</sup>

OnabotulinumtoxinA has been reported to relieve pain in a variety of conditions, including migraine.<sup>8-20</sup> Efficacy results from previous trials in patients with episodic migraine (generally understood as occurring  $< 15$  days per month) have been negative.<sup>10,21-23</sup> Results from exploratory trials in episodic migraine, chronic tension-type headache, and CDH have been mixed, but have suggested that onabotulinumtoxinA may be useful as preventive treatment for CDH, specifically patients suffering from CM.<sup>8-10,24-26</sup> Various onabotulinumtoxinA dosages and injection paradigms have been evaluated in these studies,<sup>8-10,24-26</sup> and the Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) injection protocol evolved from these paradigms. Pivotal results from the PREEMPT clinical program have established onabotulinumtoxinA as a safe, well-tolerated, and effective headache prophylactic treatment for CM.<sup>27-29</sup>

<sup>i</sup>Historically, three terms have commonly been used interchangeably to describe patients with very frequent headaches that occur on most days of the month. These terms are *chronic daily headache*, *transformed migraine*, and *chronic migraine*. In June 2006, the Headache Classification Committee (ICHD) of the International Headache Society published revised criteria for diagnosing CM (ICHD-2R) and confirmed their position that *chronic migraine* was the preferred terminology among the three.<sup>3</sup>

Although the exact mechanism of onabotulinumtoxinA in antinociception has not been fully elucidated, animal and human studies indicate that onabotulinumtoxinA inhibits the release of nociceptive mediators, such as glutamate, substance P, and calcitonin gene-related peptide, from peripheral termini of primary afferents (nociceptors).<sup>30-37</sup> Blocking release of these neurotransmitters inhibits neurogenic inflammation; this, in turn, inhibits peripheral sensitization of nociceptive (pain-conducting) nerve fibers. As a result, peripheral pain signals to the central nervous system are reduced and, indirectly, central sensitization is blocked.<sup>30,31,36,37</sup>

The goal of this review is to provide an evidence-based clinical approach for treating CM with onabotulinumtoxinA. This review discusses patient selection, dosing, injection site selection, and injection techniques.

## EVIDENCE OF ONABOTULINUMTOXINA AS PREVENTIVE TREATMENT FOR CHRONIC MIGRAINE

Localized pericranial injections of onabotulinumtoxinA were first reported to alleviate migraine symptoms in patients with episodic migraine who had received treatment for hyperfunctional facial lines in a multicenter, open-label study. The study found that 89% of patients with episodic migraine who were treated with onabotulinumtoxinA had complete or partial response of their migraine symptoms, including headache.<sup>38</sup> Other, placebo-controlled, exploratory studies of episodic migraine patients (history of  $\geq 3$  moderate to severe migraines and  $\leq 15$  headache days per month) did not demonstrate statistically superior improvement in patients treated with onabotulinumtoxinA.<sup>21-23,25</sup> However, these trials did help to identify a patient population potentially responsive to onabotulinumtoxinA treatment. In one study, a post-hoc subgroup analysis of patients with the highest baseline frequencies of headache days (ie,  $\geq 12$  and  $\leq 15$  per month) found that onabotulinumtoxinA-treated patients experienced a significant mean decrease from baseline in headache episodes at Day 180 (the primary time-point) compared with placebo-treated patients ( $P = .048$ ).<sup>25</sup> These results suggest that patients suffering very fre-

quent headache attacks may be the ones most likely to benefit from prophylactic onabotulinumtoxinA treatment.

Results of 2 additional exploratory, well-designed, randomized, double-blind, placebo-controlled trials have provided further insight into which patients, dosages, and injection protocol may yield the best results from prophylactic onabotulinumtoxinA therapy.<sup>8,24</sup> Together, these trials recruited >1000 patients with CDH (>15 headache days per month) who could have had any combination of migraine and/or episodic or chronic tension-type headache. Baseline data from these studies indicated that the majority of patients enrolled likely suffered from CM.<sup>8,24,39</sup> Each study used a different approach (fixed-site or follow-the-pain [FTP], discussed below) and different doses of onabotulinumtoxinA (75–260 U). The primary outcome measures of these exploratory trials were not met, although improvements from baseline for the treatment groups were reported in both trials.<sup>8,24</sup> In one trial, several secondary measures showed statistically significant benefit with onabotulinumtoxinA treatment vs placebo treatment,<sup>8</sup> which suggested that further analysis was warranted to identify a specific subgroup of patients.<sup>39</sup> A subgroup analysis that excluded patients taking other headache prophylactic treatments showed a statistically significant improvement in the frequency of headache-free days at 6 months, the primary end-point (10.0 days in the onabotulinumtoxinA group vs 6.7 days in the placebo group,  $P = .038$ ). A significant reduction at 6 months in the mean frequency of headaches per 30 days that favored onabotulinumtoxinA treatment was also observed ( $-7.8$  in the onabotulinumtoxinA group vs  $-4.5$  in the placebo group;  $P = .032$ ).<sup>39</sup> This subgroup analysis was conducted also based on recommendations from migraine controlled-trial guidelines that recommend monotherapy studies because concomitant treatment may confound study results.<sup>40–42</sup> Overall, these exploratory phase 2 studies provided guidance and shaped the study design and the injection paradigm of the phase 3 PREEMPT clinical program.

Another controlled study demonstrated the effectiveness of 100 U onabotulinumtoxinA in the treatment of patients with CM who specifically did

not overuse pain medication. In this study, which used a fixed-site administration approach, patients in the onabotulinumtoxinA treatment group had a statistically significant and clinically meaningful (31.0%) decrease in migraine frequency (primary end-point) compared with the 8.9% decline for those in the placebo-treated group ( $P < .001$ ).<sup>9</sup>

More recently, the PREEMPT clinical program has confirmed onabotulinumtoxinA as an effective, safe, and well-tolerated prophylactic treatment for adults with CM.<sup>27</sup> These two phase 3, multicenter studies (PREEMPT 1 & 2), each of which had a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week open-label phase, enrolled 1384 patients with CM. In these studies, all patients received a minimum intramuscular (IM) dose of 155 U of onabotulinumtoxinA administered to 31 injection sites across 7 head and neck muscles using a fixed-site, fixed-dose (FSFD) injection paradigm (each injection was 5 U in 0.1 mL). In addition, up to 40 U onabotulinumtoxinA, administered IM to 8 additional injection sites across 3 head and neck muscles, was allowed, using a FTP approach. Thus, the minimum dose was 155 U and the maximum dose was 195 U.<sup>27</sup>

Important end-points (primary and secondary) were change from 28-day baseline compared with the 28 days ending at Week 24 for frequency of headache days (primary PREEMPT 2; secondary PREEMPT 1) and headache episodes (primary PREEMPT 1; secondary PREEMPT 2). Statistically significant reductions from baseline for frequency of headache days after onabotulinumtoxinA treatment compared with placebo treatment in both PREEMPT 1 ( $P = .006$ ) and PREEMPT 2 ( $P < .001$ ) were observed.<sup>28,29</sup> Statistically significant improvement from baseline after onabotulinumtoxinA compared with placebo treatment was seen for headache episodes in PREEMPT 2 ( $P = .003$ ),<sup>29</sup> but not in PREEMPT 1.<sup>28</sup> Pooled analysis demonstrated that onabotulinumtoxinA treatment significantly reduced mean frequency of headache days ( $-8.4$  onabotulinumtoxinA,  $-6.6$  placebo;  $P < .001$ ) and headache episodes ( $-5.2$  onabotulinumtoxinA,  $-4.9$  placebo;  $P = .009$ ).<sup>27</sup> Several other efficacy variables (migraine episodes, migraine days, moderate or severe headache days,

cumulative hours of headache on headache days, and proportion of patients with severe disability) showed significant between-group differences favoring onabotulinumtoxinA. The PREEMPT results showed highly significant improvements in multiple headache symptom measures and demonstrated improvement in patients' functioning, vitality, psychological distress, and overall quality of life.<sup>27</sup>

A literature review of the randomized, double-blind, placebo-controlled clinical studies of onabotulinumtoxinA as headache prophylaxis treatment for CM reports adverse events (AEs) that were consistent with the known safety and tolerability profile of IM administration of onabotulinumtoxinA. The safety profile indicates that onabotulinumtoxinA is safe and well-tolerated in the CM population, with few patients discontinuing treatment due to AEs (1.4-3.8%).<sup>8,24,27-29,43</sup> In contrast, other prophylactic headache treatments report discontinuation rates due to AEs as high as 12.7%.<sup>43</sup> Several epidemiologic surveys indicate that preventive therapies are significantly underutilized; only a minority of patients who could benefit from preventive therapy are currently treated (6-13% in population-based surveys).<sup>7,44,45</sup> Thus, a substantial proportion of migraine sufferers who might benefit from prevention do not receive it. A study of patient adherence to prophylactic migraine medication showed that 35% of enrolled patients were nonadherent.<sup>46</sup> Another study revealed that approximately 75% of the study population ( $n = 729$ ) had stopped or switched prophylactic treatment for migraine after 1 year.<sup>47</sup> Given the substantial AEs and adherence issues associated with available pharmacotherapies for CM, the relatively mild AEs associated with onabotulinumtoxinA treatment may present an attractive treatment alternative.

## **RATIONALE AND DESIGN OF THE PREEMPT INJECTION PARADIGM**

**Patient Selection.**—Identifying headache disorder(s) that respond to onabotulinumtoxinA treatment has been the subject of clinical exploration for more than a decade. Initial research evaluated patients with various headache disorders, such as cervical-associated headache,<sup>48</sup> episodic migraine,<sup>10,38</sup> CM,<sup>8,9,24</sup> and chronic tension-type headache.<sup>26,49</sup>

PREEMPT results support previous studies,<sup>8,24,39</sup> which identified CM patients as the ones most likely to benefit from onabotulinumtoxinA treatment. Results from the onabotulinumtoxinA pivotal studies confirm that patients with CM, including those who were overusing acute headache medication during the 28-day baseline period, benefit from this treatment.<sup>27-29</sup>

**Dose.**—Between 1997 and 2000, 5 exploratory, randomized, double-blind, placebo-controlled, parallel-group design studies of episodic migraine were conducted. In these studies, each treatment arm used a FSFD IM injection paradigm with the intent of determining which muscle(s) and dose(s) were effective. Doses ranged from 6 to 75 U, and the number of injection sites ranged from 3 to 11, administered IM in up to 4 muscle groups, all in the front of the head (ie, corrugator, procerus, frontalis, and temporalis) with no posterior head or neck injections.<sup>10,21,22</sup> Two of these studies evaluated a single treatment cycle and patients were followed for approximately 16 weeks.<sup>10,21</sup> The other 3 studies evaluated multiple treatment cycles repeated at 120-day intervals in sequential follow-on studies.<sup>22</sup>

In 2001, 4 additional larger, exploratory, randomized, double-blind, placebo-controlled, parallel-group design studies were initiated: 2 in patients with episodic migraine and 2 in patients with CDH. All 4 studies utilized a FSFD treatment paradigm. In 2 of the studies, additional treatments were allowed in predefined head and neck muscles where patients had predominant pain. Doses evaluated in these studies ranged from 75 U in 20 injection sites across 7 specific head and neck muscles<sup>23,24</sup> to 260 U in 58 injection sites across 7 specific head and neck muscles.<sup>8,25</sup> In one of these phase 2 studies in CDH,<sup>24</sup> the dose included 225 U, 150 U, and 75 U groups and provided insight with regard to the optimally safe and effective dosage per injection cycle. However, in this trial a dose-response was observed for tolerability, with the 225 U dose group having more AEs (eg, muscle weakness, neck pain) than the other 2 treatment groups. With regard to efficacy, the 2 higher dose groups were both different from the 75 U group, but there was no difference in efficacy between the 225 U and 150 U groups. Therefore, it was determined that the optimal

total dose to maximize efficacy and tolerability was within the range of >150 U and <200 U. PREEMPT confirmed that 155-195 U of onabotulinumtoxinA is efficacious for treating patients with CM.<sup>27-29</sup>

**Injection Sites and Techniques.**—Dilution volume used for each 100 U vial of onabotulinumtoxinA varied across the early studies, which could have also contributed to varied findings across these studies, and this is another important factor to consider for this injectable treatment. Early exploratory studies diluted each vial with 1.33-10 mL, which resulted in onabotulinumtoxinA concentrations that ranged from 7.5 U/0.1 mL to 0.1 U/0.1 mL.<sup>10,21,22</sup> The occurrence of eyelid ptosis, which may be influenced by the dose and dilution administered to the frontal muscles (corrugator, procerus, and frontalis muscles), was seen in up to 17.5% patients<sup>10</sup> injected with a total maximum dose of 57 U (75 U group) (dilution 1.33 mL/vial) to these muscles. In another study, despite a maximum dose of only 19 U in these muscles (25 U total dose group), ptosis was reported at a rate of 14.3% when using a dilution of 4 mL/vial.<sup>21</sup> In the double-blind, placebo-controlled phase of the pivotal phase 3 PREEMPT trials, ptosis was reported at low rates (3.6% of onabotulinumtoxinA-treated and 0.3% of placebo-treated patients)<sup>27</sup> with a total dose of 35 U to the frontalis, corrugator, and procerus muscles. In PREEMPT, each 100 U vial of onabotulinumtoxinA was diluted with 2 mL preservative-free normal saline, resulting in a concentration of 5 U/0.1 mL.

To ensure the stability of the protein, the package insert for onabotulinumtoxinA (BOTOX®) recommends reconstitution with preservative-free normal saline (0.9% Sodium Chloride, USP).<sup>50</sup> Once a 100 U vial of onabotulinumtoxinA has been reconstituted, it must be injected or immediately stored in a refrigerator at 2-8°C in the original vial (not in a syringe) and used within 24 hours<sup>50</sup> or as indicated in the local package insert.

In the development of a treatment paradigm for onabotulinumtoxinA injections, perhaps the greatest evolution has been in the selection of sites for the injections. As mentioned above, 2 approaches have been widely used: fixed-site/fixed-dose and follow-the-pain. It was previously believed that the type of app-

roach depended on the type of headache, but whether one approach should be preferred over the other has not previously been firmly established. Early headache studies generally used a fixed-site approach, identifying sites in the forehead and glabellar region while generally avoiding the occipital and neck regions.<sup>10,51</sup> The fixed-site approach distributes onabotulinumtoxinA to muscles that align with the peripheral nerve distribution of the cervical and trigeminal sensory system, which is believed to be the target-end organ for onabotulinumtoxinA in treating CM. These sites remain unchanged regardless of where the patient's pain is located. The PREEMPT injection paradigm, which uses a combination of fixed and FTP injection sites, provides optimal distribution of onabotulinumtoxinA based on individual patient symptoms.<sup>8,24</sup>

The muscle groups chosen in PREEMPT were based on in-depth analysis of the interaction effects of muscle group dose on efficacy variables in patients who were not using prophylactic headache medication during baseline, and in-depth analyses of the safety and tolerability of the dose and dosage paradigm used in the 2 Allergan-sponsored phase 2 studies of patients with CDH.<sup>8,24</sup> The findings from these analyses, which are discussed further below, serve as the foundation for the choice of muscles, dose, and dilution used in the PREEMPT studies.

**Frontalis, Corrugator, and Procerus (Frontal/Glabellar Region).**—In the phase 2 trials,<sup>8,24</sup> patients reported that the frontal/glabellar region was the most frequent location where their head pain started and ended. In the first trial, doses for the frontal/glabellar region were not specified; only a total dose was specified for the overall region, which was administered across the frontalis, corrugator, and procerus muscles. In the second trial, the frontalis and corrugator muscles of the forehead were injected, but not the procerus muscle. Overall, the first trial had better signals for efficacy than the second trial. Thus, to ensure the best chance for efficacy as well as ensure consistency and standardization of treatment, the PREEMPT paradigm used the muscles that were injected in the first trial: the frontalis, corrugator, and procerus.

The AE rate of eyelid ptosis was 7.5% in the onabotulinumtoxinA-treated group in the first trial,<sup>8</sup>

and 4.8% and 6.6% in the 150 U and 225 U dose groups, respectively, in the second trial.<sup>24</sup> To reduce the potential for focal AEs such as eyelid ptosis, a slightly lower total dose (35 U) than the average dose administered to the frontal muscles in the second trial (40 U) was chosen for evaluation in the phase 3 PREEMPT studies. Furthermore, in the PREEMPT trials the exact number of injections and location for injection to these muscles was specified in the protocol and injection training to ensure optimal tolerability and to specifically reduce the eyelid ptosis AE rates observed in the phase 2 trials. Indeed, the PREEMPT injection method in these muscles appears to have achieved these goals, because the PREEMPT clinical program had statistically significant separation from placebo across multiple headache symptom measures, with an overall eyelid ptosis rate of 3.6% for onabotulinumtoxinA-treated patients in the double-blind, placebo-controlled phase of the pooled phase 3 trials.

**Temporalis.**—In the phase 2 trials,<sup>8,24</sup> patients reported that the temporalis area was the second most frequent location where their head pain started and ended. The FSFD for this muscle in the phase 3 trials was determined based on the fact that the mean dose administered to the temporalis muscle in the first trial was ~40 U (~20 U per side) and the maximum dose was 50 U. There were no emerging tolerability issues from injecting this muscle at these doses in the phase 2 trials. Because this muscle was a very common location of predominant pain for many patients in the phase 2 trials, it was decided that for the PREEMPT paradigm the total dose of 40 U (20 U per side) would be required as a minimum dose, and an allowance for an additional 10 U to this muscle area could be given using the FTP regimen.

**Cervical Paraspinal Muscle Group (Neck Muscles).**—In the phase 2 trials,<sup>8,24</sup> patients indicated that their headache pain frequently started and/or stopped in the back of the head (either in the occipitalis and/or the neck). The splenius capitis and semispinalis muscles were the neck muscles injected in both phase 2 trials. The protocols allowed investigators some discretion as to specific injection location in these muscles, and many of the investigators administered the treatment to the mid-neck region and

often injected these muscles using longer needles to ensure that they reached the semispinalis muscle. In the second trial, which was a dose-ranging, FSFD regimen trial, patients in the middle- and high-dose groups showed a relatively high incidence of neck pain (~25%). In some instances, neck muscle weakness resulted in patients needing temporary soft collars to support their head. In this trial, patients in the middle- and high-dose groups received 20 U and 30 U, respectively, to each side of the splenius capitis and semispinalis neck muscles, for total doses of 40 U and 60 U, respectively, across these 2 muscle groups. The incidence of neck pain (13.3%) in patients treated in first trial (which had variable neck dose that could range from 20 to 40 U total across the semispinalis and splenius capitis muscles) was not as high; these patients received average doses of ~18 U in each muscle group for a total mean dose in the mid-neck region of ~36 U.

Upon review of the tolerability data, the PREEMPT injection paradigm for the neck was revised. Injections were to be given to the upper neck (cervical paraspinal muscles) at the base of the skull, rather than to the mid-neck region. The FTP injection regimen was not allowed in the neck region, and injections were to be more superficial rather than deep into the neck muscles. Hence, the injection needle length and gauge were standardized to 0.5 inch and 30 gauge, respectively, which is shorter and a smaller bevel than what had been allowed in the second phase 2 trial (that trial had allowed use of up to 1.5 inch and/or larger 27-gauge needle). Furthermore, it was decided to reduce the total dose injected into the neck region. The overall dose was reduced to a FSFD of 20 U for this muscle group (10 U to each side of the head). It was anticipated that this dose would be sufficient from an efficacy perspective and that the lower neck dose would result in less neck pain and neck rigidity, and also decrease the risk of excessive neck muscle weakness, which would improve the overall tolerability profile while maintaining efficacy. The overall AE rates in the pooled analysis of the double-blind, placebo-controlled phase of the PREEMPT studies was less than what was observed in the phase 2 studies, with neck pain occurring in 8.7% of the onabotulinumtoxinA-

treated patients vs 2.7% of the placebo-treated patients.<sup>27</sup> There was only 1 patient in PREEMPT who required a soft collar due to excessive weakness, compared with 10 patients in the phase 2 studies, confirming that a reduction in the dose and needle length was appropriate.

**Occipitalis.**—In the phase 2 trials,<sup>8,24</sup> patients reported that occipitalis was the third most frequent location where their head pain started and ended. The phase 2 data were also evaluated to ascertain the frequency of FTP paradigm actually used by clinicians in the first trial, because variation in the dosage was allowed for all muscle groups in that protocol except for the occipitalis. The mean and median doses for each muscle group showed that the dosages for the temporalis and trapezius muscles were the muscle groups with the most variation across patients, which indicated FTP was most frequently used for these muscle groups. Most patients have predominant pain on one side of the head, or in the back of the head, or in the shoulders that may warrant additional treatment to those areas. Because a decision had been made to reduce the overall dose administered to the neck and to not allow FTP regimen in the neck muscles (as described above), there was concern that there would be insufficient “back of the head” dose to ensure efficacy, especially since so many patients complain of pain in that area. Thus, the minimum dose administered to the occipitalis was increased from the phase 2 dose, and, to reduce risk of neck weakness, the sites for injection into the occipitalis were located primarily above the occipital ridge, which would also reduce the risk of neck weakness. Furthermore, if patients had a complaint of predominant pain in the back of the head, additional FTP dosing would be allowed in this muscle.

**Trapezius.**—In the phase 2 trials,<sup>8,24</sup> approximately 20-30% of patients reported that their headache pain started and/or ended in the trapezius muscles. In the second trial, the total doses administered to the trapezius muscles were 20 U, 40 U, and 60 U in the 75 U, 150 U, and 225 U dose groups, respectively. The incidence of arm (shoulder) pain, which was felt to be related to injections into the trapezius muscle due to the close location and the thinness of the

muscle at the proximal location near the shoulder muscle, was higher for the 2 higher dose groups: 8.2% in the 225 U group and 8.9% in the 150 U group compared with 6.3% in the 75 U group. In the first trial, the mean dose administered to the trapezius was ~48 U and the incidence of arm (shoulder) pain was 5.8%, which is lower than that observed in the second trial. The incidence of arm (shoulder) pain in the patients who received the maximum 60 U dose was not felt to be a general safety concern, but at the same time there was a desire to minimize patient discomfort while ensuring optimum efficacy from this treatment. Thus, the dosage regimen for the trapezius muscle in the PREEMPT clinical program was standardized to a minimum dose of 30 U (15 U on each side), with the option for additional FTP treatment to a maximum dose of 50 U (up to 20 U additional administered as 5 U per injection site divided across 1 or both sides) if clinically needed. This standardization was appropriate, as demonstrated by the reduction in the incidence of arm (shoulder) pain for onabotulinumtoxinA-treated patients (2.9%) in the double-blind phase of PREEMPT.

**Masseter Muscle.**—The masseter muscle, which was an optional muscle that could have been injected in the first phase 2 trial,<sup>8</sup> was not included as a muscle to be injected in PREEMPT. The masseter muscle was injected in only 24% (84/355) of patients in that trial, and clinical data analyses suggested that patients who received masseter injections did not benefit from onabotulinumtoxinA treatment to the same extent as those who did not receive masseter injections. It was unclear from this finding whether patients who were manifesting pain in the masseter region represent a subgroup of chronic migraineurs and/or whether comorbid chronic pain conditions of temporomandibular disorder or chronic pain in or around the temporomandibular joint were potentially confounding the results. Although there was no indication of specific AEs resulting from masseter injection, neither was there evidence that including the masseter muscle enhanced the efficacy; hence, it was not included as a target muscle group for injection in the phase 3 PREEMPT trials.

**Table.—OnabotulinumtoxinA Dosing for Chronic Migraine by Muscle Using the PREEMPT Injection Paradigm**

Head/Neck Area	Recommended Dose: Total dosage (number of sites†)
Frontalis‡	20 units (in 4 sites)
Corrugator‡	10 units (in 2 sites)
Procerus	5 units (in 1 site)
Occipitalis‡	30 units (in 6 sites), rebreak up to 40 units in 8 sites
Temporalis‡	40 units (in 8 sites), rebreak up to 50 units in 10 sites
Trapezius‡	30 units (in 6 sites), rebreak up to 50 units in 10 sites
Cervical paraspinal muscle group‡	20 units (in 4 sites)
Total dose range	155 units to 195 units

†Each intramuscular injection site = 0.1 mL = 5 U onabotulinumtoxinA.

‡Dose distributed bilaterally for the minimum 155 U dose.

### THE PREEMPT INJECTION PARADIGM

Based on exploratory phase 2 CM studies detailed above,<sup>8,24</sup> the PREEMPT clinical program evaluated a standardized treatment paradigm.<sup>27-29</sup> Using this standardized paradigm, a minimum dose of 155 U of onabotulinumtoxinA was administered as 31 FSFD injections across 7 specific head/neck muscles (Table). Up to 40 U of additional onabotulinumtoxinA could have been administered at the physician's discretion using a FTP strategy into the temporalis, occipitalis, and/or trapezius muscles, with a maximum dose of 195 U administered to 39 sites (Table). When deciding on dose and location of additional onabotulinumtoxinA, physicians took into consideration the location of the patient's predominant pain and the severity of palpable muscle tenderness.

The PREEMPT injection paradigm involved a minimum of 31 injections to 7 specific head and neck muscle areas. Patients were placed supine for injections into the corrugator, procerus, frontalis, and temporalis, and these muscles were injected first, in that order. Patients were sitting for injections into the occipitalis, cervical paraspinal, and trapezius muscles. The physician palpated each muscle (bilaterally, if appropriate) prior to injection to verify muscle delineation, and determined whether there was any muscle

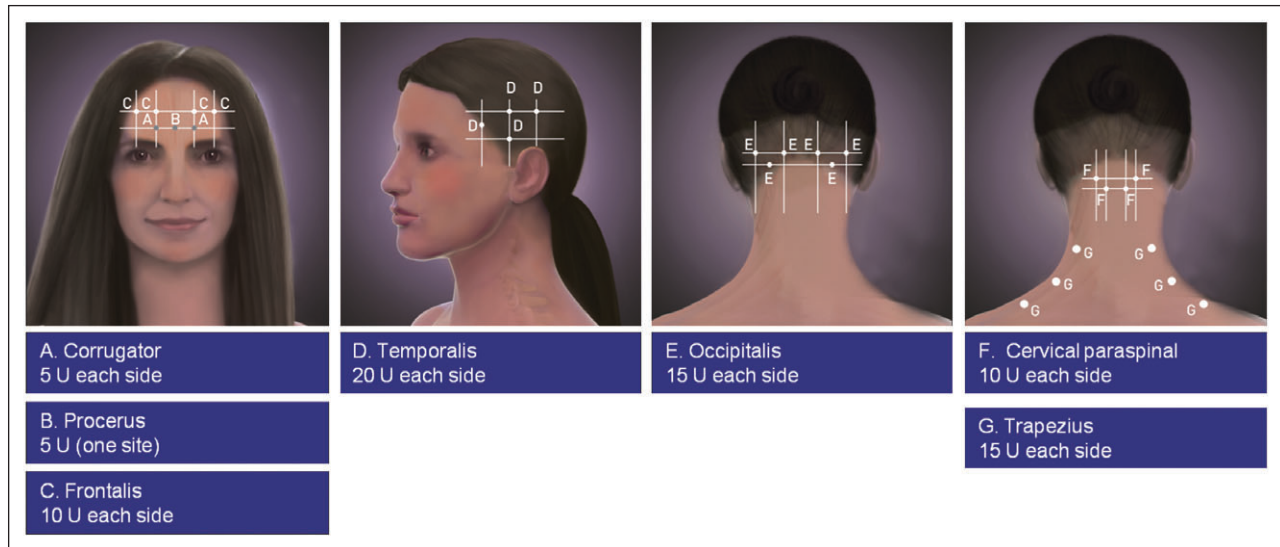
tenderness and areas of pain that required additional treatment. The PREEMPT injection paradigm dose for CM was 155-195 U administered IM using a sterile 30-gauge, 0.5-inch needle as 0.1 mL (5 U) injections per each site. A 1-inch needle was allowed in the neck region for patients with thick neck muscles. The treatment paradigm recommended wearing gloves while the treatment was administered. Prior to injection, the skin was cleansed according to standard practice for IM injections (eg, with alcohol). The needle was inserted into the muscle with the bevel up, at approximately a 45-degree angle. Once the needle was inserted into the muscle, the hub of the needle was held with one hand to ensure that the needle did not torque in the skin. The plunger was pulled back slightly with the other hand to ensure no blood return, and the plunger was then pushed to administer 0.1 mL (5 U) to each designated injection site. If bleeding or bruising occurred, gentle pressure was applied. Injections were not given intravenously.

**Corrugator and Procerus.**—Injections started in the glabellar region, which consists of the corrugator and procerus muscles. These muscles are shallow, so the needle was kept superficial to avoid hitting the periosteum. A total of 2 FSFD injections were given to the corrugator muscle, one on each side of the forehead. According to the paradigm, the injection site is located approximately 1.5 cm (1 finger's breadth) above the medial superior edge of the orbital ridge (bony landmark). The thumb was placed under the corrugator muscle and the injection was done with the needle angled up and away from the eye (toward the forehead), to prevent ptosis of the eyelid (Fig. 1A). Ptosis occurs when toxin diffuses into the medial portion of the upper eyelid where the levator palpebrae superioris muscle is located.<sup>52</sup>

According to the paradigm, the procerus muscle has 1 FSFD injection site, in the midline of the forehead approximately 1.5 cm above the medial superior aspect of the orbital ridge (bony landmark) of each eye. This injection site is midway between the 2 corrugator injections (Fig. 1B), as if there is a single horizontal line connecting all 3 of these injections.

**Frontalis.**—Each physician then injected the frontalis muscle, which is shallow, so the needle was kept superficial to avoid hitting the periosteum. Each





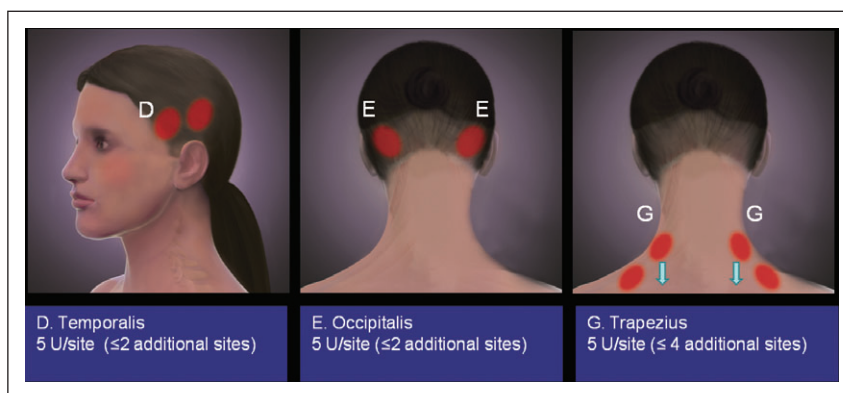
**Fig 1.**—Fixed-site, fixed-dose injection site locations: the (A) corrugators, (B) procerus, (C) frontalis, (D) temporalis, (E) occipitalis, (F) cervical paraspinal, and (G) trapezius muscle injection sites.

injection diffuses over an area about 2 cm in diameter once the needle pierces the skin (Fig. 1C), thus the needle did not need to be directed upward for these injections. According to this paradigm, there are a total of 4 FSFD frontalis injections (2 on the left side and 2 on the right). For medial injection sites, a visual line was drawn up from the medial edge of the eyebrow about 1.5 cm (1 finger's breadth) from the corrugator injection site. The lateral injection sites are parallel and approximately 1.5 cm lateral of the medial injections sites.

**Temporalis.**—The temporal area received a total of 8 FSFD injections, 4 to each side. Up to 2 additional injections using the optional FTP paradigm were allowed. Prior to any injection, the muscles on both sides of the head were palpated for tenderness or pain. Each physician started with the 4 fixed-site injections on the left side of the head as indicated in Figure 1D. The patient was instructed to clench his or her teeth to assist in the location of the anterior aspect of the temporalis muscle, which was palpated. The first injection was made just behind this point (approximately 2 fingers' breadth) behind the hairline. The second injection was made approximately 0.5 cm superior and 1.5 cm posterior to the first injection in the medial aspect of the muscle. The third injection site was found parallel and approximately

1.5 cm posterior to the second injection. The fourth fixed-site injection was 1.5 cm below and perpendicular to the second injection, into the medial aspect of the muscle (Fig. 1D). If a decision was made to inject additional onabotulinumtoxinA into the temporalis muscle, it was injected in this side before the right side of the head (Fig. 2D). The PREEMPT injection paradigm recommends that an additional injection site be used rather than increasing the volume for any given prior injection site.

**Occipitalis.**—Prior to injecting the occipital area, both the left and right sides were palpated to identify the areas of tenderness and/or pain. The external occipital protuberance was palpated to locate the occipitalis injection sites, which are superior to the supranuchal ridge on either side of this protuberance (Fig. 1E). Three injections were administered to the right and left occipitalis muscles, for a total of 6 FSFD injections (Fig. 1E). The first injection was given just above the occipital protuberance along the supranuchal ridge and approximately 1 cm left/right (depending on the side) of the external occipital protuberance. The second injection was given approximately 1 cm to the left/right and approximately 1 cm above the first injection. The third injection was given 1 cm medial and 1 cm above the first injection site. According to the FTP optional dosing paradigm, an



**Fig 2.—Follow-the-pain muscle areas: optional injections are distributed between the right and left (D) temporalis, (E) occipitalis, and (G) trapezius muscles in areas of maximal tenderness and/or pain.**

additional 2 injections could have been distributed between the right and left occipitalis muscles (1 injection on each side or 2 injections on 1 side) in the areas identified as having maximal tenderness (Fig. 2E).

**Cervical Paraspinal Muscle Group.**—Beginning on the left side, the cervical paraspinal muscle group injection sites were located by palpating the cervical spine (Fig. 1F). It was important not to go too deep into the cervical paraspinal and trapezius muscles with the injections, and the hub of the 0.5-inch needle served as a relatively accurate “depth” guide. The first injection was administered lateral to the midline, approximately 3-5 cm inferior to the occipital protuberance. A second injection was administered on the same side, 1 cm lateral and superior to the first injection (diagonally toward the ear from the first injection). This procedure was repeated symmetrically on the contralateral side, for a total of 4 FSFD injections.

**Trapezius.**—Lastly, the superior portions of the trapezius muscles were palpated to identify areas of tenderness and/or pain. Beginning on the left side, the muscle was visually divided into 3 sections (Fig. 1G). The first injection was administered in the lateral aspect of the muscle. The physician then moved medially, to the mid-portion of the trapezius, and administered the second injection. The third injection was administered medially and superiorly within the third section of the muscle. This procedure was repeated symmetrically on the contralateral side for a total of 6 FSFD injections. According to the FTP optional dosing paradigm, an additional 4 injections could

have been distributed between the right and left trapezius muscles in the areas identified as having maximal tenderness (Fig. 2G). Physicians exercised caution when deciding to inject additional units of onabotulinumtoxinA into the trapezius muscles, and avoided the infero-medial portions of the trapezius muscle (Fig. 2G; see arrow) to limit the possibility of neck weakness.

Patients were observed for 10-15 minutes following treatment. Patients were advised not to rub or massage the affected areas for 24 hours, and told that any bumps that appeared on the forehead should disappear within approximately 2 hours. Patients were advised that they may need, and should use, their acute medications for breakthrough headaches. Retreatment occurred at 12-week intervals. In the interim, patients were encouraged to maintain a headache diary.

## CONCLUSION

OnabotulinumtoxinA has been found to be effective, safe, and well-tolerated for the prophylaxis of headache in adults with CM at doses ranging from 155 to 195 U administered IM across 7 head and neck muscles every 12 weeks for up to 5 treatment cycles.<sup>27-29</sup> Discontinuation rates due to AEs were low, and most AEs reported were transient, mild to moderate in severity, and localized to the sites of injection. This tolerability profile may make onabotulinumtoxinA more appealing than systemic agents for long-term treatment as headache prophylaxis in adults with CM.

Previous studies evaluating onabotulinumtoxinA for a range of primary headache disorders employed a variety of dose ranges and injection site approaches; PREEMPT built upon those trials and established an effective injection paradigm that confirmed the efficacy, safety, and tolerability of onabotulinumtoxinA for the prophylactic treatment of headaches in adults with CM. The PREEMPT injection paradigm targets a broad distribution of V1 and C2 dermatomes and is the optimal injection strategy of onabotulinumtoxinA for patients with CM. Because onabotulinumtoxinA may be part of a comprehensive treatment program, it is recommended that injections of onabotulinumtoxinA for the prophylactic treatment of CM be utilized only by those healthcare providers who have experience in the comprehensive management of this complex patient population as well as experience in the use of onabotulinumtoxinA.

#### NOTE

Dosing and treatment paradigm are specific to the formulation of onabotulinumtoxinA manufactured by Allergan, Inc. (Irvine, CA, USA), which, as noted on US Food and Drug Administration labeling, is not interchangeable with other preparations of botulinum toxin products. As of August 31, 2010, onabotulinumtoxinA has received regulatory approval for the treatment of chronic migraine in the United Kingdom and Estonia.

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