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ADIS DRUG Q&A

OnabotulinumtoxinA in Chronic Migraine: A Profile of Its Use

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Abstract
OnabotulinumtoxinA (Botox®; a formulation of botulinum toxin type A (BoNT/A)] is indicated for the prevention of headaches in adults with chronic migraine (CM) in numerous countries, including those of Europe. In clinical trials, intramuscular administration of BoNT/A (155–195 units at 12-week intervals) to patients with CM was generally well tolerated and associated with sustained and clinically meaningful improvements in multiple assessments of headache symptoms, headache-related impact and/or disability and migraine-specific health-related quality of life over a period of 1 year (in the pivotal PREEMPT 1 and 2 studies) and 2 years (in the phase IV COMPEL study). The efficacy and safety of BoNT/A therapy have been confirmed in a number of large, prospective, real-world studies conducted in Europe, including the 2-year REPOSE study. Intramuscular BoNT/A has also demonstrated greater clinical utility than the oral prophylactic medication topiramate in a clinical practice setting (FORWARD study).

Digital Features for this Adis Drug Q&A, including a peer-reviewed video abstract, can be found at https://doi.org/10.6084/m9.figshare.13218869.

Adis evaluation of BoNT/A (Botox®) in CM
Administered intramuscularly every 3 months
Effective in CM patients with or without acute medication overuse
Effective in CM patients who have or have not previously used recognized prophylactic medications
Neck pain, (facial) muscle weakness and eyelid ptosis are the most common treatment-related adverse events

Enhanced material for this Adis Drug Q&A, including a video abstract, can be found at https://doi.org/10.6084/m9.figshare.13218869.

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1 What is the rationale for using onabotulinumtoxinA in chronic migraine?

Chronic migraine [CM; defined as ≥ 15 headache days/month for > 3 months (within the last 12 months), with ≥ 8 migraine days/month [1]] affects ≈ 1–2% of the general population [2]. It usually evolves from episodic migraine (EM; defined as < 15 headache days/month) and is associated with a greater symptomatic and socioeconomic burden, as well as higher healthcare resource utilization (HRU), compared with EM [3].

The first-line treatment of CM is pharmacological [4]; it is based on the use of acute medications to relieve or ameliorate the symptoms of a migraine attack that has already begun, and the use of preventative therapies to reduce the frequency, duration and severity of attacks (thereby limiting the need for acute medications, as these may be causing concurrent medication overuse headache) [3].

Various oral medications [e.g. β-adrenoreceptor antagonists (β-blockers), anticonvulsants, antidepressants and calcium channel blockers (CCBs)] are used for the prophylaxis of CM [4]. However, topiramate, the only oral agent currently approved for the prophylaxis of migraine headache in Europe, is not specifically licenced for the prophylaxis of CM in this region [5]. Moreover, shortcomings of these oral preventatives in terms of efficacy, tolerability and adherence have led to the development and subsequent approval of novel therapeutic modalities for the treatment of CM in

the form of onabotulinumtoxinA [Botox®; a formulation of botulinum toxin type A (BoNT/A)] [3, 6] and, more recently, monoclonal antibody calcitonin gene receptor peptide (CGRP) antagonists (e.g. erenumab, fremanezumab and galcanezumab) [4, 7].

Intramuscular administration of BoNT/A has been approved for the prevention of headaches in adults with CM in numerous countries worldwide, including those of Europe and North America [3, 8]. However, the exact wording of the indication may vary between countries, and local prescribing information should be consulted for specific details [3].

Prescribing information pertaining to the use of BoNT/A for the prophylaxis of CM in the UK [9] (as a representative of prescribing information in European countries) is summarized in Table 1. This article discusses the efficacy and tolerability of BoNT/A in the prevention of CM, primarily from a European perspective.

2 How does onabotulinumtoxinA work in chronic migraine?

Although the exact mechanism(s) of action are still being investigated, extracranial administration of BoNT/A is believed to prevent headaches in patients with CM by inhibiting peripheral sensitization and, indirectly, central sensitization within the trigeminovascular system, both of which are postulated to be involved in migraine pathophysiology and chronification (i.e. conversion of EM to CM) [3, 10, 11].

The intraneuronal target for BoNT/A is synaptosomal-associated fusion attachment protein (SNAP-25), which is one of the essential proteins of the soluble N-ethylmaleimide-sensitive fusion attachment protein receptor (SNARE) complex; BoNT/A cleaves SNAP-25, thereby disrupting SNARE-mediated vesicle trafficking [10]. Preclinical evidence indicates pericranial injections of BoNT/A in the trigeminally-innervated cranio-facial-cervical region may reduce peripheral sensitization by modulating two SNARE-dependent processes:

- Decreasing the release of pro-inflammatory and excitatory neurotransmitters and neuropeptides (e.g. substance P, CGRP and glutamate) from primary afferent fibres that transmit nociceptive pain; and
- Decreasing the upregulation of pain-sensitive ion channels [e.g. transient receptor potential vanilloid 1 (TRPV1) receptor and P2X3 purinergic receptor)] on nociceptive nerve terminals and cell bodies [10].

3 What is the clinical efficacy of onabotulinumtoxinA in chronic migraine?

The short- and longer-term efficacy of intramuscular BoNT/A for headache prophylaxis in adults with CM has been demonstrated over a period of 1 year in two pivotal phase III studies (PREEMPT 1 [12] and 2 [13]; together comprising the PREEMPT clinical programme [14, 15]) and over a period of 2 years in a phase IV study (COMPEL) [16].

3.1 In the PREEMPT clinical programme

The multicentre PREEMPT 1 and multinational PREEMPT 2 studies, which were otherwise identical in design (apart from the designation of the primary and secondary endpoints), enrolled a combined total of 1384 patients (86% females; mean age 41 years; 65% acute analgesic/medication overusers) who had ≥ 15 headache days/month (with headache lasting ≥ 4 h/day), with ≥ 50% of the days being migraine/probable migraine days [14, 15].

The method whereby BoNT/A was administered in these studies (referred to as the 'PREEMPT paradigm') is the approved dosing regimen in Europe (see Table 1). Patients received up to five treatment cycles: two with BoNT/A 155–195 U or placebo during the 24-week, randomized, double-blind phase (at weeks 0 and 12) and three with BoNT/A 155–195 U during the subsequent open-label extension phase (at weeks 24, 36 and 48) [12–15].

3.1.1 Versus placebo

Two treatment cycles of BoNT/A significantly improved all assessments of headache symptoms, including the monthly frequency of headache days (primary endpoint), compared with placebo, according to a predefined pooled analysis of the two PREEMPT trials (Table 2). At week 24, significantly ($p < 0.001$) more BoNT/A recipients than placebo recipients were responders in terms of achieving a clinically meaningful (i.e. ≥ 50%) improvement in the monthly frequency of headache days (47% vs 35%), moderate to severe headache days (49% vs 38%) and migraine days (48% vs 36%), as well as in the monthly cumulative hours of headache on headache days (50% vs 39%) [14, 15]. Improvements in headache symptoms in BoNT/A-treated patients were reflected in reduced triptan consumption, albeit overall analgesic/medication consumption was not significantly decreased relative to placebo (Table 2). A post hoc pooled analysis indicated that BoNT/A therapy had an early onset of action, with significant ($p < 0.05$ vs placebo) reductions in headache and

Table 1 Prescribing summary of onabotulinumtoxinA (Botox®) in treating chronic migraine in adults in Europe [9]

What is its approved indication?	
Prophylaxis of headaches in adults with CM (headaches on ≥ 15 d/mo for > 3 mo [within last 12 mo], of which ≥ 8 d are with migraine)	
How is it available and how should it be stored?	
Availability	Vials containing 50, 100 or 200 Allergan U[a] of BoNT/A (as powder for solution for injection)
Storage	In a refrigerator (2–8° C) or freezer (at or below -5° C)
What is the approved dosing regimen (PREEMPT paradigm)?	
Dosing	*Fixed-site, fixed-dose approach:* 155 U injected to 31 sites across seven specific head/neck muscle areas (frontalis, corrugator, procerus, occipitalis, temporalis, trapezius and cervical paraspinal) [one 5-U injection/site]
	Follow the pain strategy: Up to eight additional 5-U injections may be given unilaterally or bilaterally in up to three specific muscle areas (occipitalis, temporalis and trapezius)
	Total dose: 155–195 U
Frequency	Recommended re-treatment schedule is every 12 wk
What is its pharmacokinetic profile?	
Little systemic distribution of BoNT/A is believed to occur following intramuscular injection of therapeutic doses	
What are the contraindications to its use?	
Known hypersensitivity to botulinum toxin type A or any of the excipients	
Presence of infection at the proposed injection site or sites	
How should it be used in special populations?	
Pregnant women	Should not be used unless clearly necessary (lack of adequate data)
Breast-feeding women	Cannot be recommended (not known whether excreted in breast milk)
What other special warnings/precautions/monitoring requirements pertain to its use?	
Initiate dosing in treatment-naïve pts with lowest recommended dose	
Do not exceed recommended dosages and frequencies of administration (potential for overdose, exaggerated muscle weakness, distant spread of toxin and formation of neutralising antibodies)	
Use with extreme caution and under close (specialist) supervision in pts with subclinical or clinical evidence of defective neuromuscular transmission or those with underlying neurological disorders	
Use with extreme caution in pts with a history of dysphagia and aspiration	
Use with caution if inflammation is present at proposed injection site(s) or when excessive weakness or atrophy is present in target muscle	
Discontinue (and initiate appropriate medical therapy) if serious and/or immediate hypersensitivity reaction occurs	
Safety and efficacy not established (prophylaxis of headaches in pts with EM [HA on < 15 d/mo] or chronic tension type headache) or not studied (medication overuse headache)	
Is it associated with any potentially clinically relevant drug interactions?	
Agents interfering with neuromuscular transmission	No specific recommendation; however, theoretically, agents that interfere with neuromuscular transmission may potentiate the effect of BoNT/A
Botulinum toxins	No specific recommendation; however, excessive neuromuscular weakness may be exacerbated by the administration of another botulinum toxin product prior to the resolution of the effects of a previously administered botulinum toxin product

BoNT/A onabotulinumtoxinA (Botox®), *CM* chronic migraine, *EM* episodic migraine, *mo* months, *pts* patients, *U* unit(s), *wk* weeks

[a]Potency U of onabotulinumtoxinA (Botox®) are not interchangeable with other formulations of BoNT/A

migraine days/week apparent at week 1, and persisting from week 3 onwards, after the first treatment cycle [17].

BoNT/A therapy also significantly improved headache-related impact, assessed using the Headache Impact Test-6 (HIT-6), and migraine-specific health-related quality of life (HR-QOL), assessed using the Migraine Specific Quality of Life Questionnaire (MSQ), compared with placebo, according to the predefined pooled analysis (Table 2). Significant ($p < 0.001$) and clinically meaningful improvements in HIT-6 and MSQ role-restrictive (RR), role-preventive (RP) and emotional-functioning (EF) domain scores favouring BoNT/A over placebo were seen at all assessment points through week 24 [14, 15].

In additional pooled analyses [18–24] (post hoc [18, 21, 22, 24], where stated):

- BoNT/A improved ($p < 0.05$ vs placebo) headache symptoms in patients who were or were not acute medication overusers at baseline [19, 23], those who had or had not previously used recognized prophylactic medications [23], and those who had previously failed to respond to ≥ 3 preventative therapies [20]

Table 2 Short-term efficacy of onabotulinumtoxinA (Botox®) for prevention of headaches in adults with chronic migraine. Key results (intent-to-treat) in the pooled analysis of the PREEMPT 1 and 2 trials

Endpoint	Mean change from BL (BL[a]) at wk 24[b] [14, 15]		Mean change from BL at wk 56[c] [15]	
	BoNT/A ($n = 688$)	PL ($n = 696$)	BoNT/A → BoNT/A ($n = 688$)	PL → BoNT/A ($n = 696$)
HA d/mo	− 8.4***[d] (19.9)	− 6.6[d] (19.8)	− 11.7*	− 10.8
Moderate to severe HA d/mo	− 7.7*** (18.1)	− 5.8 (18.0)	− 10.7*	− 9.9
Cumulative h of HA on HA d/mo	− 119.7*** (296*)	− 80.5 (281)	− 169.1*	− 145.7
HA episodes/mo	− 5.2** (12.2**)	− 4.9 (13.0)	− 7.4	− 7.5
Migraine d/mo	− 8.2*** (19.1)	− 6.2 (18.9)	− 11.2*	− 10.3
Migraine episodes/mo	− 4.9** (11.4**)	− 4.5 (12.2)	− 6.8	− 7.0
HIT-6 score	− 4.8*** (65.5)	− 2.4 (65.4)	− 7.7	− 7.0
Acute analgesic intakes/mo	− 10.1 (26.9)	− 9.4 (27.8)	− 15.4	− 15.7
Acute analgesic intake d/mo	− 6.1* (14.6)	− 5.3 (14.9)	− 8.4	− 8.5
Triptan intake d/mo	− 3.2*** (NR)	− 2.1 (NR)	− 4.2	− 3.8
MSQ EF domain score	17.9*** (42.1)	9.5 (42.4)	25.0	22.1
MSQ RP domain score	13.1*** (56.0)	6.4 (56.1)	19.0	17.3
MSQ RR domain score	17.0*** (16.6)	8.6 (17.3)	25.2*	21.8

BoNT/A onabotulinumtoxinA (Botox®), *BL* baseline, DB double-blind, *EF* emotional functioning, *HA* headache, *HIT-6* headache impact test-6, *mo* month, *MSQ* Migraine-specific quality of life questionnaire, *NR* not reported, *OL* open-label, *PL* placebo, *RP* role preventive, *RR* role restrictive, *wk* weeks

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs PL, PL BL or PL → BoNT/A

[a]Assessed over the previous 4-wk period (i.e. ending at wk 0)

[b]Assessed over the previous 4-wk period. Pts received two DB treatment cycles of either BoNT/A or PL

[c]Assessed over the previous 4-wk period. Pts received up to five treatment cycles: two DB then three OL of BoNT/A (BoNT/A → BoNT/A) or two DB of PL then three OL of BoNT/A (PL → BoNT/A)

[d]Primary endpoint

- BoNT/A increased ($p < 0.001$ vs placebo) responder rates at week 24 in terms of the proportions of patients who achieved clinically meaningful improvements in monthly headache-day frequency (45% vs 34%), average daily headache severity (36% vs 22%), HIT-6 score (41% vs 25%) and MSQ RR domain score (59% vs 40%), as well as the proportions of patients who achieved at least one (72% vs 57%), at least two (54% vs 37%), at least three (34% vs 20%) or all four (20% vs 9%) of these outcomes [18]
- Among patients who did not achieve a clinically meaningful improvement in monthly headache-day frequency (i.e. monthly headache-day frequency non-responders), assessments of headache severity [21, 24], headache-related impact (HIT-6 score) [24] and migraine-specific HR-QOL (all three MSQ domain scores) [24] at week 24 were significantly improved with BoNT/A (all $p < 0.01$ vs placebo)
- More BoNT/A-treated than placebo-treated patients achieved treatment-controlled CM, defined as < 15 headache days/month during weeks 13–24 (56.1% vs 49.1%; $p = 0.01$) [22]. BoNT/A recipients, as compared with placebo recipients, who achieved treatment-controlled CM reported significantly ($p \leq 0.017$) fewer headache days/month (7.4 vs 6.8), as well as greater ($p \leq 0.012$) – and clinically meaningful – improvements in HIT-6 and MSQ RR, RP and EF domain scores at all assessments through week 24 [22].

3.1.2 Over repeated treatment cycles

Cumulative prophylactic effects were seen over successive BoNT/A treatment cycles in the PREEMPT trials [15, 17, 25]. In the predefined pooled analysis [15], all assessments of headache symptoms, acute analgesic/medication use, headache-related impact and migraine-specific HR-QOL continued to improve relative to baseline during the open-label extension phase, both in those who had previously received BoNT/A (early treatment) and those who had previously received placebo (late treatment) during the double-blind phase (Table 2). Nonetheless, multiple assessments of headache symptoms still significantly favoured the early treatment group over the late treatment group at week 56 (Table 2), indicating that patients who started treatment earlier (i.e. had been treated for longer) had better outcomes at that time point.

A post hoc pooled analysis indicated that a high proportion (61%) of patients treated with BoNT/A throughout achieved sustained treatment-controlled CM, defined as < 15 headache days/month during all 6 months of the extension phase, i.e. weeks 25–56 [22]. BoNT/A-treated patients who achieved sustained treatment-controlled CM reported a mean of 5.0 headache days/month, as well as clinically meaningful improvements in HIT-6 and MSQ RP, RR and EF domain scores at all assessments through week 56 [22].

Importantly, another post hoc pooled analysis [26] indicated that at least two or three treatment cycles may be needed to determine responsiveness to BoNT/A therapy. For example, 22% of the 349 BoNT/A recipients who were monthly headache-day frequency non-responders after the first cycle became monthly headache-day frequency responders after the second cycle; 26% of the 271 BoNT/A recipients who were monthly headache-day frequency non-responders after the first and second cycles became monthly headache-day frequency responders after the third cycle. Results for responder rates for other outcomes, including monthly moderate to severe headache-day frequency and HIT-6 score, were similar [26].

3.2 In the COMPEL study

The multinational COMPEL study [16] enrolled 716 patients (85% females; mean age 43 years; 64% acute analgesic/medication overusers) who had ≥ 15 headache days/month (with headache lasting ≥ 4 h/day). They received up to nine cycles of BoNT/A 155 U (i.e. using only the fixed-site, fixed-dose approach of the PREEMPT paradigm; see Table 1) during the 108-week open-label treatment intervention phase (at weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96). Just over one-half (52.1%) completed all nine treatment cycles [16].

The COMPEL study showed the continuing benefit of treatment with BoNT/A over a 2-year period, thereby substantiating and extending the findings of the PREEMPT clinical programme [16]. BoNT/A therapy significantly and progressively decreased the number of headache days/month at all assessment time points throughout the study, including week 24 (first post-baseline assessment) and week 108 (fourth and final post-baseline assessment; primary endpoint) (Table 3). Similarly, there were significant and progressive reductions in the number of moderate to severe headache days/month, as well as significant and sequential improvements in headache-related impact (HIT-6 score) (Table 3).

In other analyses of BoNT/A efficacy in COMPEL [16, 27–37] (post hoc [27, 35, 36], where stated):

- Assessments of migraine-related disability (MIDAS score) [28] and migraine-specific HR-QOL (all three MSQ domain scores) were improved ($p < 0.0001$ vs baseline) at week 108 [28]
- Comorbid symptoms of depression [measured using the 9-item Patient Health Questionnaire (PHQ-9)] and anxiety (7-item Generalized Anxiety Disorder Assessment), and associated symptoms of sleep disturbance (Pittsburgh Sleep Quality Index) and fatigue (Fatigue Severity Scale), were improved ($p < 0.0001$ vs baseline) at week 108; similar improvements were seen at all earlier assessments [29]
- Assessments of headache symptoms [16, 30–34], headache-related impact (HIT-6 score) [16, 30, 33], migraine-related disability (MIDAS score) [31, 32, 34] and migraine-specific HR-QOL (all three MSQ domain scores) [32, 34] were improved to a similar extent in patients with or without a history of acute medication overuse [30, 31], those receiving or not receiving oral preventive treatments at baseline [16], those with or without daily headaches at baseline [32, 33], and those with or without allodynia at baseline [34]
- The proportion of monthly headache-day frequency responders progressively increased over the course of

Table 3 Longer-term efficacy of onabotulinumtoxinA (Botox®) for prevention of headaches in adults with chronic migraine. Key results in the COMPEL study (n = 716) [16]

Endpoint	Mean BL value	Mean change from BL at			
		wk 24[a] (after tx 2)	wk 60[a] (after tx 5)	wk 84[a] (after tx 7)	wk 108[a] (after tx 9)
HA d/mo	22.0	− 7.4**	− 9.2**	− 9.8**	− 10.7**[b]
Moderate to severe HA d/mo	18.0	− 6.5**	− 8.1**	− 8.4**	− 9.5**
HIT-6 score	64.7	NR	− 6.8*	NR	− 7.1*

All nine BoNT/A tx were administered in open-label fashion

BL baseline, *HA* headache, *HIT-6* headache impact test-6, *NR* not reported, *tx* treatment cycle(s)

*$p < 0.001$, **$p < 0.0001$ vs BL

[a]Assessed over the previous 4-wk period

[b]Primary efficacy endpoint

the study (47%, 54%, 57% and 62% at weeks 24, 60, 84, 108, respectively). Among patients who completed all nine treatment cycles, a high proportion (76%) of monthly headache-day frequency responders at week 24 maintained this response through week 108 [35]

- Responder rates at week 108 were 62% for monthly headache-day frequency, 59% for HIT-6 score, 75% for MIDAS score and 66% for MSQ RR domain score; 87%, 72%, 52% and 27% of patients achieved at least one, at least two, at least three or all four of these outcomes, respectively [27]
- The proportion of patients who achieved treatment-controlled CM (defined as < 15 headache days/month in any of the 4-week periods ending at weeks 24, 60, 84 and 108) was high and increased progressively over the course of the study (56%, 69%, 70% and 74% at weeks 24, 60, 84 and 108, respectively) [36]
- Sustained treatment-controlled CM (defined as < 15 headache days/month in all of the 4-week periods ending at weeks 24, 60, 84 and 108) was achieved by 50% of evaluable patients ($n = 289$). These individuals reported a reduction in moderate-to-severe headache days/month (−10.4 , −11.0, −11.4 and −11.9 at weeks 24, 60, 84 and 108, respectively; all $p < 0.001$vs baseline); the majority were monthly headache-day frequency responders (78%, 88%, 88% and 89% at weeks 24, 60, 84 and 108, respectively) [36].

4 What is the effectiveness of onabotulinumtoxinA in clinical practice?

The effectiveness of BoNT/A administered in accordance with the PREEMPT paradigm as a real-world preventative therapy for CM has been demonstrated in a number of large, prospective, observational studies conducted in routine clinical practice in Europe [38–43], notably the multinational REPOSE study [38] (Table 4).

4.1 In the REPOSE study

Consistent with the observed efficacy of BoNT/A in the PREEMPT and COMPEL studies, the REPOSE study showed the sustained effectiveness of BoNT/A in the preventive treatment of CM over a period of up to 2 years [38].

Exclusion criteria were receipt of any botulinum toxin type A serotype in the previous 26 weeks and concurrent enrolment in a CM post-authorisation safety study (hereafter referred to as 'CM-PASS'; see Sect. 5). Enrolled patients received at least one BoNT/A treatment cycle. Most had previously received oral preventative therapies [e.g. β-blockers (72%), antidepressants (70%), antiepileptics (70%) and CCBs (30%)]; these could be continued throughout the study period. The majority (90%) of patients were BoNT/A-naïve, i.e. they had not previously received BoNT/A for CM [38].

BoNT/A significantly and progressively decreased the number of headache days/month at all assessment time points throughout the study (i.e. administration visits 2 through 8) (Table 4), when administered largely as recommended in the summary of product characteristics and following the PREEMPT paradigm. Similarly, there were significant ($p < 0.001$ vs baseline) and progressive improvements in migraine-specific HR-QOL (all three MSQ domain scores) and generic quality of life (as assessed using the EuroQol 5-Dimenion Questionnaire) at all assessment time points [38].

4.2 In other prospective studies

Treatment with up to five cycles of BoNT/A has resulted in responder rates of ≈50–80%, depending on the definition used, and sustained beneficial effects have been seen in responders who have continued treatment for up to 2–3 years (Table 4).

Long-term outcomes are available for responders in the largest study of the real-world effectiveness of BoNT/A therapy to date, which has evaluated 972 patients (who have received a total of 5745 treatment cycles) over a period of 8 years at a single centre in the UK (Hull Migraine Clinic) [39, 44]. At year 5, 44 of 186 patients who were responders after the second cycle were still receiving—and benefitting from—treatment. Moreover, 105 had stopped treatment after achieving < 10 headache days/month for 3 consecutive months (modified positive stopping rule) and continued to fulfil the criteria for EM. The remaining 37 had stopped treatment for other reasons (e.g. resistance or pregnancy) or were lost to follow-up [44].

Treatment with eight cycles of BoNT/A at the higher dose of 195 U (i.e. using the full follow-the-pain approach of the PREEMPT paradigm; $n = 132$ [45]) resulted in greater ($p < 0.05$) reductions in headache days, migraine days and HIT-6 score at all assessment time points over the 2-year study period relative to BoNT/A at the lower dose of 155 U (i.e. using only the fixed-site, fixed-dose approach; $n = 143$ [46]), based on an indirect comparison of the results of two (separate) studies conducted at the same single centre in Italy [45]. Analgesic intake was also significantly ($p < 0.001$) reduced with the higher versus the lower dose at all assessments time points from month 6 onwards [45].

Consistent with experience in Europe, an interim analysis of a Canadian, multicentre, prospective, observational study (PREDICT) [47] showed that four cycles of BoNT/A (≈ 170 U/cycle) significantly ($p < 0.0001$ vs baseline) improved

Table 4 Real-world effectiveness of onabotulinumtoxinA (Botox®) administered as per the PREEMPT protocol for prevention of headaches in adults with chronic migraine. Key results in large (n ≥ 195) prospective studies from Europe

Study [Country]	No. of pts	Key outcomes
REPOSE [38] [Germany, Italy, Norway, Russia, Sweden, Spain, UK]	633 [85% F; 45 y[a]; 36% MO]	HA d/mo (20.6 at BL) ↓ by 8.0, 9.4, 10.8,11.7, 12.1, 13.0 and 13.1 (all ***) at time of tx 1, 2, 3, 4, 5, 6, 7 and 8, respectively
Ahmed et al. [39] [UK][b]	851 [81% F; 45 y[a]; 53% MO]	53% were Rs (either ≥ 50% ↓ in HA or migraine d/mo[d] or ↑ in HA-free d/mo 2 × BL after tx 1)
Andreou et al. [40] [UK]	200 [79% F; 46 y[a]; 46% MO]	HA d/mo[c] (24.0 at BL) ↓ to 12.0* and 11.3* after tx 1 and 2, respectively Migraine d/mo[c] (13.0 at BL) ↓ to 5.7* and 5.0* after tx 1 and 2, respectively HA-free d/mo[c] (0 at BL) ↑ to 11.0* and 12.8* after tx 1 and 2, respectively HIT-6 score[c] (70 at BL) ↓ to 66* and 64* after tx 1 and 2, respectively 64% were Rs (≥ 30% ↓ in HA d/mo after tx 2) — in Rs, HA d/mo[c] (23 at BL) ↓ to 8, 8, 8 and 11 after tx 2, 5, 8 and 13, respectively 29% fulfilled criteria for EM after tx 2
Corbelli et al. [41] [Italy][b]	195 [82% F]	52% were Rs (≥ 50% ↓ in HA d/mo after tx 5) — in Rs, HA d/mo (24.2 at BL) ↓ to 7.0*** and 6.9 after tx 5 and 9, respectively 18% were PRs (<50%, but ≥ 30% ↓ in HA d/mo after tx 5) — in PRs, HA d/mo (23.8 at BL) ↓ to 17.4*** and 15.3 after tx 5 and 9, respectively
Domínguez et al. [42] [Spain][d]	725 [86% F; 47 y[a]; 58% MO]	HA d/mo (21.8 at BL) ↓ to 10.6** and 8.4**[†] after tx 1 and 4, respectively Migraine d/mo (13.8 at BL) ↓ to 7.0** and 6.0**[†] after tx 1 and 4, respectively 66% and 79% were Rs (> 50% ↓ in HA d/mo) after tx 1 and 4, respectively MIDAS score (35.9 at BL) ↓ to 19.3** and 9.1**[†] after tx 1 and 4, respectively
Torres-Ferrus et al. [43] [Spain]	395 [85% F; 47 y[a]; 61% MO]	HA d/mo (26.5 at BL) ↓ to 15.2*** after tx 2 51% were Rs (≥ 50% ↓ in HA d/mo after tx 2) 49% were disability Rs (≥ 50% ↓ in MIDAS score after tx 2)

Where explicitly stated, pts had previously failed to respond to, or were intolerant of, oral prophylactic treatments (≥ 2–3 [39, 40, 42])

BL baseline, *EM* episodic migraine, *F* females, *HA* headache, *HIT-6* headache impact test-6, *MIDAS* migraine disability assessment, *MO* acute analgesic/medication overusers, *pts* patients, *PRs* partial responders, *Rs* responders, *tx* treatment cycle(s), ↑ increase(d), ↓ decrease(d)

*$p \leq 0.05$, **$p < 0.01$, ***$p < 0.001$ vs BL; †$p < 0.01$ vs after tx 1

[a]Mean (median [39]) age

[b]Abstract

[c]Median value

[d]Multicentre study

migraine-specific HR-QOL (all three MSQ domain scores) in BoNT/A-naïve CM patients ($n = 196$ enrolled).

4.2.1 Versus topiramate

The comparative effectiveness of BoNT/A and topiramate for the preventative treatment of CM in routine clinical practice (in the USA) has been evaluated in a randomized, open-label, multicentre, post-authorization study (FORWARD) [48]. Adults with CM were randomized to receive either three cycles of BoNT/A 155 U (i.e. using only the fixed-site, fixed-dose approach of the PREEMPT paradigm) or immediate-release topiramate 50–100 mg/day for 36 weeks; those who discontinued topiramate could cross-over to BoNT/A and remain in the study until week 48.

The proportion of patients achieving a ≥ 50% improvement in the monthly frequency of headache days at week 32 (primary outcome measure) was significantly higher among those initially randomized to BoNT/A than those initially randomized to topiramate [40% vs 12%; adjusted odds ratio, 4.9 (95% CI 2.7–9.1); $p < 0.001$]. This primary analysis of the comparative effectiveness of the two treatments used a baseline observation carried forward approach to impute missing values for any reason [e.g. discontinuation due to lack of efficacy or adverse events (AEs)]; in this regard, the proportion of patients who completed the randomized treatment period was much higher among those initially assigned to BoNT/A (86% of 140 patients) than those initially assigned to topiramate (20% of 142 patients). In terms of the comparative efficaciousness of the two treatments, responder rates did not differ significantly between patients remaining on BoNT/A and those remaining on topiramate in a sensitivity analysis that used pro-rated observed data (57% vs 68%).

BoNT/A was superior ($p \leq 0.024$) to topiramate on all secondary and other outcomes [48, 49], including the ≥ 50% headache-day frequency responder rate at week 12 (46% vs 29%; post hoc analysis of observed data) [48] and

assessments of headache impact (HIT-6 score at week 30) [49] and depression (PHQ-9 score at week 36) [49].

Among the 80 patients initially assigned to topiramate who crossed-over to BoNT/A, the ≥ 50% headache-day frequency responder rates at weeks 32 and 48 (exploratory outcomes) were 39% and 28%, respectively [48].

5 What is the tolerability of onabotulinumtoxinA in chronic migraine?

Injection of up to five cycles of BoNT/A (155–195 U/cycle) at 12-week intervals is generally well tolerated, according to pooled analyses of the 56-week PREEMPT clinical programme [3, 14, 15, 25]. BoNT/A recipients mostly reported AEs that were mild or moderate in severity and resolved without sequelae; they infrequently discontinued therapy due to AEs (Table 5).

The overall incidence of treatment-related AEs (TRAEs) in BoNT/A recipients was higher than that for placebo recipients (Table 5). However, the incidence rates for individual TRAEs, which included neck pain, muscular weakness (e.g. facial paresis), eyelid ptosis, musculoskeletal pain, injection-site pain, headache and musculoskeletal stiffness, were consistent with the known pharmacology and established tolerability profile of BoNT/A when injected into head and neck muscles; no new safety events were observed, either in the 24-week double-blind phase or the 32-week open-label phase [3, 14, 15]. The overall rate of TRAEs in BoNT/A recipients progressively decreased with repeated treatments, being 48%, 37%, 38%, 26% and 19% after the first, second, third, fourth and fifth cycles of BoNT/A, respectively [25]. Neck pain (4.3%), muscular weakness (1.6%), injection site pain (2.1%), and eyelid ptosis (1.9%) were the most frequently reported TRAEs in patients who received all five cycles of onabotulinumtoxinA in the PREEMPT clinical programme [25]. Only one BoNT/A recipient in the pooled PREEMPT studies experienced a serious TRAE (migraine requiring hospitalization); no deaths were reported [14].

Tolerability findings over a period of 1 year in the PREEMPT clinical programme are supported and extended

Table 5 Tolerability of onabotulinumtoxinA (Botox®) for prophylaxis of headaches in adults with chronic migraine in clinical and real-world studies

Tolerability parameter (% of pts)	Pooled PREEMPT studies [15]			COMPEL [16]	REPOSE [38]	CM-PASS [51]
	DB		OLE	OL	OL	OL
	BoNT/A ($n = 687$)	PL ($n = 692$)	BoNT/A ($n = 1205$)	BoNT/A ($n = 716$)	BoNT/A ($n = 633$)	BoNT/A ($n = 1160$)
TEAEs	62.4**	51.7	58.3	60.9	–	41.2
Serious TEAEs	4.8*	2.3	3.8	10.5	–	5.3
TRAEs[a]	29.4**	12.7	20.3	18.3	18.3	25.1
Serious TRAEs[a]	0.1	0.0	0.1	0.1	1.3	< 0.1
Common TRAEs [a]						
Neck pain	6.7	2.2	4.6	4.1	2.8	4.4
Muscular weakness	5.5	0.3	3.9	1.4	–	2.7
Eyelid ptosis	3.3	0.3	2.5	2.5	5.4	4.1
Injection site pain	3.2	2.0	2.0	2.0	–	–
Headache	2.9	1.6	1.4	1.4	–	2.2
Myalgia	2.6	0.3	1.2	–	–	0.9
Musculoskeletal stiffness	2.3	0.7	1.7	1.7	2.7	2.0
Musculoskeletal pain	2.2	0.7	1.1	–	–	0.9
Facial paresis	2.2[b]	–	1.2[b]	1.3	–	1.3
Discontinuations due to AEs	3.8[c]	1.2[c]	2.6[c]	4.5[c] (1.8[d])	1.6[d]	4.4[c]

AEs adverse events, *ADR* adverse drug reactions, *BoNT/A* onabotulinumtoxinA (Botox®), *DB* double-blind phase, *OL(E)* open-label (extension phase), *PL* placebo, *pts* patients, *TEAEs* treatment-emergent AEs, *TRAEs* treatment-related AEs, – information not available (e.g. only ADRs occurring in > 2% of pts in REPOSE were reported)

*$p = 0.0133$, **$p < 0.0001$ vs PL

[a]ADRs (REPOSE)

[b]Included in muscular weakness in PREEMPT 1 and 2

[c]Discontinuations due to TEAEs

[d]Discontinuations due to TRAEs

by those of the 2-year (108-week) COMPEL study [16, 50], as well as those of several real-world studies from Europe, including the 64-week CM-PASS study [51] and the 24-month REPOSE study [38] (see Sect. 4). The overall rates of treatment-emergent AEs (TEAEs) and TRAEs, as well as the incidences of individual TRAEs, reported in COMPEL, CM-PASS and REPOSE are generally comparable to those reported in the open-label phase of the pooled PREEMPT studies (Table 5); no new safety concerns or cumulative tolerability issues have been identified [16, 38, 50, 51]. Only one BoNT/A recipient in the COMPEL study experienced a serious TRAE (generalized rash); no deaths were reported [16].

CM-PASS is the largest observational study to date to examine the safety of BoNT/A for the preventative treatment of CM in routine clinical practice [51]. The majority (86%) of the 1160 patients (84% women; median age 46.6 years; 24.7% medication overusers) enrolled at 58 centres across Germany, Spain, Sweden and the UK, had a diagnosis of CM or transformed (i.e. chronified) migraine at baseline, although nearly half (48%) were BoNT/A-naïve. Similar to the pooled PREEMPT and COMPEL studies, only one BoNT/A recipient in CM-PASS reported a serious TRAE (worsening of migraine); neither of the two observed fatal adverse events were considered related to treatment [51]. Special interest TRAEs included worsening of migraine (reported in 4.0% of patients), intractable migraine (0.4%), hypersensitivity (0.9%) and dysphagia (0.3%); the incidence rates of intractable migraine and dysphagia (secondary and primary outcome measures, respectively) were 1.6 and 0.4 per 1000 person-months [52].

Against a background of inadequate data on the use of BoNT/A in pregnancy (see Table 1), outcomes in 45 pregnant CM patients exposed to BoNT/A have been reported recently [53]. Among the 32 patients that consented to continue treatment during their pregnancy, there was one miscarriage and 32 full-term deliveries of healthy newborns with normal birthweight and no congenital malformations [53].

Like other BoNT/A products, BoNT/A exhibits a low immunogenic potential [3].

5.1 Versus topiramate

Intramuscular administration of BoNT/A as per the PREEMPT paradigm had a more favourable tolerability profile than oral administration of topiramate in terms of the rates of AEs and discontinuations due to AEs in the open-label FORWARD study [48]. Specifically:

- TEAEs were reported in 48% of patients initially randomized to, or who crossed-over to, BoNT/A ($n = 220$) compared with 79% of patients initially randomized to topiramate ($n = 142$); TRAEs were reported in 17% and 70% of patients, respectively
- Five (4%) of the 140 patients initially randomized to BoNT/A compared with 72 (51%) of the patients initially randomized to topiramate discontinued treatment due to adverse events
- The most common TRAEs with BoNT/A were neck pain (4%), musculoskeletal pain (2%), migraine (1%) and blurred vision (1%); the most common TRAEs with topiramate were paresthesia (29%), cognitive disorder (12%), fatigue (12%), nausea (12%), decreased appetite (11%), dizziness (11%) and attention disturbance (8%) [48].

6 What is the current clinical position of onabotulinumtoxinA in chronic migraine?

BoNT/A is one of the most widely utilized preventive medications for CM [54, 55]; it continues to be a central component of clinical practice in the era of CGRP antagonists [54]. BoNT/A is an effective and generally well tolerated treatment, as demonstrated in clinical trials (PREEMPT 1 and 2; COMPEL) and confirmed in real-world studies (e.g. REPOSE and CM-PASS). In terms of reducing the number of days with headache, the favourable effect of BoNT/A appears early, although it also appears to accumulate with successive treatment cycles, at least initially, suggesting that maximum benefit may require multiple administrations [17]. At least half of the patients treated with BoNT/A throughout the PREEMPT or COMPEL studies of 1 and 2 years' duration, respectively, achieved sustained treatment-controlled CM (i.e. they no longer met the criteria for CM) while continuing therapy.

Beyond headache-day reduction, BoNT/A therapy is associated with clinically meaningful improvements in assessments of headache severity, headache-related impact (including migraine-related disability) and migraine-specific HR-QOL, including in monthly headache-day frequency non-responders. Accordingly, headache-day reduction as a sole outcome measure may not be appropriate to assess responsiveness to BoNT/A. Treatment with BoNT/A also reportedly reduces HRU (e.g. in the COMPEL [37] and REPOSE [56] studies) and improves work productivity (e.g. in the PREDICT [47] and FORWARD [49] studies). Importantly, the results of studies evaluating onabotulinumtoxinA (Botox®) are specific to this particular formulation of BoNT/A and cannot be extrapolated to other commercially available formulations of BoNT/A.

European Headache Federation (EHF) guidelines concerning the use of BoNT/A in clinical practice are mainly based on expert opinon (Table 6). Consistent with data from the PREEMPT clinical programme, the EHF recommends attempting at least two to three cycles of BoNT/A before categorizing patients as responders or non-responders. However, like the National Institute for Health and Care Excellence (NICE) in the UK, it recommends that a monthly

Table 6 Summary of recommendations from the European Headache Federation on the use of onabotulinumtoxinA (Botox®) in chronic migraine [55]

Which patients should be offered BoNT/A?
Patients should preferably have failed 2–3 other migraine prophylactics (unless contraindicated by comorbid disorders) before starting BoNT/A
For pts with MO, should withdrawal be done before initiating BoNT/A?
If feasible, patients with MO should be withdrawn from the overused medication before initiating BoNT/A. If not, BoNT/A can be initiated from the start or before withdrawal
How should BoNT/A be administered?
BoNT/A should be administered in accordance with the PREEMPT paradigm (i.e. 155–195 U into 31–39 sites every 12 wks)
It is possible that 195 U is more effective than 155 U; the higher dose could be considered, if the patient does not respond to the lower dose
When can an BoNT/A-naive patient be considered a non-responder?
Non-responders are defined as patients with < 30% reduction in HA d/mo during first mo after the first BoNT/A treatment cycle. However, other factors (e.g. HA intensity, disability and patient preferences) should also be considered when evaluating response
Stop treatment if patient does not respond to the first 2–3 treatment cycles (negative stopping rule)
How should responders to BoNT/A be managed over time?
Evaluate response to ongoing BoNT/A therapy by comparing 4-week period before with 4-week period after each treatment cycle
Stop treatment in patients with a reduction to < 10 HA d/mo for 3 consecutive mo (positive stopping rule). However, other factors (e.g. HA intensity, disability and patient preferences) should also be considered when deciding whether to discontinue therapy
Re-evaluate patients 4–5 months after stopping treatment to ensure they continue not to meet the criteria for CM

BoNT/A onabotulinumtoxinA (Botox®), *CM* chronic migraine, *HA* headache, *MO* medication overuse

headache-day frequency responder be defined using less stringent criteria than used in the PREEMPT trials, i.e. a ≥ 30% (rather than ≥ 50%) reduction in headache days [55]. Short disease duration, high serum CGRP levels and (in women) polymorphisms in genes encoding CGRP and TRPV1 are among the potential predictors of responsiveness that have been identified, based on data collected in clinical practice [3]. Of note, the EHF acknowledges that the optimal definition of a de novo non-responder to BoNT/A has still to be determined [55].

Regarding how long treatment should be continued in responders, the EHF has adopted the modified stopping rule proposed by Gooriah and Ahmed [57], which is more stringent than the positive stopping rule proposed by NICE (i.e. the patient has to have fulfilled criteria for EM for 3 consecutive months) [20]. The EHF recommends re-evaluating patients 4–5 months after stopping BoNT/A to ensure the patient continues to fulfil the criteria for EM (Table 6).

According to the EHF, patients should be given realistic expectations about their treatment [55]. This includes advising that BoNT/A therapy may improve, but does not cure, their CM, and that a positive clinical effect may wear off before their next treatment cycle [55]. 'BoNT/A wear off' has been defined as a good initial, but short-lasting (8–10 weeks), response to treatment [58]; it is a widely recognized, albeit underexplored, phenomenon [58, 59]. Various strategies to counteract BoNT/A wear-off have been suggested. These include increasing the dose in subsequent cycles (up to the maximum of 195 U) or offering prophylactic bridging therapies (e.g. peripheral nerve blocks) between injections [58, 59]; however, the optimal approach remains to be determined [60].

Head-to-head comparisons between BoNT/A (administered as per the PREEMPT paradigm) and other medications approved for the prevention of migraine/CM are limited to the real-world FORWARD study, in which BoNT/A therapy demonstrated greater clinical utility than topiramate, largely due to tolerability issues associated with the latter (Sects. 4.2.1 and 5.1). On the basis of this result, the logic of using topiramate ahead of BoNT/A in the treatment of CM could be queried [48], although it was also observed that the two treatments were similarly efficacious in those patients who remained on them and, moreover, that the effectiveness of BoNT/A in patients who received it after failing topiramate was comparable to that in patients who received it from the outset (Sect. 4.2.1). Pending the availability of direct comparisons, the effectiveness of BoNT/A and CGRP antagonists for the prevention of CM has been [61] or is being [62] compared indirectly in network meta-analyses. According to the completed analysis [61], the efficacy of BoNT/A is seemingly comparable to that of erenumab and fremanezumab. The results of the ongoing analysis [62] are awaited with interest.

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