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CADTH COMMON DRUG REVIEW

Clinical Review Report (Resubmission)

OnabotulinumtoxinA (BOTOX)

(Allergan Inc.)

Indication: For the prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting four hours a day or longer)

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

ACM-S	Assessment of Chronic Migraine Symptoms Questionnaire
ACM-I	Assessment of Chronic Migraine Impacts Questionnaire
ADL-I	Activities of Daily Living Impact
AE	adverse event
BLOCF	baseline observation carried forward
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
CM	chronic migraine
CrI	credible interval
DB	double-blind
EMO-I	Emotions Impact
ENE-I	Energy Impact
GEN-I	General Impact
HIT	Headache Impact Test
HOS-I	Household Activities Impact
HRQoL	health-related quality of life
HRU	health care resource utilization
ICHD-III	International Classification of Headache Disorders 3rd Edition
ITT	intention-to-treat population
IVRS	interactive voice response system
LEA-I	Leisure Activities Impact
LOCF	last observation carried forward
MCID	minimal clinically important difference
MD	mean difference
MIBS	Migraine Interictal Burden Scale
mLOCF	modified last observation carried forward
MOH	medication overuse headache
MSQ	Migraine-Specific Quality of Life Questionnaire

MSQv2.1	Migraine-Specific Quality of Life Questionnaire, version 2.1
OLE	open-label extension
Ona A	onabotulinumtoxinA
PHQ-9	Patient Health Questionnaire
PP	per-protocol
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SES	Symptom Experience Score
SOC-I	Social Impact
SSS	Symptom Severity Score
WDAE	withdrawal due to adverse event
WOCF	worst observation carried forward
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem
WS-I	Work/School Impact

Drug	OnabotulinumtoxinA (Botox)
Indication	For the prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer)
Reimbursement Request	As per indication
Dosage Form(s)	Sterile vacuum-dried concentrate powder for solution for injection; 50, 100, and 200 Allergan units per vial
NOC Date	October 18, 2011
Manufacturer	Allergan Inc.

Executive Summary

Introduction

Migraine is a common, debilitating, neurological disorder characterized by recurrent headaches and symptoms of nausea, vomiting, photophobia, and/or phonophobia.[1,2] An episode may last from four to 72 hours and may be preceded by an aura (a visual or auditory disturbance). The two subtypes of migraine, episodic and chronic migraine (CM), are differentiated by the frequency of headache occurrence.[1,2] The third edition of the International Classification of Headache Disorders (ICHD-III) described CM as a headache (tension-type-like or migraine-like) occurring on 15 or more days per month for more than three months that has the features of migraine headaches on at least eight days per month.[2] Some patients may go from experiencing episodic migraine (occurring on fewer than 15 days per month) to CM.[1] It is believed that, annually, 2.5% of patients with episodic migraine will transition to CM.[3] A US population-based study published in 2012 estimated an overall prevalence of CM of 0.91% (diagnosis of CM based on ICHD-III criteria).[4] Canadian prevalence estimates are not available. The incidence of CM has not been determined.

Migraine management includes treating acute attacks and using prophylactic drug therapy to reduce attack frequency or severity. Acute attacks can be treated with acetaminophen, NSAIDs (ASA, ibuprofen, or naproxen), and triptans.[5] Prophylactic medications are usually considered for patients experiencing more than four attacks per month.[6] These medications include botulinum toxin, anti-calcitonin gene-related peptide receptors (CGRPs), and anticonvulsants, as well as others from a variety of drug classes. In clinical practice, patients on migraine prophylaxis frequently discontinue or switch treatments due to a lack of efficacy or tolerability.[7,8] In Canada, onabotulinumtoxinA (Botox, or Ona A), is the only drug indicated specifically for the prophylaxis of CM.[9] Erenumab and topiramate are both indicated for prevention of migraine in adults, for whom topiramate is indicated for the prophylaxis of migraine headaches,[10] and erenumab is indicated for prevention of migraines in adults who have at least four migraine days per month.[11] All other medications that are commonly used for the treatment of CM are used “off-label” for this indication.

Ona A is a neuromuscular paralytic agent derived from the fermentation of *Clostridium botulinum* type A and one of several immunologically distinct serotypes of the botulinum neurotoxin.[12]

On May 28, 2014, the CADTH Canadian Drug Expert Committee (CDEC) issued a recommendation that Ona A not be listed for the management of CM.[13] Key reasons for the recommendation included significant limitations with the design of the two pivotal trials, PREEMPT-1 and PREEMPT-2 (i.e., the relatively short duration of the studies for a chronic condition and a population that included patients with medication overuse headache), and the clinical significance of the absolute differences between Ona A and placebo for health-related quality of life (HRQoL) and headache outcomes was considered uncertain. The recommendation was based on evidence presented in a CADTH Common Drug Review (CDR) report for Ona A,[14] which is summarized in Appendix 6 and Appendix 7 of this report. The manufacturer provided this resubmission with additional data and information from recently conducted studies that were not available at the time of the original submission. In light of new information, this resubmission was made with the primary goal of attempting to provide and assess any clinical studies that can fill the evidence gaps identified by CDEC. The manufacturer-provided reviews of several randomized controlled trials (RCTs), one of which compared Ona A with topiramate. The manufacturer also provided several articles that present the minimal clinically important differences (MCIDs) for the outcomes that were deemed important for patients with CM. New evidence was provided to support the efficacy of Ona A in patients with CM and with or without medication overuse headache (MOH) from studies that have been published since the first CDR clinical review was conducted. Finally, the manufacturer provided details of prospective and retrospective non-randomized trials that have been published on the long-term safety and efficacy of Ona A when used as preventive treatment for CM.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of Ona A for the prophylaxis of headaches in adults with CM (≥ 15 days per month with headaches lasting 4 hours a day or longer). This clinical report is an update of the original CDR review. The main change in the review protocol in this report relative to the original CDR review is that any evidence provided by the manufacturer was assessed and included in the report on the basis of its potential for addressing research gaps identified by CDEC at the initial submission of Ona A for prevention of CM.

Results and Interpretation

Included Studies

Two RCTs (the FORWARD study and Study 545) and four single-arm trials (COMPEL, REPOSE, Negro et al. [2015], and Negro et al. [2016]) are included in this review. All trials included adult patients with CM, with the Negro et al. studies including patients with CM and MOH. The FORWARD study evaluated the efficacy, safety, and tolerability of Ona A versus topiramate over a 36-week period. Study 545 was designed to evaluate the use of the Assessment of Chronic Migraine Impacts (ACM-I) questionnaire in assessing the impact and benefit of treatment with Ona A in adults with CM. COMPEL, REPOSE, and the Negro et al. studies evaluated the efficacy and safety of treatment with Ona A for up to two years. The primary outcome in the FORWARD study was the proportion of patients with a decrease of at least 50% from baseline in the frequency of headache days per 28-day period, at the primary time point of week 32. Other outcomes included change from baseline in the frequency of headache days per 28-day period, change from baseline in total score on the six-item Headache Impact Test (HIT-6) per 28-day period, and the proportion of patients with a decrease of ≥ 70% from baseline in the frequency of headache days per 28-day period. [redacted] Many other efficacy

outcomes, including patient-reported outcomes, were assessed in the FORWARD study as exploratory. In Study 545, the primary efficacy end point was change from baseline in the ACM-I total score. Other efficacy measures were change from baseline in the ACM-I domain scores, the Assessment of CM Symptoms questionnaire, the Migraine-Specific Quality of Life Questionnaire (MSQ), and HIT-6 score. [redacted] In the COMPEL trial, the primary efficacy end point was the mean change from baseline in the number of headache days for the 28-day period ending at week 108 (following nine treatments). Secondary efficacy measures were the mean change from baseline in the frequency of headache days for the 28-day period ending at week 60 (following five treatments), and the mean change from baseline in HIT-6 total score over a four-week period at week 60 and week 108 (following nine treatments). Many other efficacy outcomes, including patient-reported outcomes, were assessed in the COMPEL study as exploratory. [redacted] In the REPOSE study, no primary variable was defined. Efficacy measures assessed were change from baseline in MSQ, change from baseline in EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L), change from baseline in patient-reported headache frequency, and health care resource utilization, which was assessed by evaluating admission to hospital for headache. No adjustments for multiplicity were performed. In the two Negro et al. studies, efficacy measures assessed were headache days, migraine days, acute pain medication intake every three months, and HIT-6 scores assessed every six months. Whether the outcomes in these two studies were adjusted for multiplicity was not reported.

The main limitation of the FORWARD trial was that it was an open-label trial; being aware of treatment allocation may have influenced the outcome measures assessed subjectively, including adverse events (AEs) and HRQoL, which could potentially be biased by knowledge of treatment received. In addition, patients' willingness to continue therapy may have been influenced by knowledge of the treatment received and the availability of the option to discontinue topiramate and switch to Ona A. That knowledge may have played a role in the large discontinuation rate in the topiramate group, in which 80.3% of patients discontinued treatment versus only 14.3% who discontinued Ona A treatment. While the main reason for discontinuation was AEs, other reasons for discontinuation, such as withdrawal of consent and loss to follow-up, were also higher in the topiramate treatment group than in the Ona A treatment group. In addition, the data-imputation method used for the base-case analysis was baseline observation carried forward, in which, if a patient had a missing entry for any reason (e.g., discontinuation due to AE, lost to follow-up, lack of efficacy), the baseline value data were utilized and the patient was considered a nonresponder. Given the high dropout rate in the topiramate treatment group, this imputation would likely favour Ona A.

[redacted]

The COMPEL, REPOSE, and Negro et al. studies were single-arm studies. There is a risk of bias with outcomes measurement in single-arm studies as patients and providers are aware of their assigned intervention. Measurement of subjective outcomes, such as HRQoL, may be at increased risk of bias if patients in the study are aware of their treatment allocation. For example, patients may report improved HRQoL simply because they are receiving a new treatment. Knowledge of their intervention may also bias results indirectly by affecting adherence. Patients may be more likely to closely adhere to therapy if they are receiving a treatment that they anticipate will be an improvement over other therapies.

Improved adherence may lead to better outcomes. Knowledge of treatment assignment can also bias harms, particularly AEs. If patients are aware that they are taking an active therapy, they might be more likely to attribute an AE to a drug, or may even be more likely to report an AE. The discontinuation rate was high in COMPEL (47.9%) and REPOSE (79.8%). The Negro et al. studies were conducted independently of the manufacturer, and as such, Clinical Study Reports were not available to the manufacturer or CADTH. A detailed and thorough assessment of these studies was therefore not possible, especially given that the extent of exposure to Ona A and the number of injections of Ona A received by patients were not reported. Also treatment-related AEs were only reported instead of treatment-emergent adverse events (TEAEs), which tend to underreport AEs experienced by patients.

In addition to the main trials reviewed, two clinical trials were reviewed and critically appraised in the original CDR clinical report for Ona A in adults with CM; PREEMPT-1 and PREEMPT-2 were summarized in Appendix 6, and the open-label extension phase of PREEMPT-1 and PREEMPT-2 was summarized in Appendix 7.

Efficacy

The first reason provided for the 2014 CDEC recommendation not to list was the uncertainty regarding both the magnitude and clinical significance of the treatment effect of Ona A, particularly with respect to HRQoL and headache and migraine outcomes. The second reason involved the limitations of the design of the PREEMPT-1 and PREEMPT-2 trials, namely the enrolled patient population and potential inclusion of patients with MOH. In addition, CDEC noted a lack of sufficient evidence regarding long-term safety and efficacy. The manufacturer provided additional studies and articles to address CDEC concerns.

The manufacturer provided an article by Cole et al.[15] that describes MCIDs for between-group comparisons of the three domains of the MSQ (role function-restrictive, role function-preventive, and emotional function). The treatment-effect sizes associated with Ona A in the PREEMPT-1 and PREEMPT-2 trials for each of the MSQ domains, with the exception of emotional function in PREEMPT-1, all exceed the between-group MCIDs identified by Cole et al.[15] However, the MCIDs estimated by Cole et al. were based on patients with a maximum of 15 headache days per month (i.e., most patients in the data sets used by Cole et al. would be below the threshold for classification of CM). The MCID reported by Cole et al.[15] therefore might not be applicable for patients with CM, especially given that most likely patient with CM would have a worse quality of life (QoL) than patients with a maximum of 15 headache days per month, and hence an improvement in QoL that would be seen as clinically meaningful for patients with a maximum of 15 headache days per month might not be generalizable to patients with CM.

The original CADTH review concluded that the absolute difference between Ona A and placebo in headache and migraine days of approximately one to two days was not clinically important.[14] To address the first reason provided for the CDEC recommendation not to list, in the resubmission the manufacturer pointed to more recent evidence by Dodick et al.[16] that a one-day reduction in headache frequency was clinically meaningful. Dodick et al. referenced a study by Silberstein et al.[17] that examined headache frequency and HRQoL. Silberstein et al. examined the characteristics of patients (N = 703) 12 years of age or older who received Ona A using data from an open-label clinical study conducted at 10 headache centres in the US.[17] The majority (65.6%) of patients had CM, although approximately 34% had other types of headache conditions, such as migraine not classified as chronic and

tension-type headache. Silberstein et al.[17] stated that: “A 1-day increase in HA [headache] frequency was associated with a greater likelihood of HA pain interfering with mood (4.0%, *P* < .001), recreational activities (4.0%, *P* = .004), or life enjoyment (4.0%, *P* = .001).” It is unclear which instruments the domains of mood, recreational activities, and life enjoyment were taken from. As well, it is unclear if the domains were selected a priori or if a relationship between headache frequency and the other domains of HRQoL of the three instruments was tested, found not to be statistically significant, and not reported. Without knowing the scale on which these domains were based, it is difficult to determine if a 4% improvement is clinically meaningful. In addition, the time point and study sample size upon which these results are based are unclear. A large number of patients (N = 221) had dropped out by the one-year point, and it is uncertain if the data for these patients were imputed or omitted from the final results. No other studies were identified that specifically examined the association between reduction in headache frequency and QoL in patients with CM. The between-group difference in the mean change from baseline in frequency of headache days per 28 days at week 24 was [redacted] in PREEMPT-1 and [redacted] in PREEMPT-2, [redacted]. The between-group difference in the mean change from baseline in frequency migraine/probable migraine days per 28 day period at week 24 was [redacted] in PREEMPT-1 and [redacted] in PREEMPT-2, [redacted]. The clinical expert consulted for this review indicated that the between-group difference in the mean change from baseline in frequency of headache days, and in frequency of migraine/probable migraine days, of one to two days is clinically meaningful for patients.

To address the second reason for the do-not-list recommendation from CDEC related to PREEMPT-1 and PREEMPT-2 trials, including patients suffering from MOH, the manufacturer pointed to the 2018 International Headache Society (IHS) Guidelines for Controlled Trials of Preventive Treatment of Chronic Migraine.[18] The IHS guidelines recommend that inclusion of patients with MOH should not be prohibited in clinical trials of CM prophylaxis due to the large and representative population of CM sufferers with MOH.[18] The guidelines recommend that patients with CM and MOH be included in trials, although they should be stratified and balanced accordingly.[18] Given the recently published IHS recommendations, and the fact that the included patients with MOH in the PREEMPT trials were stratified and balanced between groups for MOH as recommended by the guidelines, it was reasonable for the pivotal trials to enrol patients with MOH and CM. The clinical expert consulted on this review also indicated that patients with MOH should not be excluded from clinical trials of CM, and enrolling patients with MOH in the trials after adequate and careful medication overuse discontinuation might not be possible. In this resubmission, the manufacturer provided two single-arm trials (Negro et al. [2015] and [2016]) involving patients with CM and comorbid MOH. Both studies evaluated the long-term efficacy and safety of Ona A over a two-year period. The efficacy measures assessed in both studies were change from baseline in headache days, migraine days, acute pain medication intake, and HIT-6 score. Improvement in headache symptoms and acute pain medication intake were important outcomes according to the patient group input received by CADTH for this resubmission. The HIT-6 is a questionnaire that quantifies the impact of headache on a patient’s life. In Negro et al. 2015 and Negro et al. 2016 studies, the number of headache days, migraine days, acute pain medication intake, and HIT-6 scores decreased (i.e., improved) during the period of treatment from the first to the last therapy session. However, the outcomes assessed in Negro et al. 2015 and Negro et al. 2016 were

not adjusted for multiplicity, and any interpretation of results reported should consider the potential for inflated type I error.

To address the third reason for the do-not-list recommendation from CDEC (insufficient evidence regarding long-term safety and efficacy) the manufacturer provided four single-arm trials: COMPEL, REPOSE, and the Negro et al. 2015 and Negro et al. 2016 studies. Both COMPEL and REPOSE assessed Ona A 155 Allergan units (U) in patients with CM over a period of 108 and 104 weeks, respectively. In the COMPEL study, efficacy measures assessed were change from baseline in the number of headache days, change from baseline in HIT-6 total score, [redacted]. The REPOSE study assessed change from baseline in MSQ, change from baseline EQ-5D-3L, change from baseline in headache frequency, and health care resource utilization. In the COMPEL study, [redacted] A statistically significant reduction in the mean number of headache days from baseline was observed at week 108 (–10.7 [6.44] $P < 0.0001$), as well as a [redacted]. In the REPOSE study, improvements in the EQ-5D-3L total score (index), the frequency of headache days, and reduction in health care resource utilization were observed at all post-baseline treatment visits. However, both trials had many methodological limitations related to the open-label, non-comparative designs, as highlighted previously. Given these limitations and the uncertainty associated with them, the results reported in the COMPEL, REPOSE, and Negro et al. 2015, and Negro et al. 2016 trials are challenging to interpret. It is not clear if the reduction in headache days would be sustained if patients were to stop receiving Ona A.

A key limitation that was identified in the original CDR clinical review for Ona A was the lack of a head-to-head active-comparison trial. The manufacturer provided an open-label RCT (FORWARD) that evaluated the efficacy, safety, and tolerability of Ona A versus topiramate in adult patients with CM. This trial reported statistically significant results in favour of Ona A for the primary and secondary outcomes (which were adjusted for multiple testing). However, this trial had many methodological limitations, as highlighted previously. Given these limitations and the resulting uncertainty, the results reported in the FORWARD trial are challenging to interpret.

The Institute for Clinical and Economic Review conducted an indirect treatment comparison of CGRP inhibitors and placebo or commonly used preventive treatments in adults with CM.[19] Although several efficacy and safety outcomes were evaluated, IDCs could be performed only for change from baseline in monthly migraine days, change from baseline in monthly headache days, and all-cause discontinuation. In a Bayesian network meta-analysis, Ona A was not favoured over topiramate or CGRP inhibitors on these outcomes.[19] These results, however, are limited by several potential sources of heterogeneity that were not systematically evaluated, and generalizability to the patient population of interest is limited. In clinical practice, Ona A is likely to be used in patients who have failed several lines of previous treatments. However, the CGRP inhibitor trials in the network meta-analyses excluded patients who failed as few as two or three previous therapies and insufficient data were available to conduct subgroup analyses for patients who failed at least one prior preventive therapy. Other factors that limited generalizability were the failure

of trials to consistently follow Health Canada–approved Ona A dosing and the fact that indirect comparisons did not incorporate longer-term follow-up data.

Study 545 was a relatively small trial (N = 52) [redacted] This study was designed as a pilot study to investigate the utility of the ACM-I, a new instrument developed to measure the impact of CM on daily activities and patient-treatment benefits for products developed to treat CM. Study 545 was not intended to provide robust evidence of efficacy and safety of Ona A.

Harms

There were no deaths in any of the included trials. In patients who received Ona A for two years no new safety signals were identified. In the FORWARD trial, the proportions of patients who experienced AEs (78.9% versus 47.7%), serious adverse events (SAEs) (4.2% versus 1.8%) [redacted] were higher in the topiramate treatment group than in the Ona A group. In Study 545 the proportions of patients who experienced AEs and SAEs were higher in the Ona A group than placebo group. Overall, the most frequent AEs associated with Ona A were [redacted], neck pain, and [redacted]. In the FORWARD trial, no single SAE was reported by more than one patient. In the single-arm COMPEL study, SAEs were reported in 10.5% (75 of 716) of patients. The most frequently reported SAEs (i.e., in at least three patients each) were migraine (0.8%), suicidal ideation (0.7%), and headache, malignant melanoma, and non-cardiac chest pain (0.4% each). In the REPOSE study, a total of nine SAEs were reported in eight patients (1.3%). The most frequently reported SAEs were psychiatric disorders (0.5%) and nervous system disorders (0.3%). However, the clinical expert involved in the review indicated that these SAEs were unlikely to be due to Ona A treatment. [redacted] In the COMPEL study, discontinuations from the study due to AEs were reported in 4.5% of patients. The AEs leading to the most discontinuations were suicidal ideation (four patients) and eyelid ptosis, headache, and pregnancy (three patients each).

In the Negro et al. studies, treatment-related AEs were only reported rather than TEAEs, which tend to underreport AEs experienced by patients, because, while TEAEs refer to AEs temporally related to the study treatment, treatment-related AEs refer to the causality assessment by the investigator. The FDA's guidance for industry (Statistical Principles for Clinical Trials) indicates that all AEs should be reported, whether or not they are considered to be related to treatment.[20]

[redacted]

Potential Place in Therapy[a]

In clinical practice, Ona A can be expected to have a beneficial effect (defined as reduction in headache days) in approximately 70% of patients, while the remaining 30% of patients would be expected to receive no benefit from Ona A injections after two sets of injections given three months apart. Of the patients who would experience a beneficial effect, 20% would experience a reduction in the numbers of headache days they have each month and approximately 40% could be expected to continue to have headaches with approximately the same frequency, but with reduced severity. Finally, approximately 10% of patients would experience a reduction in both frequency and severity of headaches.

In practice, patients who fulfill ICHD-III criteria for CM are offered the option of a trial of Ona A or topiramate and are provided with information about both medications. Many patients eventually end up on treatment with both medications to obtain optimal results.

ICHD-III criteria are easy to apply to identify the patients most likely to benefit from Ona A therapy. This is a clinical diagnosis and no specialized testing is required.

Conclusions

Two RCTs (the FORWARD study and Study 545) and four single-arm trials (COMPEL, REPOSE, Negro et al. [2015], and Negro et al. [2016]) were included in this review. All trials included adult patients with CM, with the Negro et al. 2015, and Negro et al. 2016studies including patients with CM and MOH. While the FORWARD study demonstrated that Ona A was statistically significantly superior to topiramate in reducing headache days, [redacted] and improving patient-reported outcomes (HIT-6), the FORWARD study had many methodological limitations that could have biased the results in favour of Ona A, including the open-label design, high dropout rate in the topiramate treatment group, and imputation methods. While all of the single-arm trials reported improvement in all of the outcomes assessed, there is uncertainty in the results reported due to the absence of a control arm, high dropout rate, and the risk of inflated type I error. [redacted] and the Negro et al. trials assessed the intake of acute-headache medication, and in these trials, patients decreased the frequency of their intake of acute-headache pain medication. There is still uncertainty around the absolute numerical difference between groups of approximately one to two headache and migraine days reported in PREEMPT-1 and PREEMPT-2 in the original CDR review, whether or not they are clinically meaningful. No deaths and no evidence of toxin spread were reported, and anaphylactic reactions were reported in less than 0.1% of patients in one study. Ona A was associated with a relatively low incidence of SAEs in the included trials.

[a] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Table 1: Summary of Results

	FORWARD				
	Ona A 155 U (N = 140)	Topiramate (N = 142)	OR or MD	95% CI	*P* value
Decrease from baseline in the frequency of headache days per 28-day period – intention-to-treat set at weeks 29 to 32[a]					
N	140	142			
Headache days ≥ 50% reduction from baseline,[b] n (%)	56 (40.0)	17 (12.0)	OR = 4.94	2.681 to 9.085	< 0.001
Headache days ≥ 70% reduction from baseline, n (%)	38 (27.1)	12 (8.5)	OR = 4.05	2.014 to 8.157	< 0.001
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Changes from baseline in frequency of headache days by 28-day (4-week) intervals – intention-to-treat set at weeks 29 to 32[c]					
Baseline, mean (SD)	22.1 (4.6)	21.9 (4.8)			
Weeks 30, mean (SD)	13.8 (9.4)	19.8 (7.4)			
Change from baseline					
N	140	142			
Mean (SD)	−8.3 (8.9)	−2.1 (5.6)	MD = −6.199	–7.936 to –4.462	< 0.001
Changes from baseline in total HIT-6 score per 28-day period at week 30 – intention-to-treat set[c]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
Change from baseline					
N	110	115			
Mean (SD)	−5.6 (7.2)	−1.3 (3.9)	MD = −4.248	−5.766 to −2.731	< 0.001
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]					

[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HIT-6					
Baseline, mean (SD)	64.7 (4.2)	65.3 (5.5)			
Week 24					
N	15	18			
[redacted]	[redacted]	[redacted]			
	GMA-BTX-CM-12-545				
	Ona A 155 U (N = 19)	**Placebo (N = 26)**	**Between-groups difference**		***P* value**
Change from baseline, mean (SD)	−5.1 (4.7)	−6.7 (7.9)	[redacted]		[redacted]
MSQ – role function-restrictive					
Baseline, mean (SD)	39.8 (16.6)	40.9 (21.7)			
Week 24					
N	13	18			
[redacted]	[redacted]	[redacted]			
Change from baseline, mean (SD)	32.1 (15.4)	26.5 (28.9)	[redacted]		[redacted]
MSQ – role function-preventive					
Baseline, mean (SD)	58.9 (18.8)	62.5 (23.0)			
Week 24					
N	13	18			
[redacted]	[redacted]	[redacted]			
Change from baseline, mean (SD)	25.8 (18)	20.8 (28.9)	[redacted]		[redacted]
MSQ – emotional function					
Baseline, mean (SD)	53.3 (27.6)	58.7 (23.9)			
Week 24					
N	14	18			
[redacted]	[redacted]	[redacted]			
Change from baseline, mean (SD)	26.2 (26.3)	18.5 (34.2)	[redacted]		[redacted]

	COMPEL				
	Baseline	Week 24 (after treatment 2)	Week 60 (after treatment 5)	Week 84 (after treatment 7)	Week 108 (after treatment 9)
Change from baseline in the number of headache days per 28-day period (modified LOCF)					
N	715	715	715	715	715
Mean (SD)	22.0 (4.82)	14.6 [redacted]	12.7 [redacted]	12.2 [redacted]	11.3 [redacted]
Change from baseline, mean (95% CI)		−7.4 [redacted]	−9.2 [redacted]	−9.8 [redacted]	−10.7 [redacted]
P value for the change from baseline[e]		P < 0.0001	P < 0.0001	P < 0.0001	P < 0.0001
HIT-6 total score (modified LOCF)					
N	713	713	713	713	713
Mean (SD)	64.7 (4.82)	[redacted]	58.0 [redacted]	[redacted]	57.7 [redacted]
Change from baseline, mean (95% CI)		[redacted]	−6.8 [redacted]	[redacted]	−7.1 [redacted]
P value for the change from baseline[e]		[redacted]	P < 0.0001	[redacted]	P < 0.0001

	COMPEL				
	Baseline	Week 24 (after treatment 2)	Week 60 (after treatment 5)	Week 84 (after treatment 7)	Week 108 (after treatment 9)
[redacted]					
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
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[redacted]					[redacted]
[redacted]					[redacted]
	Negro et al. (2015); Ona A 155 U (N = 132)[f]				
	Headache days per month N = 132, mean (SD)	Migraine days per month N = 132, mean (SD)	Medication intake days per month N = 132, mean (SD)	HIT-6 N = 132, mean (SD)	Percentage of patients with severe impact (HIT-6 score ≥ 60), N = 132 n (%)
Baseline (1st injection)	22.3 (4.1)	21.4 (4.3)	20.8 (4.5)	68.9 (4.3)	124 (93.9)
6 months (3rd injection)	12.9 (2.6)[g]	12.4 (2.5)[g]	11.8 (2.4)	64.4 (5.0)[g]	102 (77.3)
12 months (5th injection)	9.4 (2.9)[g]	9.2 (2.8)[g]	8.7 (2.7)[g]	58.5 (3.7)[g]	59 (44.7)
18 months (7th injection)	8.6 (2.6)[g]	7.9 (3.0)[g]	7.6 (2.9)[g]	55.4 (4.9)[g]	49 (37.1)
24 months	7.3 (2.1)[g]	6.8 (2.3)[g]	5.3 (1.7)[g]	52.0 (5.6)[g]	29 (22)
	Negro et al. (2016); Ona A 195 U (N = 143)[f]				
	Headache days per month N = 143, mean (SD)	Migraine days per month N = 143, mean (SD)	Medication intake days per month N = 143, mean (SD)	HIT-6 N = 143, mean (SD)	Percentage of patients with severe impact (HIT-6 score ≥ 60), N = 143 n (%)
Baseline (1st injection)	22.2 (4.9)	21.6 (4.8)	21.0 (5.1)	67.9 (4.2)	137 (95.8)
6 months (3rd injection)	10.2 (2.8)[g]	9.7 (2.7)[g]	9.9 (1.9)[g]	61.0 (3.9)[g]	91 (63.6)
12 months (5th injection)	5.7 (1.7)[g]	5.4 (1.2)[g]	5.6 (1.4)[g]	56.8 (3.8)[g]	57 (39.9)
18 months (7th injection)	4.9 (1.3)[g]	4.5 (1.0)[g]	4.7 (1.3)[g]	54.0 (4.6)[g]	38 (26.5)
24 months	4.1 (1.0)[g]	3.8 (1.0)[g]	3.7 (1.3)[g]	49.0 (6.7)[g]	22 (15.4)

Adverse events	FORWARD		GMA-BTX-CM-12-545		COMPEL	REPOSE
	Ona A 155 U (N = 220)	Topiramate[h] (N = 142)	Ona A 155 U (N = 25)	Placebo (N = 27)	Ona A 155 U (N = 716)	Ona A 155 U or 195 U (N = 633)
Patients with > 0 TEAE, N (%)	105 (47.7)	112 (78.9)	9 (36.0)	[redacted]	436 (60.9)	[redacted]
Patients with > 0 SAEs, N (%)	4 (1.8)	6 (4.2)	0	1 (3.7)	75 (10.5)	[redacted]
WDAEs, N (%)	[redacted]	[redacted]	NR	NR	32 (4.5)	[redacted]

Number of deaths, N (%)	0	0	0	0	0	[redacted]
Notable harms, N (%)						
Dysphagia	[redacted]	[redacted]			[redacted]	[redacted]
Neck pain	[redacted]	[redacted]	4 (16.0)	1 (3.7)	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid ptosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diplopia	[redacted]	[redacted]			[redacted]	[redacted]
Urinary incontinence	[redacted]	[redacted]			[redacted]	[redacted]

CI = confidence interval; HIT = six-item Headache Impact Test; LOCF = last observation carried forward; MD = mean difference; MSQ = Migraine-Specific Quality of Life Questionnaire; NR = not reported; Ona A = onabotulinumtoxinA; OR = odds ratio; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event; U = Allergan units; WDAE = withdrawal due to adverse event.

[a] Odds ratio, 95% CI, and *P* value were estimated using a logistic regression model adjusted by baseline headache days.

[b] Primary efficacy end point of the study.

[c] Estimated mean difference, 95% CI, and *P* value were assessed using analysis of covariance adjusting for baseline headache days.

[d] Estimated mean difference, 95% CI, and *P* value for the final 28-day time period were assessed using nonparametric rank analysis of covariance with treatment as a factor and adjusting for baseline.

[e] Two-sided *P* value for comparing post-baseline visit to baseline was from the paired t-test.

[f] Number of patients included in the analyses at each time point in Negro et al. (2015) and Negro et al. (2016) was not reported.

[g] $P \leq 0.05$ for the change from baseline. A paired t-test was used to compare the mean headache days, migraine days, medication intake days, and HIT-6 score at baseline and at each cycle of injections after Hartley's Fmax test was used to assess equal variance of data. A chi-square test was used to compare categorical variables.

[h] Percentages used the number of patients that received each treatment as the denominator. Patients that received both Ona A and topiramate were included in the denominator for all treatment groups and overall. At each level of summarization, a patient was counted once within a treatment group and once for the total population.

Sources: Clinical Study Reports for FORWARD and GMA-BTX-CM-12-545 studies,[21,22] Clinical Study Reports for COMPEL study,[23] Negro et al.[24], and Negro et al.[25]

Reprinted and (modified) from Springerplus, Negro A, Curto M, Lionetto L, Crialesi D, Martelletti P. OnabotulinumtoxinA 155 U in medication overuse headache: a two years prospective study. 2015;4:826. Creative Commons Attribution License 4.0. http://creativecommons.org/licenses/by/4.0/legalcode. Modified by compiling data from additional file 1 Tables S1, S2, S3, S4, and S5.

Reprinted and (modified) from The Journal of Headache and Pain, Negro A, Curto M, Lionetto L, Martelletti P. A two years open-label prospective study of OnabotulinumtoxinA 195 U in medication overuse headache: a real-world experience. 2016;17:1.Creative Commons Attribution License 4.0. http://creativecommons.org/licenses/by/4.0/legalcode. Modified by compiling data from Table 3 and additional file 1 Table S1.

Introduction

Disease Prevalence and Incidence

Migraine is a common, debilitating neurological disorder characterized by recurrent headaches and symptoms of nausea, vomiting, photophobia or phonophobia.[1,2] An episode may last from four to 72 hours and may be preceded by an aura (a visual or auditory disturbance). The two subtypes of migraine, episodic and chronic migraine (CM), are differentiated by the frequency of headache occurrence.[1,2]

The third edition of the International Classification of Headache Disorders (ICHD-III) described CM as a headache (tension-type-like or migraine-like) occurring on 15 or more days per month for more than three months with the features of migraine headaches on at least eight days per month.[2]

Some patients may go from experiencing episodic migraines (occurring on fewer than 15 days per month) to CM.[1] It is believed that, annually, 2.5% of patients with episodic migraine will transition to CM.[3]

Several CM prevalence studies have been conducted, but estimates varied, most likely because of the use of heterogeneous definitions of CM. A systematic review of 12 population-based studies (published from 1991 to 2006) reported an overall prevalence of CM ranging from 0% to 5.1%.[26] Sex-specific estimates showed that the prevalence of CM was 2.5 to 6.5 times higher in women (1.7% to 4.0%) than in men (0.6% to 0.7%).[26] A US population-based study published in 2012 estimated an overall prevalence of CM of 0.91% (diagnosis of CM based on ICHD-III criteria).[4] For both males and females, the prevalence of CM increased throughout adolescence, peaked mid-life, and decreased after the age of 50 years.[4] Canadian prevalence estimates are not available. The incidence of CM has not been determined.

Patients with CM have greater headache-related disability, worse socioeconomic status and health-related quality of life (HRQoL), higher rates of comorbid conditions, and higher use of health care resources than patients with episodic migraine.[4,27] One population-based study found that, after adjusting for sociodemographic factors, headache-related disability was four times greater in patients with CM compared with those with episodic migraine (odds ratio [OR], 3.9; 95% confidence interval [CI], 3.5 to 4.3]; $P < 0.001$).[4]

Some cases of CM may be caused by the overuse of acute-headache medications, which confounds the diagnosis of CM and leads to misdiagnosis. One study found that, in patients diagnosed with CM, the prevalence of medication overuse was 31% to 69%.[26] When medications are stopped, approximately 50% of patients diagnosed with CM revert to an episodic migraine subtype. Equally, many patients who overuse medications do not improve after discontinuing the medications.[2] The ICHD-III recognizes medication overuse headache (MOH) as a distinct type of migraine, and advises that patients with CM and MOH should be coded for both, and that if migraine remained chronic after drug withdrawal, the MOH diagnosis may be rescinded.[2]

Standards of Therapy

Migraine management includes treating acute attacks and using prophylactic drug therapy to reduce attack frequency or severity. Acute attacks can be treated with acetaminophen,

NSAIDs (ASA, ibuprofen or naproxen), and triptans.[5] Prophylactic medications are usually considered for patients experiencing more than four attacks per month.[6] These medications include a variant of the botulinum toxin (onabotulinumtoxinA, Ona A), anti-calcitonin gene-related peptide receptor (erenumab), beta-blockers (e.g., propranolol, metoprolol, or atenolol), serotonin antagonist (pizotifen), tricyclic antidepressants (e.g., amitriptyline or nortriptyline), serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine), anticonvulsants (e.g., topiramate, gabapentin, or divalproex), and calcium-channel blockers (e.g., flunarizine or verapamil). In clinical practice, patients on migraine prophylaxis frequently discontinue or switch treatments due to lack of efficacy or tolerability.[7,8] In Canada, Ona A (Botox) is the only drug indicated specifically for the prophylaxis of CM.[9] Erenumab and topiramate are both indicated for prevention of migraine in adults, whereas topiramate is indicated in adults for the prophylaxis of migraine headache[10] and erenumab is indicated for prevention of migraine in adults who have at least four migraine days per month.[11] All other medications that are commonly used for the treatment of CM (e.g., beta-blockers, tricyclic antidepressants, and anticonvulsants) are being used “off-label” for this indication.

The Second International Burden of Migraine Study evaluated the use of preventive medications in 1,165 patients with CM.[28] Participants represented six countries: US, Canada, UK, Germany, France, and Australia. The survey showed that approximately 66% of respondents with CM had used or currently used a preventive medication. The rate of prior or current use of prophylaxis in Canadian respondents with CM was 56%. For all respondents, antidepressants were used most frequently (55%), followed by beta-blockers (37%), and anticonvulsants (36%). The odds of using a prophylactic treatment was higher for CM patients compared with patients with episodic migraine after adjusting for various factors (OR, 2.7; 95% CI, 2.2 to 3.6).[28]

Drug

Ona A is a neuromuscular paralytic agent derived from the fermentation of *Clostridium botulinum* type A and is one of several immunologically distinct serotypes of botulinum neurotoxin.[12] Ona A blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine.[9] A dual mechanism of action has been proposed for Ona A, whereby it exerts its therapeutic effect on both sensory and motor neurons.[9] When injected intramuscularly at therapeutic doses, Ona A causes partial chemical denervation of muscle and inhibits the release of sensory neurotransmitters and downregulates the expression of cell surface receptors as well as prevents and reverses sensitization in nociceptive sensory neurons.[9]

The Health Canada–approved CM dose is 155 Allergan units (U) administered intramuscularly (0.1 mL injection [5 U] to each of 31 sites on the head and neck).[9] Additional injections may be administered for a total maximum dose of 195 U (39 sites). The recommended retreatment is every 12 weeks. The Allergan unit upon which dosing is based is a specific measurement of toxin activity that is unique to Allergan’s formulation of botulinum toxin type A. Therefore, the Allergan units used to describe Botox activity are different from those used to describe that of other botulinum toxin preparations.[9]

The key characteristics of pharmacological treatments for prophylaxis of CM are summarized in Table 2.

Table 2: Key Characteristics of Pharmacological Prophylaxis Treatments for Chronic Migraine

Drug Class	Most Common Therapeutic Uses	Agents Most Commonly Used in CM	Common Adverse Events	Comments Related to CM
Onabotulinumtoxin	Many indications including overactive bladder, neurogenic detrusor overactivity associated with a neurological condition, equinus foot, focal spasticity, and strabismus	onabotulinumtoxinA	Headache, facial muscle weakness, drooping of the eyelids, muscle spasm, muscle tightness, injection pain and rash	As per the clinical expert, Ona A might have weakened the muscles in the neck, and then the neck has to work harder to hold up, and it is more of muscular ache because other muscles have to work harder
Anti-CGRPR	Prevention of migraine	Erenumab	Injection site reactions, constipation, muscle spasm and pruritus	Erenumab is indicated for prevention of migraine in adults who have at least 4 migraine days per month
Anticonvulsants	epilepsy	Gabapentin, topiramate, divalproex	Varies by agent	Topiramate is indicated in adults for the prophylaxis of migraine headache Cognitive side effects (such as somnolence, dizziness, confusion, difficulty concentrating, or visual effects) limit its usefulness in practice; other side effects reported include blurred vision, visual disturbances, periorbital pain, and a possible increase in the risk of suicidal thoughts and behaviour
TCA	Depression	Amitriptyline, nortriptyline	Weight gain, dry mouth, drowsy, fatigue, constipation	Start with low doses and titrate up; may be given at bedtime
Beta blockers	Angina, hypertension,	Propranolol, nadolol, metoprolol	Fatigue, bradycardia, hypotension, coldness of extremities, depression, sleep disturbance, impotence, brochospasm	Start with low doses; if failed one drug, can try another; taper when discontinuing treatment
CCB	Angina, hypertension	Verapamil	Bradycardia, hypotension, constipation, nausea, edema, headache	May take several months to see benefits
	Prophylaxis of migraine	Flunarizine	Fatigue, weight gain, depression	Flunarizine is indicated for prophylaxis of migraine (with and without aura) in patients with frequent and severe attacks who have not responded satisfactorily to other treatment and/or in whom other therapy has resulted in unacceptable side effects

Drug Class	Most Common Therapeutic Uses	Agents Most Commonly Used in CM	Common Adverse Events	Comments Related to CM
SNRI	Depression, anxiety	Venlafaxine	Dry mouth, nausea, somnolence	Fewer anticholinergic AEs than TCAs
Serotonin agonist	Prevention of migraine headaches	pizotifen	Fatigue, weight gain, weak anticholinergic effects	Somnolence, so begin at a low dose and dose at bedtime

AE = adverse event; CGRPR = calcitonin gene-related peptide receptor; CCB = calcium channel blockers; CM = chronic migraine; Ona A = onabotulinumtoxinA; SNRI = serotonin-norepinephrine reuptake inhibitors, TCA = tricyclic antidepressant.

Sources: CADTH Common Drug Review clinical expert, eCPS,[29] RxFiles,[30] and erenumab product monograph.[11]

Submission History

On May 28, 2014, the CADTH Canadian Drug Expert Committee (CDEC) issued a recommendation that Ona A not be listed for the management of CM.[13] Key reasons for the recommendation included the significant limitations with the design of the two pivotal trials (PREEMPT-1 and PREEMPT-2) and the relatively small absolute difference between the Ona A and placebo groups for this chronic condition. The recommendation was based on evidence presented in a CADTH Common Drug Review (CDR) report for Ona A,[14] which is summarized in Appendix 6 and Appendix 7 of this report. The CDR report followed a systematic review approach, which included published and unpublished phase III randomized clinical trials (RCTs) of Ona A as indicated by Health Canada for CM, along with clinical trials considered pivotal by Health Canada.

In addition, CDEC identified the following areas as constituting evidence gaps:

- magnitude and clinical significance of Ona A effects in improving HRQoL and reducing the number of headache days and migraine/probable migraine days in patients with CM
- efficacy and safety in patients with or without MOH
- inadequate data regarding the long-term safety and efficacy of Ona A used for the prophylaxis of headaches in adults with CM.

The manufacturer submitted a request for reconsideration in which it was explained that concurrent diagnosis of CM and MOH is possible and that ideal clinical management is the initiation of prophylactic therapy concurrently with a reduction in acute medication usage. It was also noted that high placebo response rates are commonly reported in the literature for pain clinical trials. The clinical expert consulted by the manufacturer indicated that in clinical practice, the assessment of clinical benefit includes a number of clinical factors such as a reduction in the number of hours per month with a headache and a decrease in headache intensity, which lead to improvement in the patient's ability to function and their quality of life (QoL). The clinical expert also mentioned that reduction in headache hours is meaningful to the patient. It could mean that a patient could engage in typical daily activities such as work. The clinical expert also stated that Ona A provides a benefit to a subset of CM patients, and that the entire PREEMPT patient sample may have diluted the treatment-effect results for this patient subset. However, the subset of patients who might respond to Ona A was not defined.

Basis of Resubmission

The manufacturer resubmitted Ona A with additional data and information from studies that were not available at the time of the original submission to CDR to address the evidence gaps identified by CDEC with the 2014 review. The manufacturer provided several randomized controlled trials, one of which compared Ona A with topiramate. The manufacturer also provided several articles that present results for the minimal clinically important differences (MCIDs) for the outcomes that were deemed important for patients with CM. New evidence was also provided to support the efficacy of Ona A in patients with CM and with or without MOH from studies that have been published since the original CDR clinical review was conducted. Finally, the manufacturer provided prospective and retrospective non-randomized trials that have been published on the long-term safety and efficacy of Ona A when used as preventive treatment for CM.

In the original submission, the requested listing criteria were: prophylaxis of headaches in adults with CM (≥ 15 days per month with headache lasting four hours a day or longer) who have failed (i.e., exhibit a lack of efficacy, intolerance, or clinical contraindication to) at least three prior oral prophylactic medications. Patients who have not obtained an adequate treatment response (≥ 30% reduction in days of headache per month) after two treatment cycles should be discontinued from further therapy.

In the resubmission, the requested listing criteria are the same as the indication, i.e., for the prophylaxis of headaches in adults with CM (≥ 15 days per month with headache lasting four hours a day or longer). The latter is less restrictive than the listing criteria in the original submission, and there is no stopping rule in the new requested listing criteria. No justification was provided for this change in the listing request.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of Ona A injection (Botox) for the prophylaxis of headaches in adults with CM (≥ 15 days per month with headache lasting four hours a day or longer).

Methods

All manufacturer-provided RCTs that used a Health Canada–approved dosage were included in the systematic review. In addition, manufacturer-provided non-randomized studies that addressed research gaps identified by CDEC for the previous submission that are not addressed by the RCTs were included in the systematic review. Published studies were selected for inclusion based on the selection criteria presented in Table 3.

Any studies included in the previous CDR review of Ona A injection for this indication were excluded from the current review. However, data from the pivotal studies (PREEMPT-1 and PREEMPT-2) are summarized in Appendix 6 and Appendix 7.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adult patients with chronic migraine (≥ 15 days per month with headache lasting four hours a day or longer) **Subgroups of interest:** • Patients who have failed (i.e., exhibit a lack of efficacy, intolerance, or clinical contraindication to) prior oral prophylactic medications • Patients who overuse acute headache pain medication versus those who don't • Duration of illness
Intervention	OnabotulinumtoxinA injection (Botox) at doses between 155 U (31 injection sites) and 195 U (39 injection sites)
Comparators	• Erenumab • Anticonvulsants (topiramate) • Tricyclic antidepressants (e.g., amitriptyline, nortriptyline) • Beta blockers (e.g., propranolol, nadolol, metoprolol) • Other anticonvulsants (e.g., gabapentin, divalproex) • Calcium-channel blockers (e.g., flunarizine, verapamil) • Serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine) • Pizotifen
Outcomes	**Efficacy outcomes:** • HRQoL using a validated scales (e.g., MSQ)[a] • Headache symptoms (e.g., HIT-6 score) • Other patient-reported outcomes (e.g., MIDAS)[a] • Acute headache pain medication intake[a] • Headache/migraine frequency (e.g., headache/migraine days, headache/migraine episodes)[a] • Treatment failure • Duration of effect and re-treatment intervals • Health care resource utilization (e.g., emergency visits) • Loss of work days **Harms outcomes:** AEs, SAEs, WDAEs, mortality, notable harms and harms of special interest (e.g., autonomic dysreflexia, cardiovascular events, dysphagia, hematological AEs, neck pain, generalized weakness, seizure, incontinence, swallowing disorder, speech disorder, ptosis, and diplopia)
Study Design	Published and unpublished phase III and IV RCTs. In addition, other study designs that address gaps in evidence as defined by the CDEC recommendation were eligible.[b]

AE = adverse event; CDEC = CADTH Canadian Drug Expert Committee; HIT-6 = six-item Headache Impact Test; HRQoL = health-related quality of life; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire; RCT = randomized controlled trial; SAE = serious adverse event; U = Allergan units; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

[b] The CDEC recommendation for onabotulinumtoxinA injection (Botox) for this indication, published May 2014, identified the following areas as having insufficient evidence regarding the efficacy and safety of onabotulinumtoxinA, specifically: magnitude and clinical significance of the treatment effect with respect to effects on health-related quality of life and migraine outcomes; efficacy and safety in patients with or without medication overuse headache; long-term safety and efficacy.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Botox (onabotulinumtoxinA) and migraines.

Methodological filters were applied to limit retrieval to RCTs. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on November 30, 2018. Regular alerts were established to update the search until the meeting of CDEC on April 10, 2019. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies**,** health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings**,** drug class reviews and databases. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Results

Findings from the Literature

Five studies were identified from the literature for inclusion in the systematic review (Figure 1). Three additional studies were provided by the manufacturer. The included studies are summarized in

Table 4 and Table 5. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

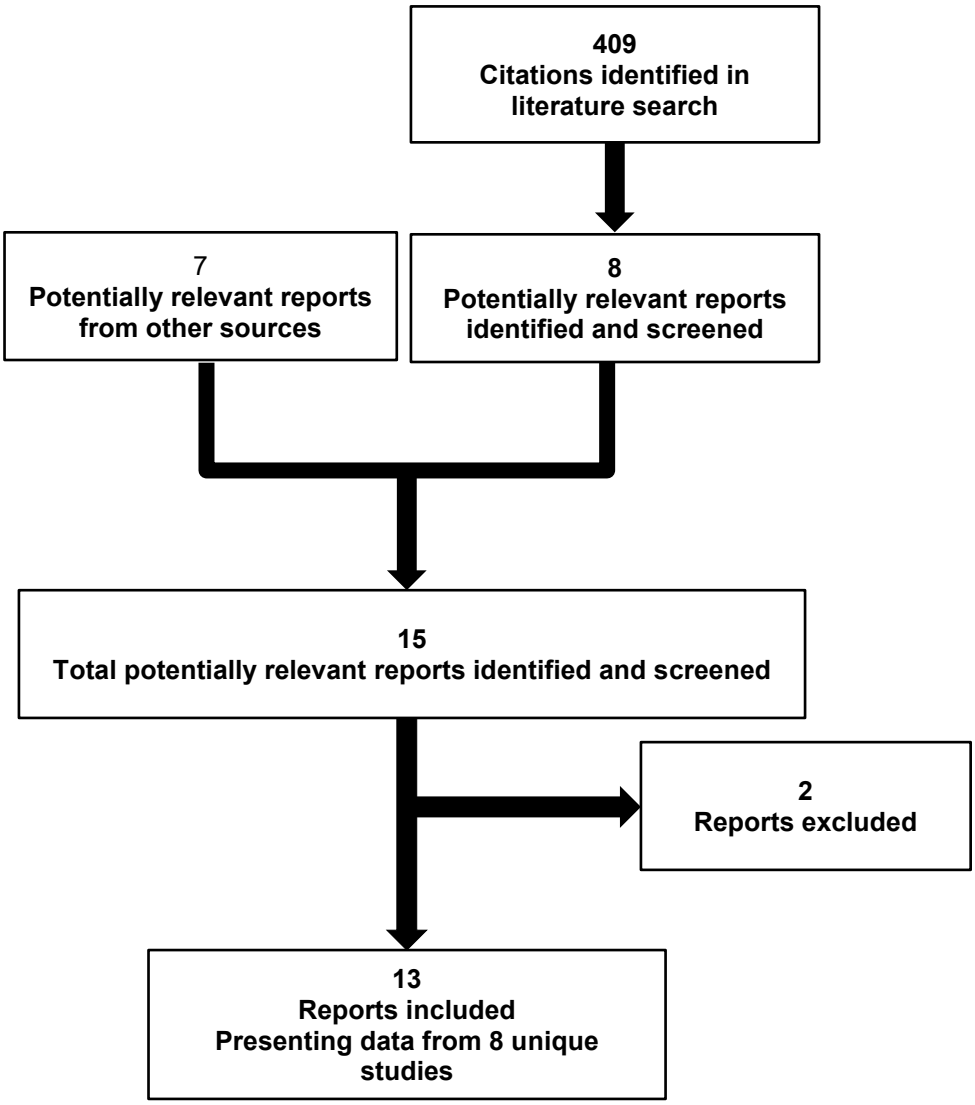

Table 4: Details of Included Randomized Controlled Trials

		FORWARD	GMA-BTX-CM-12-545
Designs & Populations	**Study design**	Open-label RCT	Double-blind RCT
	Locations	US	US
	Randomized, N	282	52
	Inclusion criteria	• Adult patients (between 18 and 65 years of age) • History of CM diagnosed according to ICHD-III beta • ≥ 15 headache days in a 28-day period (headaches that last more than 4 hours and/or require treatment with prescription medication) • Patients using medication(s) with a known headache prophylactic effect were included, if in the opinion of the investigator, the dose has been stable, and the medication(s) has been well tolerated for at least 12 weeks prior to screening and the patient was willing to maintain at a stable dose and dosage regimen during the study [redacted]	• Adult patients (between 18 and 65 years of age) • Medical history of CM for at least 6 months prior to week −4 [redacted]
	Exclusion criteria	• Was taking opioid-containing products for acute-headache treatment more than 8 days during the 28-day run-in period • Previous treatment with botulinum toxin of any serotype for any reason • Previous treatment with topiramate for any reason • History of acute myopia or increased intraocular pressure • Diagnosis of myasthenia gravis, Eaton–Lambert syndrome, amyotrophic lateral sclerosis or any other significant disease that might interfere with neuromuscular function • Acupuncture, transcutaneous electrical stimulation, cranial traction, dental splints for headache, or injection of anesthetics/steroids in the 4 weeks prior to screening [redacted]	• Conditions causing chronic facial pain such as temporomandibular disorder and fibromyalgia • Use of headache prophylaxis medication within 4 weeks of the screening visit • Diagnosis of myasthenia gravis, Eaton–Lambert syndrome, amyotrophic lateral sclerosis • Previous use of any botulinum toxin of any serotype for any reason • Skin infections or acne that would interfere with the injection sites • Acupuncture, transcutaneous electrical nerve stimulation, cranial traction, dental splints for headache, nociceptive trigeminal inhibition, occipital nerve block treatments, or injection of anesthetics/steroids within 4 weeks of screening
Drugs	**Intervention**	155 U intramuscular Ona A, as 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas repeated every 12 weeks	Ona A 155 U total dose per treatment injected into specified head and neck muscles on day 1 followed by a second treatment at week 12
	Comparator(s)	Topiramate administered orally at doses starting at 25 mg/day given once daily and titrated up to 100 mg/day (administered in 2 divided doses) given over 4 weeks, starting with an initial dose of 25 mg/day for the first week	Placebo (normal saline) injected into specified head and neck muscles on day 1 followed by a second treatment at week 12

		FORWARD	GMA-BTX-CM-12-545
Duration	**Phase**		
	Run-in	4 weeks	4 weeks
	Double-blind	NA	24 weeks
	Washout	NA	NA
	Crossover	Patients receiving topiramate could cross over to receive Ona A, while patients receiving Ona A were exited from the study	NA
	Open label	36 weeks	NA
	Follow-up	12 weeks	NA
Outcomes	**Primary End Point**	≥ 50% decrease from baseline in the frequency of headache days per 28-day period at week 32	Change from baseline in the ACM-I total score
	Other End Points	**Secondary outcome measures:** • Change from baseline in the frequency of headache days per 28-day period • Change from baseline in total HIT-6 score per 28-day period • Proportion of patients with a ≥ 70% decrease from baseline in the frequency of headache days per 28-day period **Other outcomes:** [redacted] • Reduction from baseline in the total days of acute headache pain medication use [redacted] • Change from baseline in PHQ-9 quick depression assessment score per 14-day period [redacted] • Change from baseline in WPAI-SHP score per 7-day period • Safety	• Change from baseline in the ACM-S domain scores: SSS and SES • Change from baseline in the ACM-I domain scores: ADL-I, EMO-I, WS-I, SOC-I, LEA-I, HOS-I, ENE-I, COG-I, and GEN-I • Change from baseline in the MSQ • Change from baseline in the HIT-6 • Safety
Notes	**Publications**	None	None

ACM-I = Assessment of Chronic Migraine Impacts; ACM-S = Assessment of Chronic Migraine Symptoms; ADL-I = Activities of Daily Living Impact; CM = chronic migraine; COG-I = Cognitive Impact; EMO-I = Emotions Impact; ENE-I = Energy Impact; GEN-I = General Impact; HIT-6 = six-item Headache Impact Test; LEA-I = Leisure Activities Impact; HOS-I = Household Activities Impact; MIBS-4 = Migraine Interictal Burden Scale; MSQ = Migraine-Specific Questionnaire; NA = not applicable; Ona A = onabotulinumtoxinA; PHQ-9 = Patient Health Questionnaire; SES = Symptom Experience Score; SOC-I = Social Impact; SSS = Symptom Severity Score; U = Allergan units; WPAI-SHP = Work Productivity and Activity Impairment Questionnaire – Specific Health Problem; WS-I = Work/School Impact.

Note: One additional report was included (CADTH Common Drug Review submission[31]).

Sources: Clinical Study Reports for FORWARD and GMA-BTX-CM-12-545 studies.[21,22]

Table 5: Details of Included Single-Arm Trials

		COMPEL	REPOSE	Negro et al. (2015) (155 U)	Negro et al. (2016) (195 U)
Designs and Populations	**Study design**	Prospective, open-label, single-arm trial	Prospective, open-label, single-arm trial	Prospective, open-label, single-arm trial	Prospective, open-label, single-arm trial
	Locations	Australia, Republic of Korea, and US	Germany, Italy, Norway, Russia, Spain, Sweden, and UK	Italy	Italy
	Randomized/ enrolled (N)	716	641	155	172
	Inclusion criteria	• Adults aged ≥ 18 years • Diagnosis of CM (≥ 15 days per month with headache lasting 4 hours a day or longer with or without medication overuse history)[a] • Patients not taking oral headache prophylaxis medication must have discontinued their oral prophylaxis ≥ 4 weeks prior to visit 1(the screening visit happened at −4 weeks) • For patients who were taking oral headache prophylaxis medication, patient must have been on a stable dose and regimen of a single oral prophylaxis treatment for at least 4 weeks prior to visit 2 (which took place 4 weeks after visit 1) and it was day 1, when first treatment provided, which was also defined as baseline)	• Adult patients who are prescribed Ona A for CM symptom relief	• Adult patients with CM • Patients overused acute pain medications during the one-month baseline period (Medication overuse was defined as simple analgesics intake for ≥ 15 days, or other medication classes or combination of multiple drug classes for ≥10 days, taken at least 2 days per week or more.) • Patients with criteria for MOH who had failed one or more withdrawal attempts • Patients who had received and failed other preventive therapies due to lack of efficacy or intolerable side effects	
	Exclusion criteria	• Diagnosis of myasthenia gravis, Eaton–Lambert syndrome, or amyotrophic lateral sclerosis • Headache attributed to another disorder • Infection or skin disorder at injection sites • Previous treatment with botulinum toxin of any serotype for any reason • Anticipated need for botulinum toxin of any	• Had received any botulinum toxin serotype within the previous 26 weeks • Currently participating in the Ona A CM Post-Authorisation Safety Study • Treatment with Ona A is contraindicated per the prescribing information	NR	NR

		COMPEL	REPOSE	Negro et al. (2015) (155 U)	Negro et al. (2016) (195 U)
		type for any reason during the course of the study • Previous participation in any botulinum toxin clinical trial • Had severe major depressive disorder or suicidal ideation			
DRUGS	**Intervention**	155 U intramuscular Ona A, as 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas repeated every 12 weeks	155 U Ona A, as 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas repeated every 3 months (at the investigator's discretion, dose can be increased by an additional 40 U using a "follow the pain" method) repeated every 12 weeks	155 U intramuscular Ona A, as 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas repeated every 3 months (± 1 week)	195 U intramuscular Ona A for 39 sites
	Comparator(s)	None	None	None	155 U intramuscular Ona A from Negro et al. (2015)[24]
DURATION	**Phase**				
	Run-in	4 weeks	NR	1 month	1 month
	Double-blind	NA	NA	NA	NA
	Washout	NA	NA	NA	NA
	Crossover	NA	NA	NA	NA
	Open label	108 weeks	2 years including follow-up	2 years	2 years
	Follow-up	0		NR	NR
OUTCOMES	**Primary end point**	• Change from baseline in the frequency of headache days at week 108			
	Other end points	• Change from baseline in the frequency of headache days at week 60 • Change from baseline in HIT-6 questionnaire total score at week 60 and week 108 [redacted]	• MSQ • EQ-5D-3L • Headache day frequency • Admission to hospital for headache • Safety	• Headache days • Migraine days • Acute pain medication intake • HIT-6 • Safety	• Headache days • Migraine days • Acute pain medication intake • HIT-6 • Safety

		COMPEL	REPOSE	Negro et al. (2015) (155 U)	Negro et al. (2016) (195 U)
		[redacted] • Safety			
Notes	**Publications**	Blumenfeld et al.[32]	Davies et al.[33]	Negro et al.[24]	Negro et al.[25]

CM = chronic migraine; EQ-5D-3L = EuroQoL 5-Dimensions 3-Levels questionnaire; HIT-6 = six-item Headache Impact Test; MOH = medication overuse headache; MSQ = Migraine-Specific Quality of Life Questionnaire; NR = not reported; Ona A = onabotulinumtoxinA; U = Allergan units.

[a] Medication overuse was defined as the frequency of use of abortive headache pain medication(s) during the baseline period. Criteria for medication overuse: ≥ 15 days per 1-month period and at least 2 days per week for any simple analgesic intake, or ≥ 10 days per 1-month period and at least 2 days per week for intake within a category for at least 1 category among ergotamines, triptans, opioids, and combination analgesic medications or for such intake combined across at least 2 categories among ergotamines, triptans, analgesics (including simple and combination analgesic medication) and opioids.

Note: One additional report was included (CADTH Common Drug Review submission[31]).

Sources: Blumenfeld et al.,[32] Blumenfeld et al.,[34] Negro et al.,[24] Negro et al.,[25] Davies et al.,[33] and Clinical Study Reports for COMPEL and REPOSE studies.[23,35]

Included Studies

Description of Studies

Eight studies were included in this report. As part of the resubmission, the manufacturer provided CADTH with four RCTs and four single-arm trials. Of the included studies, 10-001AL[36,37] and 12-001AL[38] will not be discussed in detail in this report because, after a thorough assessment, it was found that they did not provide evidence that could be used to address research gaps identified by CDEC due to limitations associated with their design (patients enrolled in study 10-001AL received only one treatment cycle of Ona A, making the duration of treatment shorter than that reported in the PREEMPT trials, and study 12-001AL compared Ona A with Ona A plus topiramate, which is not a comparison of interest for this review) and small sample size (only 20 patients were enrolled in each study). Data from two RCTs (FORWARD[22] and GMA-BTX-CM-12-545[21]) and four single-arm trials (COMPEL,[32] REPOSE,[33] Negro et al. [2015][24] and Negro et al. [2016][25]) are reported in detail in the current report.

The FORWARD trial (N = 282) was a prospective, multi-centre, randomized, open-label, parallel-group study that evaluated the efficacy, safety, and tolerability of Ona A versus topiramate in adult patients with CM. The study consisted of a pre-treatment period lasting four weeks, a treatment period with Ona A or topiramate lasting up to 36 weeks, and a post-treatment follow-up period lasting 12 weeks (for patients receiving Ona A). The pre-treatment period consisted of a screening visit that occurred within six weeks prior to day 1 and a prospective 28-day run-in period. The prospective run-in period began as soon as the patient completed the screening procedures. Patients who completed the run-in period and met the pre-specified entry criteria were randomly assigned on day 1 in a 1:1 ratio to receive Ona A 155 U administered approximately every 12 weeks intramuscularly as 31 fixed-site, fixed-dose injections across seven specifically defined head and neck muscle areas, or topiramate administered orally at dosages of up to 100 mg/day (minimum 50 mg/day), until week 36 or early discontinuation. Randomization was not stratified. All

patients who were randomly assigned to receive treatment with Ona A or topiramate remained in the study until week 36. However, patients who discontinued topiramate treatment for any reason at any time up to or including week 36 were permitted to cross over to receive treatment with Ona A for the remainder of the study. The first Ona A treatment was administered at the next scheduled office visit, and the patient returned every 12 weeks up to and including week 36 visit (for a maximum of three Ona A treatment sessions during the course of the study) to receive Ona A treatments, with a final exit visit at week 48. Ona A treatment could have been initiated during the topiramate dose-tapering period. Therefore, including the six-week baseline period, a patient could have remained in the study for a maximum of 54 weeks. Patients were required to maintain a daily electronic headache diary (e-diary) during the entire study period (i.e., from screening visit to exit visit). The number of headache days during the first 28 continuous days of the run-in period served as the baseline for calculating change from baseline for 28-day periods subsequent to each study visit.

Study GMA-BTX-CM-12-545, hereafter referred to as Study 545 (N = 52), was a multi-centre, randomized, double-blind, placebo-controlled study of adult patients with CM. Patients were randomly assigned [redacted] to receive either Ona A 155U or placebo. [redacted] The objective of this study was to collect preliminary data on the usefulness of the Assessment of Chronic Migraine Impacts (ACM-I) questionnaire [redacted] in assessing the impact and patient-treatment benefit of Ona A 155 U in adult patients with CM. A total dose of 155 U of Ona A or placebo was administered intramuscularly as [redacted] injections across [redacted] specifically defined head and neck muscle areas. [redacted] A second treatment session was conducted at week 12. [redacted]

The COMPEL study (N = 716) was a single-arm, open-label, multi-centre, prospective study of Ona A use in CM patients for headache prophylaxis. During each of the nine treatment sessions, each patient received 155 U of Ona A administered as 31 fixed-site, fixed-dose intramuscular injections across seven specific head and neck muscle areas. Each patient was followed for 112 weeks (a four-week run-in period and a 108-week open-label interventional period). Patient diary data were collected daily for 28 days following the screening visit (i.e., during the run-in period). Patient diaries were completed through an interactive voice response system (IVRS).

The REPOSE study (N = 641) was a single-arm, open-label, multi-centre, prospective study in patients with CM who have been prescribed Ona A. Each patient was to be observed for 24 months. A total dose of 155 U of Ona A was administered intramuscularly as 31 fixed-site, fixed-dose injections across seven specifically defined head and neck muscle areas. At the investigator's discretion, the dose could be increased by an additional 40 U using a "follow the pain" method. Consecutive patients for whom the physician decided to prescribe Ona A, and who had not received treatment with any botulinum toxin serotype in the last 26 weeks, were considered for inclusion in this study at the baseline visit. All procedures were

performed at the discretion of the participating physicians according to their clinical judgment and the local standard of medical care.

Negro et al. (2015) (N = 155) and Negro et al. (2016) (N = 173) were single-arm, open-label, multi-centre, prospective studies of patients with CM and comorbid MOH. Both studies evaluated the long-term efficacy and safety of Ona A over a two-year period. Patients enrolled in Negro et al. (2015) received 155 U of Ona A administered as 31 fixed-site, fixed-dose intramuscular injections across seven specific head and neck muscle areas. Patients enrolled in Negro et al. (2016), received 195 U of Ona A for 39 sites, where 155 U of Ona A was administered intramuscularly as 31 fixed-site, fixed-dose injections across seven specifically defined head and neck muscle areas and additional 40 U were administered using a "follow the pain" strategy in eight additional sites across three head and neck muscles. In both studies, treatment was administered every three months (± one week). Baseline data were collected from patients' headache diary entries for the month previous to starting Ona A.

Populations

Inclusion and Exclusion Criteria

The FORWARD study enrolled males or females 18 to 65 years of age with a medical history of CM, diagnosed according to the adult CM diagnostic criteria listed in ICHD-III. Patients must have had 15 or more headache days during the 28-day run-in period, with each headache day consisting of either or both of the following criteria: a total of four or more hours of headache and/or headache of any duration with the use of prescription migraine-specific acute-headache medication(s). Patients using medication(s) with a known headache preventive effect may have been included if, in the opinion of the investigator, the dose was stable, the medication(s) was well tolerated for at least 12 weeks prior to screening, and the patient was willing to maintain at a stable dose and dosage regimen during the study. Also patients had to have the ability to follow study instructions (including compliance with a daily e-diary and patient-reported outcome measures) and be likely to complete all required visits in order to be enrolled. Patients were excluded if they were taking opioid-containing products for acute-headache treatment for more than eight days during the 28-day run-in period, had an uncontrolled or unstable medical condition other than CM, received previous treatment with botulinum toxin or topiramate, or if they had a current diagnosis confirmed by the investigator of any headache disorder other than CM. Patients were also excluded if they were not in the run-in period for at least four weeks (28 continuous days) or did not record a minimum of 20 days worth of e-diary data.

Study 545 enrolled males or females 18 to 65 years of age with a medical history of CM for at least six months prior to week −4. Patients were required to have had 15 or more headache days during the four-week baseline screening period, with each headache day consisting of four or more hours of continuous headaches, and at least 50% of baseline headache days being migraine or probable migraine days, and at least four distinct headache episodes each lasting at least four hours. Patients were excluded if they had [redacted] concurrent chronic pain condition, use of headache prophylaxis medication within four weeks of the screening visit, and received previous treatment with botulinum toxin. [redacted]

The COMPEL study enrolled male or female patients who were at least 18 years of age with a diagnosis of CM (defined as ≥ 15 days per month with headache lasting four hours a day or longer) with or without medication overuse. Medication overuse was defined as the frequency of use of abortive headache pain medication(s) during the baseline period. [redacted] Patients who were not taking oral headache prophylaxis medication must have discontinued their oral prophylaxis at least four weeks prior to the first visit (defined as the screening visit that occurred at −4 weeks). For patients who were taking oral headache prophylaxis medication, the patient must have been on a stable dose and regimen of a single oral prophylaxis treatment for at least four weeks prior to the second visit (defined as the baseline visit on day 1, when the first treatment was provided). Patients also had to have the ability to follow study instructions (including compliance with a diary) and be likely to complete all required visits in order to be enrolled. Documentation of ≥ 15 days of headache per month with headache lasting four hours a day or longer by IVRS patient diary was required. [redacted] Patients were excluded if they had any medical condition that might have put the patient at increased risk of exposure to Ona A; [redacted] headache attributed to another disorder; severe major depressive disorder; presence of infection or skin disorder at injection sites; and previous exposure to any botulinum toxin. [redacted]

The REPOSE study enrolled male or female adult patients who were prescribed Ona A for the symptomatic treatment of CM. Patients were excluded if they received any botulinum toxin serotype in the previous 26 weeks or were concurrent participants in Allergan's Ona A Chronic Migraine Post-Authorisation Safety Study.

The two Negro et al. 2015 and Negro et al. 2016 studies enrolled adult patients affected by CM with MOH who had failed one or more withdrawal attempts, and who had received and failed other preventive therapies for CM due to lack of efficacy or intolerable side effects. All patients were allowed to take other preventive oral medications during treatment with Ona A. During the one-month baseline period, all patients overused acute pain medications, which were defined as intake of simple analgesics intake on at least 15 days, or intake of other medication types or combination of types for at least 10 days, with intake for at least two days/week from the category of overuse.

Baseline Characteristics

In the FORWARD study, overall patient demographics were generally well-balanced between the Ona A and topiramate treatment groups at baseline; however, there were some imbalances with respect to concomitant medications. Patients were 18 to 65 years of age (mean, 39.8 years), [redacted], and 81.2% were white. The majority (84.8%) of patients were female. The average number of headaches over 28 days was 22.1 and 21.9 in the Ona A and topiramate treatment groups respectively. [redacted]

[redacted] Headache prophylactic treatment was used in approximately 18% of patients at baseline, and it appeared to be balanced between-treatment groups.

Table 6 presents the baseline characteristics.

In Study 545, no imbalances were noted between-treatment groups with regard to demographic variables. The mean age of patients in each treatment group was similar at approximately 43 years, and the majority of patients were female, at approximately 85% of patients in each group. [redacted] The Migraine-Specific Quality of Life Questionnaire (MSQ) scores for subscales role function-restrictive (RR), role function-preventive (RP), and emotional function (EF) were higher in the placebo group than in the Ona A treatment group. [redacted]

In the COMPEL study, patients [redacted] (mean, 43.0 years), 81.3% were white, and the majority of patients were female (84.8%). The mean time since onset of CM was 10.6 years and the mean age of onset was 32.5 years. A majority of patients had a family history of migraine (62.7%). At baseline, the average number of headache days was 22.0, and the average number of moderate/severe headache days was 18.0. At baseline, 89.2% of patients were using acute headache pain medications. The most frequently used (> 20%) acute-headache medications were triptans (53.5%), simple analgesics (45.7%), and combination analgesics (31.4%). A total of 63.7% were overusing acute headache pain medications (i.e.. taking the medication at least twice a week in any week with at least five diary days during the baseline period). The most frequently overused (> 20%) acute-headache medications were triptans for > 10 days (27.1%). [redacted]

Table 7 presents the baseline characteristics.

In the REPOSE study, patients were 18 to 79 years of age (mean, 45.4 years), and the majority of patients were female (85.3%). MOH was reported in 229 patients (36.2%). The mean age of onset of headache was 18.2 ± 9.9 years. The median time since diagnosis of CM was two years, and the average was 5.6 years. Sumatriptan and ibuprofen, the most frequently used acute medications, were used by 24.0% and 19.4% of patients, respectively. A headache prophylaxis was used at baseline by 49.6% of the patients.

Topiramate, the most frequently reported prophylactic medication, was used by 16.9% of the patients. Table 7 presents the baseline characteristics.

In Negro et al. (2015) and Negro et al. (2016) the majority of patients were female (81.8% and 79.7%, respectively), with a mean age of 43.2 years (range 18 to 76) and 44.9 years (range 18 to 78), respectively. The average time from CM onset was 10.2 years (range 1 to 40 years) in Negro et al. (2015), and 9.3 years (range 1 to 40) in Negro et al. (2016). The average number of headache days was 22.3 and 22.2 in Negro et al. (2015) and Negro et al. (2016), respectively. The percentage of patients who had a severe score on the six-item Headache Impact Test (HIT-6) (≥ 60) was 93.9% and 95.8% in Negro et al. (2015) and Negro et al. (2016. Table 7 presents the baseline characteristics.

Table 6: Summary of Baseline Characteristics in FORWARD and GMA-BTX-CM-12-545 Trials

	FORWARD			GMA-BTX-CM-12-545	
	Ona A 155U (N = 140)	Topiramate (N = 142)	[redacted]	Ona A 155U (N = 19)	Placebo (N = 26)
Age (years)					
Mean (SD)	40.2 (11.7)	39.4 (12.6)	[redacted]	43.7 (13.1)	42.2 (11.8)
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min to max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)					
Male	23 (16.4)	20 (14.1)	[redacted]	3 (15.8)	3 (11.5)
Female	117 (83.6)	122 (85.9)	[redacted]	16 (84.2)	23 (88.5)
Race, n (%)					
White	111 (79.3)	118 (83.1)	[redacted]	[redacted]	[redacted]
Black	13 (9.3)	8 (5.6)	[redacted]	[redacted]	[redacted]
Asian	4 (2.9)	2 (1.4)	[redacted]	[redacted]	[redacted]
Hispanic	11 (7.9)	12 (8.5)	[redacted]		
Other	1 (0.7)	2 (1.4)	[redacted]	[redacted]	[redacted]
Use of headache prophylactic treatment(s), n (%)	26 (18.6)	25 (17.6)	[redacted]	[redacted]	[redacted]
Prior use of headache prophylactic treatment(s), n (%)	NR	NR	[redacted]	[redacted]	[redacted]
Time since onset of chronic migraine (years)	NR	NR	[redacted]	[redacted]	[redacted]
Number of headaches over 28 days, mean (SD)	22.1 (4.6)	21.9 (4.8)	[redacted]	[redacted]	[redacted]
Number of migraines over 28 days	NR	NR	[redacted]	[redacted]	[redacted]
Concomitant medications (opioids), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant medications (non-opioids), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain medication intake days, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HIT-6 total score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSQ – role function-restrictive, Mean (SD)	NR	NR	[redacted]	39.8 (16.6)	40.9 (21.7)
MSQ – role function-preventive, Mean (SD)	NR	NR	[redacted]	58.9 (18.8)	62.5 (23.0)

	FORWARD			GMA-BTX-CM-12-545	
	Ona A 155U (N = 140)	Topiramate (N = 142)	[redacted][a]	Ona A 155U (N = 19)	Placebo (N = 26)
MSQ – emotional function, mean (SD)	NR	NR	[redacted]	53.3 (27.6)	58.7 (23.9)

HIT-6 = six-item Headache Impact Test; max = maximum; min = minimum; MSQ = Migraine-Specific Quality of Life Questionnaire; NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation; U = Allergan units.

[a] Topiramate to Ona A is a subgroup of patients who initially received topiramate and switched to Ona A. Patients could be both in topiramate and topiramate to Ona A groups.

Sources: Clinical Study Reports for FORWARD and GMA-BTX-CM-12-545.[21,22]

Table 7: Summary of Baseline Characteristics in the Included Single-Arm Trials

	COMPEL	REPOSE	Negro et al. (2015)[a]	Negro et al. (2016)[a]
	Ona A 155 U (N = 716)	Ona A 155 U or 195 U (N = 633)	Ona A 155 U (N = 132)	Ona A 195 U (N = 143)
Age (years)				
Mean (SD)	43.0 (11.3)	45.4 (11.7)	43.2 (13.5)	44.9 (12.7)
Min to max	[redacted]	18 to 79	18 to 76	18 to 78
Female, n (%)	607 (84.8)	540 (85.3)	108 (81.8)	114 (79.7)
Race, n (%)				
Caucasian	582 (81.3)	NR	NR	NR
Asian	89 (12.4)	NR	NR	NR
African-American/black	41 (5.7)	NR	NR	NR
Other	4 (0.6)	NR	NR	NR
Age of onset of chronic migraine (years), mean (SD)	32.5 (13.7)	NR	NR	NR
Time since onset of chronic migraine (years) , mean (SD)	10.6 (11.0)	NR	10.2 (4.8)	9.3 (5.1)
Time since diagnosis of chronic migraine (years), mean (SD)	NR	5.6 (8.0)	7.6 (4.3)	8.4 (4.7)
Family history of migraine, n (%)	449 (62.7)	NR	NR	NR
Severity of pain during headache, n (%)				
Mild	3 (0.4)	NR	NR	NR
Moderate	296 (41.3)	NR	NR	NR
Severe	417 (58.2)	NR	NR	NR
Mean (SD) headache days	22.0 (4.8)[b]	20.6 (5.4)	22.3 (4.1)	22.2 (4.9)
Mean (SD) moderate or severe headache days	18.0 (5.7)[b]	NR	NR	NR
Mean (SD) HIT-6 total score	64.7 (4.8)[c]	NR	68.9 (4.3)	67.9 (4.2)
Patients with severe HIT-6 score, n (%)	NR	NR	124 (93.9)	137 (95.8)
MSQ – role function-restrictive, mean (SD)	[redacted]	36.4 (17.4)	NR	NR
MSQ – role function-preventive, mean (SD)	[redacted]	51.0 (21.7)	NR	NR
MSQ – emotional function, mean (SD)	[redacted]	42.7 (25.2)	NR	NR
Mean (SD) migraine days	NR	NR	21.4 (4.3)	21.6 (4.8)
Diagnosis of medication overuse headache, n (%)	NR	229 (36.2)[d]	132 (100)	143 (100)
Pain medication intake days, mean (SD)	NR	NR	20.8 (4.5)	21 (5.1)
Acute headache pain medication use, n (%)	639 (89.2)[e]	NR	132 (100)	143 (100)

	COMPEL	REPOSE	Negro et al. (2015)[a]	Negro et al. (2016)[a]
	Ona A 155 U (N = 716)	Ona A 155 U or 195 U (N = 633)	Ona A 155 U (N = 132)	Ona A 195 U (N = 143)
Triptans	383 (53.5)	NR	NR	NR
Simple analgesics	327 (45.7)	NR	NR	NR
Combination analgesics	225 (31.4)	NR	NR	NR
Opioids	117 (16.3)	NR	NR	NR
Ergotamines	53 (7.4)	NR	NR	NR
Acute headache pain medication overuse, n (%)	456 (63.7)[e,f]	262 (41.4)	132 (100)	143 (100)
Triptans (≥ 10 days)	194 (27.1)	NR	NR	NR
Combination analgesics (≥ 10 days)	88 (12.3)	NR	NR	NR
Simple analgesics (≥ 15 days)	79 (11.0)	NR	NR	NR
Opioids (≥ 10 days)	38 (5.3)	NR	NR	NR
Ergotamines (≥ 10 days)	18 (2.5)	NR	NR	NR

HIT-6 = six-item Headache Impact Test; max = maximum; min = minimum; MSQ = Migraine-Specific Quality of Life Questionnaire; NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation; U = Allergan units.

[a] Baseline data are drawn from the previous month before starting Ona A.

[b] Headache days per 28 days in the analysis population (n = 715); includes 25 patients who reported < 15 headache days per 28 days at baseline

[c] In the analysis population (n = 715).

[d] Includes any diagnosis of medication overuse, rebound, or analgesic-overuse headache, based on the treating physician's clinical judgment.

[e] Data from patients with ≥ 20 days of data in their patient diary.

[f] To qualify for acute headache pain medication overuse, a patient had to take this type of medication at least twice a week in any week with at least 5 diary days during the baseline period.

Sources: Blumenfeld et al.,[32] Blumenfeld et al.,[34] Negro et al.,[24] Negro et al.,[25] Davies et al.,[33] Clinical study reports for COMPEL and REPOSE studies.[23,35]

Reprinted and (modified) from Springerplus, Negro A, Curto M, Lionetto L, Crialesi D, Martelletti P. OnabotulinumtoxinA 155 U in medication overuse headache: a two years prospective study. 2015;4:826. Creative Commons Attribution License 4.0. http://creativecommons.org/licenses/by/4.0/legalcode. Modified by compiling data from Table 2.

Reprinted and (modified) from The Journal of Headache and Pain, Negro A, Curto M, Lionetto L, Martelletti P. A two years open-label prospective study of OnabotulinumtoxinA 195 U in medication overuse headache: a real-world experience. 2016;17:1.Creative Commons Attribution License 4.0. http://creativecommons.org/licenses/by/4.0/legalcode. Modified by compiling data from Table 2.

Interventions

In the FORWARD trial, Ona A was administered at day 1, week 12 ± 7 days, and week 24 ± 7 days at a dose of 155 U administered as 31 fixed-site, fixed-dose intramuscular injections across seven specific head and neck muscle areas. Patients randomly assigned to the topiramate group received up to 36 weeks of topiramate administered orally at doses starting at 25 mg/day given once daily and titrated in weekly increments of 25 mg/day until a dose of 100 mg/day was reached. (A stable topiramate dose of at least 50 mg/day [maximum 100 mg/day] was required.) Patients continued to receive daily doses of topiramate until week 36 or early discontinuation (with dose-tapering to commence at the time of discontinuation). Patients may have used medication(s) with a known headache preventive effect if, in the opinion of the investigator, the dose was stable and the medication(s) were well tolerated for at least 12 weeks before screening. Any medication with a known headache-preventive effect used by the patient was to be maintained at a stable dose and dosage regimen during the study. Patients could also take prescription or over-the-counter acute headache pain medications as prescribed and/or directed by the investigator. Any concurrent medication was maintained at a stable dose and dosage regimen during the study. All study drugs were to be used in accordance with the protocol

and package insert by patients under the direct supervision of an investigator. [redacted]
Administration of botulinum toxin of any serotype or topiramate for any indication during the study was prohibited, except as directed by the study.

In Study 545, 155 U of Ona A or placebo was administered at day 0 and at week 12 during the double-blind phase. [redacted]

In COMPEL study, 155 U Ona A was administered every 12 weeks for nine treatment sessions. The administration of Ona A was similar to that described in the FORWARD trial. For patients who were taking oral headache prophylaxis medication, the patient must have been on a stable dose and regimen of a single oral prophylaxis treatment for at least four weeks prior to visit 2 (day 1, treatment 1). For patients not on oral headache prophylaxis at visit 2, a single oral headache prophylaxis medication [redacted] may have been added to the patient's regimen as a component of headache prevention at or after visit 4 (week 24). For patients on a stable dose and regimen of a single oral headache prophylaxis medication for at least four weeks prior to visit 2, the dose may have been changed at or after visit 4 (week 24). [redacted]

In the REPOSE study, a total dose of 155 U of Ona A was administered intramuscularly as 31 fixed-site, fixed-dose injections across seven specifically defined head and neck muscle areas. At the investigator's discretion, the dose could be increased by an additional 40 U using a "follow the pain" method, in which, if there was a predominant pain location(s), additional injections to one or both sides could be administered in up to three specific muscle groups (occipitalis, temporalis, and trapezius), up to the maximum dose per muscle. Patients received Ona A injections approximately every three months up to 13 times. Medications that had been prescribed for headache prophylaxis and/or for acute treatment of headaches in the 26 weeks prior to the baseline visit were documented. Any changes in prophylactic and/or acute-headache medications were documented at subsequent (follow-up) visits. Ona A treatment was administered by physician trained in the PREEMPT injection paradigm.

In Negro et al. (2015), patients received 155 U of Ona A administered as 31 fixed-site, fixed-dose intramuscular injections across seven specific head and neck muscle areas. Patients enrolled in Negro et al. (2016), received 195 U of Ona A for 39 sites, where 155 U

of Ona A was administered intramuscularly as 31 fixed-site, fixed-dose injections across seven specifically defined head and neck muscle areas and additional 40 U were administered using a “follow the pain” strategy in eight additional sites across three head and neck muscles. In both studies, treatment was administered every three months (± one week). Patients in both studies were allowed to take preventive oral medication during treatment with Ona A. Ona A was administered by physicians who had received proper training as an injector, and the same physician followed each patient over the two years.

Outcomes

In the FORWARD trial, the primary efficacy end point was the proportion of patients with decrease from baseline of at least 50% in the frequency of headache days per 28-day period at the primary time point of week 32 (defined as the 28-day period ending with week 32).

The secondary end points included the following:

- change from baseline in the frequency of headache days per 28-day period
- change from baseline in total HIT-6 score per 28-day period
- proportion of patients with a ≥ 70% decrease from baseline in the frequency of headache days per 28-day period.

Exploratory end points included the following:

[redacted]

- reduction from baseline in the total days of acute headache pain medication use

[redacted]

- [redacted]
- change from baseline in the nine-item Patient Health Questionnaire (PHQ-9) quick depression assessment score per 14-day period

[redacted]

- change from baseline in Work Productivity and Activity Impairment Questionnaire – Specific Health Problem (WPAI-SHP) per seven-day period.

In Study 545, the primary efficacy end point was change from baseline in the ACM-I total score. Other efficacy measures were change from baseline in the ACM-I domain scores, the Assessment of Chronic Migraine Symptoms (ACM-S), the MSQ, and HIT-6.

In the COMPEL trial, the primary efficacy end point was the mean change from baseline in the number of headache days for the 28-day period ending at week 108 (following nine treatments). The secondary efficacy measures were the mean change from baseline in the frequency of headache days for the 28-day period ending at week 60 (following 5 treatments), and the mean change from baseline in HIT-6 total score over a four-week period at week 60 and week 108 (following 9 treatments).

[redacted]

[redacted]

- [redacted]

In the REPOSE study, no primary variable was defined. Efficacy measures assessed were change from baseline in MSQ, change from baseline in the EuroQoL 5-Dimensions 3-Levels questionnaire (EQ-5D-3L), change from baseline in patient-reported headache frequency, and health care resource utilization, which was assessed by evaluating admission to hospital for headache.

In the Negro et al. studies, the efficacy measures assessed were headache days, migraine days, and acute-pain medication intake every three months. HIT-6 was assessed every six months.

Refer to Appendix 5 for more information on the validity of the outcome measures described in this section.

Migraine-Specific Quality of Life Questionnaire, version 2.1

Migraine-Specific Quality of Life Questionnaire, version 2.1 (MSQv2.1) is a 14-item instrument that assesses the impact of migraine on a patient's HRQoL across the three role-function domains: RR (seven items assessing how migraines limit one's daily social and work-related activities), RP (four items assessing how migraines prevent these activities), and EF (three items assessing the emotions associated with migraines).[39] Participants respond to the 14 items using a six-point scale: none of the time, a little bit of the time; some of the time; a good bit of the time; most of the time; and all of the time, each of which is assigned a score of 1 to 6. Raw dimension scores are computed as a sum of item responses and are rescaled to a 0-to-100-point scale, producing an overall score for each domain. A higher score indicates better HRQoL.[39] MSQ can also be scored in the reverse fashion, with a lower score indicating higher function. In [redacted] and REPOSE, higher scores indicated better QoL. The reverse-scoring method was used in Study 545, PREEMPT-1, and PREEMPT-2, in which a negative change from baseline indicated improvement and a positive change indicated worsening. Validation of MSQv2.1 has been conducted in patients with CM. The instrument was internally consistent and demonstrated construct validity for this population.[40] One study estimated within-group MCIDs of 10.9, 8.3, and 12.2 for RR, RP, and EF, respectively, in patients with CM.[41] Between-group MCIDs of 3.2, 4.6, and 7.5 for RR, RP, and EF, respectively, were estimated in another study of patients with a maximum of 15 headache days per month.[15]

Headache Impact Test

The Headache Impact Test (HIT) is a web-based, multi-question health assessment that quantifies the impact of headache on a patient's life.[42] Eighty-four possible questions cover topics such as functional health and well-being. HIT-6 is a short form version of HIT, which was developed for practical reasons.[43] Six items (questions) were selected from a pool of 89 questions (54 questions from HIT and 35 questions suggested by clinicians).[43] HIT-6 measures pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress.[44] The patient chooses one of five responses to each question: never, rarely, sometimes, very often, or always, and the responses are assigned 6, 8, 10, 11, or 13 points, respectively. Total HIT-6 scores range from 36 to 78; a higher score indicates a greater impact of the disease on the daily life of the respondent. The scores may be also interpreted using four groupings: A score ≤ 49 points indicates little or no impact, a score of 50 to 55 points indicates some impact, a score of 56 to 59 indicates

substantial impact, and a score ≥ 60 points reflects severe impact.[44] The HIT-6 was also validated in patients with CM, demonstrating internal consistency and construct validity.[45] One study found a between-group MCID of 2.3 points in patients with chronic daily headache.[46] A within-group MCID of 2.5 points and a between-group MCID of −1.5 points were reported in a study of patients with episodic migraine.[47]

Headache and Migraine/Probable Migraine Days

The MCID for reduction in headache and migraine/probable migraine days is unclear. A study found that a one-day increase among patients with mixed types of headache conditions (a majority with CM) was associated with a greater likelihood of headache pain interfering with mood (4.0%, $P < 0.001$), recreational activities (4.0%, $P = 0.004$), or life enjoyment (4.0%, $P = 0.001$).[17] It is unclear which instruments the domains of mood, recreational activities, or life enjoyment were taken from. As well, it is unclear if the domains were selected a priori or if a relationship between headache frequency and the other domains of HRQoL of the three instruments was also tested, found not to be statistically significant, and not reported. Without knowing the scale on which these domains were based, it is difficult to determine if a 4% improvement is clinically meaningful. In addition, the time point and study sample size upon which these results are based are unclear. If it was at the one-year point, a large number of patients (N = 221) had dropped out by then and it is uncertain if data for these patients was imputed or omitted from the final results. No other studies were identified that specifically examined the association between reduction in headache frequency and QoL in patients with CM.

In the FORWARD trial, a headache day was defined as a calendar day (00:00 to 23:59) with four or more hours of headache and/or headache of any duration accompanied by the use of migraine-specific acute-headache medication(s), i.e., ergot alkaloids, ergot combinations, opioids, triptans, or combination analgesics (simple analgesics combined with opioids or barbiturates with or without caffeine). The count of headache days in a 28-day period was derived from the e-diary reports of total duration of all headaches for a given day, and was based on the count of days with a headache lasting at least four hours and/or headache of any duration with the use of migraine-specific acute-headache medication(s). The primary time point was week 32, encompassing the last 28-day period ending with week 32. The number of headache days during the first 28 continuous days of the run-in period served as the baseline for calculating change from baseline for 28-day periods subsequent to each office visit.

In the COMPEL study, a headache day was defined as a day (00:00 to 23:59) for which a patient reported a headache in the patient diary with four or more continuous hours of headache as recorded in IVRS diary. This study assessed change in the outcomes measured at two years (following nine treatments) relative to a patient's baseline levels established during the 28-day baseline period prior to the first injection.

In the REPOSE study, a headache day was defined as a day for which the patient reported a headache lasting longer than four hours. Baseline data were collected at the first visit. It does not appear that patient diaries were used.

The Negro et al. 2015 and Negro et al. 2016 studies did not report how headache days or migraine days were defined. Baseline data were collected from patients' headache diary entries for the month before starting Ona A.

Migraine Interictal Burden Scale

The Migraine Interictal Burden Scale (MIBS-4) measures migraine burden between attacks (i.e., interictal states).[22] Four domains are included in the instrument: impairment in work or school, impairment in family and social life, difficulty making plans or commitments, and emotional and/or affective and cognitive distress. The questionnaire consists of four items, is self-administered and has a total score across domains of 0 to 12, with higher scores representing more severe burden. A score of 0 indicates no burden, 1 to 2 mild, 3 to 4 moderate, and 5 + severe. There was evidence from one abstract that MIBS-4 correlated significantly with MIDAS, PHQ-9, and MSQ in patients with migraine ($P < 0.0001$). An MCID for MIBS-4 was not identified in the literature.

Patient Health Questionnaire Quick Depression Assessment Score

The PHQ-9 quick depression assessment score is a self-administered screening and diagnostic tool.[22] It consists of the nine diagnostic criteria for depressive disorders. Patients are asked to indicate the frequency with which they have been bothered by these nine symptoms over the previous two weeks on a four-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The total score ranges from 0 to 27 (from best to worst). A score of 0-4 represents no or minimal depression, 5-9 mild depression, 10-14 moderate depression,15-19 moderately severe depression and 20-27 severe depression.[48] The PHQ-9 score correlated strongly with the Beck Depression Inventory II (Spearman's rho = 0.754, $P < 0.001$), moderately with Migraine Disability Assessment Scale (MIDAS) (0.377, $P < 0.001$), strongly with HIT-6 (0.519, $P < 0.001$), and strongly with MSQ (−0.538, $P < 0.001$), demonstrating construct validity.[49]

Assessment of Chronic Migraine – Impact and Assessment of Chronic Migraine Symptoms

The ACM-I is a 24-item instrument that examines the effects of CM on a patient's life. Items include daily activities; feelings; energy level; household, leisure, and social activities; and work over the past seven days.[22] The items are rated on a Likert scale of 0 (none of the time) to 5 (all of the time). Item 22 has an additional response option, but was recoded on a 0-to-5 scale for analysis. The total ACM-I score was transformed so that higher scores indicated worse impact of CM. The ACM-S assesses the symptoms of CM and includes the domains of symptom severity and symptom experience. ACM-I and ACM-S were validated in a sample of patients from COMPEL, which is an open-label multi-centre study to examine the long-term efficacy and safety of Ona A in patients with CM.[50] Patients were also administered the MSQ, MIDAS, HIT-6, and the Short Form (36) Health Survey (SF-36). The average age of patients was 43.0 years and most patients were female (84.8%). With respect to validity, the ACM-S was correlated with MSQ and MIDAS, but had lower correlation with other measures, such as HIT-6 and SF-36. Based on MIDAS classification, the ACM-I increased with higher disease severity, suggesting that it has discriminant validity. For reliability, internal consistency was demonstrated with a Cronbach's alpha of > 0.8 for both ACM-I and ACM-S. An MCID for ACM-I or ACM-S was not identified in the literature.

Work Productivity and Activity Impairment Questionnaire – Specific Health Problem

The WPAI-SHP is a self-administered questionnaire to measure impairments in work and activities during the past seven days due to a general or specific health problem.[22] The instrument poses six questions and results in four scores: absenteeism (work time missed),

presenteeism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment or absenteeism plus presenteeism), and activity impairment. The six questions are: Q1 = currently employed; Q2 = hours missed due to health problems; Q3 = hours missed other reasons; Q4 = hours actually worked; Q5 = degree health affected productivity while working (using a 0 to 10 visual analogue scale [VAS]); Q6 = degree health affected productivity in regular unpaid activities (VAS).[51-53] The general form of the WPAI-SHP was validated with a sample of 106 employed individuals who were affected by a symptom or health problem during the seven days prior to recruitment.[52] However, no studies were found that validated the WPAI-SHP in patients with migraine. An MCID for the WPAI-SHP in patients with migraine was not identified in the literature.

EuroQol 5-Dimension 3-Levels Questionnaire

The EQ-5D-3L[54,55] is a generic HRQoL instrument that has been applied to a wide range of health conditions and treatments, including migraine.[56] The first of two parts of the questionnaire is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing “no problems,” “some problems,” and “extreme problems,” respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[54,55] The second part is a 20 cm VAS that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state,” respectively. The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states “dead” and “perfect health,” respectively. Correlation coefficients between EQ-5D-3L utility values and the HIT-6, and the RR, RP, and EF functions of MSQ in patients with CM were −0.42 (strong),[49] 0.50 (strong),[49] 0.55 (strong),[49] and 0.39 (moderate)[49] ($P < 0.0001$), respectively, suggesting that the instrument has construct validity. However, the EQ-5D-3L did not perform as well as the mental and physical components of the SF-36.[57] The MCID for the EQ-5D-3L index score ranges from 0.033 to 0.074 for general use.[58] An MCID specifically for patients with migraine was not identified in the literature.

Health Care Resource Utilization

[redacted]

In the REPOSE study, health care resource utilization was assessed by evaluating admission to hospital for headache.

Harms

Adverse events (AEs) in the form of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), withdrawals due to adverse events, and notable AEs (i.e., AEs of particular interest to this review) were reported in both RCTs, and in the COMPEL trial. In the REPOSE trial, adverse drug reactions were reported and defined as a response to a medicinal product that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function. Treatment-related AEs were reported in both Negro et al. trials. Safety and tolerability were evaluated by the incidence and type of TEAEs, SAEs, and patients, with TEAEs leading to discontinuation of study drug.

Statistical Analysis

FORWARD Study

In the FORWARD study, a sample size of 400 patients (200 per treatment group) was planned to provide 90% statistical power to detect an expected treatment difference of 16% at a two-sided significance level of 0.05. This calculation assumed a topiramate responder rate of 28% and an Ona A responder rate of 44% at the primary time point of week 32. A responder was defined as having a ≥ 50% decrease from baseline in the frequency of headache days per 28-day period. The assumed responder rate for Ona A was estimated from the PREEMPT-1 and PREEMPT-2 trials.[59,60] The topiramate responder rate was estimated from published articles by Silberstein et al.[61] and Rothrock et al.[62] [redacted]

All efficacy analyses were conducted by grouping patients according to the treatment they were randomized to receive. The primary and secondary efficacy end points were analyzed on the intention-to-treat (ITT) set. A family-wise error rate was controlled using a hierarchical-testing gatekeeping procedure. The testing began with the primary efficacy end point and continued with the first secondary end point in the ranking order, followed by the next, and so on, in a sequential fashion. If the test of the primary end point showed statistical significance at the (two-sided) 0.05 level, then testing of the next end point in the ranking order was justified; this stepwise process continued for all end points listed in the hierarchical order. However, if no statistical significance was shown at the (two-sided) 0.05 level for the test of any specified end point in the hierarchical order, then that end point and all subsequent end points below this in the ranking order were not considered as indicators of efficacy, but rather considered supportive, regardless of their nominal *P* value. The order for the hierarchical testing was as follows:

- the proportion of patients with a ≥ 50% decrease from baseline in the frequency of headache days
- change from baseline in the frequency of headache days per 28-day period
- change from baseline in HIT-6 score
- the proportion of patients with a ≥ 70% decrease from baseline in the frequency of headache days.

The primary and the secondary end points showed statistical significance at 0.05, and none of the tests failed.

For efficacy analyses, patients who discontinued topiramate and then received Ona A were considered nonresponders and baseline data were used for the remaining study days for the primary and secondary efficacy end points. No adjustments for multiplicity were performed for the exploratory end points.

The primary efficacy analysis scores were analyzed using a logistic regression model, adjusted by the baseline number of headache days as a covariate. A two-sided test with a *P* value ≤ 0.05 was considered as statistically significant. The first secondary efficacy end point (change from baseline in frequency of headache days) was analyzed using analysis of covariance with baseline headache day count as the covariate. The second secondary efficacy end point (change from baseline in HIT-6 score) was analyzed using a nonparametric rank analysis of covariance, with treatment as a factor and adjusting for the baseline value. The third secondary efficacy end point (proportion of patients with a ≥ 70% decrease from baseline in the frequency of headache days) was analyzed using the same methods used to analyze the primary end point (a logistic regression model adjusted by the baseline frequency of headache days).

If the patient reported headache data (either headache days or headache-free days) for at least 20 days but fewer than 28 days in a diary period, the data for counts were prorated accordingly and rounded to the nearest whole number. The prorating was based on the number of days with reported data in that period. For example, if there were 24 days with reported data in a 28-day diary window, the headache day count was multiplied by 28, divided by 24, and rounded to a whole number. If the patient reported total daily headache durations that indicated 16 headache days and eight headache-free days, the patient's standardized counts after prorating would be 19 headache days and nine headache-free days. If a patient reports e-diary data for fewer than 20 days in a 28-day period, the patient's entries for this time period were set to missing.

A baseline observation carried forward (BLOCF) method was utilized to impute missing values for the analyses of all outcomes. This type of imputation replaces the missing value with the baseline value; if a patient had a missing entry for any reason (e.g., discontinuation due to AE, loss to follow-up, lack of efficacy), the baseline value data were utilized and the patient was considered a nonresponder. Patients who discontinued Ona A and those randomized to topiramate who discontinued treatment and subsequently received Ona A were considered nonresponders for the analyses of the primary and secondary outcomes and thus baseline value data were utilized. The BLOCF method was used for missing values for the change from baseline in HIT-6 score and for the patient-reported outcome analyses.

Sensitivity analyses of the primary variable were performed for the ITT set in the following ways:

1. The primary analysis was repeated using Fisher's exact test.

[redacted]

3. The same logistic regression methods but applying the worst observation carried forward imputation method for missing values when there were less than 20 days of reported data in the e-diary. Specifically, this used a patient's worst-case observation within the 28-day period to populate the missing values within that time period.
4. The same logistic regression method was re-calculated on "observed data" (i.e., without imputation for missing counts when there were less than 20 days of reported data).

[redacted]

COMPEL study

The primary end point test of reduction in frequency of headache days in a 28-day period versus no reduction included data collected from every patient in the analysis population (AP). Knowing that the related subgroup analyses for the primary end point would, by definition, be testing mean responses from smaller collections of patients, the required sample size was calculated to power the study for both the primary end point within the AP as well as for the subgroup analyses of the primary end point. The sample size calculation assumed a two-tailed t-test using an alpha = 0.05 with 80% power. Standard deviation of headache day frequency reduction per 28 days was estimated to be 6.59 days based on results of the PREEMPT-1 and PREEMPT-2 trials.[59,60] In the case where the smaller of the two groups in a subgroup analysis was approximately 10.2% of the AP, it was estimated that a sample of approximately 600 patients would be necessary to detect a 2.5-day difference in mean reduction of headache days between subgroups.

[redacted]

[redacted]

If fewer than 28 days of data were recorded in a 28-day diary period, measures of headache frequency and severity and of medication use were prorated. Fractional imputed values remained as fractional headache days. This applied to all diary periods, including the baseline diary period. For patients in the AP, if fewer than 20 days were recorded by the patient using the IVRS diary in a 28-day diary period, imputation methods for the primary end point were implemented as follows: If a patient reported diary data in fewer than 10 days of a 28-day diary period, the number of headache days for the missing period was imputed by a modified last observation carried forward (mLOCF) method. The substitution was the corresponding number of headache days from the patient's previous 28-day diary period (i.e., the last observation) adjusted to match the mean change observed over all fully observed patients in the same time period. Fractional imputed values remained as fractional headache days. If a patient reported diary data for 10 to 19 of the days in a 28-day diary period, the number of headache days for the missing period was imputed by taking the average of two estimates: the estimate obtained using the mLOCF method described above, and the estimate that maintained the same proportion of headache days that were observed over the 10 to 19 days of collected data. Again, fractional imputed values were recorded as fractional headache days. The same imputation method was used for secondary outcomes. [redacted]

REPOSE Study

The REPOSE study planned to enrol 650 patients from approximately 115 participating clinics in Europe, i.e., on average five patients per site. It was estimated that 650 patients were needed to provide enough power for a subgroup-level analysis. Where a country or region with 12 sites and five patients per site will result in 60 patients, a sample size of 60 will have an 86% power to detect a difference in means of −1 headache-related hospital admission days per 90 days (i.e., a reduction from an average of five days at baseline to four days at follow-up), assuming a standard deviation of this difference of 2.5 days, using a paired t-test with a two-sided 0.05 significance level. No primary variable was defined in this study. Changes from baseline (pre- and post-comparison) were tested at the two-sided 5% level using a nonparametric testing procedure (Wilcoxon signed rank test without adjustment). For continuous data, data were analyzed "as is," with no imputation methods employed. For categorical data a category of "missing data" was provided whenever data were missing. A proportion was calculated based on the number of non-missing values if appropriate. If any EQ-5D-3L dimension score was missing, the total EQ-5D-3L score was set to missing. If the answer to one MSQ question was missing, the affected dimension score was set to missing and the total score was set to missing. No adjustments for multiplicity were performed.

Negro et al. Studies

No sample size calculation was reported. Categorical values were reported as patient counts and percentage, and continuous variables were reported as mean ± standard deviation (SD) rates. A chi-square test was used to compare categorical variables. After using Hartley's Fmax test to assess equal variances of data, a paired t-test was used to compare the mean headache days, migraine days, medication intake days, and HIT-6 score at baseline and at each cycle of injections. Only patients who completed the two years of follow-up were included in the analysis and in reporting of adverse events. Whether any imputation method was used to account for missing data were not reported. No adjustments for multiplicity were performed.

The CDR protocol included subgroups by duration of illness, by patients who have failed prior oral prophylactic medications, and by patients who overuse acute headache pain medication versus those who don't. Only the COMPEL study conducted subgroup analysis by previous use of preventive treatment and by history of acute medication overuse at baseline. None of the other studies reported subgroup analysis, and the COMPEL study did not undertake subgroup analysis by duration of illness.

Analysis Populations

Two APs were defined for the FORWARD study. The ITT set included all randomly assigned patients. Analysis based on ITT was the primary evidence of efficacy. The safety set included all patients who received at least one dose of the study drug. All safety analyses were performed using the safety set and patients were analyzed as treated.

In Study 545, two predetermined patient populations were defined: the ITT population and the safety population. Efficacy analyses were performed using the ITT population, which comprised all randomized patients. Patients were analyzed according to randomization assignment, regardless of actual treatment received. Safety analyses were performed using the safety population, which comprised all patients who received at least one injection of the study treatment. All safety analyses were performed according to actual treatment received at the study treatment visit (rather than as randomized).

In the COMPEL study, all efficacy analyses were performed using the AP, consisting of all enrolled patients who had at least one efficacy assessment at baseline or a post-baseline visit. All safety analyses were performed using the safety population, consisting of all patients who received at least one Ona A treatment.

In the REPOSE study, the analysis of all variables was based on the safety analysis set, which consisted of all patients who received at least one dose of Ona A. Effectiveness variables were also analyzed based on the per-protocol set, which included all patients in the safety analysis set who completed 24 months.

In both Negro et al. studies, only patients who completed the two years of follow-up were included in the analysis and in reporting of AEs.

Patient Disposition

A total of 282 patients were enrolled in the FORWARD study; 140 patients were randomly assigned to the Ona A treatment group, while 142 patients were randomly assigned to begin the study on topiramate. The percentage of patients who completed the treatment to which they were originally assigned was 85.7% in the Ona A treatment group and 19.7% in the topiramate group (Table 8). Among patients in the topiramate group who did not complete their assigned treatment regimen, 80 patients (56.3%) switched to Ona A treatment; 71 of these 80 patients (or 50.0% of the 142 patients who began the study on topiramate) switched to Ona A treatment by week 12. Among the 140 patients who began the study in the Ona A treatment group, 11 in the Ona A treatment group (7.9%) discontinued study treatment; the most frequently reported reasons for discontinuation were ineffective treatment and/or AEs. Among the 142 patients who began the study in the topiramate treatment group, 89 (62.7%) discontinued study treatment; 72 patients (50.7%) discontinued topiramate treatment due to AEs. A total of 25 patients (8.9%) were discontinued after being lost to follow-up. This total includes 15 of the 142 patients (10.6%) who were originally assigned to topiramate treatment, versus five (3.6%) of those who were originally assigned to Ona A. Similarly, higher consent withdrawal was reported in the topiramate treatment group (13.4%) versus 4.3% in the Ona A group. These numbers indicate a considerable imbalance in the dropout rate between-treatment groups, with lower dropout rates in the Ona A treatment group.

In Study 545, a total of 52 patients were randomized and received study treatment (25 received Ona A and 27 received placebo). Of these patients, 45 were included in what was defined as the ITT population (19 in the Ona A group and 26 in the placebo group). Seven patients were withdrawn from the study due to a randomization error and excluded from the ITT population. The safety population comprised all 52 patients. [redacted] 15 patients (79.0%) and 18 patients (69.2%) in the Ona A and placebo groups, respectively (Table 8).

Of the 960 screened patients in the COMPEL study, 716 were enrolled and received study medication. [redacted] Overall, 52.1% (373 of 716) of patients completed the study. The most common (> 10%) reasons for early discontinuation were withdrawal of consent (12.8%) and lost to follow-up (11.5%). Patients discontinued due to lack of efficacy and TEAEs were reported in 4.9% and 3.5% of patients, respectively (Table 9).

In the REPOSE study, 641 patients were enrolled and 633 patients were treated. Only 128 patients (20.2%) completed the 24-month study. Upon documentation of the last visit of a patient, physicians were asked to provide the reason for this last visit (end-of-study reason). The most frequent end-of-study reason in the safety analysis set was “no scheduled visits for a future treatment within the study period” (63.5%, n = 402); 144 patients (22.7%) discontinued the treatment with Ona A and 41 patients (6.5%) continued Ona A therapy but did not wish to continue participating in the study. No end-of-study reason was given by 46 patients (7.3%). The most common reasons for treatment discontinuation were lack of efficacy (14.2%), AE (2.4%), inconvenience of participation (2.7%), and other (5.7%) (Table 9).

The completion rate was 85.2% and 83.1% in Negro et al. (2015) and Negro et al. (2016), respectively. The most common reasons for treatment discontinuation, respectively, were lack of efficacy (5.2% in Negro et al. [2015] and 2.9% in Negro et al. [2016]), AEs (3.2% in Negro et al. [2015] and 4.1% in Negro et al. [2016]), dropout (1.8% in Negro et al. [2015] and 3.5% in Negro et al. [2016]), and personal reasons (3.2% in Negro et al. 2015 and 4.1%) (Table 9).

Table 8: Patient Disposition in FORWARD and GMA-BTX-CM-12-545 Trials

	FORWARD			GMA-BTX-CM-12-545	
	Ona A 155U	Topiramate	Topiramate to Ona A 155 U[a]	Ona A 155 U	Placebo
Screened, N	NR			NR	
Randomized	140	142	80 (switched from topiramate to Ona A 155 U[a])	25	27
Completed treatment regimen assigned to patient at start of study, N (%)	120 (85.7)	28 (19.7)			
Completed study, N (%)	113 (80.7)	28 (19.7)	55 (68.8)	[redacted]	[redacted]
Completed study for topiramate and topiramate to Ona A, N (%)		84 (59.2)[b]			
Patients who discontinued treatment regimen to which they were assigned, N (%)	11 (7.9)[c]	89 (62.7)[cd]	6 (7.5)[c]	NA	NA
Discontinued the study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reason for treatment discontinuation, N (%)					
Adverse event(s)	5 (3.6)	72 (50.7)	0	NR	NA
Noncompliant with treatment regimen	0	1 (0.7)	0	NA	NA
Treatment was ineffective	7 (5.0)	27 (19.0)	3 (3.8)	NA	
Major protocol violation	1 (0.7)	0	0	NA	NA
Other	0	3(2.1)	3 (3.8)	NA	NA
Primary reason for study discontinuation, N (%)					
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event(s)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious protocol violations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	FORWARD			GMA-BTX-CM-12-545	
	Ona A 155U	Topiramate	Topiramate to Ona A 155 U[a]	Ona A 155 U	Placebo
ITT, N	140	142		19	26
PP, N	NR	NR	NR	NR	NR
Safety, N	140	142	80	25[i]	27[i]

ITT = intention-to-treat; NA = not applicable; NR = not reported; Ona A = onabotulinumtoxinA; PP = per-protocol; U = Allergan units.

[a] Topiramate → Ona A is a subgroup of patients who initially received topiramate and switched to Ona A (n = 80).

[b] Includes topiramate → Ona A patients who completed study (n = 55) and 1 patient who completed the per protocol study (by successfully completing a week 36 visit) despite earlier discontinuation of topiramate treatment.

[c] Patients may have multiple reasons for study treatment discontinuation. Patients who discontinued Ona A treatment (either those who were originally assigned to the Ona A group or switched to Ona A after discontinuing topiramate treatment) were discontinued from the study.

[d] A total of 9 patients who were originally assigned to this group discontinued topiramate treatment and discontinued from the study. Additionally, 7 patients who were originally assigned to this group were lost to follow-up, and 2 patients withdrew consent. Finally, 1 patient discontinued topiramate treatment but also completed the study (as they successfully completed a week 36 visit despite discontinuing treatment earlier).

[e] [redacted]

[h] These patients experienced a major protocol violation that resulted in their early discontinuation from study participation and exclusion from ITT population analyses.

[i] Seven patients were withdrawn from the study at site 4 as they were re-randomized and received the study treatment of the alternate group at week 12.

Sources: Clinical Study Reports for FORWARD and GMA-BTX-CM-12-545 studies.[21,22]

Table 9: Patient Disposition in the Included Single-Arm Trials

	COMPEL	REPOSE	Negro et al. (2015)	Negro et al. (2016)
	Ona A 155 U	Ona A 155U or 195 U	Ona A 155 U	Ona A 195 U
Screened, N	960	[redacted]	NR	NR
Enrolled, N	716	[redacted]	155	172
Treated, N	716	[redacted]	NR	NR
Completed, N (%)	373 (52.1)	[redacted]	132 (85.2)[a]	143 (83.1)[a]
Not Completed, N (%)	343 (47.9)	[redacted]	23 (14.8)	29 (16.9)
Reason for treatment discontinuation, N (%)				
Adverse event	25 (3.5)	[redacted]	5 (3.2)	7 (4.1)
Lack of efficacy	35 (4.9)	[redacted]	8 (5.2)	5 (2.9)
Pregnancy	5 (0.7)	[redacted]	2 (1.3)	4 (2.3)
Lost to follow-up	82 (11.5)	[redacted]	0	0
Subject withdrew consent	92 (12.8)	[redacted]	0	0
Protocol violation	60 (8.4)	[redacted]	0	0
Other	43 (6.0)	[redacted]	0	0
Missing	1 (0.1)	[redacted]	0	0
Dropout	0	[redacted]	3 (1.8)	6 (3.5)
Personal reasons	0	[redacted]	5 (3.2)	7 (4.1)
Patient thinks it is inconvenient to come	0	[redacted]	0	0

	COMPEL	REPOSE	Negro et al. (2015)	Negro et al. (2016)
	Ona A 155 U	Ona A 155U or 195 U	Ona A 155 U	Ona A 195 U
Patient thinks the injections are too painful	0	[redacted]	0	0
Patient is concerned about risks	0	[redacted]	0	0
Patient thinks the injections take too much time	0	[redacted]	0	0
Per-protocol set	NR	[redacted]	NR	NR
Safety analysis set	716	[redacted]	132	143
Analysis set[b]	715	[redacted]	132	143

NR = not reported; Ona A = onabotulinumtoxinA; U = Allergan units.

[a] Completed 2 years of follow-up.

[b] One patient did not have post-baseline headache diary data and was therefore not included in the AP.

Sources: Blumenfeld et al.,[32] Blumenfeld et al.,[34] Negro et al.,[24] Negro et al.,[25] Davies et al.,[33] Clinical Study Reports for COMPEL and REPOSE studies.[23,35]

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Exposure to Study Treatments

[redacted]

Those who switched from topiramate to Ona A are included in the 220 patients in the Ona A treatment group.

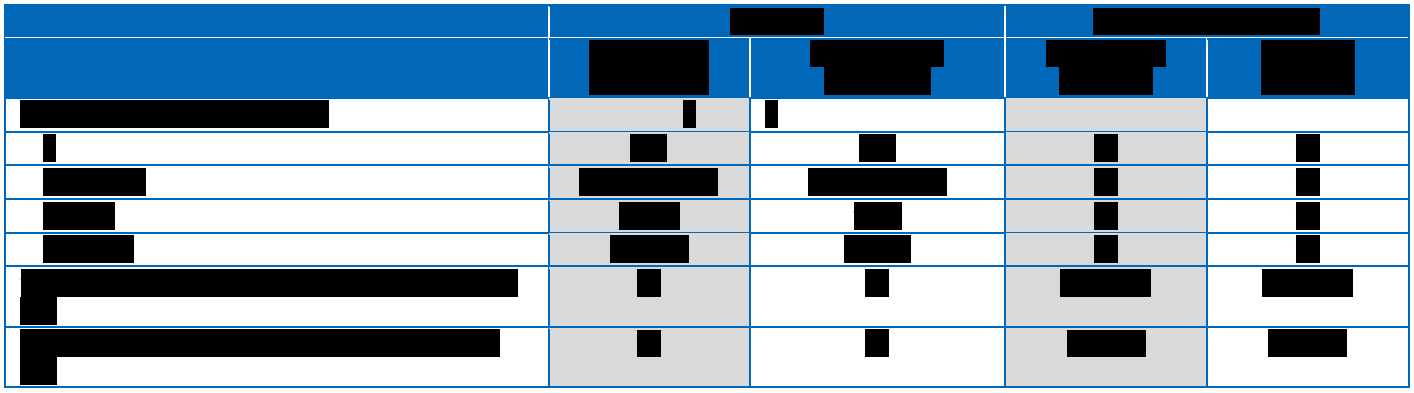
[redacted]

In the COMPEL study, 67.2% of patients (481 of 716) received 60 weeks of treatment and over half of all patients (56.1%, 402 of 716) received 108 weeks of treatment, which was the maximum duration of treatment in this study. [redacted] (Table 11).

In the REPOSE study, all 633 patients (100.0%) in the safety analysis set had at least one treatment, [redacted]

In Negro et al. (2015) and Negro et al. (2016), 132 (85.2%), and 143 (83.1%) respectively, completed the two years of follow-up and did not discontinue Ona A prior to 24 months. However, the extent of exposure to Ona A and how many injections of Ona were received by patients were not reported (Table 11).

Table 10: Exposure to Study Treatments in FORWARD and GMA-BTX-CM-12-545 Trials



max = maximum; min = minimum; NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation. U = Allergan units.

Sources: Clinical Study Reports for FORWARD and GMA-BTX-CM-12-545 studies.[21,22]

Table 11: Exposure to Study Treatments in the Included Single-Arm Trials

	COMPEL	REPOSE	Negro et al. (2015)	Negro et al. (2016)
	Ona A 155U (N = 716)	Ona A 155U or 195 U (N = 336)	Ona A 155U (N = 155)	Ona A 195U (N = 172)
Received 1 treatment, n (%)	716 (100.0)	[redacted]	NR	NR
Received treatment 2, n (%)	645 (90.1)	[redacted]	NR	NR
Received treatment 3, n (%)	585 (81.7)	[redacted]	NR	NR
Received treatment 4, n (%)	543 (75.8)	[redacted]	NR	NR
Received treatment 5, n (%)	515 (71.9)	[redacted]	NR	NR
Received treatment 6, n (%)	481 (67.2)	[redacted]	NR	NR
Received treatment 7, n (%)	444 (62.0)	[redacted]	NR	NR
Received treatment 8, n (%)	422 (58.9)	[redacted]	NR	NR
Received treatment 9, n (%)	402 (56.1)	[redacted]	NR	NR
Exit visit at week 108, n (%)	373 (52.1)	[redacted]	NR	NR
Completed the 2 years of follow-up, n (%)	NA	[redacted]	132 (85.2)	143 (83.1)
Number of treatment sessions per patient (visits with Ona A injections)				
n	[redacted]	[redacted]	NR	NR
Mean (SD)	[redacted]	[redacted]	NR	NR
Median (min to max)	[redacted]	[redacted]	NR	NR
Mean “total dose” of Ona A per patient and visit [units]				
n	NR	[redacted]	NR	NR
Mean (SD)	NR	[redacted]	NR	NR
Median (min to max)	NR	[redacted]	NR	NR

max = maximum; min = minimum; NA = not applicable; NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation; U = Allergan units.

Sources: Blumenfeld et al.,[32] Negro et al.,[24] Negro et al.,[25] and Clinical Study Reports for COMPEL and REPOSE studies.[23,35]

Critical Appraisal

Internal Validity

FORWARD study

Randomization and allocation concealment in the FORWARD trial were clearly described and distribution of baseline characteristics between different treatment arms appeared to be balanced. However, the FORWARD trial used an open-label design and therefore patient knowledge of treatment allocation may have influenced the outcome measures assessed subjectively (including AEs and HRQoL), which could potentially be biased by knowledge of treatment received. In addition, patients' willingness to continue therapy may have been influenced by knowledge of the treatment received, which may have played a role in the large discontinuation rate.

Randomization appeared to be well conducted as once informed consent was signed at the screening visit, the site staff logged on to the interactive Web response system (IWRS) and obtained a unique patient number, which was used as identification for the electronic patient e-diary, electronic case report forms, electronic clinical outcome assessments, and all source documentation throughout the study. The IWRS system provided the site with the treatment to which the patient was assigned. Sites dispensed study drug according to IWRS instructions.

A large discontinuation rate of 80.3% was reported in the topiramate group, whereas only 14.3% discontinued Ona A treatment. While the main reason for discontinuation was adverse event, other reasons, such as withdrawal of consent and lost to follow-up, were also higher in the topiramate treatment group than in the Ona A treatment group. The fact that patients knew from the beginning that if they were randomized to topiramate they had the option to cross over to Ona A if they discontinued topiramate could explain the high dropout rate in the topiramate group.

For efficacy analyses, patients who discontinued topiramate and then switched to Ona A were considered nonresponders and baseline data were used for the remaining study days for the primary and secondary efficacy end points. Also, if a patient had a missing entry for any reason (e.g., discontinuation due to an adverse event, lost to follow-up, lack of efficacy), the baseline value data were utilized, and the patient was considered a nonresponder. Given the high dropout rate in the topiramate treatment group, this method of considering these patients as nonresponders could have biased the results in favour of Ona A, given the differential discontinuation rate and imputation of nonresponse between groups.

[redacted]

If a patient reported at least 20 days of headache data (either headache days or headache-free days) but fewer than 28 days in a diary period, the data for counts were prorated accordingly and rounded to the nearest whole number. However, this approach may not have been appropriate and could have introduced bias, because data would not be missing at random and patient data would be more likely to be missing on headache days or patients would be more prompted to fill in data on headache days.

The sample size in the FORWARD trial was estimated to be 400 patients in order to have 90% statistical power to detect an expected treatment difference of 16%. [redacted]
Even with the smaller sample size, the FORWARD study showed statistically significant results for the primary and secondary end points.

[redacted]

The primary efficacy end point and all secondary end points were statistically significant, and can be interpreted as such, given that they were adjusted for multiplicity. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Single-Arm Studies

The COMPEL, REPOSE, and Negro et al. studies were single-arm studies. There is a risk of bias with outcome measurements in single-arm studies as patients and providers are aware of their assigned intervention. Measurement of subjective outcomes, such as HRQoL, may be at increased risk of bias if patients in the study are aware of their treatment allocation. For example, patients may report improved HRQoL simply because they are receiving a new treatment. Knowledge of their intervention may also bias results indirectly by affecting adherence. Patients may be more likely to closely adhere to therapy if they are receiving a treatment that they anticipate will be an improvement over existing therapies. Improved adherence may lead to better outcomes. Knowledge of treatment assignment can also bias harms, particularly AEs. If patients are aware that they are taking an active therapy, they may be more likely to attribute an AE to a drug, or may even be more likely to report an AE.

In the COMPEL study, the discontinuation rate was high, with only 52.1% completing the study, while only 5% discontinued to lack of efficacy, 11.5% of patients were lost to follow-up, and 12.8% of patients withdrew consent. However, patients who were lost to follow-up or withdrew consent might not have been experiencing a satisfactory response, and the

patients who remained in the study would more likely be patients without an AE and with better efficacy.

In the COMPEL study, missing data were imputed for all patients even if they had fewer than 10 days of data-recording in a 28-day diary period; if a patient discontinued the study, the number of headache days for the missing period was imputed by an mLOCF method. The substitution was the corresponding number of headache days from the patient's previous 28-day diary period (i.e., the last observation) adjusted to match the mean change observed over all fully observed patients in the same time period. If a patient discontinued the study after the first or the second injections, then, for the analysis of the last visit at week 108, the number of headache days for that patient for the missing period was imputed from week 12 or week 24 until week 108. Such an assumption would introduce bias in favour of Ona A because if there was good response at the last observation, then that response was carried forward until the end of the trial. This assumes that the response was sustained for that period, which might not be true. No sensitivity analyses for other imputation methods were conducted. In addition, only 373 (52.1%) of the 716 enrolled patients completed the study, indicating that a large portion of data were imputed for the week 108 analysis, and, given the issues identified with imputation method, the results were likely biased in favour of Ona A.

[redacted]

[redacted]

Subgroup analyses by previous use of preventive treatment and by history of acute medication overuse at baseline were conducted in the COMPEL study. To compare treatment effects in subgroups in any study, a test of interaction should be used. If the result of the interaction test is not significant then there is no observable subgroup effect. However, such analysis was not reported by the manufacturer. Instead a t-test was used to compare subgroups.

[redacted]

[redacted]

The COMPEL and REPOSE studies enrolled patients with a diagnosis of CM but did not describe how these patients were diagnosed with CM, nor whether ICHD-III was followed in order to properly diagnose these patients with CM.

The Negro et al. studies were conducted independent of the manufacturer, and as such, Clinical Study Reports were not available to the manufacturer or CADTH. A detailed and thorough assessment of these studies was therefore not possible, especially given that the extent of exposure to Ona A, the number of injections of Ona received by patients, and how concomitant medications were handled were not reported. In addition, because it was not reported how many patients were included in the analyses at each time point and it was not reported if any imputation method was used to account for missing data, it is not possible to know if there are any missing values or, if there are missing values, how these were handled. Also, treatment-related AEs were only reported instead of TEAEs, and treatment-related AEs tend to underreport adverse events experienced by patients because, while a TEAE refers to an adverse event temporally related to the study treatment, a treatment-related AE refers to the causality assessment by the investigator. The FDA's guidance for industry (Statistical Principles for Clinical Trials) indicates that all AEs should be reported, whether or not they are considered to be related to treatment.[20]

The potential implications of conducting multiple statistical tests were not considered in the Negro et al. studies, and no adjustment was made for multiple testing, despite secondary end point analyses that would increase the risk of type I (false-positive) error. As a result, all end points beyond the primary should be interpreted with consideration of this risk.

In addition, the Negro et al. studies did not report how headache days or migraine days were defined and measured, which is problematic, given that, if no strict clear definition for headache and migraine day is provided, this could lead to bias and overestimation of treatment effect.

In both Negro et al. studies, patients with CM and with criteria for MOH were enrolled. However, how these patients were diagnosed with CM and MOH, and whether ICHD-III was followed in order to properly diagnose them, were not described.

External Validity

There were no Canadian sites enrolled in the included studies. According to the clinical expert consulted for this review, the population enrolled in all trials was generally representative of Canadian adult patients with CM, although white patients were over-represented. The expert noted that the cut-off of 65 years of age applied in the FORWARD study is not used in clinical practice, but there is no reason that patients over 65 would

behave differently. Also in the FORWARD study, time since onset of CM was not reported. Ideally, a protocol to control for this omission would have been included, but this is not necessarily a critical oversight.

The FORWARD study excluded patients who were taking opioid-containing products for acute-headache treatment for more than eight days during the 28-day run-in period; and the generalizability of the results of the included studies to this subgroup of patients is unknown.

[redacted]

The discontinuation rates in the COMPEL and REPOSE studies were high, with only 52.1% and 20.2% completing the studies respectively. Also, 56% of patients in the FORWARD study who were randomized to topiramate discontinued treatment before the end of the study. This loss to follow up can seriously reduce the generalizability of the findings, given that the subgroup of patients completing the studies is potentially less representative of the recruited patients.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 3). See Appendix 4 for detailed efficacy data.

Headache Impact Test

In the FORWARD trial, change from baseline in total HIT-6 score per 28-day period was assessed as a secondary outcome. In Study 545, change from baseline in HIT-6 was assessed as a secondary outcome. In the COMPEL trial the mean change from baseline in HIT-6 total score over a four-week period at week 60 and week 108 was assessed as a secondary outcome, [redacted] In the Negro et al. studies, HIT-6 was assessed every six months.

In the FORWARD trial, at week 30, the mean (SD) changes from baseline for HIT-6 scores were −5.6 (7.2) for Ona A-treated patients and −1.3 (3.9) days for topiramate-treated patients, resulting in an estimated mean (95% CI) treatment difference of −4.248 (−5.766 to −2.731) in favour of Ona A ($P < 0.001$). The outcome of change from baseline in total HIT-6 score was adjusted for multiplicity, hence a claim of statistically significance is acceptable given the control of the type I error rate. This between-group difference exceeded the established MCID of 2.3 points in patients with chronic daily headache. [redacted] Results are presented in Table 16.

[redacted] Results are presented in Table 19.

In the COMPEL study, at baseline, patients reported a mean (SD) HIT-6 total score of 64.7 (4.82). Improvements from baseline on the mean HIT-6 total score were observed as early as week 12 (−4.4 [6.25]) and continued to week 60 (−6.8 [6.55]) and week 108 (−7.1 [7.24]; $P < 0.0001$ for all time points). This within-group difference exceed the established MCID of 2.5 points patients with episodic migraine. [redacted] Subgroup analyses by previous use of preventive treatment, use of preventive treatment at baseline, and history of acute medication overuse at baseline were conducted in the COMPEL study. For the change from baseline in total HIT-6 score at week 108, a greater reduction in HIT-6 (improvement) was seen in the subgroups of no previous prophylaxis-medication use, no use of prophylaxis medications at baseline, and no medication overuse at baseline compared with subgroups of previous prophylaxis-medication use, use of prophylaxis medications at baseline, and history of acute pain medication overuse, respectively. [redacted]

In the Negro et al. studies, the mean HIT-6 score decreased during the period of treatment from the first to the last injection, from 69.4 ± 4.9 at baseline to 52 ± 5.6 at 24 months; $P < 0.001$ in Negro et al. (2015), and from 67.9 ± 4.2 at baseline to 49 ± 6.7; $P < 0.001$ at 24 months in Negro et al. (2016). However, this outcome was not adjusted for multiplicity, and any interpretation of reported results should be consider the potential for inflated type I error. The proportion of patients with a severe (≥ 60) HIT-6 score decreased as well, from 93.9% at baseline to 22% at 24 months in Negro et al. (2015), and from 95.8% at baseline to 15.4% at 24 months in Negro et al. (2016). Results are presented in Table 25 and Table 26.

Migraine-Specific Quality of Life Questionnaire

In Study 545, change from baseline in MSQ was assessed as a secondary outcome. In the COMPEL trial the mean changes from baseline to each study time point for MSQ was assessed as an exploratory efficacy outcome. In the REPOSE study, change from baseline in MSQ was one of the efficacy measures.

In Study 545, the between-group mean difference in change from baseline in the RR subdomain of the MSQ was not statistically significant (5.6 in favour of Ona A, [redacted]). The between-group mean difference in change from baseline in the RP subdomain of the MSQ was not statistically significant (5.0 in favour of Ona A, [redacted]). The between-group mean difference in change from baseline in EF subdomain of the MSQ was not statistically significant (7.7 in favour of Ona A, [redacted]). Results are presented in Table 19.

[redacted]

[redacted]

In the REPOSE study's safety analysis set, improvements in all three MSQ domains were observed at all post-baseline treatment visits, based on patients with data available at baseline and the respective visits. However, this outcome was not adjusted for multiplicity, and any result reported should be interpreted with consideration for the potential of an inflated type I error. Results are presented in Table 24.

EuroQol 5-Dimensions 3-Levels Questionnaire

In the REPOSE study, change from baseline in the EQ-5D-3L was an efficacy measure. No other study assessed the EQ-5D-3L.

Improvements in the EQ-5D-3L total score (index) were observed at all post-baseline treatment visits in the safety analysis set. The median total score was 0.69 (range: −0.59 to 1.0) at baseline (n = 596), the median total score was 0.76 (range: −0.32 to 1.0) at month 6 (n = 362) and 0.80 at all later visits, i.e., month 12 (n = 227) and month 24 (n = 121), as well as at last available follow-up visit value of a patient (n = 424). While the *P* value was < 0.001 at all time points, this outcome was not adjusted for multiplicity, and any result reported should be interpreted with consideration of the potential for inflated type I error. Results are presented in Table 24.

The EQ-5D-3L health state (VAS) score ranges between 0 (worst imaginable health state) and 100 (best imaginable health state). Improvements from baseline in the health state score were seen at all post-baseline treatment visits in the safety analysis set. The median health state score was 50.0 at baseline (n = 582) and the median health state score was 70.0 at all post-baseline visits: month 6 (n = 360), month 12 (n = 228), month 24 (n = 121), and last available follow-up visit value of a patient (n = 421). While the *P* value was < 0.001 at all time points, this outcome was not adjusted for multiplicity, and any result reported should be interpreted with consideration of the potential for inflated type I error. Results are presented in Table 24.

Assessment of Chronic Migraine – Impact and Assessment of Chronic Migraine Symptoms

[redacted]In Study 545, change from baseline in the ACM-I total score was the primary efficacy end point. Change from baseline in the ACM-I domain scores and ACM-S were assessed as a secondary outcome.

[redacted]

[redacted]

Migraine Interictal Burden Scale

[redacted]

Patient Health Questionnaire Quick Depression Assessment Score

In the FORWARD trial, change from baseline in PHQ-9 quick depression assessment score per 14-day period was assessed as an exploratory end point. No other study assessed PHQ-9.

At week 36 of treatment, the mean (SD) changes from baseline for PHQ-9 scores were −2.1 (4.6) for Ona A-treated patients versus −0.5 (1.9) for patients treated with topiramate. A mean difference of −1.862 was reported in favour of Ona A over topiramate (95% CI: −2.628 to −1.095; $P < 0.001$). However, this outcome was not adjusted for multiplicity, and was assessed as an exploratory efficacy outcome, and any result reported should be interpreted with consideration of the potential for inflated type I error. Results are presented in Table 16.

Per cent Reductions in Headache Days per 28-Day Period

In the FORWARD trial, the primary efficacy end point was the proportion of patients with a decrease of at least 50% from baseline in the frequency of headache days per 28-day period, at the primary time point of week 32. The proportion of patients with a ≥ 70% decrease from baseline in the frequency of headache days per 28-day period was a secondary end point [redacted]

In the FORWARD trial, at the end of week 32, 40% of Ona A-treated patients demonstrated a ≥ 50% decrease from baseline in the mean number of headache days reported during weeks 29 to 32 versus 12.0% of topiramate-treated patients (OR, 4.94; 95% CI, 2.681 to 9.085; $P < 0.001$) [redacted]

[redacted]

The number of Ona A-treated patients who demonstrated ≥ 70% [redacted] decreases from baseline in the mean number of headache days reported during weeks 29 to 32 was higher compared with topiramate-treated patients ($P < 0.001$ for both) (Table 15). [redacted]

[redacted]

Frequency of Headache Days per 28-Day Period

In the FORWARD trial, the change from baseline in the frequency of headache days per 28-day period was a secondary end point. In the COMPEL trial, the primary efficacy end point was the mean change from baseline in the number of headache days for the 28-day period ending at week 108 (following nine treatments), and the mean change from baseline in the frequency of headache days for the 28-day period ending at week 60 (following five treatments) were secondary efficacy measures. In the REPOSE study, change from baseline in patient-reported headache frequency was an efficacy measure. In the Negro et al. studies, the average number headache days per month was one of the efficacy measures assessed.

In the FORWARD trial, during the interval from week 29 to week 32, the mean (SD) change from baseline in the number of headache days was −8.3 (8.9) days for Ona A–treated patients and −2.1 (5.6) days for topiramate-treated patients, resulting in an estimated mean (95% CI) treatment difference of −6.199 (−7.936, −4.462) headache days in favour of Ona A ($P < 0.001$) (Table 15). [redacted] Results are presented in Table 15.

In the COMPEL trial, at baseline, patients reported a mean (SD) of 22.0 (4.82) headache days per 28-day period. The primary end point was met when statistically significant reductions in the mean number of headache days from baseline were observed at week 108 (−10.7 [6.44] $P < 0.0001$). Reductions in the mean number of headache days from baseline were also observed at week 60 (−9.2 [6.22], $P < 0.0001$). However, this analysis at week 60 was not adjusted for multiplicity, and interpretation of any results reported should consider the potential for inflated type I error (Table 21). Subgroup analyses by previous use of preventive treatment, use of preventive treatment at baseline, and history of acute medication overuse at baseline were conducted in the COMPEL study. For the change from baseline in the frequency of headache days per 28-day period at week 108, a higher reduction in headache days was seen in the subgroups of no previous prophylaxis-medication use, no use of prophylaxis medications at baseline, and no medication overuse at baseline, compared with subgroups of previous prophylaxis-medication use, use of prophylaxis medications at baseline, and history of acute pain medication overuse, respectively.

[redacted]

In the Negro et al. studies, the headache days per month decreased during the period of treatment from the first to the eighth session of therapy, from 22.3 ± 4.1 at baseline to 7.3 ± 2.1 at 24 months; $P < 0.001$ in Negro et al. (2015), and from 22.2 ± 4.9 at baseline to 4.1 ± 1.0 at 24 months; $P < 0.001$ in Negro et al. (2016). However, this outcome was not adjusted for multiplicity, and any result reported should be interpreted with consideration of the potential for inflated type I error. Results are presented in Table 25 and Table 26.

Frequency of Moderate or Severe Headache Days per 28-Day Period

In the FORWARD trial, change from baseline in the frequency of severe headache days per 28-day period was assessed as an exploratory end point. No other study assessed this outcome. [redacted]

[redacted]

Frequency of Migraine Days

In the Negro et al. studies, the average number of migraine days per month was one of the efficacy measures assessed. No other study assessed migraine days. In both studies, the migraine days per month decreased during the period of treatment from the first to the eighth session of therapy, from 21.4 ± 4.3 at baseline to 6.8 ± 2.3 at 24 months; $P < 0.001$ in Negro et al. (2015) and from 21.6 ± 4.8 at baseline to 3.8 ± 1.0 at 24 months; $P < 0.001$ in Negro et al. (2016). Results are presented in Table 25 and Table 26. However, no clear definition was provided for this outcome. In addition, it was not adjusted for multiplicity, and interpretation of any results reported should consider the potential for inflated type I error.

Headache Pain Medication Intake

In the FORWARD trial, reduction from baseline in the total days of acute headache pain medication use was assessed as an exploratory end point. In the Negro et al. studies, medication intake days per month was one of the efficacy measures assessed.

[redacted]

In the Negro et al. studies, medication intake days decreased during the period of treatment from the first to the eighth session of therapy, from 20.8 ± 4.5 at baseline to 5.3 ± 1.7 at 24 months; $P < 0.001$ in Negro et al. (2015), and from 21.0 ± 5.1 at baseline to 3.7 ± 1.3 at 24 months; $P < 0.001$ in Negro et al. (2016). However, this outcome was not adjusted for multiplicity, and interpretation of any results reported should consider the potential for inflated type I error. Results are presented in Table 25 and Table 26.

Health Care Resource Utilization

[redacted]Health care resource utilization was also assessed in the REPOSE trial by evaluating admission to hospital for headache. In both studies these outcomes were not adjusted for multiplicity, and any result reported should be interpreted with consideration given to the potential for inflated type I error.

[redacted]

[redacted]

In the REPOSE trial baseline visits, the proportion of patients who had been admitted to hospital for headache in the last three months prior to baseline was 6.0% (38 of 663 patients). At last available follow-up visit, the proportion of patients admitted to hospital was 2.1% (13 of 607 patients). Results are presented in Table 24.

Work Status and Productivity

In the FORWARD trial, change from baseline in WPAI-SHP per seven-day period use was assessed as an exploratory end point. [redacted] Results are presented in Table 18.

The estimated mean Ona A–versus-topiramate differences, 95% CIs, and *P* values for all four WPAI-SHP domains calculated from week 36 results were as follows:

[redacted]

Work Productivity Loss Score: estimated mean Ona A-versus-topiramate difference of −0.669 (95% CI, −1.249 to −0.088) in favour of Ona A (*P* = 0.024).

[redacted]

Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). Table 12 and Table 13 supply detailed harms data. In the Negro et al. studies, only reported treatment-related AEs were reported, and hence AEs from these studies will not be comments on; results from these studies are presented in Table 27.

Adverse Events

In the FORWARD study, the incidence of TEAEs among topiramate-treated patients was higher than among the Ona A treatment group (78.9% of patients in the topiramate group versus 47.7% for the Ona A group). The most frequently reported TEAEs among Ona A–treated patients were sinusitis (5.9% of patients in the Ona A group; 7.5% of topiramate to Ona A patients), neck pain (4.5% of patients in the Ona A group; 6.3% of topiramate to Ona A patients), and migraine (2.7% of patients in the Ona A group; 5.0% of topiramate to Ona A patients). Sinusitis and migraine were reported with similar frequency among topiramate-treated patients (7.0% and 2.1%, respectively); 2.1% of patients assigned to topiramate treatment reported neck pain. The most frequently reported TEAEs among topiramate-

treated patients were paresthesia (31.0% of topiramate patients), nausea (13.4%), cognitive disorder and dizziness (12.7% each), decreased appetite (10.6%), disturbance in attention (8.5%), vision blurred (7.7%), sinusitis (7.0%), and depression (5.6%).

In Study 545, nine patients (36.0%) in the Ona A group and [redacted] in the placebo group reported experiencing at least one TEAE. No further details were provided in the Clinical Study Report.

In the COMPEL study, TEAEs were reported in 60.9% (436/716) of patients. The most frequently reported (> 5%) TEAEs were neck pain and sinusitis, both of which were reported in 5.3% (38 of 716) of patients.

[redacted]

Serious Adverse Events

[redacted] Serious TEAEs were reported by 1.8% of patients in the Ona A treatment group, and in 4.2 of patients in the topiramate treatment group.

In study 545, one patient (3.7%) in the placebo group experienced an SAE. No other SAE was reported.

In the COMPEL study, SAEs were reported in 10.5% (75 of 716) of patients. The most frequently reported SAEs (i.e., in at least three patients each) were migraine (0.8%, six of 716), suicidal ideation (0.7%, five of 716), and headache, malignant melanoma, and non-cardiac chest pain (0.4%, three of 716 each).

In the REPOSE study, a total of [redacted] were reported in [redacted]. The most frequently reported SAEs were psychiatric disorders (n = 3, 0.5%) and nervous system disorders (n = 2, 0.3%).

Withdrawal Due to Adverse Events

[redacted]

Discontinuations due to AEs were not reported in Study 545.

In the COMPEL study, discontinuations from the study due to TEAEs were reported in 4.5% (32 of 716) of patients. The TEAEs leading to the most discontinuations were suicidal ideation (four patients) and eyelid ptosis, headache, and pregnancy (three patients each).

[redacted]

Mortality

No death was reported in either study.

Notable Harms

Autonomic dysreflexia, cardiovascular events, dysphagia, hematological AEs, neck pain, generalized weakness, seizure, incontinence, swallowing disorder, speech disorder, ptosis, and diplopia were identified as notable harms of interest based on the review protocol.

[redacted]

In Study 545, the number of patients experiencing neck pain was 4 (16.0%) and 1 (3.7%), [redacted]

[redacted]

[redacted]

Table 12: Harms in FORWARD and GMA-BTX-CM-12-545 Trials

	FORWARD			GMA-BTX-CM-12-545	
	Ona A 155U (N = 220)	Topiramate[a] (N = 142)	Topiramate to Ona A 155 U[bc] (N = 80)	Ona A 155U (N = 25)	Placebo (N = 27)
Patients with > 0 AEs, N (%)	105 (47.7)	112 (78.9)	38 (47.5)	9 (36.0)	[redacted]
Most common AEs (5% in any group), N (%)					
Paresthesia	1 (0.5)	44 (31.0)	0		
Dizziness	6 (2.7)	18 (12.7)	1 (1.3)		
Cognitive disorder	1 (0.5)	18 (12.7)	1 (1.3)		
Disturbance in attention	0	12 (8.5)	0		
Migraine	6 (2.7)	3 (2.1)	4 (5.0)		
Sinusitis	13 (5.9)	10 (7.0)	6 (7.5)		
Nausea	1 (0.5)	19 (13.4)	0		
Neck pain	10 (4.5)	3 (2.1)	5 (6.3)	4 (16.0)	1 (3.7)
Fatigue	1 (0.5)	19 (13.4)	0		
Depression	4 (1.8)	8 (5.6)	2 (2.5)		
Vision blurred	6 (2.7)	11 (7.7)	3 (3.8)		
Decreased appetite	0	15 (10.6)	0		
[redacted]	[redacted]	[redacted]	[redacted]		

	FORWARD			GMA-BTX-CM-12-545	
	Ona A 155U (N = 220)	Topiramate[a] (N = 142)	Topiramate to Ona A 155 U[bc] (N = 80)	Ona A 155U (N = 25)	Placebo (N = 27)
[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]		
Injection site pain				2 (8.0)	1 (3.7)
Shoulder pain				3 (12)	0
Facial paresis				2 (8.0)	0
SAEs					
Patients with > 0 SAEs, N (%)	4 (1.8)	6 (4.2)	2 (2.5)	0	1 (3.7)
WDAEs					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of deaths, N (%)	0	0	0	0	0
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		

AE = adverse event; Ona A = onabotulinumtoxinA; SAE = serious adverse event; U = Allergan units; WDAE = withdrawal due to adverse event.

[a] Percentages used the number of patients that received each treatment as the denominator. Patients that received both Ona A and topiramate were included in the denominator for all treatment groups and overall. At each level of summarization, a patient was counted once within a treatment group and once for the total population.

[b] Topiramate → Ona A is a subgroup of patients who initially received topiramate and switched to Ona A.

[c] For patients who switched from topiramate to Ona A, TEAEs starting on or after the date of the first Ona A injection were counted in the treatment group related to the AE as determined by the investigator. If the AE was related to both treatments (or if relatedness was unknown), it was counted in both treatment groups, but only once for the total population.

Sources: Clinical Study Reports for FORWARD and GMA-BTX-CM-12-545 studies.[21,22]

Table 13: Harms in COMPEL and REPOSE Studies

	COMPEL	REPOSE
	Ona A 155 U (N = 716)	Ona A 155 U or 195 U (N = 633)
Patients with > 0 TEAEs, N (%)	436 (60.9)	[redacted]
Most common AEs (reported in ≥ 2%), N (%)		
Eyelid ptosis	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Musculoskeletal stiffness	[redacted]	[redacted]

	COMPEL	REPOSE
	Ona A 155 U (N = 716)	Ona A 155 U or 195 U (N = 633)
Musculoskeletal pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Migraine	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
SAEs		
Patients with > 0 SAEs, N (%)	[redacted]	[redacted]
SAEs occurring in ≥ 3 Patients		
Non-cardiac chest pain	[redacted]	[redacted]
Malignant melanoma	[redacted]	[redacted]
Migraine	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Suicidal ideation	[redacted]	[redacted]
WDAEs		
WDAEs, N (%)	[redacted]	[redacted]
TEAEs leading to study discontinuation occurring in ≥ 2 patients, N (%)		
Eyelid ptosis	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	NR
[redacted]	[redacted]	NR
Headache	3 (0.4)	NR
Pregnancy	3 (0.4)	NR
Suicidal ideation	4 (0.6)	NR
Rash	2 (0.3)	NR
Number of deaths, N (%)	0	0
Notable harms		
Dysphagia	[redacted]	3 (0.5)
Neck pain	[redacted]	18 (2.8)
Muscular weakness	[redacted]	10 (1.6)
Eyelid ptosis	[redacted]	34 (5.4)
Diplopia	[redacted]	NR
Urinary incontinence	[redacted]	NR

AE = adverse event; Ona A = onabotulinumtoxinA; SAE = serious adverse event; TEAE = treatment-emergent adverse event; U = Allergan units; WDAE = withdrawal due to adverse event.

Sources: Blumenfeld et al.,[32] Clinical Study Reports for COMPEL and REPOSE studies.[23,35]

Discussion

Summary of Available Evidence

Two RCTs (the FORWARD study and Study 545) and four single-arm trials (COMPEL, REPOSE, Negro et al. [2015], and Negro et al. [2016]) were included in this review. All trials included adult patients with CM, with the Negro et al. studies including patients with CM and MOH. The FORWARD study evaluated the efficacy, safety, and tolerability of Ona A versus topiramate over a 36-week period. Study 545 compared Ona A with placebo over a 24-week period. COMPEL, REPOSE, and the Negro et al. 2015, studies evaluated the efficacy and safety of Ona A for up to two years. The primary outcome in the FORWARD study was the proportion of patients with a decrease from baseline of at least 50% in the frequency of headache days per 28-day period, at the primary time point of week 32. Other outcomes included change from baseline in the frequency of headache days per 28-day period, change from baseline in total HIT-6 score per 28-day period, and the proportion of patients with a ≥ 70% decrease from baseline in the frequency of headache days per 28-day period. The family-wise error rate was controlled using a hierarchical-testing gatekeeping procedure in the assessment of these outcomes. Many other efficacy outcomes, including patient-reported outcomes, were assessed in the FORWARD study as exploratory. In Study 545, the primary efficacy end point was change from baseline in the ACM-I total score. Other efficacy measures were change from baseline in the ACM-I, ACM-S, MSQ, and HIT-6 scores. [redacted] In the COMPEL trial, the primary efficacy end point was the mean change from baseline in the number of headache days for the 28-day period ending at week 108 (following nine treatments). The secondary efficacy measures were the mean change from baseline in the frequency of headache days for the 28-day period ending at week 60 (following five treatments), and the mean change from baseline in HIT-6 total score over a four-week period at week 60 and week 108 (following nine treatments). Many other efficacy outcomes, including patient-reported outcomes, were assessed in the COMPEL study as exploratory. [redacted] In the REPOSE study, no primary variable was defined. Efficacy measures assessed were change from baseline in MSQ, change from baseline in EQ-5D-3L, change from baseline in patient-reported headache frequency, and health care resource utilization, which was assessed by evaluating admission to hospital for headache. No adjustments for multiplicity were performed. In both Negro et al. studies, the assessed efficacy measures were headache days, migraine days, and acute pain medication intake every three months. HIT-6 was assessed every six months.

In addition to the main trials reviewed, two clinical trials were reviewed and critically appraised in the original CDR clinical report for Ona A in adults with CM. PREEMPT-1 and PREEMPT-2 were summarized in Appendix 6, and the open-label extension of PREEMPT-1 and PREEMPT-2 was summarized in Appendix 7. In addition, an indirect treatment comparison (ITC) that compared Ona A with other therapies for CM in adults was summarized and critically appraised in Appendix 8.

Interpretation of Results

Efficacy

Ona A for prevention of CM was initially submitted to the CDR in August 2013 and subsequently considered by CDEC in March 2014 (original review) and May 2014 (request for reconsideration). The Final Recommendation issued on May 28, 2014, recommended that Ona A not be listed for the management of CM. The first reason provided for the recommendation not to list was the uncertainty regarding both the magnitude and clinical significance of the treatment effect of Ona A, particularly with respect to HRQoL and headache and migraine outcomes. The second reason involved the limitations of the design of the PREEMPT-1 and PREEMPT-2 trials, namely the enrolled patient population and potential inclusion of patients with MOH. In addition, CDEC noted a research gap such that there was insufficient evidence regarding long-term safety and efficacy. The manufacturer provided additional studies and articles to address CDEC's concerns.

Patient group input and the clinical expert involved in the review identified HRQoL as an important outcome, and as such it was chosen as a key efficacy outcome. In the PREEMPT-1 and PREEMPT-2 trials, HRQoL was measured using MSQ. To address the first reason provided for the 2014 CDEC recommendation not to list, the manufacturer provided an article by Cole et al.,[15] which describes MCIDs for between-group comparisons of the three domains of the MSQ. The group-level MCIDs for between-group differences was estimated to be as follows: RR: 3.2, RP: 4.6, and EF: 7.5. The treatment-effect sizes associated with Ona A in the PREEMPT-1 and PREEMPT-2 trials for each of the MSQ domains, with the exception of EF in PREEMPT-1, all exceeded the between-group MCIDs identified by Cole et al.[15] However, the MCIDs estimated by Cole et al.[15] were based on a maximum of 15 headache days per month (i.e., most patients in the datasets used by Cole et al. would be below the threshold for classification of CM). Hence the MCID reported by Cole et al.[15] may not be applicable to patients with CM, especially given that most patients with CM would likely have worse QoL than patients with a maximum of 15 headache days per month, and an improvement in QoL that would be seen as clinically meaningful for patients with a maximum of 15 headache days per month might not be generalizable to patients with CM.

Reducing the frequency of headache and migraine days was also an important outcome according to the patient group input and the clinical expert involved in the review, and as such was chosen as a key efficacy outcome for the review. In the PREEMPT-1 and PREEMPT-2 trials, the frequency of headache and migraine days were measured. The original CADTH review report concluded that the absolute difference between Ona A and placebo in headache and migraine days of approximately one to two days, was not clinically important.[14] To address the first reason provided for the CDEC recommendation not to list, the manufacturer in its resubmission pointed to more recent evidence by Dodick et al.[16] that a one-day reduction in headache frequency was clinically meaningful. Dodick et al. referenced a study by Silberstein et al.[17] that examined headache frequency and HRQoL. Silberstein et al. examined the characteristics of patients (N = 703), 12 years of age or older, who received Ona A using data from an open-label, clinical study, conducted at 10 headache centres in the US.[17] The majority (65.6%) of patients had CM, although approximately 34% had other types of headache conditions, such as migraine not classified as chronic and tension-type headache. Silberstein et al.[17] stated that: "A 1-day increase in HA [headache] frequency was associated with a greater likelihood of HA pain interfering with mood (4.0%, $P < .001$), recreational activities (4.0%, $P = .004$), or life enjoyment (4.0%,

P = .001)." It is unclear which instruments that the domains of mood, recreational activities, or life enjoyment were taken from. As well, it is unclear if the domains were selected a priori or if a relationship between headache frequency and the other domains of HRQoL of the three instruments was also tested, found not to be statistically significant and not reported. Without knowing the scale on which these domains were based, it is difficult to determine if a 4% improvement was clinically meaningful. In addition, the time point and study sample size upon which these results are based are unclear. If it was at the one-year point, a large number of patients (N = 221) had dropped out by then and it is uncertain if data for these patients was imputed or omitted from the final results. No other studies were identified that specifically examined the association between reduction in headache frequency and QoL in patients with CM. The between-group difference in the mean change from baseline in frequency of headache days per 28 days at week 24 was [redacted] in PREEMPT-1 and [redacted] in PREEMPT-2, [redacted]. The between-group difference in the mean change from baseline in frequency of migraine/probable migraine days per 28-day period at week 24 was [redacted] in PREEMPT-1 and [redacted] in PREEMPT-2, [redacted]. The clinical expert consulted on this review indicated that the between-group difference in the mean change from baseline in frequency of headache days, and in frequency of migraine/probable migraine days of one to two days was clinically meaningful for patients.

To address the second reason for the do-not-list recommendation from CDEC related to the inclusion of patients suffering from MOH in the PREEMPT-1 and PREEMPT-2 trials, the manufacturer pointed to the 2018 International Headache Society (IHS) Guidelines for Controlled Trials of Preventive Treatment of Chronic Migraine.[18] The IHS guidelines specifically address medication overuse in chronic migraine trials as they acknowledge that many patients diagnosed with CM also overuse acute medications and so also fulfill criteria for MOH. Moreover, the IHS guidelines recommend that inclusion of patients with MOH should not be prohibited in clinical trials of CM prophylaxis due to the large and representative population of CM sufferers with MOH.[18] Rather, the guidelines recommend that patients with CM and MOH be included in trials that are stratified and balanced accordingly.[18] It is also recommended that no changes should be made to overused drugs during the screening phase, baseline, and double-blind periods to avoid potentially confounding the outcome measures, unless required by the nature of the trial.[18] Given the recently published IHS recommendations, and the fact that the included patients with MOH in the PREEMPT trials were stratified and balanced between groups for MOH as recommended by the guideline, it was reasonable for the pivotal trials to enrol patients with MOH and CM. The clinical expert consulted on this review also indicated that patients with MOH should not be excluded from clinical trials of CM, and enrolling patients with MOH in the trials after adequate and careful medication overuse discontinuation might not be possible. In this resubmission, the manufacturer provided two single-arm trials (Negro et al. [2015] and Negro et al. [2016]) that enrolled patients with CM and comorbid MOH and evaluated the long-term efficacy and safety of Ona A over a two-year period. In both studies, efficacy measures assessed were change from baseline in headache days, migraine days, acute-pain medication intake, and HIT-6. Improvement in headache symptoms and acute headache pain medication intake was an important outcome according to the patient group input. The HIT-6 is a questionnaire that quantifies the impact of headache on a patient's life. In the Negro et al. studies, the number of headache days, migraine days, acute-pain medication intake, and HIT-6 score decreased during the period of treatment from the first to the last session of therapy. However, none of the outcomes

assessed in the Negro et al. studies were adjusted for multiplicity, and interpretation of any reported results should consider the potential for inflated type I error. Also, both studies were single-arm studies. There is a risk of bias with outcome measurements in single-arm studies as patients and providers are aware of their assigned intervention. Measurement of subjective outcomes such as HIT-6 may be at increased risk of bias if patients in the study are aware of their treatment allocation. In addition, Clinical Study Reports were not provided by the manufacturer for these studies. A detailed and thorough assessment of these studies was therefore not possible, especially given that the extent of exposure to Ona A, the number of injections of Ona received by patients, and how concomitant medications were handled were not reported. In addition, it was not reported how many patients were included in the analyses at each time point or whether any imputation method was used to account for missing data, making it impossible to know if there was any missing values, or, if there were missing values, how these were handled.

To address the third reason for the do-not-list recommendation from CDEC (insufficient evidence regarding long-term safety and efficacy), the manufacturer provided four single-arm trials: COMPEL, REPOSE, Negro et al. (2015), and Negro et al. (2016). The Negro et al. studies are summarized in the preceding paragraph. Both COMPEL and REPOSE assessed administration of 155 U of Ona A in patients with CM over a period of 108 weeks and 104 weeks respectively. In the COMPEL study, efficacy measures assessed were change from baseline in the number of headache days, change from baseline in HIT-6 total score, [redacted]. The efficacy measures assessed in the REPOSE study were change from baseline in MSQ questionnaire, change from baseline in EQ-5D-3L, change from baseline in headache frequency, and health care resource utilization. In the COMPEL study, [redacted] −10.7 [6.44] $P < 0.0001$), and a reduction in health resource utilization was also reported. In the REPOSE study, improvements in the EQ-5D-3L total score (index) and the frequency of headache days and a reduction in health resource utilization were observed at all post-baseline treatment visits. However, both trials had limitations, mainly the open-label design. There is a risk of bias with outcomes measured in single-arm studies as patients and providers are aware of their assigned intervention. Measurement of subjective outcomes such as HRQoL may be at increased risk of bias if patients in the study are aware of their treatment allocation. The lack of a control group makes it difficult to interpret the findings. Also, the discontinuation rate was high in the COMPEL and REPOSE studies, in which only 52.1% and 20.2% completed the study, respectively. This could seriously reduce the generalizability of the findings, given that the subgroup of patients completing the studies are potentially less representative of the recruited patients, and patients who remained in the study would more likely be patients without AEs and with better efficacy. In addition, in the analyses of changes from baseline for MSQ, change from baseline in the frequency of headache days and changes from baseline in health care resource utilization in the COMPEL study, and for all outcomes in the REPOSE study, data were analyzed “as is,” with no imputation methods employed for missing data. This is problematic, given that data for more than 50% of patients were not available at the last time point analysis, which would introduce bias in favour of Ona A and produce overestimated results. [redacted] In addition, none of these studies assessed stopping criteria or reported what

happened to patients who discontinued treatment. It is not clear if the reduction in headache days would be sustained if patients were to stop receiving Ona A.

A key limitation identified in the original CDR clinical review report for Ona A was the lack of a head-to-head active-comparison trial. The manufacturer provided an open-label RCT (FORWARD) that evaluated the efficacy, safety, and tolerability of Ona A versus topiramate in adult patients with CM. This trial reported statistically significant results in favour of Ona A for the primary and secondary outcomes (which were adjusted for multiple testing). [redacted] in which 80.3% of patients in the topiramate group discontinued topiramate treatment and only 14.3% discontinued Ona A treatment. While the main reason of discontinuation was an adverse event, other reasons for discontinuation such as withdrawal of consent and loss to follow-up were also higher in the topiramate treatment group than in the Ona A treatment group. In addition, the data-imputation method used for the base-case analysis was BLOCF, in which, if a patient has a missing entry for any reason (e.g., discontinuation due to AE, lost to follow-up, lack of efficacy), the baseline value data were utilized and the patient was considered a nonresponder. [redacted] Given these limitations, the results reported in the FORWARD trial are uncertain.

The Institute for Clinical and Economic Review conducted an ITC to examine calcitonin gene-related peptide (CGRP) inhibitors compared with placebo or commonly used preventive treatments in adults with CM.[19] Although several efficacy and safety outcomes were evaluated, ITCs could be performed only for change from baseline in monthly migraine days, change from baseline in monthly headache days, and all-cause discontinuation. In a Bayesian network meta-analysis, Ona A was not favoured over topiramate or CGRP inhibitors on these outcomes.[19] However, these results are limited by several potential sources of heterogeneity, which were not systematically evaluated, and generalizability to the patient population of interest is limited. In clinical practice, Ona A is likely to be used in patients who have failed several lines of previous treatments. However, the CGRP inhibitor trials in the network meta-analyses excluded patients who failed as few as two or three previous therapies and insufficient data were available to conduct subgroup analyses for patients who failed at least one prior preventive therapy. Other factors that limit generalizability were the failure of the trials to consistently follow Health Canada–approved Ona A dosing and the fact that the ITCs did not incorporate longer-term follow-up data.

[redacted]

[redacted]

In the original submission,[14] the manufacturer-requested reimbursement criteria were:

- Prophylaxis of headaches in adults with CM (≥ 15 days per month with headache lasting four hours a day or longer) who have failed (i.e., exhibit a lack of efficacy, intolerance, or clinical contraindication to) at least three prior oral prophylactic medications. Patients who have not obtained an adequate treatment response (≥ 30% reduction in days of headache per month) after two treatment cycles should be discontinued from further therapy.

In the resubmission, the requested reimbursement criteria are the same as the indication, i.e., for the prophylaxis of headaches in adults with CM (≥ 15 days per month with headache lasting four hours a day or longer). This is less restrictive than the reimbursement criteria in the original submission and no stopping rule has been suggested in the new requested reimbursement criteria. The European Headache Federation's published guidelines on the use of Ona A for CM indicate that response to Ona A should be continuously monitored by headache calendars, and that there are no convincing data supporting one definition of responders to Ona A over another.[64] These guidelines recommend that if patients experience a reduction in headache days of less than 30% during the first month after treatment with Ona A compared with the month before first treatment, then patients should be defined as nonresponders. They also recommend stopping Ona A if the patient does not respond during the first two or three treatment cycles.[64]

Harms

There were no deaths in any of the included trials. In patients who received Ona A for two years, no new safety signals were identified. In the FORWARD trial, the proportion of patients who experienced AEs, SAEs and withdrawals due to AEs was higher in the topiramate treatment group than Ona A group. In Study 545 the proportion of patients who experienced AEs and SAEs was higher in the Ona A group than in the placebo group. Overall, the most frequent AEs associated with Ona A were sinusitis, neck pain, eyelid ptosis, and migraine. In the FORWARD trial, no single SAE was reported by more than one patient; and SAEs were reported by 1.8% of patients in the Ona A treatment group. In the single-arm COMPEL study, SAEs were reported in 10.5% (75 of 716) of patients. The most frequently reported SAEs (i.e., by at least three patients each) were migraine (0.8), suicidal ideation (0.7%), and headache, malignant melanoma, and non-cardiac chest pain (0.4% each), while in the [redacted]
The most frequently reported SAEs were psychiatric disorders (0.5%) and nervous system disorders (0.3%). However, the clinical expert involved in the review indicated that these SAEs were unlikely to be due to Ona A treatment. [redacted] In the COMPEL study, discontinuations from the study due to AEs were reported in 4.5% of patients. The TEAEs leading to the most discontinuations were suicidal ideation (four patients) and eyelid ptosis, headache, and pregnancy (three patients each). [redacted]

[redacted]

In the Negro et al. studies, treatment-related AEs were only reported rather than TEAEs. This approach can underreport AEs experienced by patients because, while the TEAEs refer to adverse events temporally related to the study treatment, the treatment-related AEs refer to the causality assessment by the investigator. The FDA's guidance for industry (Statistical Principles for Clinical Trials) indicates that all AEs should be reported, whether or not they are considered to be related to treatment.[20]

Potential Place in Therapy[b]

In clinical practice Ona A can be expected to have a beneficial effect (defined as reduction in headache days) in approximately 70% of patients, while the remaining 30% of patients would be expected to receive no benefit from Ona A injections after two sets of injections given three months apart. Of the patients who would experience a beneficial effect, 20% will experience a reduction in the numbers of headaches days they have each month and approximately 40% can be expected to continue to have headaches with the same frequency but with reduced severity. Finally, approximately 10% of patients would experience a reduction in both frequency and severity of headaches.

In practice, patients who fulfil ICHD-III criteria for CM are offered the option of a trial of Ona A or topiramate and are provided with information about both medications. Many patients end up on treatment with both medications to obtain optimal results.

ICHD-III criteria are easy to apply to identify the patients most likely to benefit from Ona A therapy. This is a clinical diagnosis and no specialized testing is required.

[b] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

Two RCTs (FORWARD and Study 545) and four single-arm trials (COMPEL, REPOSE, Negro et al. [2015], and Negro et al. [2016]) were included in this review. All trials included adult patients with CM, with the Negro et al. studies including patients with CM and MOH. While the FORWARD study demonstrated that Ona A was statistically significantly superior to topiramate in reducing headache days, [redacted] and improving patient reported outcomes (HIT-6). However, FORWARD suffered from many methodological limitations that could potentially bias the results in favour of Ona A, including the open-label design, high dropout rate in the topiramate treatment group, and imputation methods. While all of the single-arm trials reported improvement in all of the outcomes assessed, there is uncertainty in the reported results due to the absence of a control arm, high dropout rate, and the risk of inflated type I error. [redacted], in the Negro et al. trials, which assessed the intake of acute-headache medication, patients decreased the frequency of their intake of acute headache pain medication. Whether the absolute numerical difference between groups of approximately one to two headache and migraine days reported in PREEMPT-1 and PREEMPT-2 in the original CDR review is clinically meaningful is uncertain. There were no deaths and no evidence of toxin spread, and anaphylactic reactions were reported in less than 0.1% of patients in one study. Ona A was associated with a relatively low incidence of SAEs in the included trials.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group, Migraine Canada, provided input for this submission. Migraine Canada is a national organization that supports, educates, and advocates for people living with migraines. The work of the organization is carried out through a volunteer board of directors, composed of patients and health care professionals. Migraine Canada educates and raises awareness about migraines through electronic and print materials, a website, social media, workshops, and forums. The organization received financial payments over the past two years from Allergan, the manufacturer of Botox, Eli Lily, and Novartis. In addition, the organization used funding from Allergan to pay the contractor who posted and collated the raw results for the online surveys.

2. Condition-Related Information

Migraine Canada, in partnership with Partage Migraine Québec, conducted two online surveys to gather information. Survey A was designed and analyzed by the Volunteer Board of Migraine Canada. It was promoted on Facebook, Migraine Canada's Twitter account, and through migraine clinics in Canada. The survey was open from June 4 to July 4, 2018. Responses were received from 251 participants with chronic migraine (CM). Survey B was also designed and analyzed by the Volunteer Board of Migraine Canada; however, it was targeted to patients with CM who received Botox. It was posted on the websites of Migraine Canada and Migraine Québec from September 24 to October 19, 2018, and was promoted on the Facebook communities of both organizations. Responses were received from 161 participants.

Migraine is a neurological disease that can be episodic (attacks on 14 days or fewer per month) or chronic (attacks on 15 days or more per month). The disease is differentiated into the active attack phase (ictal state) and the in-between attack phase (interictal state). During attacks, the headaches may be severe, throbbing, and with recurring pain, usually on one side. Patients often experience nausea, vomiting, dizziness, extreme sensitivity to sound, light, touch, and smell, and tingling or numbness in the extremities or face. There may also be auras that cause disturbances in vision, speech, sensations, and muscle strength. The attacks may last from four to 72 hours. Patients experience lower QoL during the in-between attack phase as well. Patients fear the next attack and may limit activities to avoid triggers and migraine onset. Planning ahead may be difficult — as one caregiver expressed, "There is a feeling of helplessness, and lack of control where scheduling life is concerned. We are at the mercy of these attacks."

Migraines have a significant impact on patients' lives. During attacks, the ability to accomplish tasks, work, and interact with others is compromised. Cognition is affected, with slowed thinking, lack of focus, and difficulty in reading and speaking. Nausea and vomiting may be disruptive and affect the intake of oral medications. The experience of sensory hypersensitivity may lead patients to isolate themselves in a dark room and stop all activities. In the survey, less than 1% indicated that they have no limitations and 2% reported that they avoid triggers but otherwise function well. Fifteen per cent missed work on five or more days per month and 19% indicated they are disabled (not working) but could still do some desired activities. However, 26% reported that they are disabled and dependent on others to accomplish the activities of daily living. One patient stated, "I am always managing migraines, or living in a darkened room. I am currently not working

because of migraine. Migraines are ruining my life." Another patient said, "It isolates and diminishes you. Constant pain symptoms from migraine wear on the body and soul." The disease affects family relationships, with 57% reporting major negative impacts. CM may also lead to anxiety and depression. In the survey, 42% reported mild effects on mood and 51% moderate or severe effects that required counselling and/or medications.

Patients also reported feeling stigmatized and blamed for wasting health care resources and the time of health care providers.

3. Current Therapy-Related Information

Patients have low satisfaction with the care received by physicians, with 16% very dissatisfied and 46% dissatisfied. No improvement in disease was reported by 38% of respondents, mild improvement by 51%, and marked improvement by 6%; five per cent reported worsening, which may be due to side effects of treatments. Patients often try multiple medications with no success and seek alternative therapies. In Surveys A and B, 76% and 85%, respectively, reported experiencing side effects that led to discontinuation of medication. Side effects include somnolence, fatigue, weight gain, gastrointestinal upset, depression, anxiety or mood difficulties, dizziness, cognitive problems, low blood pressure, syncope, exercise intolerance, and allergies.

Patients require more effective therapies to manage CM with fewer side effects.

4. Expectations About the Drug Being Reviewed

For patients, the most important aspect of a treatment is efficacy, followed by safety and tolerability. While patients do not expect a cure, they do expect that treatments will reduce the frequency of migraines, reduce dependence on medications, and improve quality of life (QoL). For example, patients expressed a need for "something that brings the frequency of the migraines down to a manageable level … and helps to stop the full migraine attack…," "Anything that would give me relief enough to have somewhat of a normal life," and "… allows me to return to a fully contributing member of the workforce and in my relationships."

In Survey B, 65% had tried five or more preventive medications before Botox. With Botox, patients experienced a decrease in the number of headache days, although 11% were still experiencing daily headaches. Patients reported a decrease in medication use after starting Botox; 50% of users completely stopped opioids or used them rarely and 26% stopped other preventive medications. Some patients may combine Botox with other medications to manage their condition. Improvements were noted in QoL, with 34% reporting a major impact, 35% a moderate impact, and 16% a minor impact. However, 12% reported no impact on QoL and 3% experienced a negative impact. Side effects were reported by 16% of respondents, such as minor cosmetic-related neck pain and transient increase in headache or neck pain prior to improvement. After treatment with Botox, 15% reported that they could go back to part-time or full-time work, 37% were missing fewer work days, and 79% indicated that attacks were easier to control (45% said a little easier and 34% much easier). After attempts to stop Botox or lengthen the interval between injections, patients reported that migraine recurred or that symptoms were too difficult to manage.

5. Additional Information

Migraine Canada expressed concern that migraine is a neglected, stigmatized, unrecognized, and under-diagnosed condition compared with other diseases and that these factors may restrict public access to Botox.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–) Embase (1974–) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 30, 2018
Alerts:	Bi-weekly search updates until April 10, 2019
Study Types:	Randomized controlled trials; controlled clinical trials
Limits:	No date or languate limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.nm	Name of substance word
.pt	Publication type
.mp	Mapped term
.rn	Registry number
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	exp Botulinum Toxins, Type A/
2	(onabotulin* or Botox or botulin* or BoNTA* or BoNT A or BoNT serotype A or BTXA or BTX A or BtA or Vistabel or Oculinum or Onaclostox or GSK 1358820 or GSK1358820 or AGN 191622 or AGN191622 or E211KPY694 or Daxibotulin* or dyslor or evabotulin* or letibotulin* or mt 10109 or mt10109 or nivobotulin* or prosigne or purtox or reloxin or rtt 150 or rtt150 or vistabex or xeomeen or Abobotulin* or Azzalure or CNT 52120 or CNT52120 or Dysport or Incobotulin* or Bocouture or NT 201 or NT201 or Xeomin or Prabotulin* or DWP450 or DWP 450 or Medytoxin or Meditoxin or Neuronox or Evabotulinumtoxina).ti,ab,ot,kf,hw,rn,nm.
3	1 or 2
4	exp Migraine Disorders/
5	(migraine or migraines or migrainous or sick headach* or (chronic adj2 headach*) or migrainosus or migraineur* or antimigrain* or hemicran*).ti,ab,ot,kf.
6	4 or 5
7	3 and 6
8	7 use medall
9	*botulinum toxin A/ or *Clostridium botulinum type A/
10	(onabotulin* or Botox or botulin* or BoNTA* or BoNT A or BoNT serotype A or BTXA or BTX A or BtA or Vistabel or Oculinum or Onaclostox or GSK 1358820 or GSK1358820 or AGN 191622 or AGN191622 or Daxibotulin* or dyslor or evabotulin* or letibotulin* or mt 10109 or mt10109 or nivobotulin* or prosigne or purtox or reloxin or rtt 150 or rtt150 or vistabex or xeomeen or Abobotulin* or Azzalure or CNT 52120 or CNT52120 or Dysport or Incobotulin* or Bocouture or NT 201 or NT201 or Xeomin or Prabotulin* or DWP450 or DWP 450 or Medytoxin or Meditoxin or Neuronox or Evabotulinumtoxina).ti,ab,kw,dq.
11	9 or 10
12	exp migraine/
13	(migraine or migraines or migrainous or sick headach* or (chronic adj2 headach*) or migrainosus or migraineur* or antimigrain* or hemicran*).ti,ab,kw,dq.
14	12 or 13
15	11 and 14
16	15 use oemezd
17	16 not (conference review or conference abstract).pt.
18	8 or 17
19	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
20	Randomized Controlled Trial/
21	exp Randomized Controlled Trials as Topic/
22	"Randomized Controlled Trial (topic)"/
23	Controlled Clinical Trial/
24	exp Controlled Clinical Trials as Topic/
25	"Controlled Clinical Trial (topic)"/
26	Randomization/

MULTI-DATABASE STRATEGY	
27	Random Allocation/
28	Double-Blind Method/
29	Double Blind Procedure/
30	Double-Blind Studies/
31	Single-Blind Method/
32	Single Blind Procedure/
33	Single-Blind Studies/
34	Placebos/
35	Placebo/
36	Control Groups/
37	Control Group/
38	(random* or sham or placebo*).ti,ab,hw,kf,kw.
39	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
40	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
41	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.
42	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
43	allocated.ti,ab,hw.
44	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
45	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
46	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
47	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
48	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
49	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.
50	or/19-49
51	18 and 50
52	remove duplicates from 51

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (ClinicalTrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	November 2018
Keywords:	Botox (onabotulinumtoxinA), migraines
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Appendix 3: Excluded Studies

Table 14: Excluded Studies

Reference	Reason for Exclusion
Cady RK, Schreiber CP, Porter JA, Blumenfeld AM, Farmer KU. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. Headache. 2011;51(1):21-32. Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. Headache. 2009;49(10):1466-1478.	Inappropriate dosage

Appendix 4: Detailed Outcome Data

Table 15: Summary of Headache Outcomes and Acute Headache Pain Medication Usage in FORWARD Trial

	FORWARD				
	Ona A 155 U (N = 140)	Topiramate (N = 142)	OR MD	95% CI	*P* value
Decrease from baseline in the frequency of headache days per 28-day period – ITT set at weeks 29 to 32[a]					
N	140	142			
Headache days ≥ 50% reduction from baseline,[bc] n (%)	56 (40.0)	17 (12.0)	OR = 4.94	2.681, 9.085	< 0.001
Headache days ≥ 70% reduction from baseline,[c] n (%)	38 (27.1)	12 (8.5)	OR = 4.05	2.014, 8.157	< 0.001
[redacted]					
Changes from baseline in frequency of headache days by 28-day (four-week) intervals – ITT set at weeks 29 to 32[ch]					
Baseline					
N	140	142			
Mean (SD)	22.1 (4.6)	21.9 (4.8)			
Weeks 29-32, N					
N	140	142			
Mean (SD)	13.8 (9.4)	19.8 (7.4)			
Change from baseline, mean (SD)					
N	140	142			

	FORWARD				
	Ona A 155 U (N = 140)	Topiramate (N = 142)	OR MD	95% CI	*P* value
Mean (SD)	−8.3 (8.9)	−2.1 (5.6)	MD = −6.199	−7.936 to −4.462	< 0.001
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]					

	FORWARD				
	Ona A 155 U (N = 140)	Topiramate (N = 142)	OR MD	95% CI	*P* value
[redacted]					
[redacted]					

BLOCF = baseline observation carried forward; CI = confidence interval; ITT = intention-to-treat; MD = mean difference; mLOCF = modified last observation carried forward; NR = not reported; Ona A = onabotulinumtoxinA; OR = odds ratio; SD = standard deviation; U = Allergan units; WOCF = worst observation carried forward.

[a] Odds ratio, 95% CI, and *P* value were estimated using a logistic regression model adjusted by baseline headache days. Baseline was defined as the first 28 days of the screening period starting on the day of e-diary setup. Missing data were handled using the BLOCF.

[b] Primary efficacy end point of the study.

[c] Outcomes have been adjusted for multiplicity.

[d] OR, 95% CI, and *P* value for weeks 29 to 32 are estimated using Fisher's exact test adjusted by baseline headache days.

[e] OR, 95% CI, and *P* value for weeks 29 to 32 are estimated using a logistic regression model adjusted by baseline headache days applying mLOCF imputation for missing values when there are fewer than 20 days of reported data in the e-diary. Baseline was defined as the first 28 days of the screening period starting on the day of e-diary setup.

[f] OR 95% CI, and *P* value for weeks 29 to 32 are estimated using a logistic regression model adjusted by baseline headache days applying (OCF imputation for missing values when there are fewer than 20 days of reported data in the e-diary. Baseline was defined as the first 28 days of the screening period starting on the day of e-diary setup.

[g] OR, 95% CI, and *P* value for weeks 29 to 32 are estimated using a logistic regression model adjusted by baseline headache days using observed data only. Baseline was defined as the first 28 days of the screening period starting on the day of e-diary setup.

[h] Estimated MD, 95% CI, and *P* value for the final 28-day period were assessed using nonparametric rank analysis of covariance with treatment as a factor and adjusting for baseline. Baseline was defined as the first 28 days of the screening period starting on the day of e-diary setup. Missing data were handled using the BLOCF imputation method.

[i] Estimated MD, 95% CI, and *P* value for the final 28-day period were assessed using analysis of covariance adjusting for baseline headache days. Baseline was defined as the first 28 days of the screening period starting on the day of e-diary setup. Missing data were handled using the mLOCF imputation method.

[j] Estimated MD, 95% CI, and *P* value for the final 28-day period are assessed using analysis of covariance adjusting for baseline headache days. Baseline is defined as the first 28 days of the screening period starting on the day of e-diary setup.

Source: Clinical Study Report for FORWARD study.[22]

Table 16: Summary of HIT-6, MIBS-4, and PHQ-9 Outcomes in FORWARD Trial

	FORWARD				
	Ona A 155 U (N = 140)	Topiramate (N = 142)	MD	95% CI	*P* value
Changes from baseline in total HIT-6 score per 28-day period at week 30 – ITT set[ab]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
Change from baseline					
N	110	115			
Mean (SD)	−5.6 (7.2)	−1.3 (3.9)	−4.248	−5.766 to −2.731	< 0.001
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

	FORWARD				
	Ona A 155 U (N = 140)	Topiramate (N = 142)	MD	95% CI	*P* value
[redacted]					
Change from baseline in total Patient Health Questionnaire score – ITT set at week 36[d]					
Baseline					
N	137	140			
Mean (SD)	6.5 (5.03)	7.6 (5.56)			
Weeks 36					
N	138	140			
Mean (SD)	4.4 (4.17)	7.1 (5.81)			
Change from baseline					
N	137	140			
Mean (SD)	−2.1 (4.59)	−0.5 (1.92)	−1.862	−2.628 to −1.095	< 0.001

BLOCF = baseline observation carried forward; CI = confidence interval; HIT-6 = six-item Headache Impact Test; ITT = intention-to-treat; MIBS-4= Migraine Interictal Burden Scale; MD = mean difference; mLOCF = modified last observation carried forward; NR = not reported; Ona A = onabotulinumtoxinA; PHQ-9 = Patient Health Questionnaire; SD = standard deviation; U = Allergan units.

[a] Estimated MD, 95% CI, and *P* value for the final week-30 assessment are assessed using nonparametric rank analysis of covariance with treatment as a factor and adjusting for baseline. Baseline was defined as assessments collected at randomization (day 1). For the change from baseline, only patients with a value at both baseline visit and the specific post-baseline visit were included.

[b] Outcomes have been adjusted for multiplicity.

[c] Baseline was defined as the first 28 days of the screening period starting on the day of e-diary setup. Missing data were handled using the BLOCF imputation method. Only assessments taken on days when a patient does not experience a headache were included. Total scores were averaged over each 28-day period (Total score divided by number of headache-free days). For the change from baseline, only patients with a value at both baseline visit and the specific post-baseline visit were included.

[d] Baseline was defined as assessments collected at randomization (Day 1). Missing data are handled using the BLOCF imputation method. For the change from baseline, only patients with a value at both baseline visit and the specific post-baseline visit were included.

Source: Clinical Study Report for FORWARD study.[22]

Table 17: [redacted]

	FORWARD				
	Ona A 155 U (N = 140)	Topiramate (N = 142)	MD	95% CI	*P* value
[redacted]					

	FORWARD				
	Ona A 155 U (N = 140)	Topiramate (N = 142)	MD	95% CI	*P* value
[redacted]					

	FORWARD				
	Ona A 155 U (N = 140)	Topiramate (N = 142)	MD	95% CI	*P* value
[redacted]					

CI = confidence interval; MD = mean difference; Ona A = onabotulinumtoxinA; SD = standard deviation; U = Allergan units.

[redacted]

Table 18: Work Productivity and Activity Impairment Questionnaire in the FORWARD Trial at Week 36

	FORWARD				
	Ona A 155 U (N = 140)	Topiramate (N = 142)	MD	95% CI	*P* value
Change from baseline in Work Productivity and Activity Impairment Questionnaire score – ITT set at week 36[a]					
Absenteeism score					
[redacted]					
Change from baseline, mean (SD)	−1.1 (9.64)	−0.8 (3.76)	[redacted]	[redacted]	[redacted]
Presenteeism score					
[redacted]					
Change from baseline, mean (SD)	−2.2 (18.93)	1.5 (5.73)	[redacted]	[redacted]	[redacted]
Work productivity loss score					
Baseline, N	107	101			
Baseline, mean (SD)	4.8 (2.64)	5.1 (2.33)			
Weeks 36, N	114	103			
Weeks 36, mean (SD)	3.5 (2.55)	4.3 (2.57)			
Change from baseline, N	107	101			
Change from baseline, mean (SD)	−1.3 (2.62)	−0.7 (2.05)	−0.669	−1.249 to −0.088	0.024
[redacted]					

	FORWARD				
	Ona A 155 U (N = 140)	Topiramate (N = 142)	MD	95% CI	*P* value
[redacted]					
[redacted]					
[redacted]					

BLOCF = baseline observation carried forward; CI = confidence interval; ITT = intention-to-treat; MD = mean difference; NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation; U = Allergan units.

[a] Baseline was defined as assessments collected at randomization (day 1). Missing data are handled using the BLOCF imputation method. For the change from baseline, only patients with a value at both baseline visit and the specific post-baseline visit were included.

Source: Clinical Study Report for FORWARD study.[22]

Table 19: Summary of Efficacy HIT-6 and MSQ in GMA-BTX-CM-12-545 Trial at Week 24

	GMA-BTX-CM-12-545			
	Ona A 155 U (N = 19)	Placebo (N = 26)	Between-groups difference	*P* value
HIT-6				
Baseline				
N	19	26		
Mean (SD)	64.7 (4.2)	65.3 (5.5)		
Week 24				
N	15	18		
[redacted]				
Change from baseline, mean (SD)	−5.1 (4.7)	−6.7 (7.9)	1.7 [redacted]	[redacted]
MSQ – role function-restrictive				
Baseline				
N	19	26		
Mean (SD)	39.8 (16.6)	40.9 (21.7)		
Week 24				
N	13	18		
[redacted]				
Change from baseline, mean (SD)	32.1 (15.4)	26.5 (28.9)	5.6 [redacted]	[redacted]
MSQ – role function-preventive				
Baseline				
N	19	26		
Mean (SD)	58.9 (18.8)	62.5 (23.0)		
Week 24				
N	13	18		
[redacted]				
Change from baseline, mean (SD)	25.8 (18)	20.8 (28.9)	4.9 [redacted]	[redacted]
MSQ – emotional function				
Baseline				
N	19	26		
Mean (SD)	53.3 (27.6)	58.7 (23.9)		
Week 24				

	GMA-BTX-CM-12-545			
	Ona A 155 U (N = 19)	Placebo (N = 26)	Between-groups difference	*P* value
N	14	18		
[redacted]	[redacted]	[redacted]		
Change from baseline, mean (SD)	26.2 (26.3)	18.5 (34.2)	7.7 [redacted]	[redacted]

HIT-6 = six-item Headache Impact Test; MD = mean difference; MSQ = Migraine-Specific Quality of Life Questionnaire; NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation; U = Allergan units.

Source: Clinical Study Reports for GMA-BTX-CM-12-545 study.[21]

Table 20: Summary of ACM-I and ACM-S Outcomes in GMA-BTX-CM-12-545 Trial at Week 24

	GMA-BTX-CM-12-545			
	Ona A 155 U (N = 19)	Placebo (N = 26)	Between-groups difference	*P* value
ACM-I global score				
Baseline				
N	19	26		
Mean (SD)	50.5 (17.6)	47.2 (22)		
Week 24				
N	15	18		
[redacted]	[redacted]	[redacted]		
Change from baseline, mean (SD)	−25.2 (23.5)	−20.5 (24.6)	−4.7 [redacted]	[redacted]
Symptom severity score subdomain of the ACM-S				
Baseline				
N	19	26		
Mean (SD)	54.3 (22.1)	45.9 (25.9)		
Week 24				
N	14	18		
[redacted]	[redacted]	[redacted]		
Change from baseline, mean (SD)	−18.5 (39.2)	−17.5 (30.1)	−0.9 [redacted]	[redacted]
Symptom experience score subdomain of the ACM-S				
Baseline				
N	19	26		
[redacted]	[redacted]	[redacted]		
Week 24				
N	14	18		
Mean (SD)	6.9 (3.8)	6.5 (4.0)		
Change from baseline, mean (SD)	−1.6 (5.4)	−1.9 (5.1)	0.3 [redacted]	[redacted]
Activities of daily living impact domain of the ACM-I				
Baseline				
N	19	26		
Mean (SD)	45 (16.6)	43.3 (21.1)		
Week 24				
N	15	18		
[redacted]	[redacted]	[redacted]		
Change from baseline, mean (SD)	−24 (24.8)	−21.9 (24.8)	−2.1 [redacted]	[redacted]
Emotions impact domain of the ACM-I				
Baseline				

	GMA-BTX-CM-12-545			
	Ona A 155 U (N = 19)	Placebo (N = 26)	Between-groups difference	*P* value
N	19	26		
Mean (SD)	51.9 (23.1)	42.3 (25.4)		
Week 24				
N	15	18		
[redacted]	[redacted]	[redacted]		
Change from baseline, mean (SD)	−26.2 (28.4)	−16.3 (21)	−9.9 [redacted]	[redacted]
Work/school impact domain of the ACM-I				
Baseline				
N	19	26		
Mean (SD)	47.9 (23.2)	43.1 (26.9)		
Week 24				
N	15	18		
[redacted]	[redacted]	[redacted]		
Change from baseline, mean (SD)	−30 (28.0)	−18.9 (33.1)	−11.1 [redacted]	[redacted]
Social impact domain of the ACM-I				
Baseline				
N	19	26		
Mean (SD)	39.6 (22.8)	43.1 (26.3)		
Week 24				
N	15	18		
[redacted]	[redacted]	[redacted]		
Change from baseline, mean (SD)	−18.7 (25.5)	−19.6 (29.3)	1.0 [redacted]	[redacted]
Leisure activities impact domain of the ACM-I				
Baseline				
N	19	26		
Mean (SD)	51.6 (21.4)	55.4 (31.1)		
Week 24				
N	15	18		
[redacted]	[redacted]	[redacted]		
Change from baseline, mean (SD)	−26.7 (24.7)	−30.0 (37.7)	3.3 [redacted]	[redacted]
Household activities impact domain of the ACM-I				
Baseline				
N	19	26		
Mean (SD)	45.3 (19.8)	48.5 (23.4)		
Week 24				
N	15	18		
[redacted]	[redacted]	[redacted]		
Change from baseline, Mean (SD)	−24 (28.5)	−24.4 (29.6)	0.4 [redacted]	[redacted]
Energy impact domain of the ACM-I				
Baseline				
N	19	26		
Mean (SD)	58.2 (22.2)	60.2 (19.9)		
Week 24				
N	15	18		
[redacted]	[redacted]	[redacted]		

	GMA-BTX-CM-12-545			
	Ona A 155 U (N = 19)	Placebo (N = 26)	Between-groups difference	*P* value
Change from baseline, mean (SD)	−26.3 (27.3)	−23.3 (27.8)	−3.0 [redacted]	[redacted]
Cognitive impact domain of the ACM-I				
Baseline				
N	18	26		
Mean (SD)	60.0 (19.9)	52.6 (27.0)		
Week 24				
N	14	18		
[redacted]	[redacted]	[redacted]		
Change from baseline, mean (SD)	−31.8 (29.3)	−26.3 (27.3)	−5.5 [redacted]	[redacted]
General impact domain of the ACM-I				
Baseline				
N	19	26		
Mean (SD)	57.9 (23)	53.1 (29.9)		
Week 24				
N	14	18		
[redacted]	[redacted]	[redacted]		
Change from baseline, mean (SD)	−28.6 (31.1)	−15.6 (45.3)	−13.0 [redacted]	[redacted]

ACM-I = Chronic Migraine – Impact; ACM-S = Assessment of Chronic Migraine Symptoms; MD = mean difference; NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation; U = Allergan units.

Source: Clinical Study Reports for GMA-BTX-CM-12-545 study.[21]

Table 21: Summary of Headache Outcomes in COMPEL Study Using Ona A 155 U

	COMPEL Study				
	Baseline	Week 24 (after treatment 2)	Week 60 (after treatment 5)	Week 84 (after treatment 7)	Week 108 (after treatment 9)
Change from baseline in the number of headache days per 28-day period (modified LOCF)					
N	715	715	715	715	715
Mean (SD)	22.0 (4.82)	14.6 (7.81)	12.7 (7.56)	12.2 (7.80)	11.3 (7.43)
Change from baseline, mean (95% CI)		−7.4 to [redacted]	−9.2 to [redacted]	−9.8 to [redacted]	−10.7 to [redacted]
P value for the change from baseline[a]		P < 0.0001	P < 0.0001	P < 0.0001	P < 0.0001
Subgroup: history of acute medication overuse at baseline					
N	456	456	456	456	456
Mean (SD)	21.8 (4.58)	14.4 (7.72)	12.6 (7.51)	12.2 (7.74)	11.2 (7.39)
Change from baseline, mean (95% CI)		−7.4 (−7.9 to −6.8)	−9.2 (−9.8 to −8.6)	−9.6 (−10 to −9.0)	−10.6 (−11 to −10)
Subgroup: no medication overuse at baseline					
N	259	259	259	259	259
Mean (SD)	22.3 (5.21)	14.9 (7.98)	13.0 (7.66)	12.3 (7.91)	11.3 (7.53)
Change from baseline, mean (95% CI)		−7.3 (−8.1 to −6.5)	−9.3 (−10 to −8.5)	−10.0 (−11 to −9.2)	−11.0 (−12 to −10)
Subgroup: use of oral preventive treatment at baseline					
N	348	348	348	348	348
Mean (SD)	22.3 (4.79)	15.4 (7.86)	13.6 (7.67)	13.0 (7.84)	12.1 (7.55)

	COMPEL Study				
	Baseline	Week 24 (after treatment 2)	Week 60 (after treatment 5)	Week 84 (after treatment 7)	Week 108 (after treatment 9)
Change from baseline, mean (95% CI)		−6.9 (−7.6 to −6.3)	−8.7 (−9.4 to −8.1)	−9.3 (−10 to −8.7)	−10.2 (−11 to −9.5)
Subgroup: no preventive treatment at baseline					
N	367	367	367	367	367
Mean (SD)	21.7 (4.84)	13.9 (7.71)	12.0 (7.38)	11.5 (7.69)	10.4 (7.23)
Change from baseline, mean (95% CI)		−7.8 (−8.4 to −7.1)	−9.7 (−10 to −9.0)	−10.2 (−11 to −9.5)	−11.2 (−12 to −11)
Subgroup previous use of preventive treatment					
N	349	349	349	349	349
Mean (SD)	22.3 (4.82)	15.4 (7.86)	13.5 (7.67)	13.0 (7.84)	12.1 (7.55)
Change from baseline, mean (95% CI)		−6.9 (−7.5 to −6.3)	−8.7 (−9.4 to −8.1)	−9.3 (−10 to −8.6)	−10.2 (−11 to −9.5)
Subgroup: no previous preventive treatment					
N	366	366	366	366	366
Mean (SD)	21.7 (4.81)	13.9 (7.72)	12.0 (7.39)	11.5 (7.70)	10.5 (7.24)
Change from baseline, mean (95% CI)		−7.8 (−8.4 to −7.1)	−9.7 (−10 to −9.1)	−10.2 (−11 to −9.5)	−11.2 (−12 to −11)
[redacted]					
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LOCF = last observation carried forward; NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation; U = Allergan units.

[a] Two-sided *P* value for comparing post-baseline visit to baseline was from the paired t-test.

Source: Clinical Study Reports for COMPEL study.[23]

Table 22: Summary of HIT-6 and MSQ Outcomes in COMPEL Study Using Ona A 155 U

	COMPEL Study				
	Baseline	Week 24 (after treatment 2)	Week 60 (after treatment 5)	Week 84 (after treatment 7)	Week 108 (after treatment 9)
HIT-6 total score (modified LOCF)					
N	713	713	713	713	713
Mean (SD)	64.7 (4.82)	[redacted]	58.0 (7.02)	[redacted]	57.7 (7.81)
Change from baseline, mean (95% CI)		[redacted]	−6.8 to [redacted]	[redacted]	−7.1 to [redacted]
P value for the change from baseline[a]		P < 0.0001	P < 0.0001	P < 0.0001	P < 0.0001
Subgroup: history of acute medication overuse at baseline					
N	456	456	456	456	456
Mean (SD)	65.0 (4.55)	59.6 (6.73)	58.2 (7.01)	57.2 (7.07)	58.0 (7.80)
Change from baseline, mean (95% CI)		−5.3 (−5.9 to −4.8)	−6.8 (−7.4 to −6.2)	−7.8 (−8.4 to −7.2)	−7.0 (−7.6 to −6.3)
Subgroup: no medication overuse at baseline					
N	257	257	257	257	257

	COMPEL Study				
	Baseline	Week 24 (after treatment 2)	Week 60 (after treatment 5)	Week 84 (after treatment 7)	Week 108 (after treatment 9)
Mean (SD)	64.3 (5.25)	58.8 (6.98)	57.6 (7.05)	56.5 (7.37)	57.1 (7.81)
Change from baseline, mean (95% CI)		−5.5 (−6.2 to −4.7)	−6.7 (−7.4 to −5.9)	−7.8 (−8.7 to −7.0)	−7.2 (−8.1 to −6.3)
Subgroup: use of oral preventive treatment at baseline					
N	346	346	346	346	346
Mean (SD)	64.9 (4.70)	60.2 (6.38)	58.7 (6.78)	57.9 (6.75)	58.8 (7.38)
Change from baseline, mean (95% CI)		−4.6 (−5.2 to −4.0)	−6.1 (−6.8 to −5.5)	−7.0 (−7.6 to −6.3)	−6.1 (−6.8 to −5.4)
Subgroup: no preventive treatment at baseline					
N	367	367	367	367	367
Mean (SD)	64.6 (4.95)	58.5 (7.13)	57.3 (7.18)	56.0 (7.45)	56.7 (8.08)
Change from baseline, mean (95% CI)		−6.1 (−6.8 to −5.5)	−7.4 (−8.1 to −6.6)	−8.6 (−9.4 to −7.9)	−8.0 (−8.8 to −7.2)
Subgroup: previous use of preventive treatment					
N	347	347	347	347	347
Mean (SD)	64.8 (4.69)	60.2 (6.38)	58.7 (6.77)	57.9 (6.75)	58.7 (7.37)
Change from baseline, Mean (95% CI)		−4.6 (−5.2 to −4.0)	−6.1 (−6.8 to −5.5)	−7.0 (−7.6 to −6.3)	−6.1 (−6.8 to −5.4)
Subgroup: no previous preventive treatment					
N	366	366	366	366	366
Mean (SD)	64.6 (4.95)	58.5 (7.14)	57.3 (7.19)	56.0 (7.46)	56.7 (8.08)
Change from baseline, mean (95% CI)		−6.1 (−6.8 to −5.5)	−7.4 (−8.1 to −6.6)	−8.6 (−9.4 to −7.9)	−8.0 (−8.8 to −7.2)
[redacted]					
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	COMPEL Study				
	Baseline	Week 24 (after treatment 2)	Week 60 (after treatment 5)	Week 84 (after treatment 7)	Week 108 (after treatment 9)
[redacted]					
[redacted]					

CI = confidence interval; HIT-6 = six-item Headache Impact Test; LOCF = last observation carried forward; MSQ = Migraine-Specific Quality of Life Questionnaire; NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation; U = Allergan units.

[a] Two-sided *P* value for comparing post-baseline visit to baseline was from the paired t-test.

Source: Clinical Study Reports for COMPEL study.[23]

Table 23: [redacted]

	COMPEL Study				
	Baseline	Week 24 (after treatment 2)	Week 48 (after treatment 4)	Week 72 (after treatment 6)	Week 96 (after treatment 8)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
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Table 24: [redacted]

	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
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[redacted]					
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	[redacted]				
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[redacted]					
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		[redacted]	[redacted]		
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[redacted]

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[redacted][35]

Table 25: Summary of Efficacy Outcomes in Negro et al. (2015) Using Ona A 155 U

	Negro et al. (2015), Ona A 155 U (N = 132)[a]				
	Headache Days per Month N = 132 Mean (SD)	Migraine Days per Month N = 132 Mean (SD)	Medication Intake Days per Month N = 132 Mean (SD)	HIT-6 N = 132 Mean (SD)	Percentage of Patients With Severe Impact (HIT-6 score ≥ 60), N = 132, n (%)
Baseline (1st injection)	22.3 (4.1)	21.4 (4.3)	20.8 (4.5)	68.9 (4.3)	124 (93.9)
3 months (2nd injection)	16.3 (2.7)[b]	15.9 (2.8)[b]	14.2 (2.8)[b]		
6 months (3rd injection)	12.9 (2.6)[b]	12.4 (2.5)[b]	11.8 (2.4)	64.4 (5.0)[b]	102 (77.3)
9 months (4th injection)	11.6 (2.2)[b]	11.3 (2.3)[b]	11 (2.1)[b]		
12 months (5th injection)	9.4 (2.9)[b]	9.2 (2.8)[b]	8.7 (2.7)[b]	58.5 (3.7)[b]	59 (44.7)
15 months (6th injection)	9.0 (2.8)[b]	8.3 (3.0)[b]	8.3 (3.0)[b]		
18 months (7th injection)	8.6 (2.6)[b]	7.9 (3.0)[b]	7.6 (2.9)[b]	55.4 (4.9)[b]	49 (37.1)
21 months (8th injection)	8.0 (2.3)[b]	7.3 (2.7)[b]	6.0 (2.3)[b]		
24 months	7.3 (2.1)[b]	6.8 (2.3)[b]	5.3 (1.7)[b]	52.0 (5.6)[b]	29 (22)

HIT-6 = six-item Headache Impact Test; Ona A = onabotulinumtoxinA; SD = standard deviation; U = Allergan units.

[a] It was not reported how many patients were included in the analysis of each outcome at all time points.

[b] $P \leq 0.05$ for the change from baseline. A paired t-test was used to compare the mean headache days, migraine days, medication intake days, and HIT-6 score at baseline and at each cycle of injections after Hartley's Fmax test to assess equal variance of data. A chi-square test was used to compare categorical variables.

Source: Negro et al.[24]

Reprinted and (modified) from Springerplus, Negro A, Curto M, Lionetto L, Crialesi D, Martelletti P. onabotulinumtoxinA 155 U in medication overuse headache: a two years prospective study. 2015;4:826. Creative Commons Attribution License 4.0. http://creativecommons.org/licenses/by/4.0/legalcode. Modified by compiling data from additional file 1 Tables S1, S2, S3, S4, and S5.

Table 26: Summary of Efficacy Outcomes in Negro et al. (2016) Using Ona A 195 U

	Negro et al. (2016), Ona A 195 U (N = 143)[a]				
	Headache days per month N = 143 Mean (SD)	Migraine Days per Month N = 143 Mean (SD)	Medication Intake Days per Month N = 143 Mean (SD)	HIT-6 N = 143 Mean (SD)	Percentage of Patients With Severe Impact (HIT-6 score ≥ 60), N = 143 n (%)
Baseline (1st injection)	22.2 (4.9)	21.6 (4.8)	21.0 (5.1)	67.9 (4.2)	137 (95.8)
3 months (2nd injection)	14.1 (3.4)[b]	13.5 (3.6)[b]	13.8 (3.2)[b]	-	
6 months (3rd injection)	10.2 (2.8)[b]	9.7 (2.7)[b]	9.9 (1.9)[b]	61.0 (3.9)[b]	91 (63.6)
9 months (4th injection)	7.4 (2.2)[b]	6.9 (1.6)[b]	7.0 (1.6)[b]	-	
12 months (5th injection)	5.7 (1.7)[b]	5.4 (1.2)[b]	5.6 (1.4)[b]	56.8 (3.8)[b]	57 (39.9)
15 months (6th injection)	5.4 (1.2)[b]	4.8 (1.0)[b]	5.1 (1.3)[b]	-	
18 months (7th injection)	4.9 (1.3)[b]	4.5 (1.0)[b]	4.7 (1.3)[b]	54.0 (4.6)[b]	38 (26.5)
21 months (8th injection)	4.4 (1.2)[b]	4.1 (1.0)[b]	4.2 (1.4)[b]	-	
24 months	4.1 (1.0)[b]	3.8 (1.0)[b]	3.7 (1.3)[b]	49.0 (6.7)[b]	22 (15.4)

HIT-6 = six-item Headache Impact Test; Ona A = onabotulinumtoxinA; SD = standard deviation; U = Allergan units.

[a] It was not reported how many patients were included in the analysis of each outcome at all time points.

[b] $P \leq 0.05$ for the change from baseline. A paired t-test was used to compare the mean headache days, migraine days, medication intake days, and HIT-6 score at baseline and at each cycle of injections after Hartley's Fmax test to assess equal variance of data. A chi-square test was used to compare categorical variables.

Source: Negro et al.[25]

Reprinted and (modified) from The Journal of Headache and Pain, Negro A, Curto M, Lionetto L, Martelletti P. A two years open-label prospective study of onabotulinumtoxinA 195 U in medication overuse headache: a real-world experience. 2016;17:1.Creative Commons Attribution License 4.0. http://creativecommons.org/licenses/by/4.0/legalcode. Modified by compiling data from Table 3 and additional file 1 Table S1.

Table 27: Harms in Negro et al. (2015) and Negro et al. (2016) Studies

	Negro et al. (2015)	Negro et al. (2016)
	Ona A 155 U (N = 132)	Ona A 195 U (N = 143)
Patients with > 0 TRAEs, N (%)	23 (17.5)	29 (20.3)
Severe TRAE	0	0
TRAE observed		
Neck pain	5 (3.8)	6 (4.2)
Injection site pain	4 (3.3)	5 (3.5)
Headache	5 (3.7)	7 (4.9)
Muscular weakness	5 (3.8)	7 (4.9)
Eyelid ptosis	4 (2.9)	4 (2.8)

Ona A = onabotulinumtoxinA; TRAE = treatment-related adverse event; U = Allergan units.

Sources: Negro et al.,[24] Negro et al.[25]

Appendix 5: Validity of Outcome Measures

Aim

The purpose of this appendix is to evaluate the validity and reliability of health-related quality of life (HRQoL) and patient-reported outcome measures for chronic migraine (CM).

In the original CADTH Common Drug Review clinical report,[14] the Migraine-Specific Quality of Life Questionnaire (MSQ) version 2.1 (MSQv2.1) and the six-item Headache Impact Test (HIT-6) were described. An updated literature search was performed for MSQ and HIT-6. The findings from the original report and updated literature search are included here. In addition, the results of Cole et al.[15] for between-group differences and minimal clinically important differences (MCIDs) for the three domains of the MSQv2.1 are described.

The studies in this review evaluated a number of additional outcomes that were not in the original report. This appendix additionally evaluates the validity and reliability of the following outcomes:

- Headache and migraine/probable migraine days
- Migraine Interictal Burden Scale (MIBS-4)
- Patient Health Questionnaire (PHQ-9) quick depression assessment score
- Assessment of Chronic Migraine – Impact (ACM-I) score and Assessment of Chronic Migraine Symptoms (ACM-S)
- Work Productivity and Activity Impairment Questionnaire – Specific Health Problem (WPAI-SHP)
- EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L).

Findings

Table 28: Summary of Outcome Measures and Their Measurement Properties

Outcome Measure	Type	Conclusions about Measurement Properties	MCID	References
MSQ (version 2.1)	14-items and 3 domains: • RR • RP • EF Each item rated on a 6-point scale.	**Validity:** Patients with CM: construct validity (weak to strong correlation with HIT-6, MIDAS, and PHQ-4;[39] strong correlation with HIT-6)[40] **Reliability:** Patients with CM: internal consistency demonstrated (Cronbach's alpha = RR 0.95, RP 0.90, EF 0.85;[39] Cronbach's alpha range = 0.90-0.97 across the 3 domains)[40] **Responsiveness:** Patients with CM: large effect size for patients with ≥ 50% improvement and moderate effect	Patients with CM: within-group MCIDs (anchor-based) RR = 10.9 RP = 8.3 EF = 12.2 Patients with max. 15 headache days per month: group-level MCIDs (distribution-based)[a] RR = 3.2 RP = 4.6 EF = 7.5	Bagley (2012)[39] Rendas-Baum (2013)[40] Dodick (2007)[41] Cole (2009)[15]

Outcome Measure	Type	Conclusions about Measurement Properties	MCID	References
		size for patients with 30% to 50% improvement		
HIT-6	6 items: pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. Each item rated on a 5-point scale.	**Validity:** Patients with CM: strong correlation with MSQ (r = −0.86 to −0.59) **Reliability:** Patients with CM: internal consistency (Cronbach's alpha of 0.75 to 0.92) and test-retest reliability demonstrated (ICC = 0.77) **Responsiveness:** Patients with CM: Scores detected changes in disease status based on headache frequency and cumulative hours of headache	Patients with EM: within-group MCID = 2.5 Patients with chronic daily headaches: between-group MCID = 2.3	Kosinski (2003)[43] Kawata (2005)[44] Yang (2011)[65] Rendas-Baum (2014)[45] Coeytaux (2006)[46] Smelt (2014)[47]
Headache and migraine/ probable migraine days	Reduction in the number of headaches, migraines, or probable migraine days. May be recorded by a patient diary.	Not available	Patients with mixed headache conditions: 1-day increase in headache frequency associated with quality of life domains[b]	Silberstein (2010)[17]
MIBS-4	Measurement of migraine burden between attacks with 4 domains and 4 items	**Validity:** Patients with migraine: correlation with MIDAS, PHQ-4, and MSQ	Not identified	Buse (2007)[66]
PHQ-9	9 items for depressive disorders. Each item rated on a 4-point scale	**Validity:** Patients with migraine: strong correlation with BDI-II, (r = 0.75), moderate correlation with MIDAS (r = 0.38), strong correlation with HIT-6 (r = 0.52), and strong correlation with MSQ (r = −0.54); relative to the MINI, sensitivity = 79.5%, specificity = 81.7%, PPV = 64.6%, NPV = 90.5% **Reliability:** Patients with migraine: internal consistency demonstrated (Cronbach's alpha = 0.894)	Not applicable	Seo (2015)[67]
ACM-I and ACM-S	ACM-I: 24-items to measure effects of CM on life Each item (except for item 22) is rated on a Likert scale of 0 to 5	**Validity:** Patients with CM: ACM-S correlated with MIDAS and MSQ, lower correlation with HIT-6 and SF-36 Patients with CM: ACM-I increased with higher MIDAS disease severity	Not identified	Blumenfeld (2014)[50]

Outcome Measure	Type	Conclusions about Measurement Properties	MCID	References
	ACM-S: Measures symptoms of CM	**Reliability:** Patients with CM: internal consistency demonstrated for both ACM-I and ACM-S (Cronbach's alpha > 0.8)		
WPAI-SHP	6 items to measure impairments in work and activities	The general form has been validated; however, no evidence found in patients with migraine	Not identified for migraine	Reilly (1993)[52]
EQ-5D-3L	Generic instrument applied to many health conditions. First part: Descriptive system to classify respondents into one of 243 health states – 5 dimensions with 3 possible levels Second part: 20 cm VAS with end points labelled 0 (worst imaginable health state) to 100 (best imaginable health state) Score generated with a multi-attribute utility function.	**Validity** (1) Patients with CM: strong correlation with the HIT-6 (−0.42), RR (0.50), and RP (0.55), and moderate correlation with EF (0.39) (2) The instrument could distinguish between patients with and without migraine, although it did not perform as well as the SF-36 **Responsiveness:** The utility values distinguished between mild, moderate, and severe levels of migraine pain	Not identified for migraine	Gillard (2012)[68] Essink-Bot (1997)[57] Stafford (2012)[56]

ACM-I = Assessment of Chronic Migraine – Impact; ACM-S = Assessment of Chronic Migraine – Symptoms; BDI-II = Beck Depression Inventory-II; CM = chronic migraine; EF = emotional function; EM = episodic migraine; EQ-5D-3L = EuroQoL 5-Dimension 3-Levels questionnaire; max = maximum; HIT-6 = six-item Headache Impact Test; ICC = intra-class correlation coefficient; MCID = minimal clinically important difference; MIBS-4 = Migraine Interictal Burden Scale-4; MIDAS = Migraine Disability Assessment Scale; MINI = Mini International Neuropsychiatric Interview; MSQ = Migraine-Specific Quality of Life; NPV = negative predictive value; PHQ-4 = Patient Health Questionnaire-4; PHQ-9 = Patient Health Questionnaire-9; PPV = positive predictive value; r = correlation coefficient; RP = role function-preventive; RR = role function-restrictive; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale; WPAI-SHP = Work Productivity and Activity Impairment Questionnaire – Specific Health Problem.

[a] This study also presented within-group MCIDs for the MSQ based on distribution and anchor-based techniques. However, these results are presented in the main text only and not in this table because they were based on patients with a maximum of 15 headache days per month (i.e., not exclusively in patients with chronic migraine).

[b] It is unclear how the quality-of-life domains were evaluated in this study and whether the differences observed were clinically meaningful.

Migraine-Specific Quality of Life Questionnaire

The MSQ is a disease-specific instrument that assesses the impact of migraine on a patient's HRQoL. Version 1.0 of MSQ was a 16-item instrument developed and validated by Jhingran et al.[69] MSQv2.1 is a 14-item instrument developed from MSQ version 1.0. MSQ content was improved by rewording different items for greater clarification and by shortening the questionnaire for easier administration. MSQv2.1 was used by the studies in the review.

HRQoL is assessed across three domains: role function-restrictive (RR, seven items assessing how migraines limit one's daily social and work-related activities), role function-preventive (RP, four items assessing how migraines prevent these activities), and emotional function (EF, three items assessing the emotions associated with migraines).[39]

Participants respond to the 14 items using a six-point scale: none of the time, a little bit of the time, some of the time, a good bit of the time, most of the time, and all of the time, each of which is assigned scores of 1 to 6, respectively. Raw dimension scores are computed as a sum of item responses and are rescaled to a 0-to-100-point scale, producing an overall score for each domain. A higher score indicates better HRQoL.[39] MSQ can also be scored in the reverse fashion, with a lower score indicating higher function. In COMPEL and REPOSE, higher scores indicated better quality of life. The reverse-scoring method was used in [redacted], PREEMPT-1, and PREEMPT-2, with a negative number change from baseline indicating improvement and a positive number change indicating worsening.

A study by Bagley et al. provided evidence of the validity and reliability of MSQ v2.1 in patients with CM.[39] The study was a web-based, cross-sectional survey conducted in 8,726 patients with episodic migraine (< 15 headache days per month [HDPM]) or CM (≥ 15 HDPM) from nine different countries. Of these, 499 (6%) patients had CM and their MSQ domain scores were RR = 44.4 (standard deviation [SD], 22.10), RP = 61.4 (SD, 26.1), and EF = 48.3 (SD, 28.1). With respect to reliability, internal consistency (measured with Cronbach's alpha) for the overall sample for RR, RP, and EF was 0.96, 0.90, and 0.87, respectively, and was acceptable based on a threshold of 0.70. Internal consistency (measured with Cronbach's alpha) was also acceptable for the CM sample for RR, RP, and EF (0.95, 0.90, and 0.85 respectively). For construct validity, Correlations were strong between MSQ and HIT-6 (r = –0.60 to –0.71), moderate for MSQ and Migraine Disability Assessment Scale (MIDAS) (r = –0.38 to –0.39), and weak-moderate for MSQ and Patient Health Questionnaire (PHQ) (r = –0.21 to –0.42) in patients with CM. [39,49]

Rendas-Baum et al. provided further validation of MSQv2.1 in patients with chronic migraine undergoing prophylactic treatment.[40] Data were pooled from the PREEMPT-1 and PREEMPT-2 trial, and included 1,376 patients. With respect to reliability, internal consistency at baseline was acceptable, with a Cronbach's alpha of at least 0.80 for all three scales, varying between 0.80 for EF and 0.93 for RR. At 24 weeks, Cronbach's alpha remained acceptable and ranged from 0.90 to 0.97 across the three domains and the two studies. For construct validity, MSQ and HIT-6 scores were strongly correlated, Pearson values ranging from r = –0.59 (EF) to r = –0.75 (RR) at baseline and r = –0.74 (EF and RP) and r = –0.86 (RR) at 24 weeks. For responsiveness, MSQ change scores indicated large and moderate effect-sizes for patients who experienced ≥ 50% improvement and improvement between 30% and 50%, respectively.[40]

MCID: The MCID in the MSQv2.1 score was determined from a multi-centre, double-blind, placebo-controlled randomized trial of 328 patients with chronic migraine.[41] CM was defined as the presence of at least 15 headache days over the last 28 days, of which at least half were migraines. Patients were randomized in a 1:1 ratio to receive topiramate at a maximum dose of 100 mg per day (n = 165) or placebo (n = 163) for 16 weeks. Mean age was 38.2 years (range 18 to 74 years) and 85% were female. The patients had suffered from chronic daily headaches for approximately nine years and reported 20 HDPM at baseline. Outcomes measured included MIDAS, MSQv2.1, Subject's Global Impression of Change (SGIC), and Physician's Global Impression of Change. The latter two outcomes, completed at the end of the study, used a seven-point scale with 1 indicating very much improved and 7 indicating very much worse.[41]

MCID was established using an anchor-based approach, with the SGIC as the anchor. The MCID was estimated as the change in MSQ domain score that corresponded to a unit improvement on the SGIC (i.e., the beta coefficient of the regression equation of MSQ

domain with SGIC was the MCID). For change from baseline in RR versus SGIC, there was an improvement in RR, with a regression-estimated MCID of 10.9. For change from baseline in RP versus SGIC, there was an improvement in RP, with a regression-estimated MCID of 8.3. For change from baseline in EF versus SGIC, there was improvement in EF, with a regression-estimated MCID of 12.2 (Table 29).[41]

Table 29: MCID for Each MSQ Domain – Within-Group Difference in Patients with Chronic Migraine

MSQ Domain	Regression-Estimated MCID (95% CI) Within-Group Differences
Role function-restrictive	10.9 (9.4, 12.4)
Role function-preventive	8.3 (6.7, 9.9)
Emotional function	12.2 (10.2, 14.3)

CI = confidence interval; MCID = minimal clinically important difference; MSQ = Migraine-Specific Quality of Life Questionnaire.

Source: Dodick et al.[41]

Cole et al. identified group-level and individual-level MCIDs for the RR, RP, and EF domains of MSQv.2.1.[15] The analyses were performed on pooled data from two clinical trials of topiramate for migraine prophylaxis (N = 916) and the QualityMetric National Headache Survey (N = 1,016). The two trials were randomized, double-blind, and placebo-controlled from Canada and the US. Patients were 12 to 65 years of age, had a minimum six-month history of migraine, and experienced three to 12 migraines per month (but not more than 15 HDPM during the 28-day baseline period). Patients were randomized to placebo or topiramate 50, 100, or 200 mg/day and continued on treatment for 18 weeks. The QualityMetric database included adults who resided in the contiguous 48 states of the US, were 18 to 65 years of age, were able to converse in English, and experienced a headache at least once in the past four weeks prior to the phone interview. No intervention was administered to patients in the QualityMetric survey.

Group-level MCIDs were determined using a distribution-based technique, with Cohen's d effect sizes from the pooled topiramate trial data. Table 30 shows the group-level MCIDs for RR, RP, and EF domains of the MSQ.

Table 30: Group-Level MCIDs for the MSQ in Patients With a Maximum of 15 Headache Days Per Month

MSQ Domain	Distribution-Based: MCID
Role function-restrictive	3.2
Role function-preventive	4.6
Emotional function	7.5

MCID = minimal clinically important difference; MSQ = Migraine-Specific Quality of Life Questionnaire.

Source: Cole et al.[15]

Cole et al. also calculated individual-level MCIDs with anchor-based distribution and techniques.[15] In anchor-based techniques, the anchors were average monthly migraine rate (30%, 40%, or 50% reduction), migraine status (yes/no), MIDAS, more or less headaches compared with three months ago (yes/no), bothered by headaches more now compared with three months age (yes/no), and impact of migraine on life (i.e., everyday physical activities, feeling frustrated or irritable, limitations in daily activities, and overall quality of life). The individual-level MCIDs determined by Cole et al. from anchor-based techniques (Table 31) were generally smaller than those reported in Dodick et al. (Table 29). The

MCIDs were 4.9 and 5.0 for RR, 5.0 and 7.9 for RP, and 8.0 and 10.6 for EF. Importantly, the MCIDs derived by Dodick et al. were based on patients with CM, whereas the datasets used by Cole et al. included patients with a maximum of 15 HDPM (i.e., most patients in the datasets used by Cole et al. would be below the threshold for classification of CM).

In one distribution-based technique, the MCIDs were calculated from one-half the standard deviation (SD) of each MSQ domain, from the pooled topiramate trial data set and the QualityMetric data set separately. In a second distribution-based technique, the MCIDs were calculated from the standard error of the mean of the MSQ domains in the pooled clinical trial data set. The MCIDs from distribution-based techniques ranged from 4.8 to 8.6 (RR), 7.9 to 9.9 (RP), and 10.6 to 12.4 (EF). The anchor-based MCIDs were similar to the distribution-based MCIDs using standard error of the mean, but were less than the distribution-based MCIDs using one-half SD (Table 31). The estimates based on anchor techniques are preferred to those of distribution techniques.

Table 31: Individual-Level MCIDs for MSQ in Patients With a Maximum of 15 Headache Days per Month

MSQ Domain	Anchor-Based: MCID	Distribution-Based (One-Half SD): MCID[a]	Distribution-Based (SEM): MCID
Role function-restrictive	4.9[a]; 5.0[b]	8.3[c]; 8.6[d]	4.8
Role function-preventive	5.0[b]; 7.9[a]	9.9[c]; 8.5[d]	7.9
Emotional function	8.0[b]; 10.6[a]	12.4[c]; 11.5[d]	10.6

MCID = minimal clinically important difference; MSQ = Migraine-Specific Quality of Life Questionnaire; SD = standard deviation; SEM = standard error of mean.

Source: Cole et al.[15]

[a] Estimates based on better-same-worse analysis.

[b] Estimates based on logistic analysis.

[c] Estimates based on pooled topiramate trial data set.

[d] Estimates based on QualityMetric data set.

Headache Impact Test

The Headache Impact Test (HIT) is a Web-based, multi-question health assessment that quantifies the impact of headache on a patient's life.[42] It uses computerized adaptive testing technology to select and ask only survey questions that are relevant to the respondent. A total of 84 possible questions cover topics such as functional health and well-being. Optional questions may be used to obtain information on pain, medications, and treatment satisfaction.[42]

The six-item HIT (HIT-6) is a short form version of HIT, which was developed for practical reasons.[43] The six items (questions) were selected from a pool of 89 questions (54 questions from HIT and 35 questions suggested by clinicians).[43]

HIT-6 measures pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress.[44] The patient chooses one of five responses to each question: never, rarely, sometimes, very often, or always and the responses are assigned 6, 8, 10, 11, or 13 points respectively. Total HIT-6 scores range from 36 to 78; a higher score indicates a greater impact of the disease on the daily life of the respondent. The scores may be also interpreted using four groupings: A score ≤ 49 points indicates little or no impact, a score of 50 to 55 points reflects some impact, a score of 56 to 59 indicates substantial impact, and a score ≥ 60 points reflects severe impact.[44]

HIT-6 was first tested by conducting an Internet-based survey of 1,103 adults who had experienced a headache in the past four weeks (that was not due to cold, flu, head injury, or a hangover).[43] A follow-up survey of 540 of the original respondents was conducted 14 days after the first survey. With respect to reliability, the instrument showed good internal consistency (Cronbach's alpha was 0.89 and 0.90 for the first and second survey, respectively) and test-retest reliability (intra-class correlation coefficient: 0.78, n = 540). For construct validity, correlation between HIT-6 and the Short Form (8) Health Survey scales and summaries were obtained. Moderate correlations were observed between HIT-6 and role-physical and social functioning (r = –0.36 and r = –0.37, respectively) and weak correlations with bodily pain and mental health (: r = –0.25 and r = –0.27., respectively).[49] HIT-6 correlated moderately with physical summary (r = –0.35) and mental summary (r = –0.31). The authors of the study suggested that the weak-to-moderate correlation with other instruments may be due to the heterogeneity of the HIT-6 content. For responsiveness, the instrument was responsive to self-reported changes in headache impact. Scores improved with respondents who self-reported improved headache impact, whereas scores declined with respondents who self-reported worsening headache impact.[43]

A study by Kawata et al. was conducted in patients with chronic daily headaches (≥ 15 HDPM).[44] New patients at a headache clinic were asked to complete a set of questions on their first visit (N = 309). All patients were mailed a follow-up survey four months after their baseline assessment. Mean HIT-6 score was 65.6 (SD 7.0), and 87% of patients reported having a score of 60 or more. With respect to reliability, the instrument showed good internal consistency (Cronbach's alpha = 0.87). For construct validity, correlation between HIT-6 scores and the Short-Form (36) Health Survey (SF-36) domain scores were obtained. Strong correlations were observed between HIT-6 scores and role-physical (r = –0.52) and social-functioning subscales(r = –0.57). Correlations were weak with the mental health (r = –0.22) and general health (r = –0.29) subscales of SF-36.[44]

Further testing of HIT-6 was completed by Yang et al. in 2,049 patients with episodic or chronic migraine.[65] Adults who had been participants in two studies (the National Survey of Headache Impact study and the HIT-6 validation study) were selected. Both studies had similar inclusion and exclusion criteria, and data were pooled. A total of 6.4% of respondents had CM with a HIT-6 score of 62.5 ± 7.8 (mean ± SD). Adults with episodic migraine represented 42.1% of the population (HIT-6 score, 60.2 ± 6.8), while the remainder (51.5%) had non-migraine headaches (HIT-6 score, 49.1 ± 8.7). With respect to reliability, the instrument showed strong[49] internal consistency (Cronbach's alpha was 0.83 and 0.90 for the first and second interview, respectively, in the total sample) and test-retest reliability (intra-class correlation coefficient 0.77 for HIT-6 validation study respondents). For construct validity, correlation between HIT-6 scores and other scores (MIDAS, headache pain severity, and number of HDPM) were also obtained. Strong correlation was observed between HIT-6 scores and total MIDAS scores (r = 0.56), demonstrating construct validity. Correlation was moderate (r = 0.46) and weak (r = 0.29) with headache pain intensity and number of HDPM respectively. For discriminant validity, HIT-6 scores differed significantly between subgroups of chronic migraine (mean ± SD = 62.5 ± 7.8), episodic migraine (60.2 ± 7.8), and non-migraine headaches (49.1 ± 8.7; $P < 0.0001$). Chronic migraine patients were more likely to report substantial or severe headache impact compared with patients with episodic migraine and non-migraine headaches.[65]

Rendas-Baum et al. validated the HIT-6 in 1,384 patients with chronic migraine, pooled from PREEMPT-1 and PREEMPT-2.[45] Validity, reliability, and responsiveness (i.e., ability to detect change) were evaluated. Convergent validity was assessed by correlation of HIT-6

with MSQ; if correlation coefficients were < −0.40, then the HIT-6 was deemed to have convergent validity. Construct validity was examined by comparing mean scores across groups known to differ in number of headache days within a 28-day period (i.e., < 10, 10 to 14, and ≥ 15) and cumulative hours of headache within a 28-day period (i.e., < 140, 140 to < 280, 280 to < 420, and ≥ 420) at week 24. Test-retest reliability was assessed with the intra-class correlation coefficient in a stable subsample at weeks 8 and 12. Internal consistency was assessed with Cronbach's alpha, the average inter-item correlation, and the item-total correlation at baseline and week 24. Ability to detect change was evaluated by the difference in HIT-6 scores among patients who were "much improved" (i.e., ≥ 50% decrease in headache frequency), "moderately improved" (i.e., ≥ 30% to < 50% decrease in headache frequency), or "not improved or worsening" (i.e., < 30% decrease in headache frequency or worsening). With respect to validity, the HIT-6 correlated strongly with the MSQ (−0.86 to −0.59) and demonstrated convergent validity. HIT-6 scores also differed significantly across patient groups classified by headache frequency and cumulative hours of headache, demonstrating construct validity. With respect to reliability, test-retest reliability was demonstrated with intra-class correlation coefficients of 0.76 to 0.80. The HIT-6 also demonstrated internal consistency, with Cronbach's alpha of 0.75 to 0.92, and average inter-item correlation and item-total correlation above the threshold of 0.40. For responsiveness, HIT-6 scores were significantly higher for patients with greater improvement in headache frequency and cumulative hours of headache, showing that the instrument was able to detect changes in disease status.

The MCID in HIT-6 score was determined by Coeytaux et al. from a study involving 71 patients who suffered from chronic daily headaches (≥ 15 HDPM).[46] Patients were randomly assigned to 10 acupuncture sessions administered over six weeks along with usual medical care (n = 34) or to usual medical care alone (n = 37). Patients' mean age was 46 years (range 19 years to 83 years) and 80% were female. Patients suffered from a mean of 24.2 headaches (SD, 5.8) in the month prior to study enrolment. The mean pain severity was 6.4 (SD 2.0) on an 11-point scale. There were no significant differences in baseline characteristics between the two groups.[46]

Before randomization, HIT-6 was administered at baseline and again at six weeks. At six weeks, the follow-up test included one additional question to determine the patients' perceived clinical change: "Compared with six weeks ago, my headache condition is a) much better; b) somewhat better; c) about the same; d) somewhat worse; or e) much worse."[46]

The MCID was established using an anchor-based approach that compared the HIT-6 scores of patients who reported clinical improvement to the HIT-6 scores of patients who reported no clinical change. Four different anchors were used: Method 1 related HIT-6 change scores to levels of perceived improvement in clinical status; Method 2 compared HIT-6 change scores associated with some perceived clinical change to scores associated with no change; Method 3 compared HIT-6 follow-up scores between two levels of clinical improvement; and Method 4 compared HIT-6 change scores associated with each level of change to scores associated with no perceived clinical change, using a linear regression model.[46]

Baseline HIT-6 scores were 64.9 (95% confidence interval [CI], 62.7 to 67.1) in the acupuncture group and 64.1 (95% CI, 62.2 to 66.1) in the medical care only group. At 6 weeks, HIT-6 scores were 61.4 (95% CI, 59.2 to 63.5) in the acupuncture group and 63.7 (95% CI, 62.0 to 65.5) in the medical care only group.[46] Similar MCID estimates were

obtained using different anchors (Table 32). A between-group difference of HIT change scores of 2.3 units suggests an improvement in a patient's headache condition that may be considered clinically important.

Table 32: MCIDs for HIT-6 Based on Four Methods

Method	Description	MCID, Mean (95% CI)
Method 1	HIT-6 change: "somewhat better" minus "about the same"	−2.3 (−4.6 to −0.3)
Method 2	HIT-6 change: "somewhat better/worse" minus "about the same"	−2.7 (−4.4 to −1.0)
Method 3	Follow-up HIT-6: "somewhat better" minus "about the same"	−2.3 (−4.9 to −0.2)
Method 4	HIT-6 change: "somewhat better" compared with "about the same"	−2.3 (−4.3 to −0.3)

CI = confidence interval; HIT-6 = six-item Headache Impact Test; MCID = minimally clinically important difference.

Source: Coeytaux et al.[46]

Accuracy of recall may have been a limitation of the study, given that patients had to recall their headache condition of six weeks before.

Smelt et al. developed within-group and between-group MCIDs for the HIT-6 in patients with episodic migraine.[47] The data set consisted of patients (N = 490) with migraine who participated in a randomized trial that compared a proactive approach by general practitioners with usual care in the Netherlands. The average age of patients was about 48 years, 86% were female, and patients experienced an average of approximately six headache days per month. However, the diagnosis of migraine was not based on the International Headache Society criteria. Change scores on the HIT-6 from baseline to month 3 (N = 368) were compared with two anchor questions: (1) Compared with three months ago, how is your headache condition? a. much better, b. somewhat better, c. about the same, d. somewhat worse, e. much worse; and (2) Compared with three months ago, how often do headaches limit your usual daily activities? a. a lot less often now, b. somewhat less often now, c. about the same, d. somewhat more often now, e. a lot more often now. A within-group MCID was determined by a mean-change approach, which defines the MCID as the mean change in HIT-6 score of the group of patients who reported being "somewhat better." The between-group MCID was determined by subtracting the mean-change score in the group that reported to be "about the same" from the mean-change score of the group that reported to be "somewhat better." An additional, receiver-operating characteristic (ROC) curve analysis was conducted to determine within-group MCID. The within-group MCID was estimated to be −2.5 points based on the mean change approach and −6.0 points based on the ROC curve approach. The between-group MCID was estimated to be −1.5 points.

Headache and Migraine/Probable Migraine Days

The original CADTH report concluded that the absolute difference between onabotulinumtoxinA (Ona A) and placebo in headache and migraine days of about one to two days was not clinically important.[14] In the resubmission, the manufacturer pointed to more recent evidence by Dodick et al. that a one-day reduction in headache frequency was clinically meaningful.[31] Dodick et al.[16] reference a study by Silberstein et al.[17] that examined headache frequency and HRQoL. Silberstein et al. examined the characteristics of patients (N = 703), 12 years of age or older, who received Ona A using data from an open-label, clinical study, conducted at 10 headache centres in the US.[17] The majority (65.6%) of patients had CM (defined as the presence of at least 15 headache days per 28 days, of which at least half were migraine or migrainous headache), although about 34% had other types of headache conditions, such as migraine not classified as chronic and tension-type

headache. Headache frequency was measured with a patient-maintained daily headache record. Patients responded to the Headache Impact Test, the Headache Pain-Specific Quality of Life questionnaire, and the MIDAS questionnaire and data were collected prospectively for up to one year, with 482 (68.6%) patients completing the entire one-year follow-up. The results state that: "A 1-day increase in HA [headache] frequency was associated with a greater likelihood of HA pain interfering with mood (4.0%, $P < .001$), recreational activities (4.0%, $P = .004$), or life enjoyment (4.0%, $P = .001$)." It is unclear which instruments that the domains of mood, recreational activities, or life enjoyment were taken from. As well, it is unclear if the domains were selected a priori or if a relationship between headache frequency and the other domains of HRQoL of the three instruments was also tested, found not to be statistically significant and not reported. Without knowing the scale on which these domains were based, it is difficult to determine if a 4% improvement was clinically meaningful. In addition, the time point and study sample size upon which these results are based are unclear. If it was at the one-year point, a large number of patients (N = 221) had dropped out by then and it is uncertain if data for these patients was imputed or omitted from the final results. No other studies were identified that specifically informed the MCID for reduction in headache frequency in patients with CM. Rendas-Baum's 2013 study found that the MSQ differed significantly in patients with < 10 headache days, 10 to 14 headache days, and ≥ 15 HDPM.[40] The change in MSQ was greater among groups who experienced a greater decline in headache frequency. Rendas-Baum's 2014 study found that the HIT-6 differed significantly across levels of headache frequency (i.e., < 10 days, 10 to 14 days, and ≥ 15 days per month).[45] Patients who experienced at least 50% improvement in number of headache days had about a seven-point decrease in HIT-6, ≥ 30 to < 50% improvement (a decrease of 2.9 or 3.3 points), and < 30% improvement (a change of −0.7 points).[45]

Migraine Interictal Burden Scale

The MIBS-4 measures migraine burden between attacks (i.e., interictal states).[22] Four domains are included in the instrument: impairment in work or school, impairment in family and social life, difficulty making plans or commitments, and emotional/affective and cognitive distress. The questionnaire consists of four items, is self-administered, and has a total score across domains of 0 to 12, with higher scores representing more severe burden. A score of 0 indicates no burden, 1 to 2 mild, 3 to 4 moderate, and 5 or higher severe.

Buse et al. administered 30 candidate items of the MIBS-4 as a mailed survey to 2,500 previously identified patients with migraine.[66] Patients were also mailed a validated diagnostic screener, the MIDAS, MSQ, and the PHQ. Of the 1,691 surveys returned, 1,353 met the criteria from the second edition of the International Classification of Headache Disorders (ICHD) for migraine. Categorical confirmatory factor analysis yielded the four domains of the MIBS-4. With respect to validity, the domains correlated significantly with MIDAS, PHQ, and MSQ ($P < 0.0001$). In a regression model, total MIBS-4 predicted MIDAS disability with R^2 of 0.15, suggesting that ictal and interictal burden are correlated, but distinct.

An MCID for MIBS-4 was not identified in the literature.

Patient Health Questionnaire Quick Depression Assessment Score

The PHQ-9 quick depression assessment score is a self-administered screening and diagnostic tool.[22] It consists of the nine diagnostic criteria for depressive disorders (i.e., interest or pleasure in doing things; feeling down, depressed or hopeless; trouble falling or

staying asleep or sleeping too much; feeling tired or having little energy; poor appetite or overeating; feeling bad about oneself; trouble concentrating; moving or speaking slowly or being fidgety or restless; and thoughts of suicide or hurting oneself) from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders. Patients are asked to indicate the frequency with which they have been bothered by these nine symptoms over the previous two weeks, on a four-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The total score ranges from 0 to 27 (from best to worst). A score of 0 to 4 represents none/minimal depression, 5 to 9 mild depression, 10 to 14 moderate depression, 15 to 19 moderately severe depression, and 20 to 27 severe depression.[48]

The validity and reliability of the PHQ-9 in patients with migraine was assessed by Seo et al.[67] Consecutive patients (N = 132) visiting a hospital headache clinic in Korea were recruited. Patients were diagnosed with migraine based on criteria from the third edition of the ICHD and were 16 to 70 years of age. Patients were administered the PHQ-9, as well as the Mini International Neuropsychiatric Interview-Plus Version 5.0.0, the Beck Depression Inventory-II, the MIDAS, HIT-6, and MSQ. The PHQ-9 was translated into Korean and was deemed to be identical to the English version. Of the 132 patients, 73 (55%) had chronic migraine. With respect to validity, the PHQ-9 score correlated strongly with the Beck Depression Inventory-II (Spearman's rho = 0.754, $P < 0.001$), moderately with MIDAS (0.377, $P < 0.001$), strongly with HIT-6 (0.519, $P < 0.001$), and strongly with MSQ (−0.538, $P < 0.001$), demonstrating construct validity.[49] In ROC analyses, at a cut-off score of 7, relative to the Mini International Neuropsychiatric Interview the sensitivity of the PHQ-9 was 79.5%, specificity 81.7%, positive predictive value 64.6%, and negative predictive value 90.5%. Reliability: Cronbach's alpha for the PHQ-9 was 0.894, indicating internal consistency.

Assessment of Chronic Migraine – Impact Score and Assessment of Chronic Migraine Symptoms

The ACM-I is a 24-item instrument that examines the effects of chronic migraine on a patient's life. Items include daily activities, feelings, energy level, household, leisure, and social activities, and work over the past seven days.[22] The items are rated on a Likert scale of 0 (none of the time) to 5 (all of the time). Item 22 has an additional response option, but was recoded on a 0 to 5 scale for analysis. The total ACM-I score was transformed so that higher scores indicated worse impact of chronic migraine. The ACM-S assesses the symptoms of chronic migraine and includes the domains of symptom severity and symptom experience.

ACM-I and ACM-S were validated in a sample of patients from COMPEL, which is an open-label multi-centre study to examine the long-term efficacy and safety of Ona A in patients with chronic migraine.[50] Patients were also administered the MSQ, MIDAS, HIT-6, and SF-36. The average age of patients was 43.0 years, and most were female (84.8%). Validity: The ACM-S was correlated with MSQ and MIDAS, but had lower correlation with other measures, such as HIT-6 and SF-36. Based on MIDAS classification, the ACM-I increased with higher disease severity, suggesting that it has discriminant validity. Reliability: Internal consistency was demonstrated with Cronbach's alpha of > 0.8 for both ACM-I and ACM-S.

An MCID for ACM-I or ACM-S was not identified in the literature.

Work Productivity and Activity Impairment Questionnaire – Specific Health Problem

The WPAI-SHP is a self-administered questionnaire to measure impairments in work and activities during the past seven days due to general health or a specific health problem.[22] The instrument poses six questions and results in four scores: absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism), and activity impairment. The six questions are: Q1 = currently employed; Q2 = hours missed due to health problems; Q3 = hours missed other reasons; Q4 = hours actually worked; Q5 = degree health affected productivity while working, using a 0-to-10 visual analogue scale (VAS); Q6 = degree health affected productivity in regular unpaid activities (VAS).[51-53] The questionnaire elicits information on the number of days or hours missed from work, days or hours worked, days during which the performing of work was challenging, and the extent to which the patient was limited at work (work impairment). The work impairment domain is the sum of impairment in work productivity due to absenteeism (productivity loss due to a health-related absence from work, including personal time off, sick days off work, duration of short- or long-term disability, or worker's compensation days) and impairment due to decreased productivity while at work (reduced performance of productivity while at work due to health reasons, including time not being on a task and decreased work quality and quantity). The activity impairment domain refers to impairment in daily activities other than work. Four main outcomes can be generated from the WPAI-SHP and expressed in percentages by multiplying the following scores by 100: 1) per cent work time missed due to health = Q2/(Q2 + Q4) for those who were currently employed; 2) per cent impairment while working due to health = Q5/10 for those who were currently employed and actually worked in the past seven days; 3) per cent overall work impairment due to health = Q2/(Q2 + Q4) + ([1 - Q2]/[Q2 + Q4]) × [Q5/10]) for those who were currently employed; and 4) per cent activity impairment due to health = Q6/10 for all respondents. For those who missed work and did not actually work in the past seven days, the per cent overall work impairment due to health will be equal to the per cent work time missed due to health. The outcomes are reported as percentages in impairment, with higher numbers indicating greater impairment and less productivity. The WPAI-SHP is adapted to a specific disease or condition by replacing the word "problem" in the questions with the name of the disease or condition.[70] The general form of the WPAI was validated on a sample of 106 employed individuals who were affected by a symptom or health problem during the past seven days of recruitment.[52] However, no studies were found that validated the WPAI-SHP in patients with migraine.

An MCID for the WPAI-SHP in patients with migraine was not identified in the literature.

EuroQol 5-Dimensions 3-Levels Questionnaire

The EQ-5D-3L[54,55] is a generic quality of life instrument that has been applied to a wide range of health conditions and treatments, including migraine.[56] The first of two parts of the EQ-5D-3L constitute a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[54,55] The second part is a 20 cm VAS that has

end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state,” respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the VAS that best represents their own health on that day. Hence, the EQ-5D-3L produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the VAS.

The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores below 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states “dead” and “perfect health,” respectively.

Gillard et al. compared the EQ-5D-3L with the HIT-6 and MSQv.2.1 among participants with episodic and CM in the International Burden of Migraine Study (N = 9,048 all migraine and N = 547 CM).[68] Validity: Correlation coefficients between EQ-5D-3L utility values and the HIT-6, MSQ-RR, MSQ-RP, and MSQ-EF in patients with chronic migraine were −0.42 (strong),[49] 0.50 (strong),[49] 0.55 (strong),[49] and 0.39 (moderate)[49] ($P < 0.0001$), respectively, suggesting that the instrument has construct validity. Essink-Bot et al. administered the EQ-5D-3L and three other generic health status measures, including the SF-36, to Dutch patients with migraine (N = 436) diagnosed based on the International Headache Society criteria and to a control group without migraine (N = 575).[57] With respect to validity of the ROC analysis, the EQ-5D-3L could distinguish between individuals with and without migraine, although it did not perform as well as the mental and physical components of the SF-36. Stafford et al. administered the EQ-5D-3L and MIDAS to patients with a history of physician-diagnosed migraine for at least six months, in the UK (N = 106).[56] At the study visit, patients completed the EQ-5D-3L for their current (without migraine) status. They were then asked to recall the most recent migraine attack over the past four weeks and subjectively categorize the severity of pain as mild, moderate, or severe. Patients then completed the EQ-5D-3L for each level of migraine pain severity that they experienced during the last attack. Responsiveness: The EQ-5D-3L utility value was lowest for severe levels of migraine pain (mean [SD]: −0.20 [0.29]), followed by moderate pain (0.53 [0.27]) and mild pain (0.66 [0.23]), and highest for current status without migraine (0.87 [0.15]). All utility values at each level were significantly different from 1.00 (i.e., perfect health). Also, the utility values for mild, moderate, and severe pain levels were significantly different from one another. There is a risk of recall bias as patients were asked to recall their last migraine attack.

An MCID specifically for patients with migraine was not identified in the literature. The MCID for the EQ-5D-3L index score ranges from 0.033 to 0.074 for general use.[58]

Appendix 6: Summary of Original CADTH Common Drug Review Report for Onabotulinum Toxin A for Chronic Migraine

Aim

In the original CADTH Common Drug Review clinical report for onabotulinumtoxinA (Ona A) in adults with chronic migraine (CM), two clinical trials were reviewed and critically appraised, PREEMPT-1 (191622-079) and PREEMPT-2 (191622-080).[14] The purpose of this appendix is to provide a summary of the characteristics and findings of these two studies, the critical appraisal, and the conclusions from the original report.

Study Characteristics

PREEMPT-1 and PREEMPT-2 were manufacturer-sponsored, multi-centre, randomized, double-blind (DB), parallel-group, placebo-controlled, phase III superiority trials (Table 33). The duration of the studies was 60 weeks, which included a four-week pre-randomization (run-in) phase, a 24-week DB treatment phase and a 32-week open-label extension (OLE) phase.

Both trials investigated the efficacy and safety of onabotulinum toxin A as headache prophylaxis and enrolled patients between the ages of 18 to 65 years with a history of migraine headache disorder meeting any of the diagnostic criteria listed in the second edition of the International Classification of Headache Disorders (Section 1, Migraine), with the exception of complicated migraine (i.e., basilar migraine, hemiplegic migraine, migrainous infarction, or ophthalmoplegic migraine). Patients were required to have 15 or more headache days with each day consisting of four or more hours of continuous headaches, and at least 50% of baseline headache days being migraine or probable migraine days, and at least four distinct headache episodes each lasting at least four hours.

Following the run-in phase (week –4 to day 0), patients who continued to meet the inclusion and exclusion criteria at day 0 were stratified according to medication overuse (yes/no), with medication overuse determined by the frequency of use of acute headache pain medications during the run-in phase. Overuse of acute headache pain medications was defined as an intake of medication at least two days per week and at least 10 to 15 days per 28-day period (varying with medication category). After stratification according to medication overuse, patients were randomly allocated in a blinded fashion to receive Ona A or placebo in a 1:1 ratio.

In both trials, Ona A (purified neurotoxin complex) or placebo (saline) was administered at day 0 and at week 12 during the DB phase. The active treatment and placebo were supplied in identical glass vials. A total dose of 155 Allergan units (U) of Ona A or placebo was administered intramuscularly at 31 fixed-site, fixed-dose injections across seven specifically defined head and neck muscle areas. At the investigator's discretion, the dose could be increased by an additional 40 U, using a "follow the pain" method, in up to three specific head and neck muscle areas that took into consideration the patient-reported usual location of predominant pain. These additional injections did not need to be consistent across treatment visits with respect to dose or number of injection sites. The mean (median) total dose of Ona A received by patients in the active group at day 0 and week 12 ranged from 165.1 U (155.0 U) to 165.8 U (155.0 U) in PREEMPT-1 and from 163.0 U

(155.0 U) to 164.3 U (155.0 U) in PREEMPT-2. In both treatment groups, the mean number of injection sites was around 33 in PREEMPT-1 and 32.5 in PREEMPT-2.

The primary efficacy end point in PREEMPT-1 was the frequency of headache episodes per 28-day period, ending with week 24 and compared with baseline. Secondary efficacy outcomes were frequency of headache days per 28-day period, the frequency of migraine/probable migraine headache episodes per 28-day period, the frequency of migraine/probable migraine days per 28-day period, and the frequency of acute headache pain medication intakes per 28-day period. In addition, post hoc efficacy analyses were frequency of moderate/severe headache days, total cumulative hours of headache occurring on headache days, and proportion of patients with severe category scores on the six-item Headache Impact Test-6 (HIT-6). In PREEMPT-2, the primary efficacy end point was the frequency of headache days per 28-day period, ending with week 24 and compared with baseline. Secondary efficacy outcomes were frequency of migraine/probable migraine days per 28-day period, frequency of moderate/severe headache days per 28-day period, total cumulative hours of headache occurring on headache days per 28-day period, proportion of patients with severe HIT-6 category score per 28-day period, and frequency of headache episodes per 28-day period. In addition, the Migraine-Specific Quality of Life Questionnaire (MSQ) was completed by patients at day 0, week 12, week 24, and week 56, and the generic Euro-QoL visual analogue scale (EQ-VAS) was completed on day 0 and week 24 in both studies. Safety data were presented through week 24.

The data required for the evaluation of all headache characteristics and use of acute headache pain medications were derived from self-reported diaries in which efficacy measures were recorded daily by patients for the duration of the study using a validated electronic telephone diary. The start/stop times of each headache, headache-specific characteristic, symptoms associated with headache, the effect of physical activity on headache, and use of acute headache pain medication were reported by patients.

Table 33: Study Characteristics of PREEMPT-1 and PREEMPT-2

		PREEMPT-1	PREEMPT-2
Designs & Populations	**Study design**	Phase III, multi-centre, randomized, double-blind, placebo-controlled, parallel-group trial, followed by an open-label extension phase	
	Locations	US (51 centres) and Canada (5 centres)	US (44 centres), Germany (8 centres), Canada (6 centres), UK (3 centres), Croatia (3 centres) and Switzerland (2 centres)
	Randomized (N)	679	705
	Inclusion criteria	Adult patients (between 18 and 65 years of age) with ≥ 15 HA days per 4-week period with each day consisting of ≥ 4 hours of continuous HAs, and ≥ 50% of baseline HA days being migraine/probable migraine days, and ≥ 4 distinct HA episodes each lasting ≥ 4 hours	
	Exclusion criteria	Diagnosis of other HA disorders (e.g., complicated migraine, chronic tension-type HA, hypnic HA, hemicranias continua, new daily persistent HA), use of prophylactic HA medication within 28 days prior to start of baseline, previous use of botulinum toxin, any medical condition that puts patient at increased risk if exposed to botulinum toxin (for example neuromuscular diseases), temporomandibular disorders, fibromyalgia, psychiatric disorder, Beck Depression Inventory score of ≥ 24 at baseline	
Drugs	**Intervention**	155 U intramuscular botulinum toxin type A, as 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas repeated every 12 weeks (at the investigator's discretion, dose can be increased by an additional 40 U using a "follow the pain" method)	
	Comparator(s)	155 U to 195 U intramuscular placebo (saline) repeated every 12 weeks	

		PREEMPT-1	PREEMPT-2
DURATION	**Phase**		
	Run-in	4 weeks	
	Double-blind	24 weeks	
	Follow-up	32 weeks (after DB phase) open-label extension phase	
OUTCOMES	**Primary end point**	Frequency of HA episodes per 28 day period	Frequency of HA days per 28 day period
	Other end points	Frequency of: HA days, migraine days, moderate/severe HA days, migraine episodes, and acute HA pain medication intakes per 28-day period; total cumulative hours of HA on HA days; HRQoL	Frequency of: migraine days, moderate/severe HA days, HA episodes, migraine episodes, and acute HA pain medication intakes per 28-day period; total cumulative hours of HA on HA days; HRQoL
NOTES	**Publications**	Aurora et al. (2010)[59]	Diener et al. (2010)[60]

DB = double-blind; HA = headache; HRQoL = health-related quality of life; IM = intramuscular; OLE = open-label extension; U = Allergan units.

Source: Original CADTH Clinical Review report.[14]

Patient Characteristics

Of the 1,713 patients screened for PREEMPT-1, a total of 679 patients were randomized and 674 received at least one dose of study drug (Table 34). In PREEMPT-2, 1,621 patients were screened, of which 705 were randomized, and all received at least one dose of the study drug. The primary reason for screening failure in both studies was failure to meet all of the inclusion/exclusion criteria, especially the criterion regarding the minimum number of headache days during the pre-randomization phase.

Table 34: Patient Disposition for PREEMPT-1 and PREEMPT-2

	PREEMPT-1		PREEMPT-2	
Screened, N	1713		1621	
	Ona A	**Placebo**	**Ona A**	**Placebo**
Randomized, N	341	338	347	358
Not Treated, N (%)	1 (< 1)	4 (1.2)	0	0
Completed DB phase (week 24), N (%)	296 (86.8)	295 (87.3)	311 (89.6)	334 (93.3)
Discontinued prior to week 24, N (%)	45 (13.2)	43 (12.7)	36 (10.4)	24 (6.7)
AEs	11 (3.2)	2 (0.6)	8 (2.3)	3 (0.8)
Lack of efficacy	1 (0.3)	0 (0.0)	4 (1.2)	1 (0.3)
Pregnancy	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)
Lost to follow up	6 (1.8)	15 (4.4)	7 (2.0)	8 (2.2)
Personal reasons	12 (3.5)	11 (3.3)	7 (2.0)	5 (1.4)
Protocol violations	0 (0.0)	3 (0.9)	1 (0.3)	0 (0.0)
Other	13 (3.8)	11 (3.3)	8 (2.3)	6 (1.7)
Analysis populations				
ITT, N (%)	341	338	347	358
Safety, N (%)	340	334	347	358

AE = adverse event; DB = double-blind; ITT = intention-to-treat; Ona A = onabotulinumtoxinA.

Source: Original CADTH Clinical Review report.[14]

The baseline characteristics of patients randomized in PREEMPT-1 and PREEMPT-2 are presented in Table 35. The median age of the included patients was approximately 42 years and approximately 58% of the patients were > 40 years of age. The majority of patients (84.6% to 89.1%) were female. Patients were predominantly white (89.4% to 91.4%). The mean time since onset of CM was 17.6 to 20.6 years across treatment arms in the two trials, with 47.2% and 38.8% of patients having a time since onset of CM greater than 20 years in PREEMPT-1 and PREEMPT-2, respectively. The mean age of onset of CM was 20.3 to 22.8 years, respectively, across treatment arms in the two trials, with age of onset ranging between 1 and 57 years, respectively.

Table 35: Summary of Baseline Characteristics for PREEMPT-1 and PREEMPT-2

Characteristic	PREEMPT-1		PREEMPT-2	
	Ona A (N = 341)	Placebo (N = 338)	Ona A (N = 347)	Placebo (N = 358)
Age (years)				
Mean (SD)	41.2 (10.49)	42.1 (10.46)	41.0 (10.39)	40.9 (10.82)
Median	42.0	42.0	42.0	41
Min to max	19 to 65	18 to 64	18 to 65	18 to 65
Age, n (%)				
< 40 years	144 (42.2)	128 (37.9)	149 (42.9)	160 (44.7)
≥ 40 years	197 (57.8)	210 (62.1)	198 (57.1)	198 (55.3)
Gender, n (%)				
Male	37 (10.9)	48 (14.2)	48 (13.8)	55 (15.4)
Female	304 (89.1)	290 (85.8)	299 (86.2)	303 (84.6)
Race, n (%)				
Caucasian	305 (89.4)	309 (91.4)	312 (89.9)	321 (89.7)
Non-Caucasian	36 (10.6)	29 (8.6)	35 (10.1)	37 (10.3)
Black	16 (4.7)	14 (4.1)	18 (5.2)	26 (7.3)
Asian	1 (0.3)	2 (0.6)	3 (0.9)	1 (0.3)
Hispanic	18 (5.3)	11 (3.3)	9 (2.6)	8 (2.2)
Other	1 (0.3)	2 (0.6)	5 (1.4)	2 (0.6)
BMI (kg/m^2)				
Mean (SD)	26.7 (6.18)	27.3 (6.40)	26.7 (6.55)	27.1 (6.39)
Time since onset of chronic migraine (years)				
Mean (SD)	20.3 (12.79)	20.6 (13.17)	18.5 (12.03)	17.6 (12.06)
Time since onset of chronic migraine, n (%)				
< 10 years	85 (24.9)	90 (26.6)	96 (27.7)	108 (30.2)
10 to 20 years	93 (27.3)	90 (26.6)	107 (30.8)	120 (33.5)
> 20 years	163 (47.8)	158 (46.7)	144 (41.5)	130 (36.3)
Age of onset of chronic migraine (years)				
Mean (SD)	20.3 (11.16)	20.9 (11.90)	22.0 (10.79)	22.8 (11.91)
Median (min to max)	17.0 (2 to 53)	18.0 (1 to 55)	20.0 (2 to 56)	20.0 (1 to 57)
Age of onset of chronic migraine, n (%)				
< 12 years	76 (22.3)	77 (22.8)	56 (16.1)	53 (14.8)
12 to 17 years	96 (28.2)	85 (25.1)	79 (22.8)	90 (25.1)
18 to 40 years	148 (43.4)	155 (45.9)	191 (55.0)	182 (50.8)

Characteristic	PREEMPT-1		PREEMPT-2	
	Ona A (N = 341)	Placebo (N = 338)	Ona A (N = 347)	Placebo (N = 358)
> 40 years	21 (6.2)	21 (6.2)	21 (6.1)	33 (9.2)
Disease characteristics during the 28-day run-in period				
HIT-6 score, mean (SD)	65.4 (3.82)	65.8 (4.14)	65.6 (4.26)	65.0 (4.46)
Patients with severe HIT-6 category score, n (%)	322 (94.4)	320 (94.7)	321 (92.5)	325 (90.8)
Headache days, mean (SD)	20.0 (3.73)	19.8 (3.71)	19.9 (3.63)	19.7 (3.65)
Migraine/probable migraine days, mean (SD)	19.1 (4.04)	19.1 (4.05)	19.2 (3.94)	18.7 (4.05)
Moderate/severe headache days, mean (SD)	18.1 (4.22)	18.3 (4.23)	18.1 (4.03)	17.7 (4.26)
Total cumulative hours of headache occurring on headache days, mean (SD)	295.66 (116.81)	274.88 (110.90)	296.18 (121.04)	287.20 (118.08)
Headache episodes, mean (SD)	12.3 (5.23)	13.4 (5.71)	12.0 (5.27)	12.7 (5.29)
Migraine/probable migraine episodes, mean (SD)	11.5 (5.06)	12.7 (5.72)	11.3 (4.99)	11.7 (5.08)

BMI = body mass index; HIT-6 = six-item Headache Impact Test; max = maximum; min = minimum; Ona A = onabotulinumtoxinA; SD = standard deviation.

Source: Original CADTH Clinical Review report.[14]

A total of 97.5% (662/679) and 97.6% (688/705) of patients used acute medications to treat headache pain, with mean intake of medication(s) at baseline of around 30 and 25 in PREEMPT-1 and PREEMPT-2, respectively. A total of 68.1% (462/679) and 63.0% (444/705) of patients overused acute headache pain medications at baseline in PREEMPT-1 and PREEMPT-2, respectively.

Summary of Main Findings

The data presented are for the 24-week DB treatment phase from each trial. The key outcomes that were identified a priori for the review were health-related quality of life (HRQoL), other patient-reported outcomes, and acute headache pain medication intake. HRQoL was measured with the MSQ and EQ-VAS in both studies. The results for MSQ, HIT-6, and acute-pain medication use for headache are presented in Table 36, Table 37, and Table 38, respectively.

Health-Related Quality of Life (Migraine-Specific Quality of Life Questionnaire and EuroQoL visual analogue survey)

In PREEMPT-1, patients treated with Ona A had a greater decrease from baseline in mean scores for the three HRQoL domains of MSQ than patients treated with placebo (Table 36). Similar results were found in PREEMPT-2. In both studies, patients who received Ona A treatment had mean changes from baseline scores that exceeded the established within-group minimal clinically important differences (MCIDs) of –10.9 (role function-restrictive), –8.3 (role function-preventive) and –12.2 (emotional function), while patients receiving placebo did not exceed the abovementioned MCIDs. There were no statistically significant between-group differences in EQ-VAS at week 24 (data not shown).

Table 36: Baseline and Mean Change from Baseline at Week 24 in MSQ Scores for PREEMPT-1 and PREEMPT-2 (Observed Data without Imputation for Missing Values)[a]

Outcome	PREEMPT-1			PREEMPT-2		
	Ona A	Placebo	*P* value	Ona A	Placebo	*P* value
Role function – restrictive						
Week 24, n	297	288		313	334	
Change from baseline at week 24, mean (SD)	−16.8 (22.19)	−8.8 (20.35)	< 0.001	−17.2 (22.29)	−8.4 (20.15)	< 0.001
Median (min to max)	−11.4 (−83 to 29)	−2.9 (−80 to 40)		−14.3 (−91 to 34)	−5.7 (−89 to 49)	
MD (Ona A vs. placebo)	NR			NR		
Role function-preventive						
Week 24, n	297	287		313	334	
Change from baseline at week 24, mean (SD)	−12.6 (21.58)	−7.6 (19.65)	0.005	−13.5 (22.04)	−5.4 (20.07)	< 0.001
Median (min to max)	−10.0 (−95 to 45)	−5.0 (−80 to 65)		−10.0 (−80 to 40)	−2.5 (−95 to 60)	
MD (Ona A vs. placebo)	NR			NR		
Role function-emotional function						
Week 24, n	296	285		313	333	
Change from baseline at week 24, mean (SD)	−16.9 (27.05)	−10.0 (25.04)	0.001	−19.0 (27.14)	−9.1 (24.46)	< 0.001
Median (min to max)	−13.3 (−87 to 60)	−6.7 (−100 to 47)		−13.3 (−100 to 53)	−6.7 (−100 to 60)	
MD (Ona A vs. placebo)	NR			NR		

max = maximum; MD = mean difference; min = minimum; MSQ = Migraine-Specific Quality of Life Questionnaire; NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation.

[a] *P* values for between-treatment comparisons were determined by the Wilcoxon rank sum test.

Source: Original CADTH Clinical Review report.[14]

Other Patient-Reported Outcomes

Mean changes from baseline in total HIT-6 score favoured Ona A over placebo with $P < 0.001$ for between-group differences in both studies (Table 37). The between-group difference at week 24 was 2.3 in PREEMPT-1 and 2.5 in PREEMPT-2. This between-group difference met the MCID of 2.3. When the four groupings of HIT-6 (little or no impact, some impact, substantial impact, and severe impact) were compared at week 24, results also favoured Ona A over placebo, with $P < 0.001$ in both studies.

Table 37: Change from Baseline at Week 24 in HIT-6 for PREEMPT-1 and PREEMPT-2 (mLOCF)[a]

Outcome	PREEMPT-1			PREEMPT-2		
	Ona A (N = 341)	Placebo (N = 338)	*P* value	Ona A (N = 347)	Placebo (N = 358)	*P* value
Little or no impact (total HIT-6 score range 36 to 49), n (%)	33 (9.7)	11 (3.3)	< 0.001[b]	31 (8.9)	16 (4.5)	< 0.001[b]
Some impact (total HIT-6 score range 50 to 55), n (%)	36 (10.6)	30 (8.9)		50 (14.4)	29 (8.1)	
Substantial impact (total HIT-6 score range 56 to 59), n (%)	37 (10.9)	27 (8.0)		36 (10.4)	39 (10.9)	
Severe impact (Total HIT-6 score range 60 to 78), n (%)	235 (68.9)	270 (79.9)		230 (66.3)	274 (76.5)	

Outcome	PREEMPT-1			PREEMPT-2		
	Ona A (N = 341)	Placebo (N = 338)	*P* value	Ona A (N = 347)	Placebo (N = 358)	*P* value
Change from baseline in HIT-6 score, mean (SD)	−4.7 (7.11)	−2.4 (5.63)		−4.9 (6.97)	−2.4 (6.50)	
MD (95% CI) (Ona A vs. placebo)	−2.3 (−3.3 to −1.3)		< 0.001[b]	−2.5 (−3.5 to −1.6)		< 0.001[b]

CI = confidence interval; HIT-6 = six-item Headache Impact Test; MD = mean difference; mLOCF = modified last observation carried forward; Ona A = onabotulinum toxin A; SD = standard deviation.

[a] The HIT-6 scores range from 36 to 78, with 36 being the best score (no impact) and 78 being the worst score (most severe impact). A total score of ≤ 49 indicates little or no impact, 50 to 55 indicates some impact, 56 to 59 indicates substantial impact, and ≥ 60 indicates severe impact.

[b] *P* values for between-treatment comparisons were determined by the Wilcoxon rank sum test.

Sources: Original CADTH Clinical Review report,[14] Aurora (2010),[59] and Diener (2010).[60]

Acute Headache Main Medication Intake

At week 24 in PREEMPT-1, the mean decrease from baseline in the frequency of acute headache pain medication intake was −10.1 for Ona A versus –9.7 for placebo (*P* = non-significant) and for acute headache pain medication days was –5.8 days for Ona A versus –5.8 days for placebo (*P* = non-significant) per 28-day period (Table 38). In addition, there was an overall reduction in the use and overuse of acute headache pain medications.

Table 38: Acute Headache Pain Medication Intake for PREEMPT-1 and PREEMPT-2

Outcome	PREEMPT-1			PREEMPT-2		
	Ona A (N = 341)	Placebo (N = 338)	*P* value	Ona A (N = 347)	Placebo (N = 358)	*P* value
Acute headache pain medication intakes per 28 day period (mLOCF)[a]						
Baseline, LSM (SD)	25.2 (19.27)	25.7 (22.29)		21.9 (18.76)	22.8 (18.87)	
Change from baseline at week 24, LSM (SD)	−10.1 (18.67)	−9.8 (18.54)		−9.7 (15.53)	−8.1 (14.92)	
	MD (99% CI) (Ona A vs. Placebo) −0.3 (−3.8 to 3.1)		0.795	**MD (99% CI) (Ona A vs. Placebo)** NR		0.132
Acute headache pain medications days per 28 day period (observed data)[b]						
Baseline, LSM (SD)	15.0 (6.32)	15.4 (6.38)		14.3 (6.42)	14.4 (6.30)	
Change from baseline at week 24, LSM (SD)	−5.8 (6.63)	−5.8 (6.22)	0.996	−6.4 (5.73)	−4.8 (5.93)	< 0.001
[redacted]	[redacted]			[redacted]		
Acute headache pain medication use (observed data)[c]						
Baseline, n/total (%)	335/341 (98.2)	327/338 (96.7)		337/347 (97.1)	351/358 (98.0)	
At week 24, n/total (%)	239/260 (91.9)	233/261 (89.3)	0.300	251/279 (90.0)	267/294 (90.8)	0.729
Acute headache pain medication overuse (observed data)[c]						
Baseline, n/total (%)	226/341 (66.3)	236/338 (69.8)		220/347 (63.4)	224/358 (62.6)	
At week 24, n/total (%)	81/260 (31.2)	85/261 (32.6)	0.729	66/279 (23.7)	96/294 (32.7)	0.017

CI = confidence interval; LSM = least squares mean; MD = mean difference; mLOCF = modified last observation carried forward; NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation.

Note: SD is for the mean. LSM and mean were approximately the same.

[a] *P* values for between-treatment comparisons are from analysis of covariance (ANCOVA), with baseline frequency of acute headache pain medication intakes as covariate. The main effects in the ANCOVA included treatment and medication-overuse strata.

[b] *P* values for between-treatment comparisons in the ANCOVA, with baseline frequency of acute headache pain medication days as covariate. The main effect in the ANCOVA was treatment.

[c] *P* values for between-treatment comparisons were determined by Pearson's chi-square or Fisher's exact (f) tests (if ≥ 25% of the expected cell counts are less than 5).

Sources: Original CADTH Clinical Report[14] and product monograph.[9]

Other Efficacy Outcomes

Results for headache and migraine days are presented in Table 39.

- Reduction in headache days per 28-day period: In both studies, a greater proportion of patients in the Ona A group had a 25% reduction, a 50% reduction, and a 75% reduction in headache days per 28-day period compared with placebo. The proportion of patients with a 100% reduction in headache days was similar between both treatment groups.
- Frequency of headache days per 28-day period: Patients treated with Ona A had a greater decrease from baseline in frequency of headache days per 28-day period at week 24 (least squares means [LSM] = –7.8 in PREEMPT-1 and –9.2 in PREEMPT-2) than patients treated with placebo (LSM = –6.4 in PREEMPT-1 and –6.9 in PREEMPT-2).
- Frequency of moderate/severe headache days per 28-day period: The between-group difference in the mean change from baseline in frequency moderate/severe headache days per 28-day period at week 24 was not reported in PREEMPT-1 and –2.4 days in PREEMPT-2 ($P < 0.001$), with fewer moderate/severe headache days with Ona A.
- Total cumulative hours of headache occurring on headache days per 28-day period: The between-group difference in the mean change from baseline in total cumulative hours of headache at week 24 was approximately –30 hours in PREEMPT-1 and –40 hours in PREEMPT-2 ($P < 0.001$), with fewer total cumulative hours of headache with Ona A.
- Frequency of headache episodes per 28-day period: The between-group difference in the mean change from baseline in frequency of headache episodes per 28-day period at week 24 was –0.4 episodes in PREEMPT-1 (P = non-significant) and –1.0 episodes in PREEMPT-2 ($P = 0.003$), with fewer headache episodes with Ona A (data not shown).
- Reduction in migraine/probable migraine days per 28-day period: In both studies, a greater proportion of patients in the Ona A group had a 25% reduction, a 50% reduction, and a 75% reduction in migraine/probable migraine days per 28-day period compared with placebo. The proportion of patients with 100% reduction in migraine/probable migraine days was approximately similar between both treatment groups.
- Frequency of migraine/probable migraine days per 28-day period: Patients treated with Ona A experienced a greater decrease from baseline in frequency of migraine/probable migraine days per 28-day period at week 24 (LSM = –7.6 in PREEMPT-1 and –8.8 in PREEMPT-2) than patients treated with placebo (LSM = –6.0 in PREEMPT-1 and –6.5 in PREEMPT-2).
- Frequency of migraine/probable migraine episodes per 28-day period: The between-group difference in the mean change from baseline in frequency migraine/probable migraine episodes per 28-day period at week 24 was –0.5 episodes in PREEMPT-1 (P = non-significant) and –0.9 episodes in PREEMPT-2, with fewer migraine/probable migraine episodes with Ona A (data not shown).
- Emergency room visits and hospital visits due to migraine symptoms: The baseline numbers of emergency room visits and overnight stays were less than one episode in the previous three-month period. At the end of the DB phase, the within-group differences and the between-group differences were less than 0.2 episodes (data not shown). The frequency of visits was too low for interpreting these results.
- Work status and productivity: The mean change in number of hours worked, days of work missed, days of reduced work productivity and the proportion of patients not working due to migraine were assessed using observed data. Between-group differences were similar, except for PREEMPT-2, in which the proportion of patients not working due to migraine at week 24 was 4.6% for Ona A and 9.2% for placebo (data not shown).

Table 39: Improvement from Baseline in Headache and Migraine Days for PREEMPT-1 and PREEMPT-2

Outcome	PREEMPT-1			PREEMPT-2		
	Ona A (N = 341)	Placebo (N = 338)	*P* value	Ona A (N = 347)	Placebo (N = 358)	*P* value
Results for headache days						
Reduction from baseline in headache days per 28-day period at week 24 (observed data)[a]						
[redacted]						
Frequency of headache days per 28-day period (mLOCF)[b]						
[redacted]						
Number of moderate/severe headache days per 28-day period (mLOCF)[c]						
[redacted]						
Total cumulative hours of headache occurring on headache days per 28-day period (mLOCF)[d]						
[redacted]						

Outcome	PREEMPT-1			PREEMPT-2		
	Ona A (N = 341)	Placebo (N = 338)	*P* value	Ona A (N = 347)	Placebo (N = 358)	*P* value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; MD = mean difference; mLOCF = modified last observation carried forward; NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation.

Note: SD is for the mean. LSM and mean were approximately the same. ANCOVA included treatment and medication-overuse strata.

[a] *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of acute headache pain medication intakes as covariate. The main effect in the ANCOVA was treatment.

[b] *P* values for between-treatment comparisons are from ANCOVA, with baseline values as covariate. The main effects in the ANCOVA included treatment and medication-overuse strata.

Sources: Original CADTH Clinical Review report[14] and product monograph.[9]

Harms

The results for harms are presented in Table 40. In the DB phase, the proportion of patients who experienced at least one adverse event was higher in the Ona A group (60% in PREEMPT-1 and 65% in PREEMPT-2) compared with the placebo group (47% in PREEMPT-1 and 56% in PREEMPT-2). Overall, the most frequent adverse events associated with Ona A were neck pain, muscular weakness, headache, eyelid ptosis, injection site pain, musculoskeletal pain, muscle spasms, musculoskeletal stiffness, myalgia, and migraine. The proportion of patients with at least one serious adverse event was higher in the Ona A group (5% in PREEMPT-1 and 4% in PREEMPT-2) compared with the placebo group (2% each in PREEMPT-1 and PREEMPT-2). Withdrawals due to adverse events were higher in Ona A-treated patients compared with placebo-treated patients. The most frequent reasons for withdrawals due to adverse events were headache in PREEMPT-1 and migraine in PREEMPT-2, which may be more due to a lack of efficacy rather than an adverse event.

Over the course of the entire trial (DB + OLE phases), approximately 10% of patients reported neck pain. There were no notable safety issues, including no reports of distant toxin spread and anaphylaxis. There were no deaths during the DB and OLE phases of the included trials.

Table 40: Harms for PREEMPT-1 and PREEMPT-2

	PREEMPT-1		PREEMPT-2	
	Ona A (N = 340)	Placebo (N = 334)	Ona A (N = 347)	Placebo (N = 358)
AEs, n (%)				
Patients with > 0 AEs, n (%)	203 (59.7)	156 (46.7)	226 (65.1)	202 (56.4)
Most common AEs (≥ 2% in any treatment group), n (%)				
Eyelid Ptosis	13 (3.8)	1 (0.3)	11 (3.2)	1 (0.3)
Nausea	7 (2.1)	7 (2.1)	7 (2.0)	10 (2.8)
Injection site pain	7 (2.1)	4 (1.2)	16 (4.6)	10 (2.8)
Fatigue	1 (0.3)	3 (0.9)	2 (0.6)	10 (2.8)
Sinusitis	15 (4.4)	17 (5.1)	13 (3.7)	10 (2.8)
Upper respiratory tract infection	13 (3.8)	20 (6.0)	14 (4.0)	17 (4.7)
Nasopharyngitis	12 (3.5)	16 (4.8)	16 (4.6)	14 (3.9)

	PREEMPT-1		PREEMPT-2	
	Ona A (N = 340)	Placebo (N = 334)	Ona A (N = 347)	Placebo (N = 358)
Bronchitis	9 (2.6)	4 (1.2)	8 (2.3)	7 (2.0)
Gastroenteritis viral	5 (1.5)	8 (2.4)	4 (1.2)	5 (1.4)
Influenza	4 (1.2)	7 (2.1)	7 (2.0)	9 (2.5)
Neck pain	28 (8.2)	11 (3.3)	34 (9.8)	8 (2.2)
Muscular weakness	20 (5.9)	0 (0.0)	18 (5.2)	2 (0.6)
Musculoskeletal pain	10 (2.9)	4 (1.2)	8 (2.3)	6 (1.7)
Arthralgia	7 (2.1)	3 (0.9)	5 (1.4)	6 (1.7)
Muscle spasms	7 (2.1)	2 (0.6)	6 (1.7)	4 (1.1)
Back pain	4 (1.2)	0 (0.0)	4 (1.2)	9 (2.5)
Musculoskeletal stiffness	6 (1.8)	3 (0.9)	16 (4.6)	3 (0.8)
Myalgia	6 (1.8)	3 (0.9)	15 (4.3)	3 (0.8)
Headache	15 (4.4)	10 (3.0)	16 (4.6)	12 (3.4)
Migraine	12 (3.5)	4 (1.2)	14 (4.0)	14 (3.9)
Dizziness	3 (0.9)	2 (0.6)	8 (2.3)	10 (2.8)
Depression	2 (0.6)	0 (0.0)	6 (1.7)	9 (2.5)
Insomnia	3 (0.9)	0 (0.0)	5 (1.4)	8 (2.2)
Anxiety	2 (0.6)	4 (1.2)	3 (0.9)	8 (2.2)
Cough	1 (0.3)	3 (0.9)	6 (1.7)	7 (2.0)
SAEs, n (%)				
Patients with > 0 SAEs, n (%)	18 (5.3)	8 (2.4)	15 (4.3)	8 (2.2)
SAEs reported by 2 or more in any treatment group, n (%)				
Pneumonia	0	0	2 (0.6)	1 (0.3)
Breast cancer	0	0	2 (0.6)	0 (0.0)
Uterine leiomyoma	2 (0.6)	0	0	0
Migraine	1 (0.3)	0	3 (0.9)	1 (0.3)
WDAEs, n (%)				
WDAEs, n (%)	14 (4.1)	3 (0.9)	12 (3.5)	5 (1.4)
WDAEs reported by 2 or more in any treatment group, n (%)				
Neck pain	2 (0.6)	0	2 (0.6)	0
Muscular weakness	1 (0.3)	0	2 (0.6)	0
Breast cancer	0	0	2 (0.6)	0
Headache	3 (0.9)	0	0	1 (0.3)
Migraine	0	1 (0.3)	3 (0.9)	0
Deaths, n (%)				
Deaths, n (%)	0	0	0	0
AEs of special interest reported by 2 or more in any treatment group, n (%)				
Drug hypersensitivity	1 (0.3)	0	2 (0.6)	1 (0.3)
Cardiac disorders				
Palpitations	0	0	0 (0.0)	2 (0.6)
Dysphagia	3 (0.9)	1 (0.3)	2 (0.6)	0 (0.0)

AE = adverse event; Ona A = onabotulinumtoxinA; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: Original CADTH Clinical Review report.[14]

Summary of Critical Appraisal

Internal Validity

Statistical significance should be viewed with consideration of the potential for inflated type I error rates and different alpha levels required to claim statistical significance, where a *P* value less than 0.05 would not indicate statistical significance. In PREEMPT-2, two weeks prior to the primary database lock and treatment unblinding, the initial pre-specified primary end point was changed from frequency of headache episodes to frequency of headache days. Blinding may have been broken due to adverse effects (such as paralysis of the forehead muscles) associated with Ona A. However, in neither PREEMPT-1 nor PREEMPT-2 were patients asked if they could determine whether they were on intervention or placebo treatment. The efficacy of Ona A may have been overestimated, and this would affect the results of patient-reported outcomes and the more subjective outcomes, such as days of headache/migraine and episodes of headache/migraine. Furthermore, investigators may also have been able to determine the allocated treatment group.

In PREEMPT-1 there was a baseline imbalance between the two treatment groups in terms of headache and migraine episodes. These were higher in the placebo group than the Ona A group. In addition, the total cumulative hours of headache were higher in the Ona A group than in the placebo group. This imbalance between the two groups may have explained why the effect sizes obtained in PREEMPT-1 were not as great as those obtained in PREEMPT-2.

No standardized approach was used to determine which patients would require a dose > 155 U. At the investigator's discretion, the dose could be increased by up to an additional 40 U using a "follow the pain" method. In addition, the study was not designed to determine the clinical benefit of treatment at a dose higher than 155 U.

Headache/migraine episodes and days were derived from patient diaries; however, self-reporting is subject to individual variability in reporting accuracy and completion. The number of patients included in the observed data analyses was approximately 10% lower than the number of patients who completed the DB phase. This indicates approximately 10% of the patients did not complete their diaries. This may have introduced bias that may have affected the internal validity of both trials. Furthermore, no descriptions of this electronic telephone diary and its validation were provided. Acute headache pain medication use was measured as intake of medication(s) to treat headache pain where patients reported that they took medication, regardless of the dose or number of types of medication taken at the same time. This method did not measure accurately the use of acute headache pain medication.

External Validity

PREEMPT-1 and PREEMPT-2 were designed when criteria from the second edition of the International Classification of Headache Disorders (ICHD) were still in use and prior to the publication of the third edition of the ICHD (ICHD-III). The second edition used a strict definition of CM (migraine occurring on 15 or more days per month for more than three months), whereas the ICHD-III describes CM as a headache (tension-type-like or migraine-like) occurring on 15 or more days per month for more than three months, which has the features of migraine headaches on at least eight days per month. This latter definition of CM was meant to better reflect the population of patients seen in clinical practice. Although

patients with tension-type headaches were specifically excluded from PREEMPT-1 and PREEMPT-2, the inclusion criteria used in both studies were more in line with ICHD-III.

The ICHD-III excludes medication overuse headache (MOH) from the diagnosis of CM. However, neither study excluded patients with MOH. Both studies stratified patients according to history of acute medication overuse to account for this, but some patients could still have been misclassified as CM patients when in fact they should have been diagnosed with MOH. In clinical practice there is considerable overlap between MOH and CM, making it difficult to distinguish between them. The trials likely reflect the real-world situation.

The exclusion of patients who were on therapy that is also used as prophylactic headache treatment (for example beta blockers used for hypertension and antidepressants used for depression) may have excluded CM patients with comorbid illnesses and hence the efficacy of Ona A has not been explored in such subgroup of patients.

Both trials compared Ona A versus placebo. Despite the lack of other approved prophylactic medications for CM in Canada, there are medically accepted therapies such as propranolol, amitriptyline, and topiramate that are used off-label. A comparative trial against one of these agents would have been clinically relevant.

Conclusion of Original CADTH Common Drug Report

The original CADTH report concluded that Ona A was superior to placebo in improving HRQoL and patient-reported outcomes, as measured with MSQ and HIT-6, and other efficacy outcomes, such as fewer headache and migraine days. However, the absolute difference in headache and migraine days, about one to two days, was deemed to be not clinically important. The trials were limited by short duration, lack of active comparators, imbalances in patient characteristics (PREEMPT-1), the use of subjective outcome measures, and the possibility of unblinding.

Appendix 7: Summary of Other Studies

Aim

To review the efficacy and harms data reported from the open-label extension (OLE) phase of PREEMPT-1 and PREEMPT-2.

Findings

Study/Phase Design

The 24-week, double-blind (DB), randomized, placebo-controlled, parallel-group phase of PREEMPT-1 and PREEMPT-2 was followed by a 32-week OLE phase. The OLE phase began with the week-24 visit and consisted of three treatment cycles of 12 weeks each, with all patients receiving onabotulinumtoxinA (Ona A) at week 24, week 36, and week 48. Patients completed study visits every four weeks (weeks 28, 32, 36, 40, 44, 48, 52, and 56).

Patient Disposition

Patients who had previously received Ona A in the DB phase are referred to as the Ona A / Ona A group in the OLE phase, while patients who had previously received placebo in the DB phase are referred to as the placebo / Ona A group in the OLE phase.

The rate of discontinuation was high, with more than 25% of patients discontinuing treatment before week 56. Of the 679 patients enrolled in PREEMPT-1, 71.1% of patients completed the OLE phase. In PREEMPT-2, 74.0% of patients completed the OLE phase of the study. The main reasons for treatment discontinuation in the OLE phase and for the entire study were “other” causes, which were not defined (Table 41). Few patients (2% to 4%) discontinued the study due to lack of efficacy.

Table 41: Patient Disposition

	PREEMPT-1		PREEMPT-2	
	Ona A / Ona A	Placebo / Ona A	Ona A / Ona A	Placebo / Ona A
Enrolled	341	338	347	358
Completed open-label phase (week 56), n (%)	252 (73.9)	231 (68.3)	261 (75.2)	261 (72.9)
Discontinued after week 24 and prior to week 56, n (%)	44 (12.9)	64 (18.9)	50 (14.1)	73 (20.4)
Adverse events	7 (2.1)	6 (1.8)	12 (3.5)	15 (4.2)
Lack of efficacy	5 (1.5)	6 (1.8)	6 (1.7)	14 (3.9)
Pregnancy	0	3 (0.9)	3 (0.9)	1 (0.3)
Lost to follow-up	8 (2.3)	15 (4.4)	3 (0.9)	14 (3.9)
Personal reasons	9 (2.6)	13 (3.8)	13 (3.7)	8 (2.2)
Protocol violations	2 (0.6)	3 (0.9)	1 (0.3)	1 (0.3)
Other	13 (3.8)	18 (5.3)	12 (3.5)	20 (5.6)
Discontinued the entire study, n (%)	89 (26.1)	107 (31.7)	86 (24.8)	97 (27.1)
Adverse events	18 (5.3)	8 (2.4)	20 (5.8)	18 (5.0)
Lack of efficacy	6 (1.8)	6 (1.8)	10 (2.9)	15 (4.2)
Pregnancy	2 (0.6)	4 (1.2)	4 (1.2)	2 (0.6)

	PREEMPT-1		PREEMPT-2	
	Ona A / Ona A	Placebo / Ona A	Ona A / Ona A	Placebo / Ona A
Lost to follow-up	14 (4.1)	30 (8.9)	10 (2.9)	22 (6.1)
Personal reasons	21 (6.2)	24 (7.1)	20 (5.8)	13 (3.6)
Protocol violations	2 (0.6)	6 (1.8)	2 (0.6)	1 (0.3)
Other	26 (7.6)	29 (8.6)	20 (5.8)	26 (7.3)

Ona A = onabotulinumtoxinA.

Source: Original CADTH Clinical Review report.[14]

Drug Exposure

In the OLE phase, patients received three doses of Ona A of approximately 164 Allergan units (U) each at 33 injection sites at weeks 24, 36, and 48 (Table 42). The mean dose of Ona A across all five cycles was 164 U (standard deviation [SD], 12.9) for 32.8 injection sites (SD, 2.6). The overall treatment duration was a mean 292.1 days (SD, 112.6).

Table 42: Drug Exposure in the OLE Phase and Across All Five Cycles

	PREEMPT-1 and PREEMPT-2 Combined			
Drug Exposure	**Week 24 treatment cycle 3**	**Week 36 treatment cycle 4**	**Week 48 treatment cycle 5**	**Weeks 0 to 48 treatment cycles 1 to 5**
n	1092	558	518	1300
Units, mean (SD)	164.5 (13.3)	164.9 (13.5)	164.4 (14.6)	164.0 (12.9)
Units, median (min to max)	155 (130 to 195)	155.0 (130 to 195)	155.0 (65 to 195)	158.3 (15 to 195)
Injections sites, mean (SD)	32.9 (2.7)	33.0 (2.7)	32.9 (2.9)	32.8 (2.6)
Treatment cycle durations, mean days (SD)	74.8 (16.6)	87.1 (12.1)	61.9 (10.4)	292.1 (112.6)

max = maximum, min = minimum, SD = standard deviation.

Source: Original CADTH Clinical Review report.[14]

Results

Efficacy

Migraine-Specific Quality of Life Questionnaire (MSQ) within-group comparison: Irrespective of the group assignment in the DB phase, there was a clinically important improvement in MSQ scores at the end of the study compared with baseline in both PREEMPT-1 and PREEMPT-2 for both the Ona A / Ona A group and the placebo / Ona A group (Table 43). Some patients went from the worst possible health-related quality of life (HRQoL) to the best possible HRQoL (MSQ score of 100 at baseline and improved by 100 at week 56). Some patients had a worse MSQ score compared with baseline.

Between-group comparison: In both studies, there were no statistically significant differences between Ona A / Ona A and placebo / Ona A for any of the domains (role function-restrictive, role function-preventive, and emotional function) at week 56.

Six-item Headache Impact Test (HIT-6) within-group comparison: Irrespective of the group assignment in the DB phase, there was an improvement in mean HIT-6 scores at the end of the study compared with baseline in both PREEMPT-1 and PREEMPT-2 for the Ona A / Ona A group and the placebo / Ona A group (Table 44). Whether this finding is clinically important is unknown because the within-group minimal clinically important difference has

not been determined. Nonetheless, patients went from a score of greater than 60 points at baseline (severe impact on the daily life of the respondent) to a score of 56 to 59 (substantial impact on the daily life of the respondent) at the end of the study (data not shown).

Between-group comparison: In both studies, there were no statistically significant differences in mean HIT-6 scores between the Ona A / Ona A and placebo / Ona A groups at week 56.

Acute headache pain medication intake within-group comparison: The frequency of acute pain medication intake decreased at week 56 compared with baseline for both groups in both studies (Table 45). Similarly, the number of medication days decreased from 14 to 15 days per month at baseline, by eight to nine days per month at week 52. The intake of acute pain medications could not be completely stopped; more than 70% of patients still required acute pain medications at week 56. However, the overuse of acute-pain medications decreased to less than 20% of patients at week 56, compared with more than 60% at baseline.

Between-group comparison: Statistically significant differences were obtained in acute headache pain medication days and acute headache pain medication overuse at week 56. The Ona A / Ona A group had a greater improvement in medication days and medication overuse compared with the placebo / Ona A group; however, the differences were small and not likely to be clinically important.

Headache/migraine days within-group comparison: Patients experienced a decrease in the frequency of headache days by 11 or 12 days per month at week 56, from approximately 20 days per month at baseline (Table 46). Similarly, the frequency of migraine/probable migraine days decreased by 10 or 11 days per month at week 56 from approximately 19 days per month at baseline. This means that patients experienced on average eight to nine migraines per month, reverting back to a diagnosis of CM.

Between-group comparison: In PREEMPT-1, there were no statistically significant differences between the Ona A / Ona A group and the placebo / Ona A group for any of the measures related to headache/migraine days, whereas in PREEMPT-2 all between-group differences were statistically significant.

Table 43: Baseline and Mean Change From Baseline at Week 56 in MSQ Scores

	PREEMPT-1			PREEMPT-2		
	Ona A / Ona A	**Placebo / Ona A**	***P* value**	**Ona A / Ona A**	**Placebo / Ona A**	***P* value**
Migraine-Specific Quality of Life Questionnaire (MSQ)						
Role function-restrictive						
Baseline, n	337	335		347	358	
Mean (SD)	61.3 (16.6)	63.1 (17.1)		61.7 (16.5)	59.7 (17.3)	
Median (min to max)	60.0 (9 to 100)	62.9 (23 to 100)		60 (14 to 100)	60.0 (9 to 100)	
Week 56, n	266	258		292	310	
Change from baseline at week 56, mean (SD)	–25.6 (25.0)	–22.8 (25.6)	0.329	–24.8 (25.6)	–20.9 (26.6)	0.073
Median (min to max)	–25.7 (–91 to 37)	–20.00 (–100 to 49)		–22.9 (-100 to 40)	–18.8 (–100 to 46)	

	PREEMPT-1			PREEMPT-2		
	Ona A / Ona A	**Placebo / Ona A**	***P* value**	**Ona A / Ona A**	**Placebo / Ona A**	***P* value**
Role function-preventive						
Baseline, n	337	335		347	358	
Mean (SD)	43.2 (20.9)	46.0 (21.2)		44.7 (21.6)	42.0 (22.1)	
Median (min, max)	40.0 (0 to 100)	45 (0 to 100)		40.0 (0 to 100)	40.0 (0 to 100)	
Week 56, n	266	258		293	310	
Change from baseline at week 56, mean (SD)	–18.8 (24.1)	-18.1 (24.5)	0.948	–19.2 (24.7)	–16.7 (25.7)	0.182
Median (min to max)	–20.0 (–95 to 40)	–17.5 (–90 to 55)		–15.0 (–100 to 55)	–15.0 (–100 to 70)	
Role function-emotional function						
Baseline, n	337	334		347	357	
Mean (SD)	59.1 (23.5)	60.3 (24.6)		56.8 (24.6)	55.0 (25.0)	
Median (min, max)	60.0 (7 to 100)	60.0 (0 to 100)		53.3 (0 to 100)	53.3 (0 to 100)	
Week 56, n	266	258		293	309	
Change from baseline at week 56, mean (SD)	–25.1 (29.0)	–22.3 (30.3)	0.263	–24.9 (29.1)	–22.0 (31.1)	0.098
Median (min, max)	–20.0 (-93 to 47)	–20 (–93 to 47)		–20 (–100 to 53)	–20 (–100 to 73)	

max = maximum; min = minimum; Ona A = onabotulinumtoxinA; SD = standard deviation.

Source: Original CADTH Common Drug Review report.[14]

Table 44: Baseline and Mean Change From Baseline at Week 56 in HIT-6 and Headache Impact Scores

	PREEMPT-1			PREEMPT-2		
	Ona A / Ona A (n = 341)	**Placebo / Ona A (n = 338)**	***P* value**	**Ona A / Ona A (n = 347)**	**Placebo / Ona A (n = 358)**	***P* value**
Total HIT-6 scores (mLOCF)						
Baseline, mean (SD)	65.4 (3.8)	65.8 (4.1)		65.6 (4.3)	65.0 (4.5)	
Change from baseline at week 56, mean (SD)	–7.6 (8.0)	–6.9 (7.6)	0.378	–7.7 (7.8)	–7. 1(8.7)	0.088
Baseline, median (min to max)	65.0 (51 to 78)	66.0 (53 to 78)		66.0 (50 to 78)	65.0 (46 to 78)	
Change from baseline at week 56, median (min to max)	–6.0 (–32 to 14)	–6.0 (–30 to 10)		–7.0 (–42 to 15)	–5.5 (–42 to 11)	

max = maximum; min = minimum; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.

Source: Original CADTH Clinical Review report.[14]

Table 45: Acute Headache Pain Medication Intake

	PREEMPT-1			PREEMPT-2		
	Ona A / Ona A (n = 341)	Placebo / Ona A (n = 338)	*P* value	Ona A / Ona A (n = 347)	Placebo / Ona A (n = 358)	*P* value
Acute headache pain medication intakes per 28-day period (mLOCF)						
Baseline, LSM (SD)	25.2 (19.3)	25.7 (22.3)		21.9 (18.8)	22.8 (18.9)	
Change from baseline at week 56, LSM (SD)	–16.0 (20.0)	–17.1 (19.9)	0.400	–15.1 (15.7)	–13.6 (16.4)	0.097
Acute headache pain medication intakes per 28-day period (mLOCF)						
Baseline, LSM (SD)	15.0 (6.3)	15.4 (6.4)		14.3 (6.4)	14.4 (6.3)	
Week 56, n	195	177		205	204	
Change from baseline at week 56, LSM (SD)	–8.6 (7.1)	–9.1 (7.0)	0.420	–8.7 (6.2)	–7.6 (6.3)	0.027
Acute headache pain medication intakes per 28-day period (mLOCF)						
Baseline, n/total (%)	335/341 (98.2)	327/338 (96.7)		337/347 (97.1)	351/358 (98.0)	
At week 56, n/total (%)	152/195 (77.9)	142/177 (80.2)	0.590	151/205 (73.7)	164/204 (80.4)	0.106
Acute headache pain medication intakes per 28-day period (mLOCF)						
Baseline, n/total (%)	226/341 (66.3)	236/338 (69.8)		220/347 (63.4)	224/358 (62.6)	
At week 56, n/total (%)	34/195 (17.4)	31/177 (17.5)	0.984	18/205 (8.8)	37/204 (13.4)	0.006

LSM = least squares mean; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.

Source: Original CADTH Common Drug Review report.[14]

Table 46: Improvement from Baseline in Headache and Migraine Days

	PREEMPT-1			PREEMPT-2		
	Ona A / Ona A	Placebo / Ona A	*P* value	Ona A / Ona A	Placebo/ Ona A	*P* value
Results for headache days						
Frequency of headache days per 28-day period (ANCOVA using mLOCF)						
Baseline, LSM (SD)	19.9 (3.7)	19.7 (3.7)		19.8 (3.6)	19.7 (3.7)	
Change from baseline at week 56, LSM (SD)	–11.5 (6.6)	–11.0 (6.6)	0.378	–12.1 (6.4)	–10.9 (7.0)	0.014
Number of moderate/severe headache days per 28-day period (ANCOVA using mLOCF)						
Baseline, LSM (SD)	17.9 (4.2)	18.0 (4.2)		18.0 (4.0)	17.6 (4.3)	
Change from baseline at week 56, LSM (SD)	–10.2 (6.5)	–10.1 (6.4)	0.805	–11.2 (5.9)	–9.9 (6.9)	0.004
Total cumulative hours of headache occurring on headache days per 28-day period (ANCOVA using mLOCF)						
Baseline, LSM (SD)	299.2 (116.8)	279.2 (110.9)		299.1 (121.0)	290.0 (118.9)	
Change from baseline at week 56, LSM (SD)	–162.1 (139.2)	–148.0 (138.0)	0.150	–172.9 (135.1)	–154.9 (139.1)	0.051
Results for migraine/probable migraine days						
Frequency of migraine/probable migraine days per 28-day period (ANCOVA using mLOCF)						
Baseline, LSM (SD)	19.0 (4.0)	19.0 (4.0)		19.1 (3.9)	18.7 (4.1)	

	PREEMPT-1			PREEMPT-2		
	Ona A / Ona A	Placebo / Ona A	*P* value	Ona A / Ona A	Placebo/ Ona A	*P* value
Change from baseline at week 56, LSM (SD)	–11.0 (7.0)	–10.6 (6.7)	0.405	–11.5 (6.4)	–10.3 (7.0)	0.015

ANCOVA = analysis of covariance; LSM = least squares mean; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.

Source: Original CADTH Clinical Review report.[14]

Harms

An event occurring during the DB phase and continuing into the open-label phase was only counted in the DB phase. In addition, an event occurring during the DB phase and continuing into the open-label phase whose severity increased in the open-label phase was only counted in the DB phase.

The number and percentage of patients with adverse events (AEs), serious adverse events (SAEs) and withdrawals due to adverse events are presented in Table 47 and Table 48. A patient was counted once for each adverse event when multiple occurrences of the same adverse events were reported.

There were no deaths. In the OLE phases of PREEMPT-1 and PREEMPT-2, 58% of patients experienced an AE with Ona A. Over the course of the five treatment cycles, 74% of patients exposed to Ona A reported an AE.

In the OLE phases of PREEMPT-1 and PREEMPT-2, the most common AEs were neck pain, sinusitis, and nasopharyngitis (Table 48). SAEs were infrequent. There were four cases of severe migraine, three cases of non-cardiac chest pain, three cases of uterine leiomyoma, and two cases of squamous cell carcinoma. Less than 5% of patients withdrew from the OLE phase due to an AE.

Dysphagia, neck pain, and cardiac events were identified as AEs of special interest (Table 47). Considering the entire study, approximately 10% of patients reported neck pain. Few patients reported dysphagia or a cardiac event. Other AEs of special interest included:

- Systemic toxicity: There was no evidence of distant toxin spread.
- Anaphylaxis reaction: There was no report of anaphylaxis reactions.
- Antibody formation: Serum samples for toxin-neutralizing antibody titer analysis were not collected in PREEMPT-1 and PREEMPT-2. However, the sponsor indicated that “there is no heightened risk for immunogenicity in this patient population.” (Clinical Summary Module 2.7.4, page 118).
- Autonomic dysreflexia: There was no report of autonomic dysreflexia.

Table 47: Overall Harms

	PREEMPT-1		PREEMPT-2	
	Ona A / Ona A	Placebo / Ona A	Ona A / Ona A	Placebo / Ona A
Open-label phase, n	287	284	305	329
All adverse events, n (%)	155 (54.0)	165 (58.1)	174 (57.0)	209 (63.5)
Serious adverse events, n (%)	20 (7.0)	8 (2.8)	7 (2.3)	11 (3.3)
Discontinuation due to adverse events, n (%)	4 (1.4)	5 (1.8)	9 (3.0)	13 (4.0)
Deaths, n	0	0	0	0
Entire study, n	340	334	347	358
All adverse events, n (%)	254 (74.7)	220 (65.9)	268 (77.2)	280 (78.2)
Serious adverse events, n (%)	34 (10.0)	15 (4.5)	22 (6.3)	19 (5.3)
Discontinuation due to adverse events, n (%)	18 (5.3)	8 (2.4)	20 (5.8)	18 (5.0)
Deaths, n	0	0	0	0
Adverse events of special interest (entire study)				
Neck pain	72 (10.6)		69 (9.8)	
Dysphagia	6 (< 1)		5 (< 1)	
Cardiac events	11 (1.6)		13 (1.8)	

Ona A = onabotulinumtoxinA.

Source: Original CADTH Clinical Review report.[14]

Table 48: Detailed Harms, Open-Label Phase

	PREEMPT-1 and PREEMPT-2 Combined		
	Ona A / Ona A (n = 592)	Placebo / Ona A (n = 613)	Total (n = 1205)
Adverse events in ≥ 2% of patients, n (%)	329 (55.6)	374 (61.0)	703 (58.3)
Eyelid ptosis	13 (2.2)	17 (2.8)	30 (2.5)
Nausea	12 (2.0)	10 (1.6)	22 (1.8)
Injection site pain	15 (2.5)	11 (1.8)	26 (2.6)
Sinusitis	32 (5.4)	29 (4.7)	61 (5.1)
Nasopharyngitis	26 (4.4)	31 (5.1)	57 (4.7)
Upper respiratory tract infection	24 (4.1)	24 (3.9)	48 (4.0)
Influenza	12 (2.0)	13 (2.1)	25 (2.1)
Urinary tract infection	12 (2.0)	13 (2.0)	25 (2.1)
Bronchitis	8 (1.4)	15 (2.4)	23 (1.9)
Neck pain	27 (4.6)	43 (7.0)	70 (5.8)
Muscular weakness	9 (1.5)	27 (4.4)	36 (3.0)
Muscle tightness	7 (1.2)	22 (3.6)	29 (2.4)
Musculoskeletal stiffness	5 (0.8)	19 (3.1)	24 (2.0)
Musculoskeletal pain	4 (0.7)	21 (3.4)	25 (2.1)
Myalgia	4 (0.7)	16 (2.6)	20 (1.7)
Migraine	22 (3.7)	17 (2.8)	39 (3.2)
Headache	12 (2.0)	22 (3.6)	34 (2.8)
Dizziness	12 (2.0)	9 (1.5)	21 (1.8)
Facial paresis	3 (0.5)	12 (2.0)	15 (1.2)

	PREEMPT-1 and PREEMPT-2 Combined		
Depression	3 (0.5)	13 (2.1)	16 (1.3)
Serious adverse events reported in ≥ 2 patients, n (%)	27 (4.6)	19 (3.1)	46 (3.8)
Non-cardiac chest pain	3 (0.05)	0	3 (< 1)
Uterine leiomyoma	3 (0.5)	0	3 (< 1)
Squamous cell carcinoma	0	2 (0.3)	2 (< 1)
Migraine	4 (0.7)	0	4 (< 1)
Withdrawals due to adverse events in ≥ 2 patients, n (%)	13 (2.2)	18 (2.9)	31 (2.6)
Neck pain	1 (0.2)	4 (0.7)	5 (< 1)
Muscle spasms	2 (0.3)	2 (0.3)	4 (< 1)
Muscular weakness	0	3 (0.5)	3 (< 1)
Joint stiffness	2 (0.3)	0	2 (< 1)
Muscle tightness	0	2 (0.3)	2 (< 1)
Musculoskeletal pain	0	2 (0.3)	2 (< 1)
Headache	1 (0.2)	2 (0.3)	3 (< 1)
Migraine	1 (0.2)	2 (0.3)	3 (< 1)

Ona A = onabotulinumtoxinA.

Source: Original CADTH Clinical Review report.[14]

Summary

The 32-week OLE phase began at the week-24 visit. Patients received on average 164 U of Ona A at 33 injection sites every 12 weeks (weeks 24, 36, 48). Patients completed study visits every four weeks, with the last visit recorded at week 56. The mean overall treatment duration was 292.1 days (SD, 112.6). In the OLE phase, the rate of discontinuation was high, with more than 25% of patients discontinuing treatment before week 56. However, few patients (2% to 4%) discontinued the study due to a lack of treatment efficacy. Irrespective of group assignment in the DB phase, there were improvements in MSQ and HIT-6 scores at the end of the study compared with baseline in both PREEMPT-1 and PREEMPT-2. Acute headache pain medications could not be completely stopped, with more than 70% of patients still requiring acute pain medications at week 56. However, less than 20% of patients overused acute pain medications at week 56. The frequency of headache days and migraine/probable migraine days decreased by 10 or 11 days per month at week 56, from approximately 19 to 20 days per month at baseline. This means that patients experienced on average of eight to nine migraines per month, reverting back to a diagnosis of episodic migraines. There were no deaths reported in PREEMPT-1 and PREEMPT-2. SAEs were infrequent. Less than 5% of patients withdrew from the OLE phase due to an AE. In the OLE phase, the most common AEs were neck pain, sinusitis, and nasopharyngitis. Across the entire study, 10% of patients reported neck pain. There was no evidence of distant toxin spread. There was no report of anaphylaxis reaction.

Appendix 8: Summary of Indirect Comparisons

Introduction and Background

Limited head-to-head data are available to assess the efficacy and safety of onabotulinum toxin A (Ona A) compared with other therapies for chronic migraine (CM) in adults. The purpose of this appendix was to identify, summarize, and critically appraise the data available from indirect treatment comparisons (ITCs).

Methods

CADTH Common Drug Review conducted an independent literature search for ITCs that compared Ona A with other relevant comparators for the treatment of CM in adults. One relevant publication was identified in the grey literature.[19] No ITC was submitted by the manufacturer and none were identified in the published literature.

Description of Indirect Treatment Comparisons Identified

The Institute for Clinical and Economic Review (ICER) conducted a network meta-analysis (NMA) to examine the clinical effectiveness, tolerability, and safety of calcitonin gene-related peptide (CGRP) inhibitors compared with placebo or commonly used preventive treatments in adults with chronic or episodic migraine.[19] This appendix focuses on the NMAs that compared Ona A with CGRP inhibitors and other preventive therapies in adults with chronic migraine. The population, intervention, comparators, outcomes, and design of studies included in the NMAs are provided below in Table 49.

Table 49: Populations, Interventions, Comparisons, Outcomes, and Study Design Criteria for Inclusion in Network Meta-Analyses

	ICER (2018)[19]
Population	Adults (≥ 18 years) with episodic or chronic migraine[a] and eligible for preventive migraine therapy • Chronic migraine defined as ≥ 15 headache days per month for at least 3 months and migraine features present on at least 8 days per month
Intervention	CGRP inhibitors: • Erenumab • Fremanezumab • Galcanezumab
Comparators	• Placebo • Topiramate • Propranolol • Amitryptyline • OnabotulinumtoxinA[a]
Outcomes	• Change from baseline in monthly migraine days • Change from baseline in headache days • Change from baseline in days using acute medication per month • ≥ 50% reduction in migraine days • Quality of life (MIDAS, HIT-6, MSQ) • All-cause discontinuations • Discontinuations from adverse events • Adverse events reported by ≥ 5% patients in a trial arm • SAEs
Study Design	• RCTs • Crossover studies if results prior to crossover were presented • Non-randomized comparative studies with at least 100 patients • OLEs of RCTs • Non-comparative observational studies with at least 100 patients and 6-month follow-up
Other	English language

CGRP = calcitonin gene-related peptide; HIT-6 = six-item Headache Impact Test; ICER = Institute for Clinical and Economic Review; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire; OLE = open-label extension; RCT = randomized controlled trial; SAE = serious adverse event.

[a] Focus of this appendix.

Source: Institute for Clinical and Economic Review.[19]

Review and Appraisal of ITCs

Methods of the Indirect Comparison

Study Eligibility and Selection Process

Two reviewers screened abstracts and full texts independently and studies were selected based on the eligibility criteria outlined in Table 49. Published randomized controlled trials (RCTs) of any sample size were included. Non-randomized comparative studies were selected if they had at least 100 patients and crossover studies were eligible if data were reported prior to the crossover period. To assess long-term efficacy and safety, open-label extension (OLE) trials of RCTs of any size and duration were considered in the ICER review, as were non-comparative observational studies with at least 100 patients and six months of follow-up. However, these studies are not described here. The population of interest for this appendix was adult patients (≥ 18 years) with CM who were eligible for preventive therapy. Studies of patients with other types of headache or migraine conditions,

such as tension-type, cluster, or secondary headaches were excluded. The primary intervention was CGRP inhibitors, which included subcutaneous injections of erenumab, fremanezumab, and galcanezumab, at any dose or frequency. The comparator of relevance for this appendix was Ona A and any other preventive therapies for which comparative data with Ona A were available through the NMA (i.e., topiramate). Key outcomes were change from baseline in monthly migraine days, change from baseline in headache days, change from baseline in days using acute medication per month, 50% or greater reduction in migraine days, quality of life as assessed by the Migraine Disability Assessment (MIDAS), the Migraine-Specific Quality of Life Questionnaire (MSQ), or the six-item Headache Impact Test (HIT-6), all-cause discontinuations, discontinuations from adverse events (AEs), and AEs reported by at least five per cent of patients in a trial arm.

Data Extraction

One reviewer extracted data on patient population, sample size, duration of follow-up, funding source, study design, intervention, outcome assessment (definition, timing, and method of assessment), and results. A second reviewer independently verified the extracted data. Table 50, Table 51, and Table 52 provide sample sizes, doses, and selected baseline population characteristics for the included Ona A, topiramate, and CGRP inhibitor studies, respectively. Table 53 provides the design features of the studies.

Fourteen trials were included for the assessment of clinical benefit of Ona A, topiramate, and CGRP inhibitors in CM. In the three CGRP inhibitor trials (Tepper 2017,[71] Bigal 2015,[72] and Silberstein 2017[73]) and two of the Ona A trials (Aurora 2010[59] and Diener 2010[60]), patients who showed at least 80% compliance with a daily electronic headache diary and who continued to meet the criteria for CM during the four-week baseline phase continued to the randomized phase. Criteria related to compliance with a daily headache diary were not reported in the other trials. One topiramate trial and both fremanezumab trials permitted concomitant preventive migraine therapy, which was not permitted in the other trials. Both factors — compliance with headache diary and use of concomitant preventive migraine therapy — are sources of potential heterogeneity in the NMAs. The average age was approximately 40 years, and over 80% of the patients were female. The included patients had a history of CM for an average of 20 years. Four trials reported the proportion of patients with medication overuse headache, which ranged from 41% to 68%, and five trials excluded patients with medication overuse headaches. None of the fremanezumab trial reported this information. The mean number of migraine days per month ranged from 15 to 25 at baseline across the 14 trials of onabotulinum toxin A, topiramate, and CGRP inhibitors. The time point of analysis ranged from 12 to 26 weeks.

Table 50: Selected Baseline Population Characteristics in Studies of OnabotulinumtoxinA versus placebo and OnabotulinumtoxinA versus topiramate

Study	Arm	N	Mean Age (SD)	Mean Years Since Onset (SD)	Mean Migraine Days per Month (SD)	Mean Headache Days per Month (SD)	Mean Days of Acute Medication Use per Month (SD)
Aurora (2010) (PREEMPT-1)	Ona A 155 U	341	41.2 (NR)	20.3 (NR)	19.1 (4.0)	20.0 (3.7)	NR
	Placebo	338	42.1 (NR)	20.6 (NR)	19.1 (4.1)	19.8 (3.7)	NR
Diener (2010) (PREEMPT-2)	Ona A 155 U	347	41.0 (NR)	18.5 (NR)	19.2 (3.9)	19.9 (3.6)	NR
	Placebo	358	40.9 (NR)	17.6 (NR)	18.7 (4.1)	19.7 (3.7)	NR
Cady (2014)	Ona A 155 U	10	NR	NR	23.4 (1.9)[a]	NR	NR
	Placebo	10	NR	NR	24.8 (1.9)[a]	NR	NR
Freitag (2008)	Ona A 100 U	30	42.2 (NR)	NR	NR	23 (NR)	NR
	Placebo	30	42.4 (NR)	NR	NR	23 (NR)	NR
Sandrini (2011)	Ona A 100 U	33	48.5 (9.2)	19.7 (NR)	NR	24.2 (5.0)	22.7 (6.4)
	Placebo	35	49.0 (10.1)	20.3 (NR)	NR	25.5 (5.6)	23.6 (6.6)
Cady (2011)	Ona A 200 U	29	NR	NR	11.9 (NR)	21.8 (NR)	13.9 (NR)
	Topiramate 200 mg/day	30	NR	NR	10.3 (NR)	20.5 (NR)	15.1 (NR)
Mathew (2009)	Ona A 200 U	30	NR	NR	NR	15.6 (7.0)	NR
	Topiramate 100 mg/day	30	NR	NR	NR	15.5 (7.2)	NR

NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation; U = Allergan units.

[a] Standard error.

Source: Institute for Clinical and Economic Review.[19]

Table 51: Selected Baseline Characteristics in Studies of Topiramate versus Placebo

Study	Arm	N	Mean Age (SD)	Mean Years Since Onset (SD)	Mean Migraine Days per Month (SD)	Mean Headache Days per Month (SD)	Mean Days of Acute Medication Use per Month (SD)
Silberstein (2007)	Topiramate 100 mg/day	165	37.8 (12.4)	9.3 (10.5)	17.1 (5.4)	20.4 (4.8)	11.9 (7.0)
	Placebo	163	38.6 (11.8)	9.1 (10.6)	17.0 (5.0)	20.8 (4.6)	11.4 (6.6)
Diener (2007)	Topiramate 100 mg/day	32	47.8 (9.4)	NR	15.5 (4.6)	NR	NR
	Placebo	27	44.4 (9.6)	NR	16.4 (4.4)	NR	NR
Mei (2006)	Topiramate 100 mg/day	30	45.8 (9.1)	5.0 (1.9)	NR	24.4 (3.9)	NR
	Placebo	20	45.9 (8.4)	5.0 (2.2)	NR	23.5 (3.7)	NR
Silvestrini (2003)	Topiramate 50 mg/day	14	43 (NR)	3 (NR)	NR	20 (NR)	NR
	Placebo	14	44 (NR)	3 (NR)	NR	20 (NR)	NR

NR = not reported; SD = standard deviation.

Source: Institute for Clinical and Economic Review.[19]

Table 52: Selected Baseline Population Characteristics in Studies of Calcitonin Gene-Related Peptide Inhibitor versus Placebo

Study	Arm	N	Mean Age (SD)	Mean Years Since Onset (SD)	Mean Migraine Days per Month (SD)	Mean Headache Days per Month (SD)	Mean Days of Acute Medication Use per Month (SD)
Erenumab							
Tepper (2017) (Phase II)	Erenumab 70 mg/month	191	41.4 (11.3)	20.7 (12.8)	17.9 (4.4)	20.5 (3.8)	8.8 (7.2)
	Erenumab 140 mg/month	190	42.9 (11.1)	21.9 (11.8)	17.8 (4.7)	20.7 (3.8)	9.7 (7.0)
	Placebo	286	42.1 (11.3)	22.2 (12.6)	18.2 (4.7)	21.1 (3.9)	9.5 (7.6)
Fremanezumab							
Bigal (2015) (Phase II)	Fremanezumab 675/225 mg/month	88	40.0 (11.6)	15.8 (11.2)	17.2 (5.4)	16.5 (6.7)	15.1 (7.0)
	Fremanezumab 900 mg/month	87	41.5 (12.9)	18.8 (12.2)	16.4 (5.3)	15.9 (6.5)	16.2 (6.7)
	Placebo	89	40.7 (11.5)	20.4 (13.1)	16.8 (5.0)	16.5 (6.3)	15.7 (6.2)
Silberstein (2017) (Phase III)	Fremanezumab 675 mg/3 months	376	42 (12.4)	19.7 (12.8)	16.2 (4.9)	20.4 (3.9)	13.1 (6.8)
	Fremanezumab 675/225 mg/month	379	40.6 (12.0)	20.1 (12.0)	16.0 (5.2)	20.3 (4.3)	13.1 (7.2)
	Placebo	375	41.4 (12.0)	19.9 (12.9)	16.4 (5.2)	20.3 (4.2)	13.0 (6.9)

SD = standard deviation.

Source: Institute for Clinical and Economic Review.[19]

Table 53: Design Features of Studies in Patients with Chronic Migraine

Study	Number of Centres Funding	Location	Baseline (Weeks)	Intervention (Weeks)	Total Follow-up (Weeks)	Inclusion: Migraine History Exclusion: Prior Failures	Ongoing Preventive Therapy
Ona A vs. placebo							
Aurora (2010) (PREEMPT-1) (RCT)	Multi-centre Industry	North America	4	24	56	ICHD-II NA	Not allowed
Diener (2010) (PREEMPT-2) (RCT)	Multi-centre Industry	North America; Europe	4	24	56	ICHD-II NA	Not allowed
Cady (2014) (RCT Crossover)	Multi-centre Industry	US	NR	16	28	ICHD-II NA	Allowed
Freitag (2008) (RCT)	Unclear Industry	US	4	16	16	ICHD-I NA	Allowed
Sandrini (2011) (RCT)	Multi-centre Industry	Italy	4	12	24	ICHD-II NA	Not allowed
Cady (2011) (RCT)	Multi-centre NR	US	4	12	24	ICHD-II NA	Allowed

Study	Number of Centres Funding	Location	Baseline (Weeks)	Intervention (Weeks)	Total Follow-up (Weeks)	Inclusion: Migraine History Exclusion: Prior Failures	Ongoing Preventive Therapy
Mathew (2009) (RCT)	Single center Industry	US	4	36	38	NR NA	Not allowed
Silberstein (2007) (RCT)	Multi-centre Industry	US	4	16	18	≥ 15 HA d/month with ≥ 8 d migraine > 2 preventive medications or topiramate	Not allowed
Diener (2007) (RCT)	Multi-centre Industry	Europe	4	16	23	ICHD-II NA	Allowed
Mei (2006) (RCT)	Unclear NR	Italy	4	12	12	ICHD-II NA	Not allowed
Silvestrini (2003) (RCT)	Single center NR	Italy	8	9	9	NR < 4 preventive medications	Not allowed
Tepper (2017) (RCT)	Multi-centre Industry	North America; Europe	4	12	24	≥ 15 HA d/month with ≥ 8 d migraine > 3 preventive medications	Not allowed
Bigal (2015) (RCT)	Multi-centre Industry	US	4	12	12	ICHD-III beta > 2 medication categories or > 3 preventive medications	Allowed
Silberstein (2017) (RCT)	Multi-centre Industry	Global	4	12	12	ICHD-III beta > 2 preventive medication categories	Allowed

CGRP = calcitonin gene-related peptide; d = days; HA = headache; ICHD-II = International Classification of Headache Disorders, 2nd edition; ICHD-III = International Classification of Headache Disorders, 3rd edition; NA = not applicable; NA not available; NR = not reported; Ona A = onabotulinumtoxinA; RCT = randomized controlled trial.

Source: Institute for Clinical and Economic Review.[19]

Quality Assessment of Included Studies

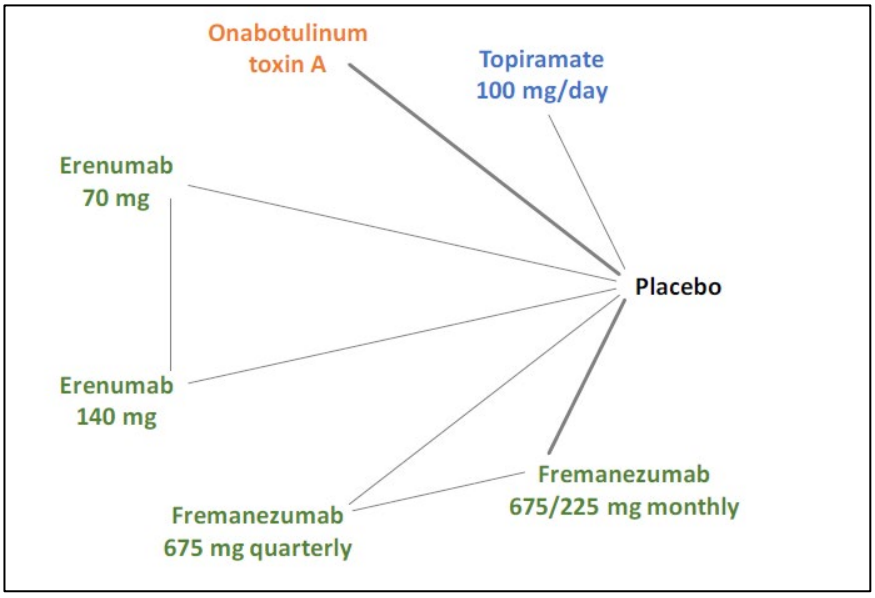
The quality of RCTs, crossover studies, and comparative non-randomized studies was assessed based on the US Preventive Services Task Force criteria. These criteria assess comparability of groups, non-differential follow-up, patient and physician blinding, clear definitions of intervention and outcomes, and approaches to missing data. An overall rating of "good," "fair," or "poor" was given to each study. The Ona A studies were rated as good

(the PREEMPT-1 and PREEMPT-2 trials of Aurora[59] and Diener[60], respectively), fair (Sandrini[74]), and poor (Cady[37] and Freitag[75]). Sandrini was rated as fair because the approach to missing data were not described. In Cady and Freitag, there was insufficient data to assess the comparability of groups. The topiramate trials were rated as good (Silberstein[63]), fair (Mei[76]), and poor (Diener[77] and Silvestrini[78]). Mei was rated as fair because the approach to missing data were not described. In Diener, groups were not comparable, there was non-differential follow-up, and outcomes were not clearly defined. In Silvestrini, there was insufficient information to assess patient/physician blinding and approaches to missing data, and outcomes were not clearly defined. The CGRP inhibitor studies[71-73] were rated to be of good quality. The head-to-head studies that compared Ona A with topiramate were rated as fair (Mathew[79]; groups were not comparable), and poor (Cady[80]; no imputation of missing data and outcomes were not clearly defined).

Evidence Network

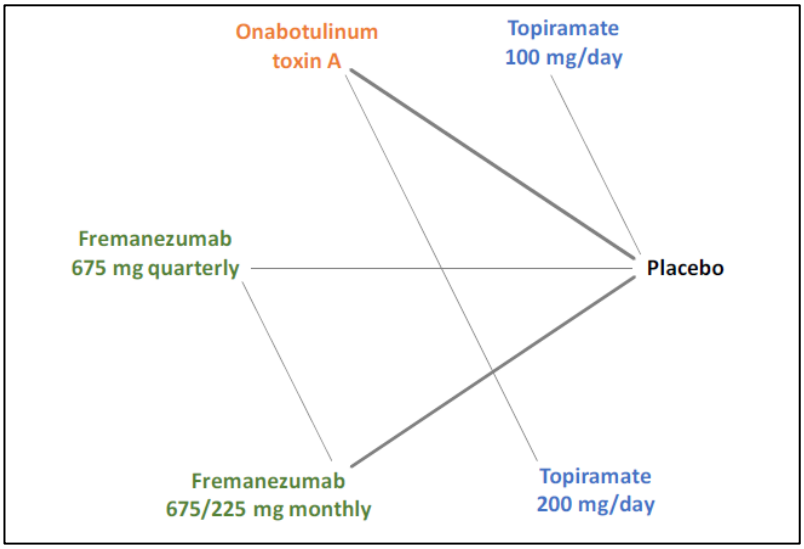
The relevant networks available for Ona A in patients with CM are shown in Figure 2, Figure 3, and Figure 4. These networks describe change from baseline in monthly migraine days, change from baseline in monthly headache days, and all-cause discontinuation, respectively. Limited data were available for ≥ 50% reduction in migraine days and quality of life, and networks were therefore not available for these outcomes. Networks for discontinuations due to AEs and serious adverse events (SAEs) were available for the chronic and episodic patient population combined and have not been presented in this appendix.

Figure 2: Network of Studies – Monthly Migraine Days (Extracted from ICER [2018], p.197)



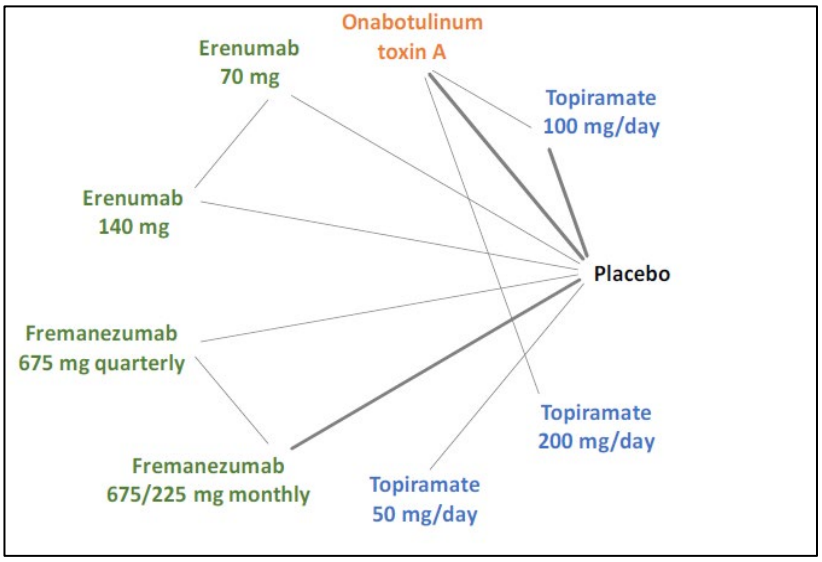
Source: Institute for Clinical and Economic Review.[19]

Figure 3: Network of Studies – Monthly Headache Days (Extracted from ICER [2018], p.199)



Source: Institute for Clinical and Economic Review.[19]

Figure 4: Network of Studies — All-Cause Discontinuation (Extracted from ICER [2018], p.207)



Source: Institute for Clinical and Economic Review.[19]

Indirect Treatment Comparison Methods

An NMA was conducted if data were available from at least three similar studies, with respect to characteristics such as population, intervention, outcome, and time point. Sufficient data were available for the following outcomes in the CM population: change from baseline in monthly migraine days, change from baseline in monthly headache days, change from baseline in days per month using acute medications, and all-cause discontinuations. Aside from monthly acute medication use, the networks for these

outcomes (Figure 2, Figure 3, and Figure 4) included Ona A, with comparisons against placebo, topiramate, and CGRP inhibitors. There were insufficient data to conduct an NMA for ≥ 50% reduction in migraine days or quality of life (MIDAS, MSQ, or HIT-6). In addition, NMAs for discontinuations due to adverse events, AEs reported by at least 5% of patients in a trial arm, and SAEs were not available for patients with chronic migraine. A meta-regression with a covariate for time point was also conducted. A treatment was concluded to favour another if the credible interval (CrI) excluded the null.

The NMAs followed a Bayesian framework, with random effects on the treatment parameters and a between-study variance that was assumed to be constant across treatment comparisons. Continuous outcomes were analyzed with a normal likelihood and identity link and binary outcomes with a binomial likelihood and logit link. The treatment effects were presented as mean differences with 95% CrIs for continuous outcomes and odd ratios with 95% CrIs for binary outcomes. Non-informative prior distributions were used for all model parameters. The first 50,000 iterations were discarded as “burn-in” and base inferences were made on an additional 50,000 iterations using three chains, and chain convergence was assessed visually with trace plots. If studies reported multiple time points, the NMAs included the latest time point data. Separate NMAs were conducted at monthly time points (e.g., four, eight, 12, and 26 weeks) where data were available. A subgroup of patients who had failed at least one prior preventive treatment was also analyzed.

Results

Fourteen trials were available in patients with chronic migraine. Of these, four RCTs and one crossover trial compared Ona A with placebo (Table 50), two RCTs compared Ona A with topiramate (Table 50), four RCTs compared topiramate with placebo (Table 51), and three RCTs compared CGRP inhibitors (i.e., erenumab and fremanezumab) with placebo (Table 52). Sample sizes, baseline characteristics, and treatment doses in these trials are provided in Table 50, Table 51, and Table 52.

Six trials (Tepper,[71] Bigal,[72] Silberstein,[73] Aurora,[59] Diener,[60] and Silberstein[63]) were included in the NMA for the mean change from baseline in monthly migraine days. The time point of analysis was the full 16-week period for the topiramate trial, the full 24-week period for the two Ona A trials, and the last four weeks of the randomization period for the three CGRP inhibitor trials, and is a potential source of heterogeneity. An average change from baseline of 3.8 to 6.3 fewer migraine days per month was reported in patients receiving placebo across the individual trials.

Eight trials (Bigal,[72] Cohen,[81] Aurora,[59] Diener,[60] Cady,[37] Freitag,[75] Silberstein,[82] and Cady[80]) were included in the NMA for the mean change in monthly headache days. The analysis time point was the last four weeks of the randomization period for two of the Ona A trials (Freitag[75] and Cady[37]) and the two fremanezumab trials,[72,81] the full 12-week period for the head-to-head Ona A and topiramate trial,[80] and the full 24-week period for the two PREEMPT trials,[59,60] and is a potential source of heterogeneity. An average change from baseline of 3.3 to 8.0 fewer headache days per month was reported in patients receiving placebo across the individual trials.

In Table 54, Table 55, and Table 56, the results for change from baseline in monthly migraine days, change from baseline in monthly headache days, and all-cause discontinuation, respectively, for Ona A from NMAs are shown. No treatment was favoured for monthly migraine days or monthly headache days. For monthly migraine days, Ona A favoured placebo (mean difference = −1.95; 95% CrI, −3.62 to −0.28) and change from

baseline in monthly headache days (mean difference = −2.06; 95% CrI, −3.48 to −0.63). No treatment was favoured for all-cause discontinuation compared with placebo, topiramate, or CGRP inhibitors.

Table 54: Network Meta-Analysis Results for Change from Baseline in Monthly Migraine Days

Comparison	Mean Difference (95% CrI)
Erenumab 140 mg vs. Ona A	−0.45 (−3.34 to 2.47)
Erenumab 70 mg vs. Ona A	−0.45 (−3.35 to 2.48)
Ona A vs. topiramate 100 mg/d	−0.26 (−3.26 to 2.73)
Ona A vs. fremanezumab 675/225 mg	−0.29 (−2.74 to 2.17)
Ona A vs. fremanezumab 675 mg quarterly	−0.65 (−3.45 to 2.15)
Ona A vs. placebo	−1.95 (−3.62 to −0.28)

CrI = credible interval; Ona A = onabotulinumtoxinA.

Source: Institute for Clinical and Economic Review.[19]

Table 55: Network Meta-Analysis Results for Change from Baseline in Monthly Headache Days

Comparison	Mean Difference (95% CrI)
Ona A vs. topiramate 200 mg/d	0.10 (−3.69 to 3.88)
Ona A vs. fremanezumab 675/225 mg	−0.21 (−2.50 to 2.07)
Ona A vs. fremanezumab 675 mg quarterly	−0.58 (−3.26 to 2.07)
Ona A vs. topiramate 100 mg/d	−0.95 (−3.82 to 1.88)
Ona A vs. placebo	−2.06 (−3.48 to −0.63)

CrI = credible interval; Ona A = onabotulinumtoxinA.

Source: Institute for Clinical and Economic Review.[19]

Table 56: Network Meta-Analysis Results for All-Cause Discontinuation

Comparison	OR (95% CrI)
Erenumab 140 mg vs. Ona A	0.50 (0.14 to 1.76)
Erenumab 70 mg vs. Ona A	0.66 (0.20 to 2.24)
Fremanezumab 675 mg quarterly vs. Ona A	0.76 (0.30, 2.19)
Topiramate 100 mg/d vs. Ona A	0.83 (0.43, 1.67)
Placebo vs. Ona A	0.91 (0.57, 1.58)
Ona A vs. topiramate 200 mg/d	0.87 (0.21, 3.56)
Ona A vs. fremanezumab 675/225 mg	0.93 (0.36, 2.01)

CrI = credible interval; Ona A = onabotulinumtoxinA; OR = odds ratio.

Source: Institute for Clinical and Economic Review.[19]

An NMA was conducted at multiple time points (i.e., four weeks, eight weeks, and 12 weeks) and, additionally, a network meta-regression was performed with study duration as a covariate. The results for monthly migraine days and monthly headache days by time point were available for Ona A 155 U versus placebo and are provided in Table 57. For monthly migraine days, Ona A favoured placebo at week 4 and week 8, but at week 12

there was no difference. No treatment was favoured for monthly headache days at any time point.

Table 57: Network Meta-Analysis Results by Time Point (onabotulinumtoxinA 155 U versus Placebo)

Time Point	Change from Baseline in Monthly Migraine Days (Mean Difference, 95% CrI)	Change from Baseline in Monthly Headache Days (Mean Difference, 95% CrI)
4 weeks	−2.10 (−3.99 to −0.20)	−1.25 (−2.68 to 0.05)
8 weeks	−1.80 (−3.57 to −0.04)	−1.84 (−5.05 to 0.42)
12 weeks	−1.40 (−2.94 to 0.13)	−1.46 (−4.65 to 0.39)
Covariate for time point	−2.15 (−21.39 to 8.62)	−2.40 (−5.38 to 0.47)
No covariate for time point	−1.95 (−3.88 to −0.02)	−2.06 (−3.48 to −0.63)

CrI = credible interval; U = Allergan units.

Source: Institute for Clinical and Economic Review.[19]

Critical Appraisal

The NMAs were based on a systematic review of the literature to identify all relevant published trials from multiple databases, although the focus of the review was on CGRP inhibitors as the intervention, rather than Ona A. Of note, the FORWARD study, which was an open-label RCT that compared Ona A (155 U) with topiramate (up to 200 mg/d) in 282 patients with CM, was not included in the NMAs.[22] The FORWARD study was available to CADTH as a Clinical Study Report and has not been published to date. While the patient population (i.e., adults with CM and eligible for preventive migraine therapy) was in alignment with the reimbursement request, there were limited data available for patients who failed previous therapies. The CGRP inhibitor trials excluded patients who experienced failures from two or three previous treatments and therefore the applicability of the evidence to the patient population of interest is limited. This is also a potential source of heterogeneity in the NMAs. The Health Canada–approved dosing for Ona A is 155 U up to 195 U. While the main trials in the NMA (i.e., PREEMPT-1 and PREEMPT-2) followed the Health Canada–approved dosing, several trials used either a smaller dose (i.e., 100 U) or a higher dose (200 U). This is another factor that limits the applicability of the NMA results to the patient population of interest and is a source of heterogeneity. A comprehensive set of safety and efficacy outcomes was evaluated, and included quality-of-life scales such as MIDAS, MSQ, and HIT-6. However, the data available for quality of life were insufficient for NMA and follow-up on all outcomes was limited from 12 to 26 weeks.

The evidence base for monthly migraine days, monthly headache days, and all-cause discontinuation formed connected networks of trials. Direct and indirect evidence was available only for Ona A versus topiramate 100 mg/d for all-cause discontinuation (Figure 4). The ICER report did not present the direct and indirect estimates separately for this treatment comparison, and the consistency of the direct and indirect estimates is therefore unclear. However, the report did indicate that for networks that were loops, the assumption of consistency among indirect and direct estimates was examined empirically using a node-splitting approach, and that no evidence of inconsistency was observed.

The report did not provide a discussion about whether the transitivity assumption was met in the networks of trials. Table 50 to Table 52 show that there were differences among the trials in the mean number of years since onset (i.e., shorter in the topiramate trials). There

were also differences among the trials in the exclusion of previous treatment failures, whether ongoing preventive therapy was allowed, and the percentage of patients with medication overuse headache (trials either excluded these patients or prevalence ranged from 41% to 68%). These factors may be important treatment-effect modifiers, but they were not examined in analyses.

The NMA considered time points in meta-regression, and attempted a subgroup analysis for patients who had failed previous therapies. However, no other sources of potential heterogeneity, such as number of previous treatment failures, use of concomitant migraine preventive therapy, compliance with headache diary, Ona A dose, or study quality, were considered.

The clinical expert consulted on this review indicated that placebo response would vary based on the method placebo was received (i.e., injection versus oral tablets) and that placebo response is higher when it is received as an injection. Across the trials included in the NMA, the average change from baseline for placebo ranged from 3.8 to 6.3 fewer migraine days per month and 3.3 to 8.0 fewer headache days per month, which suggests that the placebo response was different between trials. The ICER report did not perform an NMA meta-regression on placebo response where meta-regression models impose a common interaction effect between baseline risk and relative effectiveness that account for variation in reference arm response across trials. While adjusting for placebo response might be the preferred approach, there are limitations to the approach, because there is an assumption that study and patient characteristics (the effect modifiers of the relative treatment effect) are also prognostic factors of the outcome with placebo.[83,84] And given that the extent to which placebo response is an adequate proxy for specific characteristics or effect modifiers is unclear, uncertainty remains in such analysis.

The strength of the network was low, with only six studies for seven treatment options (for change from baseline in monthly migraine days) and only eight studies for seven treatment options (change in monthly headache days). The networks were centered on placebo and most comparisons were indirect. All of the studies included in the analysis for change from baseline in monthly migraine days were of good quality; however, three of the eight studies included in the analysis for the mean change in monthly headache days were of poor quality. A sensitivity analysis based on study quality was not conducted.

The ITC did not include any health-related quality-of-life data, patient-reported symptoms, or key safety outcome SAEs, and withdrawals due to an adverse event.

As with all NMA, inclusion of the null value in the 95% CrIs of the difference between treatments does not necessarily imply that the treatments are equivalent or noninferior.

Discussion

The ICER conducted NMAs to examine CGRP inhibitors compared with placebo or commonly used preventive treatments in adults with chronic migraine. For this appendix, relevant data were available to indirectly compare Ona A with topiramate and Ona A with CGRP inhibitors. Although several efficacy and safety outcomes were evaluated, NMAs could be performed only for change from baseline in monthly migraine days, change from baseline in monthly headache days, and all-cause discontinuation. In a Bayesian NMA, Ona A was not favoured over topiramate or CGRP inhibitors on these outcomes.

The estimates from the NMAs were compared with PREEMPT−1[59] and PREEMPT−2,[60] FORWARD,[22] and a Cochrane review.[85] In PREEMPT−1 and PREEMPT−2, the Ona A and placebo between-group difference in monthly headache days from baseline to week 24 was about one to two fewer days.[14] This corresponded with the NMA results for Ona A versus placebo of −2.1 (95% CrI, −3.5 to −0.6) for monthly headache days and −2.0 (95% CrI, −3.6 to −0.3) for monthly migraine days. In FORWARD, the mean change from baseline in frequency of headache days over 28 days for Ona A versus topiramate was −6.2 (95% CI, −7.9 to −4.4).[22] This varied considerably from the NMA estimate of 0.10 (95% CrI, −3.69, 3.88) for change from baseline in monthly headache days for Ona A versus topiramate 200 mg/d. In FORWARD, a large number of patients crossed over from topiramate to Ona A and these patients were considered as nonresponders with imputation of baseline observations, which favoured Ona A. When imputation was based on last observation carried forward, the estimate was much smaller (–0.38; 95% CI, –1.94 to 1.18) and closer to the NMA estimate. The FORWARD trial used the Health Canada–approved Ona A dosing of 155 U, whereas the estimate in the NMA was based on a single, and much smaller, trial that used 200 U. A Cochrane review pooled the results from five RCTs that compared Ona A with placebo in patients with chronic migraine and found a reduction of −3.1 (95% CI, −4.7 to −1.4) in migraine days per month at 12 weeks post-treatment. In sensitivity analyses that restricted the analysis to larger RCTs (i.e., PREEMPT−1 and PREEMPT−2), a reduction of −2.0 (95% CI, −2.8 to −1.1) migraine days per month was obtained.[85] The latter result aligned with the NMA.

Several potential sources of heterogeneity were not systematically evaluated and generalizability to the patient population of interest is limited. In clinical practice, Ona A is likely to be used in patients who have failed several lines of previous treatments. However, the CGRP inhibitor trials in the NMAs excluded patients who failed as few as two or three previous therapies and insufficient data were available to conduct subgroup analyses for patients who failed at least one prior preventive therapy. Other factors that limit generalizability were that the trials did not consistently follow Health Canada–approved Ona A dosing and the NMAs did not incorporate longer-term follow-up data.

Conclusion

The primary gap filled by the NMAs is the comparison of Ona A with the CGRP inhibitors erenumab and fremanezumab on monthly migraine days, monthly headache days, and all-cause discontinuation, as currently no direct comparative data exists. Although the NMAs suggest that Ona A is not favoured over these treatments, in terms of reduction in monthly migraine days, reduction in monthly headache days, and all-cause discontinuation, further data on quality of life, safety, and patients who failed previous therapies are needed to fully characterize benefits and harms.

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