Common Drug Review
Clinical Review Report

July 2015

Drug	onabotulinumtoxinA for injection (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).
Listing request	Prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer) who have failed (i.e., lack of efficacy, intolerance, or clinical contraindication) ≥ 3 prior oral prophylactic medications. Patients who have not obtained an adequate treatment response (≥ 30% reduction in days of headache per month) after 2 treatment cycles should be discontinued from further therapy.
Manufacturer	Allergan Inc.

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ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
BSC	best supportive care
CDR	CADTH Common Drug Review
CI	confidence interval
CM	chronic migraines
DB	double-blind
EF	emotional function
EM	episodic migraine
ER	emergency room
EQ-VAS	Euro-Qol Visual Analog Scale
HC	Health Canada
HDPM	headache days per month
HIT	Headache Impact Test
HNC	Headache Network Canada
HRQoL	health-related quality of life
ICHD-2	International Classification of Headache Disorders, 2nd edition
ICHD-3	International Classification of Headache Disorders, 3rd edition
IM	intramuscularly
ITT	intention-to-treat
MCID	minimally clinically important difference
MIDAS	Migraine Disability Assessment Scale
mLOCF	modified last observation carried forward
MOH	medication-overuse headache
MSQ	Migraine-Specific Quality of Life Questionnaire
OLE	open-label extension
PGIC	physician's global impression of change
RP	role function – preventive
RR	role function – restrictive
SAE	serious adverse event
SD	standard deviation
SGIC	subject's global impression of change
U	unit
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Migraine is a common, debilitating neurological disorder characterized by recurrent headaches and symptoms of nausea, vomiting, photophobia, or phonophobia. An episode may last from four to 72 hours and may be preceded by an aura (a visual or auditory disturbance). There are two subtypes of migraine, episodic migraine (EM) and chronic migraine (CM), which are differentiated by the frequency of headache occurrence. CM is described in the beta version of the International Classification of Headache Disorders, 3rd edition (ICHD-3) as a headache occurring on 15 or more days per month for more than three months, and which has the features of a migraine headache on at least eight days per month.[1] Some patients may go from experiencing EM, which occur on fewer than 15 days per month, to CM.[1] It is believed that, annually, 2.5% of patients with EM will transform to CM.

OnabotulinumtoxinA is a purified neurotoxin complex produced from the fermentation of *Clostridium botulinum* type A. In Canada, onabotulinumtoxinA is the only drug approved by Health Canada for the prophylaxis of CM. Other medications used off-label in the prophylaxis of CM include beta blockers and tricyclic antidepressants.

The indication under review is listed below:

Indication under review
For the prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).
Listing criteria requested by sponsor
Prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer) in patients who have failed (i.e. lack of efficacy, intolerance or clinical contraindication) ≥ 3 prior oral prophylactics medications. Patients who have not obtained an adequate treatment response (≥ 30% reduction in days of headache per month) after 2 treatment cycles should be discontinued from further therapy.

The objective of this review was to evaluate the beneficial and harmful effects of onabotulinumtoxinA injection (Botox) at doses of 155 units (U) to 195 U for the prophylaxis of headaches in adults with CM.

Results and Interpretation

Included Studies

Two manufacturer-sponsored, multi-centre, randomized, double-blind, parallel-group, placebo-controlled phase 3 superiority trials met the inclusion criteria for this review. Study 079 (N = 679) and Study 080 (N = 705) were identical in design. Both trials enrolled patients between the ages of 18 and 65 years with a history of migraine headache disorder defined as 15 or more headache days per month (HDPM), with each headache day consisting of four or more hours of continuous headaches; at least 50% of baseline headache days were migraine or probable migraine days, and at least four distinct headache episodes lasted at least four hours. The duration of both studies was 60 weeks and included a four-week pre-randomization (baseline) phase, a 24-week double-blind (DB) treatment phase, and a 32-week open-label extension (OLE) phase.

Patients were randomized in the DB phase to receive 155 U of onabotulinumtoxinA or placebo administered intramuscularly (IM) at day 0 and at week 12 at fixed points on the head and neck. The dose could be increased at the investigator's discretion by an additional 40 U using a "follow-the-pain" method. The primary efficacy outcome for Study 079 was the frequency of headache episodes per 28-day period ending with week 24 compared with baseline. The primary efficacy outcome for Study 080 was the frequency of headache days per 28-day period ending with week 24 compared with baseline.

The key limitations of the available evidence included the lack of trials to assess the comparative efficacy and safety of onabotulinumtoxinA with standard prophylactic CM treatments, the difficulty in maintaining blinding, and the baseline imbalance in some patient characteristics between the onabotulinumtoxinA and placebo groups in Study 079. The long-term efficacy and safety of onabotulinumtoxinA have yet to be determined; only two doses of onabotulinumtoxinA were administered in the DB phase of both studies, and the total study duration (DB plus OLE phases) was short (one year) for both studies. Adjustments for type 1 error were done for some, but not all, secondary efficacy outcomes. In addition, given the characteristics of the patients included in the trials, there is limited evidence for male patients, for patients with a comorbid illnesses, and for patients with less severe disease (Headache Impact Test [HIT]-6 score less than 65).

Efficacy

The key outcomes identified a priori for this review were health-related quality of life (HRQoL), other patient-reported outcomes, and acute headache pain medication intake. HRQoL was measured using the Migraine-Specific Quality of Life Questionnaire (MSQ) in both studies. The mean changes from baseline for the three MSQ domains (role restrictive, role preventive, and emotional function) in patients who received onabotulinumtoxinA demonstrated clinically important and consistent results across both trials at week 12 and at the end of the DB phase (week 24). The magnitude of the observed reductions in all three domains was confirmed to be clinically important by the clinical expert involved in the review. Furthermore, comparing onabotulinumtoxinA and placebo, the between-group differences were statistically significant at weeks 12 and 24; however, a minimally clinically important difference (MCID) for the between-group difference has not been determined.

The HIT-6 is a multi-question health assessment that quantifies the impact of headache on a patient's life. Mean total HIT-6 score changes from baseline were statistically significant in favour of onabotulinumtoxinA versus placebo ($P < 0.001$) in both studies. The between-group difference at week 24 was 2.3 points in Study 079 and 2.5 points in Study 080, which met the MCID of 2.3.

The frequency of headache days decreased by approximately 8 to 9 days per month (from 20 days per month) for onabotulinumtoxinA patients at the end of the DB phase of both studies. Placebo patients achieved a decrease of six to seven HDPM. The between-group difference was statistically significant in favour of onabotulinumtoxinA versus placebo with approximately one to two fewer HDPM in the onabotulinumtoxinA group, which is unlikely to be clinically important. The greater decrease in headache days seen with onabotulinumtoxinA compared with placebo was not reflected in a greater reduction in acute headache pain medication intake. Both treatment groups decreased their medication use by eight to 10 intakes per month without completely eliminating the need for breakthrough pain medications. A statistically significant reduction in headache episodes in favour of onabotulinumtoxinA was found only in Study 080.

Other secondary efficacy outcomes of interest for which statistical significance in favour of onabotulinumtoxinA versus placebo was reached included the frequency of migraine/probable migraine

days in Studies 079 and 080, and severe HIT-6 category score, moderate/severe headache days, and total cumulative hours of headache occurring on headache days in Study 080. The effect sizes obtained in Study 080 were generally greater than those of Study 079 and statistical significance was reached for more outcomes in Study 080. The reasons for this were unclear, but may be related to baseline differences in Study 079 where patients in the placebo group had more headache and migraine episodes compared with the onabotulinumtoxinA group. In addition, the greatest improvement for all efficacy end points was noticed at week 12, with a small incremental benefit at week 24, indicating that the main response was achieved after the first treatment.

Patients with a history of medication usage of three or more prophylactic agents had a response consistent with the overall results for all outcomes. However, these analyses were done post hoc and these findings will require confirmation.

In the OLE phase, all patients received onabotulinumtoxinA treatment for 32 weeks. Irrespective of the group assignment in the DB phase, there were no between-group differences at the end of the OLE phase for most of the outcomes measured. Irrespective of the group assignment in the DB phase, there were improvements in MSQ and HIT-6 scores at the end of the study compared with baseline of the DB phase in both Studies 079 and 080. The frequency of headache days and migraine/probable migraine days decreased by 10 to 11 days per month at week 56, from approximately 19 to 20 days per month at baseline. Acute headache pain medications could not be completely stopped, with more than 70% of patients still requiring acute pain medications at week 56. The proportion of patients stopping treatment was approximately 25% by week 56, but less than 5% were due to lack of efficacy.

Harms

There were no deaths during the DB and OLE phases of the included trials.

In the DB phase, the proportion of patients who experienced at least one adverse event (AE) was higher in the onabotulinumtoxinA group (60% in Study 079 and 65% in Study 080) compared with the placebo group (47% in Study 079 and 56% in Study 080). Overall, the most frequent AEs associated with onabotulinumtoxinA 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 (SAE) was higher in the onabotulinumtoxinA group (5% in Study 079 and 4% in Study 080) compared with the placebo group (2% each in Studies 079 and 080). Withdrawals due to AEs (WDAEs) were higher in onabotulinumtoxinA-treated patients compared with placebo-treated patients. The most frequent reasons for WDAEs were headache in Study 079 and migraine in Study 080, which may be more due to a lack of efficacy rather than an AE.

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 or anaphylaxis.

Pharmacoeconomic Summary

The manufacturer submitted a cost-utility analysis of onabotulinumtoxinA compared with best supportive care (BSC) for the prophylaxis of headache in adults who have failed three or more prior oral prophylactic medications. The target population was a subpopulation of the Health Canada (HC) indication, as the HC indication does not limit use to patients who have failed prior therapy. The analysis was based on a Markov model with seven health states, six of them based on the number of migraine days experienced per 28-day cycle (0 to 3 days, 4 to 9 days, 10 to 14 days, 15 to 19 days, 20 to 23 days, and 24 days or more) and a discontinuation state. Patients entered the model at one of the three health

states defined as CM (≥ 15 days) and transitioned to the other health states based upon pooled patient-level data from the PREEMPT-1 and PREEMPT-2 studies. The manufacturer captured treatment costs associated with onabotulinumtoxinA and BSC, as well as the costs of medical resource utilization. Utility values for each health state were obtained through mapping disease-specific quality-of-life data captured in the clinical trials by the EuroQol 5-Dimensions (EQ-5D) utility instrument. The manufacturer included various scenario analyses, including one from the societal perspective taking into account lost productivity. The time horizon for the analysis was set at three years, with a cycle length of 12 weeks. The result of the manufacturer's economic evaluation for the full HC population was an incremental cost of $28,940 per quality-adjusted life-year (QALY) gained for onabotulinumtoxinA compared with BSC. For the analysis of the requested subpopulation (patients who failed to respond to prior treatment with three or more oral prophylactic agents), the incremental cost was $25,470 per QALY gained.

Interpretations and Key Limitations

The key limitation of the manufacturer's submitted economic evaluation is whether the submitted economic evaluation presents a good representation of the chronic nature of CM and expected treatment, where key assumptions include:

- The model included health states that represent EM (< 15 HDPM); onabotulinumtoxinA is not indicated for use in this population. Including patients no longer in CM may have overestimated the benefits of onabotulinumtoxinA.
- The choice of a 30% stopping rule is arbitrary, given that only 25%, 50%, and 75% improvements were captured in the clinical trials. Treatment guidelines and Common Drug Review (CDR) clinical guidance has indicated that a 50% reduction or return to EM is the clinical goal of treatment.
- CM is a long-term condition; however, a three-year time horizon was used in the economic model. The manufacturer stated that onabotulinumtoxinA is a preventive therapy, and continued treatment is needed for most patients in order to maintain treatment response and benefit, similar to any other preventive medication.[2] This leads to the assumption that a longer time horizon may be more appropriate, where patients are expected continue on onabotulinumtoxinA indefinitely. Long-term use of onabotulinumtoxinA has not been studied, so it is unclear whether treatment effects would be maintained over time.
- The costs associated with physician visits, drug administration, and drug acquisition for onabotulinumtoxinA were likely underestimated in the manufacturer's economic evaluation.

Results of CADTH Common Drug Review Analysis

The structure of the manufacturer's economic evaluation did not permit modification for reanalyses that would better inform reimbursement recommendations and decisions. However, revisions to the cost data as indicated above increased the incremental cost-utility ratio (ICUR) between 10% and 28% individually from the manufacturer's base-case results for both the full and restricted populations, and between 63% to 65% when considered collectively (see the range in the Conclusions section).

Conclusions

Given the limitations with the model structure, full exploration of CDR-identified limitations was not possible. Consequently there is some uncertainty regarding the likely cost-effectiveness of onabotulinumtoxinA. When accounting for more likely cost inputs, CDR calculated ICURs in the range of $42,000 to $47,000 per QALY.

OnabotulinumtoxinA is available in 50 U ($179), 100 U ($357) and 200 U ($714) single-use vials. At the recommended dose of 155 U to 195 U every 12 weeks, the cost per 12-week course is $714 based on submitted prices.

Two manufacturer-sponsored, multi-centre, randomized, DB, parallel-group, placebo-controlled, phase 3 superiority trials evaluating the efficacy and safety of onabotulinumtoxinA in patients with CM were included in this systematic review. The results of Study 079 and Study 080 suggest that onabotulinumtoxinA was superior to placebo in improving patient-reported outcomes as measured with MSQ and HIT-6. Furthermore, onabotulinumtoxinA patients experienced fewer headache and migraine days than patients in the placebo group at the end of the DB phase; however, the absolute numerical difference between groups was approximately one to two days and is unlikely to be clinically important. Patients decreased the frequency of, but could not completely discontinue their intake of, acute headache pain medication. Improvement in both treatment groups was observed after the first dose, with a smaller improvement noticed after the second dose. There were no deaths, no evidence of toxin spread, and no anaphylactic reactions reported. OnabotulinumtoxinA was associated with a relatively low incidence of SAEs in the included trials. The trials are limited by the lack of an active comparator, their short duration, the imbalance of patient characteristics at baseline in Study 079, the use of subjective outcome measures, and the possibility that patients could have guessed the treatment they were receiving. The results of the trial may not be generalizable to male patients, to patients with migraines that are less severe, or in patients with comorbid illnesses.

TABLE 1: SUMMARY OF RESULTS

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Migraine-Specific Quality of Life Questionnaire (Observed Data)[a]						
Role Function–Restrictive						
Baseline, n	337	335		347	358	
Baseline, Mean (SD)	61.3 (16.58)	63.1 (17.06)		61.7 (16.54)	59.7 (17.30)	
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
Role Function–Preventive						
Baseline, n	337	335		347	358	
Baseline, Mean (SD)	43.2 (20.85)	46.0 (21.17)		44.7 (21.61)	42.0 (22.12)	
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
Role Function–Emotional Function						
Baseline, n	337	334		347	357	
Baseline, Mean (SD)	59.1 (23.54)	60.3 (24.61)		56.8 (24.61)	55.0 (25.03)	
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
HIT (mLOCF)						
Severe Impact (Total HIT-6 Score Range 60–78), n (%)						
N	341	338		347	358	
Baseline	322 (94.4)	320 (94.7)		321 (92.5)	325 (90.8)	

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Week 24	235 (68.9)	270 (79.9)		230 (66.3)	274 (76.5)	
HIT-6 Score, Mean (SD)						
N	341	338		347	358	
Baseline	65.4 (3.82)	65.8 (4.14)		65.6 (4.26)	65.0 (4.46)	
Change From Baseline at Week 24	–4.7 (7.11)	–2.4 (5.63)	< 0.001[b]	–4.9 (6.97)	–2.4 (6.50)	< 0.001[b]
Acute Headache Pain Medication (mLOCF)						
Acute Headache Pain Medication Intakes per 28-day Period						
N	341	338		347	358	
Baseline, LSMean (SD)	25.2 (19.27)	25.7 (22.29)		21.9 (18.76)	22.8 (18.87)	
Change From Baseline at Week 24, LSMean (SD)	–10.1 (18.67)	–9.8 (18.54)	0.795[c]	–9.7 (15.53)	–8.1 (14.92)	0.132[c]
Harms						
N	340	334		347	358	
Patients With at Least One AE, n (%)	203 (59.7)	156 (46.7)		226 (65.1)	202 (56.4)	
Patients With at Least One SAE, n (%)	18 (5.3)	8 (2.4)		15 (4.3)	8 (2.2)	
WDAEs, n (%)	14 (4.1)	3 (0.9)		12 (3.5)	5 (1.4)	
Deaths, n (%)	0	0		0	0	

AE = adverse event; LSMean = least squares means; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.
[a] *P* values for between-treatment comparisons were determined by the Wilcoxon rank-sum test.
[b] *P* values for between-treatment comparisons were determined by the Wilcoxon rank-sum test.
[c] *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.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Migraine is a common, debilitating neurological disorder characterized by recurrent headaches and symptoms of nausea, vomiting, photophobia, or phonophobia.[3] An episode may last from four to 72 hours and may be preceded by an aura (a visual or auditory disturbance). There are two subtypes of migraine, EM and CM, which are differentiated by the frequency of headache occurrence.[3]

The International Classification of Headache Disorders, 2nd edition (ICHD-2) described CM as migraine headache occurring on 15 or more days per month for more than three months.[4] The definition of CM was subsequently revised to better reflect the population of patients seen in clinical practice.[5] CM is described by the ICHD-3 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.[1]

Some patients may go from experiencing EM (occurring on fewer than 15 days per month) to CM.[3] It is believed that, annually, 2.5% of patients with EM will transform to CM.[6]

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 between 1991 and 2006) reported an overall prevalence of CM ranging from 0% to 5.1%.[7] 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%).[7] A recent US population-based study estimated an overall prevalence of CM of 0.91% (diagnosis of CM based on the ICHD-3 criteria).[8] For both males and females, the prevalence of CM increased throughout adolescence, peaked at mid-life, and decreased after age 50 years.[8] 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 HRQoL, higher rates of comorbid conditions, and higher use of health care resources than patients with EM.[8,9] One population-based study found that, after adjusting for socio-demographic factors, headache-related disability was four times greater in patients with CM compared with those with EM (odds ratio 3.9 [95% confidence interval, 3.5 to 4.3], $P < 0.001$).[8]

Some cases of CM may be caused by the overuse of acute headache medications, which confounds the diagnosis of CM, leading to misdiagnosis. One study found that, in patients diagnosed with CM, the prevalence of medication overuse was 31% to 69%.[7] When medications are stopped, approximately 50% of patients diagnosed with CM will revert to an EM sub-type. Equally many patients who overuse medications do not improve after discontinuing the medications.[1] The ICHD-3 recognizes medication-overuse headaches (MOH) as a distinct type of migraine. However, according to the clinical expert consulted for this review, in clinical practice it is challenging to differentiate patients who suffer from MOH from those who suffer from CM.

1.2 Standards of Therapy

In Canada, onabotulinumtoxinA (Botox) is the only drug indicated for the prophylaxis of CM (Notice of Compliance granted in October 2011).[10] Some medications may be used off-label to prevent CM; the clinical expert consulted for this review indicated that first-line prophylactic treatments include low-dose tricyclic antidepressants and beta blockers (Table 2). The newer anticonvulsants, calcium channel blockers, and serotonin-norepinephrine reuptake inhibitors are also used in clinical practice. The choice

of agent depends on the adverse effect profile and patient preference. Non-pharmacological treatments may also be tried, such as relaxation training, biofeedback, and lifestyle modification (e.g., good sleep hygiene and regular exercise).

TABLE 2: KEY CHARACTERISTICS OF PHARMACOLOGICAL TREATMENTS FOR CHRONIC MIGRAINE

Drug Class	Most Common Therapeutic Uses	Agents Most Commonly Used in CM	Common AEs	Comments Related to CM
TCA	Depression	Amitriptyline, nortriptyline	Weight gain, insomnia, dry mouth, constipation	Start with low doses; may be given at bedtime
Beta Blockers	Angina, hypertension, CHF	Propranolol, nadolol, metoprolol	Fatigue, bradycardia, hypotension, depression, sleep disturbance	Start with low doses; if failed one drug, can try another; taper when discontinuing treatment
Anticonvulsants	Epilepsy	Gabapentin, topiramate	Varies by agent	AEs common with topiramate
CCB	Angina, hypertension	Flunarizine, verapamil	Varies by agent	May take several months to see benefits
SNRI	Depression, anxiety	Venlafaxine	Dry mouth, nausea, somnolence	Fewer anticholinergic AEs than TCAs

AEs = adverse events; CCB = calcium channel blockers; CHF = congestive heart failure; CM = chronic migraine; SNRI = serotonin-norepinephrine reuptake inhibitors; TCA = tricyclic antidepressants.
Source: CADTH Common Drug Review clinical expert; eCPS;[11] RxFiles.[12]

The Second International Burden of Migraine Study (IBMS-II) evaluated the use of preventive medications in 1,165 patients with CM.[13] 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 EM after adjusting for various factors (odds ratio 2.7 [95% CI, 2.2 to 3.6]).[13]

1.3 Drug

OnabotulinumtoxinA is a purified neurotoxin complex produced from the fermentation of *Clostridium botulinium* type A.[3] The toxin exerts its action by paralytic effects (muscle relaxation) and by anhidrotic effects (blockade of the release of acetylcholine from the presynaptic terminals of motor neurons). There is also in vitro evidence that onabotulinumtoxinA exerts direct analgesic effect through the inhibition of the release of neurotransmitters and neuropeptides (such as substance P).[3]

The HC-approved CM dose is 155 units (U) administered IM (0.1 mL injection [5 U] to each of 31 sites on the head and neck).[14] Additional injections may be administered for a total maximum dose of 195 U (39 sites). The recommended retreatment is every 12 weeks. The "unit" (U) 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.[14]

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2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of onabotulinumtoxinA injection (Botox) for the prophylaxis of headaches in adults with CM.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with CM (≥ 15 days per month with headache lasting 4 hours a day or longer) **Subgroups of interest:** • Patients who have failed (i.e., lack of efficacy, intolerance, or clinical contraindication) ≥ 3 prior oral prophylactic medications • Patients who overuse acute headache pain medication versus those who do not • Males versus females • Duration of illness
Intervention	onabotulinumtoxinA (Botox) injection at doses between 155 U (31 sites) and 195 U (39 sites)
Comparators	Pharmacotherapy Interventions • Tricyclic antidepressants • Beta blockers • Anticonvulsants • Calcium channel blockers • Serotonin-norepinephrine reuptake inhibitors Non-pharmacological Interventions (e.g., behavioural therapies, physical therapy, lifestyle modifications, natural health products) Placebo
Outcomes	**Key outcomes:** • HRQoL using validated scales • Other patient-reported outcomes (e.g., HIT-6 Score) • Acute headache pain medication intake

Outcomes	**Other outcomes:** • Improvement in headache/migraine days • Improvement in headache/migraine episodes • Effect of treatment over time • Treatment failure (reduction in headache days by ≥ 30% not achieved) • Emergency room visits • Loss of work days • Prophylactic medication intake **Harms outcomes:** AEs, SAEs, WDAEs, AEs of special interest (e.g., anaphylaxis/hypersensitivity reactions, antibody formation, autonomic dysreflexia, cardiovascular events, dysphagia, hematological AEs, systemic toxicity, neck pain)
Study Design	Published and unpublished DB RCTs

AE = adverse event; CM = chronic migraine; DB = Double-blind; HIT-6 = Headache Impact Test; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; U = units; WDAE = withdrawal due to adverse event.

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 (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through 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 migraine.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. 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.

The initial search was completed on October 17th, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) held on March 19th, 2014. 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 (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search and Open Access Journals. 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.

3. RESULTS

3.1 Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

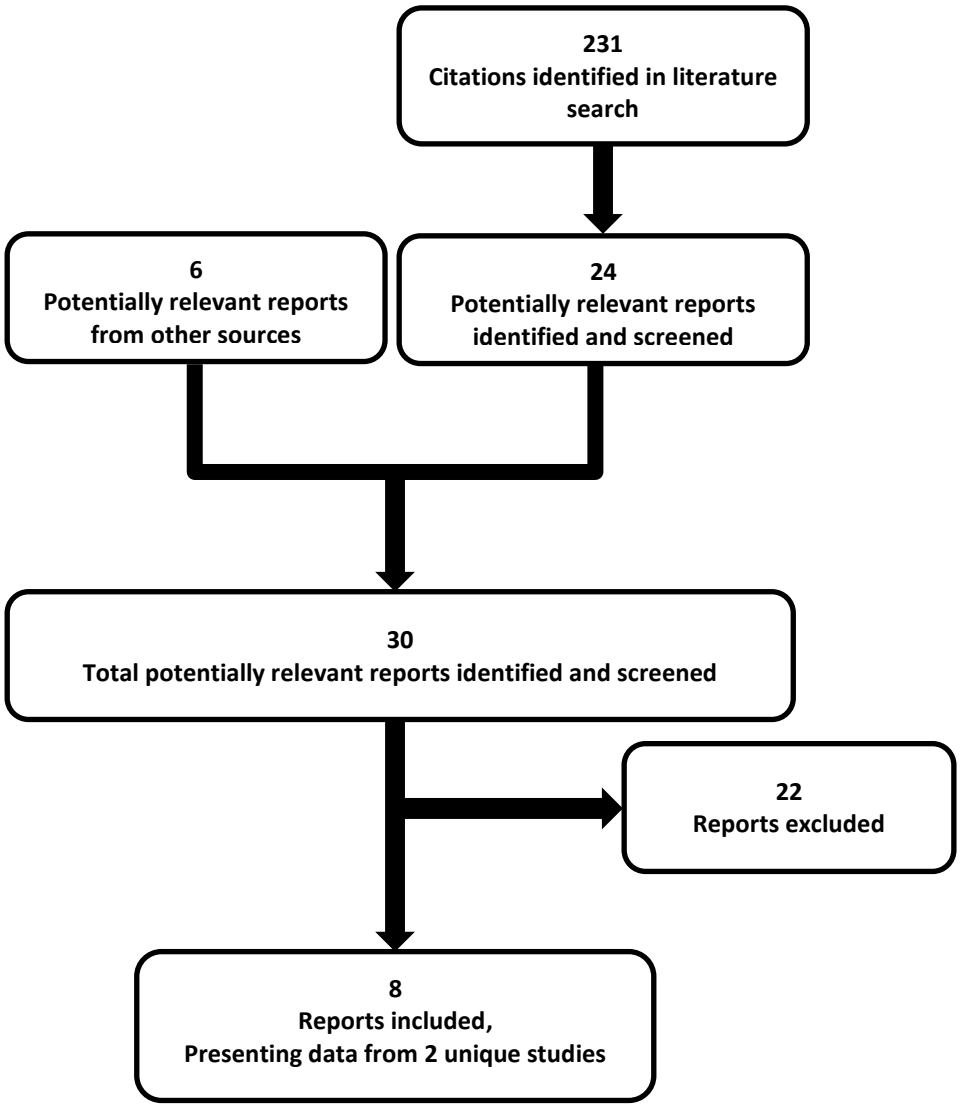

TABLE 4: DETAILS OF INCLUDED STUDIES

		Study 191622-079	Study 191622-080
DESIGNS & POPULATIONS	**Study Design**	Phase 3, multi-centre, randomized, DB, placebo-controlled, parallel-group trial, followed by an OLE 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 another HA disorder (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 the patient at increased risk if exposed to botulinum toxin (e.g., a neuromuscular disease), a temporomandibular disorder, fibromyalgia, a psychiatric disorder, and/or a Beck Depression Inventory score of ≥ 24 at baseline	
DRUGS	**Intervention**	155 U IM 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	
DURATION	**Phase**		
	Run-in	4 weeks	
	Double-blind	24 weeks	
	Follow-up	32 weeks (after DB phase) OLE 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[15]	Diener et al., 2010[16]

CDR = CADTH Common Drug Review; CSR = Clinical Study Report; DB = double-blind; HA = headache; HRQoL = health-related quality of life; IM = intramuscular; OLE = open-label extension; U = units.
Source: Study 191622-079 CSR);[17] Study 191622-080 CSR;[18] Aurora et al.,[15] Diener et al.[16]
Note: Four additional reports were used in the CDR review.[10,19-21]

3.2 Included Studies

3.2.1 Description of studies

Two manufacturer-sponsored, multi-centre, randomized, DB, parallel-group, placebo-controlled, phase 3 superiority trials were included in this systematic review. Study 191622-079 (PREEMPT-1) will be referred to as Study 079 (N = 679),[15,17] and Study 191622-080 (PREEMPT-2) will be referred to as Study 080 (N = 705).[16,18] Both trials investigated the efficacy and safety of onabotulinumtoxinA as a headache prophylaxis in patients between 18 and 65 years of age. Patients had to have experienced 15 or more headache days per four-week period. A total dose of 155 U of onabotulinumtoxinA or placebo was administered IM as 31 fixed-site, fixed-dose injections across seven specifically-defined head/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/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. Both studies were identical in design (Figure 2).

Study duration was 60 weeks, which included a four-week pre-randomization (baseline) phase, a 24-week, DB treatment phase and a 32-week OLE phase. Following the baseline phase (week –4 to day 0), patients who continued to meet the inclusion/exclusion criteria at day 0 were stratified according to medication overuse (yes/no), where medication overuse was determined by the frequency of use of acute headache pain medications during the baseline 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, within each stratum within each site, patients were randomly allocated in a blinded fashion to receive onabotulinumtoxinA or placebo in a 1:1 ratio.

Data presented in the systematic review are for the 24-week DB treatment phase from each trial. Data from the OLE phase are summarized in APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION PHASE OF STUDY 079 AND STUDY 080.

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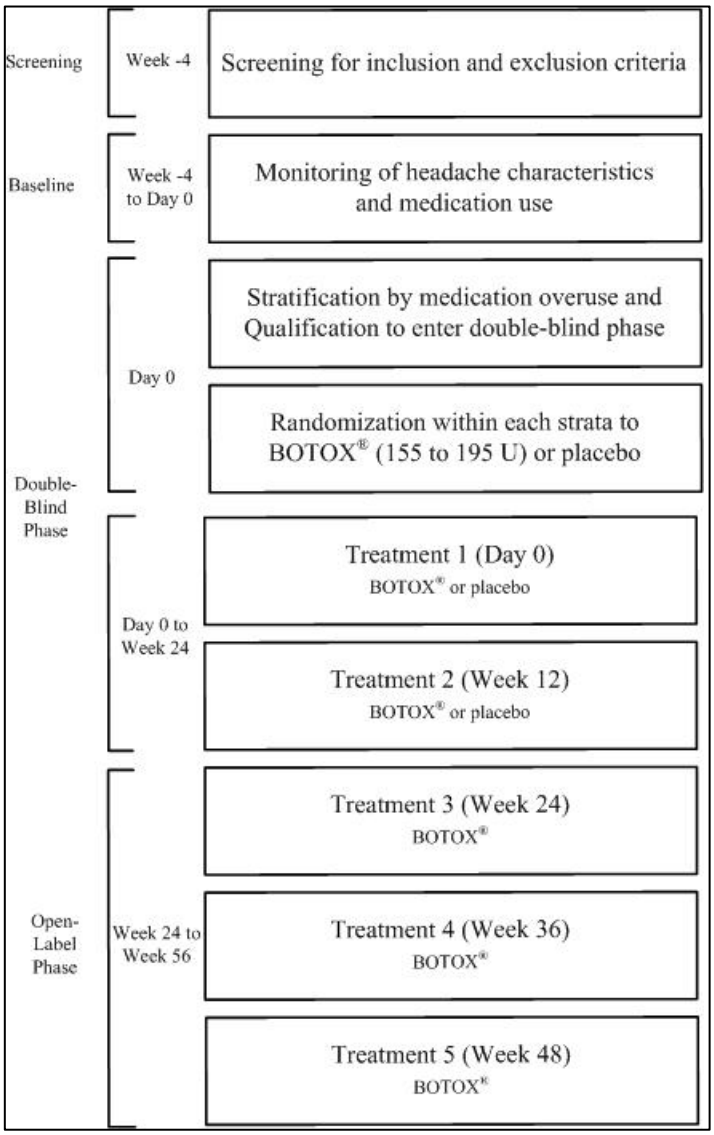
FIGURE 2: STUDY DESIGN (STUDIES 191622-079 AND 191622-080)



Source: Study 191622-079 Clinical Study Report,[17] Study 191622-080 Clinical Study Report.[18]

3.2.2 Populations

a) Inclusion and exclusion criteria

Both trials were designed to enrol male or female 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 ICHD-2, *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, during the four-week baseline phase, 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.

Key exclusion criteria were the presence of a medical condition that might have put the patient at increased risk with exposure to onabotulinumtoxinA (e.g., a neuromuscular disease), the presence of any uncontrolled clinically important medical condition other than CM, a diagnosis of another headache disorder (e.g., complicated migraine, chronic tension-type headache, hypnic headache, hemicranias continua, new daily persistent headache), use of prophylactic headache medication within 28 days prior to start of baseline, previous use of botulinum toxin, a temporomandibular disorder, fibromyalgia, a psychiatric disorder, and/or a Beck Depression Inventory score of ≥ 24 at baseline.

b) Baseline characteristics

In both trials, there were no between-group differences with respect to baseline demographic characteristics. Median age of the included patients was approximately 42 years of age, and approximately 58% of patients were ≥ 40 years of age. The majority of patients (84.6% to 89.1%) were female. Patients were predominantly Caucasian (89.4% to 91.4%). The mean time since the onset of CM was 17.6 years 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 Studies 079 and 080, respectively. The mean age of onset of CM was 20.3 to 22.8 years of age across treatment arms in the two trials, with age of onset ranging between 1 year and 57 years of age. Table 5 below presents the baseline characteristics.

In Study 079, during the 28-day baseline period, when compared with the placebo group, the onabotulinumtoxinA group had fewer headache episodes (12.3 versus 13.4), and migraine/probable migraine episodes (11.5 versus 12.7). The onabotulinumtoxinA group had more cumulative hours of headache occurring on headache days (295.66 versus 274.88). No between-group differences were seen in other disease characteristics. The mean Headache Impact Test (HIT)-6 score was close to 65, and 94.5% of patients had a severe (≥ 60) HIT-6 category score. The mean number of headache days (as per patient diaries) was approximately 20.0 days, and the mean number of moderate to severe headache days (defined as four or more continuous hours of headache and a maximum severity of moderate or severe as per patient diary) was approximately 18 days in both treatment groups. The mean number of migraine/probable migraine days was approximately 19 days in both groups.

In Study 080, there were no between-group differences with respect to baseline disease characteristics. The mean HIT-6 score was approximately 65, and approximately 91% of patients had a severe HIT-6 category score. In both treatment groups, the mean number of headache days was approximately 20 days and the mean number of moderate to severe headache days was approximately 18 days. The mean number of migraine/probable migraine days was approximately 19 days in both treatment groups. Total mean cumulative hours of headache occurring on headache days was close to 290 hours. In both treatment groups, the mean number of headache episodes and migraine/probable migraine episodes was approximately 12 episodes and 11 episodes, respectively.

A total of 97.5% (662 out of 679) and 97.6% (688 out of 705) of patients used acute medications to treat headache pain, with a mean intake of medication(s) at baseline of approximately 30 intakes and 25 intakes in Studies 079 and 080, respectively. A total of 68.1% (462 out of 679) and 63.0% (444 out of 705) of patients overused acute headache pain medications at baseline in Studies 079 and 080, respectively. A total of 61.9% (420 out of 679) and 65.1% (459 out of 705) of patients had previously used other headache prophylactic medications prior to study enrolment in Studies 079 and 080, respectively. Table 6 presents baseline medication use.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	Study 191622-079		Study 191622-080	
	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, Max	19, 65	18, 64	18, 65	18, 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 CM (Years)				
Mean (SD)	20.3 (12.79)	20.6 (13.17)	18.5 (12.03)	17.6 (12.06)
Time Since Onset of CM, 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 CM (Years)				
Mean (SD)	20.3 (11.16)	20.9 (11.90)	22.0 (10.79)	22.8 (11.91)
Median (Min, Max)	17.0 (2, 53)	18.0 (1, 55)	20.0 (2, 56)	20.0 (1, 57)
Age of onset of CM, 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)
> 40 Years	21 (6.2)	21 (6.2)	21 (6.1)	33 (9.2)
Disease Characteristics during the 28 days prior to baseline				
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)

Characteristic	Study 191622-079		Study 191622-080	
	Ona A (N = 341)	Placebo (N = 338)	Ona A (N = 347)	Placebo (N = 358)
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; CSR = Clinical Study Report; HC = Health Canada; HIT = Headache Impact Test; Min = minimum; Max = maximum; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Study 191622-079 CSR,[17] Study 191622-080 CSR,[18] HC Module.[19]

TABLE 6: BASELINE MEDICATION USE

Characteristic	Study 191622-079		Study 191622-080	
	Ona A (N = 341)	Placebo (N = 338)	Ona A (N = 347)	Placebo (N = 358)
Acute Headache Pain Medications Use During Baseline, Mean (SD)	29.1 (19.27)	30.4 (22.9)	24.7 (18.76)	25.4 (18.87)
Patients With Acute Headache Pain Medications Use During Baseline, N (%)	335 (98.2)	327 (96.7)	337 (97.1)	351 (98.0)
Simple Analgesics	239 (70.1)	220 (65.1)	231 (66.6)	238 (66.5)
Ergotamines	16 (4.7)	12 (3.6)	10 (2.9)	2 (0.6)
Triptans	221 (64.8)	209 (61.8)	220 (63.4)	226 (63.1)
Opioids	36 (10.6)	35 (10.4)	21 (6.1)	23 (6.4)
Combination Analgesics	199 (58.4)	211 (62.4)	169 (48.7)	189 (52.8)
Combined Categories	215 (63.0)	207 (61.2)	187 (53.9)	196 (54.7)
Patients With Acute Headache Pain Medications Overuse During Baseline, N (%)	226 (66.3)	236 (69.8)	220 (63.4)	224 (62.6)
Simple Analgesics (≥ 15 Days)	43 (12.6)	51 (15.1)	52 (15.0)	36 (10.1)
Ergotamines (≥ 10 Days)	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)
Triptans (≥ 10 Days)	78 (22.9)	81 (24.0)	83 (23.9)	85 (23.7)
Opioids (≥ 10 Days)	7 (2.1)	10 (3.0)	3 (0.9)	4 (1.1)
Combination Analgesics (≥ 10 Days)	87 (25.5)	98 (29.0)	55 (15.9)	69 (19.3)
Combined Categories (≥ 10 Days)	165 (48.4)	174 (51.5)	143 (41.2)	150 (41.9)
Patients With Pre-study Headache Prophylaxis Medications, N (%)	203 (59.5)	217 (64.2)	222 (64.0)	237 (66.2)
Beta Blockers	94 (27.6)	95 (28.1)	108 (31.1)	123 (34.4)
Calcium Blockers	46 (13.5)	45 (13.3)	56 (16.1)	50 (14.0)
Anticonvulsants	149 (43.7)	163 (48.2)	162 (46.7)	178 (49.7)
Antidepressants	120 (35.2)	110 (32.5)	129 (37.2)	139 (38.8)
Other	79 (23.2)	79 (21.3)	99 (28.5)	101 (28.2)
Patients With 3 or More Prior Prophylactics, N (%)	107 (31.4)	109 (32.2)	124 (35.7)	139 (38.8)

CSR = Clinical Study Report; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Study 191622-079 CSR,[17] Study 191622-080 CSR.[18]

3.2.3 Interventions

a) Double-blind phase (day 0 to week 24)

In both trials, onabotulinumtoxinA or placebo was administered at day 0 and at week 12 during the DB phase.

A minimum dose of 155 U onabotulinumtoxinA (purified neurotoxin complex) or placebo (saline) was administered IM as 31 fixed-site, fixed-dose injections across seven specific head/neck muscle areas. In addition, at the investigator's discretion, an additional 40 U of onabotulinumtoxinA or placebo could be administered using a "follow-the-pain" paradigm in up to three specific head/neck muscle areas. The active treatment and placebo were supplied in identical glass vials.

The onabotulinumtoxinA dose, the number of injection sites per muscle, the areas to be injected, and the total dose were based on the results of two exploratory phase 2 studies (191622-038 and 191622-039).

b) Open-label extension phase (week 24 to week 56)

All patients who continued into the OLE phase received onabotulinumtoxinA injections at week 24, week 36, and week 48. The same doses and regimens were used as described in the DB phase.

c) Concomitant medications

Patients were allowed to take acute headache pain medications, which were recorded using a daily diary. Any headache prophylactic medication was prohibited during the trial and within 28 days prior to baseline of Studies 079 and 080 (week –4 to day 0).

3.2.4 Outcomes

a) Efficacy

Study 079

Primary efficacy end point: In Study 079, the primary efficacy end point was the frequency of headache episodes per 28-day period ending with week 24 compared with baseline. The 28-day period ending with week 24 was defined as day 57 to day 84 following the second injection. The number of headache episodes during the 28-day run-in period prior to randomization served as the "baseline."

Secondary efficacy end points: The 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.

Other: The following post hoc efficacy analyses were undertaken: frequency of moderate/severe headache days, total cumulative hours of headache occurring on headache days, and proportion of patients with severe HIT-6 category scores.

Study 080

Primary efficacy end point: In the first study protocol of Study 080, the efficacy end points were the same as Study 079; however, two weeks prior to the time at which the database was locked and treatment unblinded, the protocol was amended. The primary efficacy end point was changed from the frequency of headache *episodes* per 28-day period to the frequency of headache *days* per 28-day period, ending with week 24 compared with baseline.

Secondary efficacy end points: With the protocol change, the secondary outcomes became 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 impact category score per 28-day period, and frequency of headache episodes per 28-day period.

In both studies, data required for the evaluation of all the headache characteristics and the 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 characteristics, symptoms associated with headache, the effect of physical activity on each headache, and use of acute headache pain medication were reported by patients on a daily basis using the electronic telephone diary.

Definitions of efficacy outcomes used in Studies 079 and 080:

- Headache episode: patient-reported headache pain that lasted at least four continuous hours per patient diary.
- Headache day: a day (00:00 to 23:59) with four or more continuous hours of headache.
- Migraine episode: pain that lasted at least four continuous hours and that met the ICHD-2 criteria of migraine without aura or migraine with aura.
- Probable migraine episode: pain that lasted at least four continuous hours and that met the ICHD-2 criteria of probable migraine.
- Migraine/probable migraine days: a day (00:00 to 23:59) with four or more continuous hours of migraine or probable migraine headache.
- Acute headache pain medication use: a patient-reported intake of medication(s) to treat headache pain where a patient reported that they took medication, regardless of the dose or number of types of medication taken at the same time. It was possible to have multiple intakes within a given day for each patient.
- Acute headache pain medication overuse: ≥ 15 days per four-week period and at least two days per week for any simple analgesic intake, or ≥ 10 days per four-week period and at least two days per week for intake within a category for at least one category among ergotamines, triptans, opioids, and combination analgesic medications, or for such intake combined across at least two categories among ergotamines, triptans, analgesics (including simple and combination analgesic medication), and opioids.
- Moderate/severe headache day: a day (00:00 to 23:59) with four or more continuous hours of headache and a maximum severity of moderate or severe as per patient diary.

Of note, some of the efficacy analyses mentioned above were not defined a priori as parameters to be measured in the protocol. Specifically, in Studies 079 and 080, the efficacy analyses assessed per 28-day period, but not defined a priori, included: 25%, 50%, 75%, and 100% decrease from baseline in the frequency of headache days, headache episodes, migraine/probable migraine headache days, migraine/probable migraine headache episodes, and daily headache impact score. Daily headache impact scores were collected from electronic patient diaries and derived from daily patient-reported assessments of headache impact. The scores ranged from 1 to 5 with 1 = no impact, 2 = little impact, 3 = moderate impact, 4 = severe impact, and 5 = unable to do anything. However, this instrument has not been validated in patients with CM, and no MCID is available. Furthermore, in Study 080, the frequency of migraine/probable migraine episodes and the frequency of acute headache pain medication intakes per 28-day period were not defined a priori.

MSQ is a disease-specific instrument which assesses the impact of migraine on a patient's HRQoL. MSQ version 2.1 is a 14-item instrument measuring the following 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). For each domain, scores range from 0 (high function) to 100 (low function). MCIDs for the within-group differences for MSQ-RR, MSQ-RP, and MSQ-EF were estimated to be 10.9, 8.3, and 12.2, respectively. The MSQ was completed by patients at day 0, at week 12, at week 24, and at week 56. Please see APPENDIX 5: VALIDITY OF OUTCOME MEASURES for additional information regarding the description and validation of the MSQ.

HIT-6 comprises six items that measure pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress.[22] Total HIT-6 scores range from 36 to 78. 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 of the disease on the daily life of the respondent. A between-group difference of HIT change scores of 2.3 units suggests a clinical improvement in a patient's headache condition. HIT-6 was completed by patients at all scheduled DB visits beginning on day 0, as well as at all office visits in the OLE phase. Please see APPENDIX 5: VALIDITY OF OUTCOME MEASURES for additional information regarding the description and validation of the HIT-6 instrument.

In addition the generic questionnaire Euro-QoL Visual Analogue Scale (EQ-VAS) was completed by patients at day 0 and week 24. This instrument is not disease specific and no MCID for CM is available.

Harms: Safety data were presented for each included study through week 24 (DB treatment phase). Long-term safety and tolerability data are presented from the OLE phase in APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION PHASE OF STUDY 079 AND STUDY 080.

3.2.5 Statistical analysis

a) Study 079

The primary efficacy analysis was change from baseline in the frequency of headache episodes per 28- day period ending with week 24 in the intention-to-treat (ITT) analysis set, as defined in the Analysis Populations section below. An analysis of covariance (ANCOVA) of the change from baseline was conducted, with treatment and medication-overuse strata as the main effects and the baseline frequency of headache episodes as covariate, using modified last observation carried forward (mLOCF [the mean across all patients in the previous 28-day period]). The analyses of secondary outcomes (frequency of headache days per 28-day period, frequency of migraine/probable migraine days per 28-day period, frequency of migraine/probable migraine episodes per 28-day period, and frequency of acute headache pain medication intakes per 28-day period) were conducted in a similar manner as the primary outcome using ANCOVA of the change from baseline in the ITT analysis set, with treatment and medication-overuse strata as the main effects and the baseline count for each of the outcomes as covariate, using mLOCF.

For the primary outcome, a two-sided test with *P* value less than or equal to 0.05 was considered as statistically significant; treatment-by-subgroup interactions were examined at the 0.10 level. In order to adjust the pre-specified type 1 error rate of 0.05 for all five pre-specified primary or secondary outcomes, a Bonferroni adjustment was applied post hoc to compare *P* values at a critical level of 0.01.

Study 080

The primary efficacy analysis was change from baseline in the frequency of headache days per 28-day period ending with week 24 in the ITT analysis set, as defined in the Analysis Populations section below. An ANCOVA of the change from baseline was conducted, with treatment and medication-overuse strata as the main effects and the baseline frequency of headache days as covariate, using mLOCF. The analyses of secondary outcomes (frequency of migraine/probable migraine days, frequency of moderate/severe headache days, total cumulative hours of headache occurring on headache days, and frequency of headache episodes) were conducted in a similar manner as the primary outcome using ANCOVA of the change from baseline in the ITT analysis set, with treatment and medication-overuse strata as the main effects and the baseline count for each of the outcomes as covariate, using mLOCF. Proportions of patients with severe HIT-6 total scores were compared between-treatment groups by Pearson's chi-square tests.

For the primary outcome, a two-sided test with *P* value less than or equal to 0.05 was considered as statistically significant; treatment-by-subgroup interactions were examined at the 0.10 level. In order to control the type 1 error rate for multiple secondary end points, a gatekeeping approach for five ranked secondary outcomes was used, in which the test of any lower-ranked secondary end point was not considered statistically significant if the *P* value of a higher ranked secondary end point was > 0.05. The hierarchical order of the secondary end points was as follows: frequency of migraine/probable migraine days, frequency of moderate/severe headache days, total cumulative hours of headache occurring on headache days, proportion of patients with severe HIT-6 category scores, and frequency of headache episodes.

In both Studies 079 and 080, in order to analyze other efficacy outcomes, the Wilcoxon rank-sum test was used in the comparisons of the change from baseline between-treatment groups for outcomes with ordered response categories and for continuous outcomes. ANCOVA with a baseline covariate included in the analysis was used for outcomes with a continuous response range, and Pearson's chi-square tests or Fisher's exact test were used for the comparisons between-treatment groups for outcomes where the data were essentially binomial.

In both Studies 079 and 080, primary and secondary efficacy outcomes were summarized using the following subgroup factors:

- investigator centre
- age (< 40/> 40 years)
- gender (male/female)
- race (Caucasian/non-Caucasian)
- acute headache pain medication overuse (yes/no)
- patients who have failed three or more prior oral prophylactic medications (post hoc analysis)

The CDR protocol included a subgroup by duration of illness; however, such analysis was not undertaken by the manufacturer.

For primary and secondary efficacy outcomes, in order to have data for all patients in the ITT population for the ITT analysis, missing values were estimated according to the following method:

- If at least 20 but less than 28 days of data were reported, data were prorated to a 28-day period equivalence.

- If less than 20 days of a 28-day period data were reported, then the scores were imputed using a mLOCF imputation analysis, which involved the mean across all patients in the previous 28-day period.

a) Analysis populations

The primary analysis population used for the efficacy analyses in both studies was the ITT analysis set. The various analyses populations are defined below:

- Safety Analysis Set: safety analyses were performed using the safety population, consisting of all patients who received the study treatment at day 0. For the DB phase, the patients were analyzed for safety as treated at the first treatment.
- ITT Analysis Set: Patients were analyzed according to the randomization assignment, regardless of actual treatment received. In order to have data for all patients in the ITT population for the ITT analysis, missing values were imputed for the ITT analysis, as described above.

3.3 Patient Disposition

Of the 1,713 patients screened for Study 079, a total of 679 patients were randomized and 674 received at least one dose of the study drug. Five randomized patients did not receive any study drug (four in the placebo treatment group and one in the onabotulinumtoxinA treatment group). In Study 080, 1,621 patients were screened, of which 705 were randomized; all of them received at least one dose of the study drug. The primary reason for screening failure in both studies was the failure to meet all of the inclusion/exclusion criteria, especially the criterion regarding the minimum number headache days during the pre-randomization phase.

Across both studies, discontinuations ranged from 6.7% to 13.2% in individual treatment arms as detailed in Table 7. Overall, the primary reasons for discontinuation were: AEs (highest proportions in the onabotulinumtoxinA treatment groups of Study 079 [3.2%] and Study 080 [2.3%]); lost to follow-up (highest proportions in the placebo treatment groups of Study 079 [4.4%] and Study 080 [2.2%]); personal reasons (highest proportions in both treatment groups of Study 079); and “other” (it was unclear how “other” was defined).

TABLE 7: PATIENT DISPOSITION

	Study 191622-079		Study 191622-080	
Screened, N	**1,713**		**1,621**	
	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; CSR = Clinical Study Report; DB = double-blind; ITT = intention-to-treat; Ona A = onabotulinumtoxinA.
Source: Study 191622-079 CSR,[17] Study 191622-080 CSR.[18]

3.4 Exposure to Study Treatments

The mean (median) total dose of onabotulinumtoxinA received by patients in the active group at day 0 and at week 12 ranged from 165.1 U (155.0 U) to 165.8 U (155.0 U) in Study 079, and from 163.0 U (155.0 U) to 164.3 U (155.0 U) in Study 080. In both treatment groups, the mean number of injection sites was approximately 33 in Study 079 and 32.5 in Study 080. Table 8 summarizes the exposure by randomized treatment for both included trials.

TABLE 8: EXPOSURE TO STUDY TREATMENTS (SAFETY POPULATION)

	Study 191622-079		Study 191622-080	
	Ona A (N = 340)	**Placebo (N = 334)**	**Ona A (N = 347)**	**Placebo (N = 358)**
Day 0 (Treatment Cycle 1)	N = 340	N = 0	N = 347	N = 0
Units, Mean (SD)	165.1 (15.62)	NA	163.0 (12.35)	NA
Units, (Median)	155.0	NA	155.0	NA
Injection Sites, Mean (SD)	33.0 (3.13)	33.1 (2.60)	32.6 (2.47)	32.5 (2.38)
Week 12 (Treatment Cycle 2)	N = 305	N = 0	N = 320	N = 0
Units, Mean (SD)	165.8 (14.38)	NA	163.1 (12.32)	NA
Units, (Median)	155.0	NA	155.0	NA
Injection Sites, Mean (SD)	33.1 (2.87)	33.1 (2.58)	32.6 (2.46)	32.5 (2.38)

CSR = Clinical Study Report; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Study 191622-079 CSR,[17] Study 191622-080 CSR.[18]

3.5 Critical Appraisal

3.5.1 Internal validity

a) Study Design

Statistical significance should be viewed with caution due to inflated type 1 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 Study 079, in order to adjust the pre-specified type 1 error rate of 0.05 for all pre-specified primary or secondary outcomes, a Bonferroni adjustment was applied post hoc to compare *P* values at a critical level of 0.01. This adjustment did not take into consideration all the outcomes measured, including HRQoL measures. In Study 080, in order to control the type 1 error rate for multiple secondary end points, a gatekeeping approach for five ranked secondary outcomes was used, in which the test of any lower-ranked secondary end point was not considered statistically significant if the *P* value of a higher ranked secondary end point was > 0.05. The type 1 error was not adjusted for HRQoL outcomes and subgroup analyses. The problem with this approach is that only certain outcomes were selected; hence, the gatekeeping approach did not take into consideration all outcomes measured, including HRQoL measures. In addition, no criteria were stated on how the outcomes were ranked, and the ranking used was different than the ranking stated in the protocol of this review. This indicates selective reporting.

In Study 080, two weeks before the primary database lock and treatment unblinding, the initial pre-specified primary end point was changed from being "frequency of headache episodes" to "frequency of headache days." These changes were driven by the results from Study 079; however, it is unlikely these changes affected the analysis of the study.

Even though the study was blinded, blinding could have been broken. Because of AEs (such as paralysis of the forehead muscles), patients may have guessed that they were receiving onabotulinumtoxinA. The guidelines for controlled trials of prophylactic treatment of CM in adults mention that "*unblinding may be a significant factor in acute and prophylactic placebo-controlled migraine trials. Subjects and investigators should be questioned at the end of the trial regarding their opinion as to what treatment group (active or placebo) the subject was assigned to during the study*."[5] In Studies 079 and 080, patients were not asked at any time if they could determine whether they were on onabotulinumtoxinA or placebo treatment. In addition, in two phase 2 studies (191622-038 and 191622-039), approximately 86% of patients correctly determined that they were receiving onabotulinumtoxinA and 58% correctly guessed they were receiving placebo.[23] In Studies 079 and 080, it may be that the efficacy of onabotulinumtoxinA was overestimated; 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.

To compare treatment effects in subgroups in a randomized controlled trial (RCT), 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.

b) Population

In Study 079, 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 onabotulinumtoxinA group. Furthermore, the total cumulative hours of headache was higher in the onabotulinumtoxinA group than in the placebo group. This imbalance between the two groups may have explained why the effect sizes obtained in Study 079 were not as great as those obtained in Study 080.

It was reported in both studies that the minimum age of onset of CM was one year old, putting into question the internal validity of the data or the diagnosis. If there was an error in data entry, then one would question why it was not fixed. Furthermore, a diagnosis of CM at one year of age would be highly improbable.

c) Interventions

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.

Both trials compared onabotulinumtoxinA 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, which are used off-label. A comparative trial against one of these agents would have been clinically relevant. In fact, several onabotulinumtoxinA trials have been conducted against medically accepted prophylactic medications. Head-to-head trials have compared onabotulinumtoxinA to topiramate,[24,25] to divalproex sodium,[26] and to amitriptyline for the prevention of CM.[27] All trials used a CM dosing regimen of onabotulinumtoxinA that is not approved by HC.

d) Outcomes

Patients were withdrawn from prophylaxis medications four weeks prior to the trial run-in phase. Improvement in outcomes from baseline may have been exaggerated (i.e., less well controlled at baseline).

A definition of what constituted a pain-free interval between two headache or migraine episodes was not provided, and hence, the reliability of frequency of episodes as an outcome may be questioned.

Headache/migraine episodes and days were derived from patient diaries; however, self-reporting is subject to individual variability in reporting accuracy and completion. Furthermore, no descriptions of the electronic telephone diary and its validation were provided.

A patient with an incomplete response to acute headache pain medication taken for a headache, or a patient getting temporary relief from acute medication, could count one headache episode as two headache episodes.

The subgroup analysis for patients who failed three or more prior prophylaxis medications was post hoc. No interaction test for this subgroup was undertaken. The result of this analysis must be interpreted with caution. In addition, a subgroup analysis for patients who did not fail three or more prior prophylaxis medications was not provided. Hence, a conclusion about these two subgroups cannot be made.

The reduction in acute medication use could potentially confound the interpretation of the results, as it may lead to a reduction in headache frequency/severity if the headaches are due to medication overuse. Approximately 65% of patients included in the study were overusing acute headache pain medication; a change in acute medication use might be reflected as a change in headache status, especially if patients had a diagnosis of MOH instead of CM.

When patients reported that they used acute headache pain medication, that use was measured as "the intake of medication(s) to treat headache pain", regardless of the dose or the number of types of medication taken at the same time. This method did not accurately measure the use of acute headache pain medication.

The use of mLOCF imputation might have biased the results. Specifically, the mLOCF method of imputation involved calculating the mean result for the outcome of interest across all patients in the previous 28-day period. Since pain could change from day to day, imputation using the previous 28-day period might not be appropriate. In addition, imputations at week 24 were performed in about 20% of the patients in both Study 079 and 080.[19] But when sensitivity analysis using "observed data" without imputing for missing values was performed, there was no change in the direction of results, indicating that the mLOCF was appropriate.

The proportion of patients who withdrew from the trials was approximately 13% for Study 079 and 9% for Study 080. One reason given was classified as "other," which was undefined. The Food and Drug Administration (FDA) clinical reviewer report identified that, in Study 079, five patients in the onabotulinumtoxinA treatment arm and four patients in the placebo treatment arm discontinued treatment due to a lack of efficacy, yet eight of these patients were reported in the "other" category in the CSR.[21] If the "other" category included withdrawals due to lack of efficacy, then the reasons for withdrawals have not been reported adequately in the studies. Furthermore, 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 that approximately 10% of patients did not complete their diaries. This may have introduced bias, which may have affected the internal validity of both trials.

3.5.2 External validity

Studies 079 and 080 were designed when ICHD-2 criteria were still in use and prior to the publication of ICHD-3. ICHD-2 used a strict definition of migraine (migraine occurring on 15 or more days per month for more than three months), whereas the ICHD-3 describes CM as a headache (tension-type-like or migraine-like) occurring on 15 or more days per month for more than three months, and 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 Studies 079 and 08, the inclusion criteria used in both studies were more in line with ICHD-3.

The ICHD-3 excludes medication-overuse headache from the diagnosis of CM. It is believed that approximately 50% of patients are wrongly diagnosed with CM while they should be diagnosed with MOH.[1] 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. As per the clinical expert involved in the review, in clinical practice there is considerable overlap between MOH and CM, making it very difficult to distinguish between them. Thus, the trials examined 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; hence, the efficacy of onabotulinumtoxinA has not been explored in such a subgroup of patients.

Patients continued to receive onabotulinumtoxinA even after the number of headache days decreased to < 15 days, which would change the diagnosis of CM to EM. It is not clear if the reduction in headache days would be sustained if patients were to stop receiving onabotulinumtoxinA. Previous onabotulinumtoxinA trials conducted in patients with EM showed limited benefits.[10,28]

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See APPENDIX 4: DETAILED OUTCOME DATA *for detailed efficacy data.*

3.6.1 Health-related quality of life

a) MSQ

Change in HRQoL from baseline to week 12 and to the primary end point (week 24) was measured using the MSQ (see APPENDIX 5: VALIDITY OF OUTCOME MEASURES). This end point was not listed within the pre-specified primary and secondary outcomes, and it is unclear if an adjustment for type 1 error for this outcome was made.

In Study 079, at week 24, patients treated with onabotulinumtoxinA had a greater decrease from baseline in mean scores for the three MSQ domains than patients treated with placebo. Changes from baseline for RR scores were –16.8 for onabotulinumtoxinA versus –8.8 for placebo ($P < 0.001$ for between-group difference). Changes from baseline for RP scores were –12.6 for onabotulinumtoxinA versus –7.6 for placebo ($P = 0.005$ for between-group difference). Changes from baseline for EF scores were –16.9 for onabotulinumtoxinA versus –10.0 for placebo ($P = 0.001$ for between-group difference).

Similar results were found in Study 080, where changes from baseline were –17.2 for onabotulinumtoxinA versus –8.4 for placebo in RR scores ($P < 0.001$ for between-group difference), –13.5 for onabotulinumtoxinA versus –5.4 for placebo in RP scores ($P < 0.001$ for between-group difference), and –19.0 for onabotulinumtoxinA versus –9.1 for placebo in EF scores ($P < 0.001$ for between-group difference).

In both studies, patients who received onabotulinumtoxinA treatment had a mean change from baseline scores that exceeded the established MCID within-group differences of –10.9 (RR), –8.3 (RP) and –12.2 (EF), while patients receiving placebo did not exceed the respective MCIDs of 10.9, 8.3, and 12.2 points. Results were presented for observed data without imputation for missing values (Table 9 and Table 14).

b) EQ-VAS

There were no statistically significant between-group differences in EQ-VAS at week 24.

TABLE 9: BASELINE AND MEAN CHANGE FROM BASELINE AT WEEK 24 IN MSQ SCORES (OBSERVED DATA WITHOUT IMPUTATION FOR MISSING VALUES)[A]

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* value	Ona A	Placebo	*P* value
MSQ 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, Max)	–11.4 (–83, 29)	–2.9 (–80, 40)		–14.3 (–91, 34)	–5.7 (–89, 49)	
MSQ 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, Max)	–10.0 (–95, 45)	–5.0 (–80, 65)		–10.0 (–80, 40)	–2.5 (–95, 60)	
MSQ 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, Max)	–13.3 (–87, 60)	–6.7 (–100, 47)		–13.3 (–100, 53)	–6.7 (–100, 60)	

CSR = Clinical Study Report; Max = maximum; Min = minimum; MSQ = Migraine-Specific Quality of Life Questionnaire; Ona A = onabotulinumtoxinA; SD = standard deviation.

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

Source: Additional information from the manufacturer;[29] Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

Subgroup Analyses

Subpopulation: Patients with Three or More Prior Prophylactics: In Study 079 at week 24, patients treated with onabotulinumtoxinA had a greater decrease in mean MSQ scores for two domains (RR with *P* = 0.010 and EF with *P* = 0.024 for between-group differences) from baseline than patients treated with placebo. The RP domain score change was not statistically significantly different between onabotulinumtoxinA and placebo. Patients who received onabotulinumtoxinA treatment had a change from baseline scores that exceeded the established MCID for the RR and EF domains of MSQ.

In Study 080, patients treated with onabotulinumtoxinA had a greater reduction in mean scores for all three MSQ domains (RR with *P* < 0.001, RP with *P* < 0.001, and EF with *P* = 0.007 for between-group differences) from baseline than patients treated with placebo. Patients who received onabotulinumtoxinA treatment had a change from baseline MSQ scores that exceeded the established MCID for all three domains (RR, RP, and EF). Detailed results are presented in Table 15.

Other Subpopulations: In both studies for male patients, there was no statistically significant difference between onabotulinumtoxinA and placebo for all MSQ domains. Patients in both treatment groups had a change from baseline scores that exceeded the established MCID for some domains. Results for female patients were consistent with the results obtained overall (Table 16).

In both studies, the onabotulinumtoxinA subgroup of patients who overused acute headache medication had a change from baseline scores that exceeded the established MCID for all domains, while for those in the placebo group, the change did not exceeded the established MCID for any of the three domains. Similarly, in the subgroup of patients who did not overuse acute headache medication, patients in placebo group achieved the established MCID except for the RP domain in Study 079 and RR domain in Study 080 (Table 17).

3.6.2 Other Patient-Reported Outcomes

In Study 080, the proportion of patients with a "severe" HIT-6 category score (≥ 60) was listed as a secondary outcome, and statistical adjustments for type 1 error were made. Other HIT-6 outcomes were not listed within the pre-specified primary and secondary outcomes.

Mean changes from baseline in total HIT-6 score favoured onabotulinumtoxinA over placebo with $P < 0.001$ for between-group differences in both studies. The between-group difference at week 24 was 2.3 in Study 079 and 2.5 in Study 080. This between-group difference met the MCID of 2.3 (Table 10).

When the four groupings of HIT-6 (little or no impact, some impact, substantial impact, or severe impact) were compared at week 24, results also favoured onabotulinumtoxinA over placebo, with $P < 0.001$ in both studies. Detailed results are presented in Table 18. In addition, Figure 3 and Figure 4 present, respectively, the proportion of patients with a "severe" HIT-6 score (≥ 60) and the mean change from baseline in HIT-6 scores at different time points. These figures showed that benefit was obtained after the first treatment, with little additional benefit after the second treatment at week 12.

Patients treated with onabotulinumtoxinA had a greater mean decrease from baseline in daily headache impact score than patients treated with placebo at week 24, with $P = 0.002$ and $P < 0.001$ in Study 079 and Study 080, respectively. No MCID in CM is available for this instrument. Detailed results are presented in Table 18.

TABLE 10: CHANGE FROM BASELINE AT WEEK 24 IN HIT-6 (MLOCF)[A]

Outcome	Study 191622-079			Study 191622-080		
	Ona A (N = 341)	Placebo (N = 338)	*P* value	Ona A (N = 347)	Placebo (N = 358)	*P* value
At Week 24						
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)	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)	
Change From Baseline in HIT-6 Score, Mean (SD)	–4.7 (7.11)	–2.4 (5.63)	< 0.001[c]	–4.9 (6.97)	–2.4 (6.50)	< 0.001[c]

CSR = Clinical Study Report; HIT = Headache Impact Test; Ona A = onabotulinumtoxinA; 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.
[c] *P* values for between-treatment comparisons were determined by the Wilcoxon rank-sum test.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

a) Subgroup Analyses

Subpopulations: Patients With Three or More Prior Prophylactics

In Study 079, the difference in the mean changes from baseline in total HIT-6 scores between the onabotulinumtoxinA group and the placebo group did not meet the established MCID of 2.3 at week 24, while in Study 080 the difference was 2.9, exceeding the established MCID. Detailed results are presented in Table 19.

Other Subpopulations

In both studies, the difference in the mean changes from baseline in total HIT-6 scores between the onabotulinumtoxinA group and the placebo group did not meet the established MCID of 2.3 for male patients at week 24, but the MCID was exceeded for female patients. Detailed results are presented in Table 20.

In both studies, among patients coded as medication overuse "Yes" or "No" the difference in the mean changes from baseline in total HIT-6 scores between the onabotulinumtoxinA group and the placebo group met or exceeded the MCID (Table 21).

Patients treated in the onabotulinumtoxinA group had a greater mean decrease from baseline in daily headache impact score than patients treated with placebo at week 24 for the subpopulations of patients with three or more prior prophylactic, females, patients who overused and did not overuse acute headache pain medication, while for the subpopulation of male patients the difference was not statistically significant in both studies (Table 22).

In both studies, the difference in the mean changes from baseline in total HIT-6 scores between the onabotulinumtoxinA group and the placebo group met the established MCID of 2.3 for the subgroup of patients who overused acute headache medication, while in the subgroup of patients who did not overuse acute headache medication, the difference exceeded the established MCID in Study 080 only (Table 23).

3.6.3 Acute headache pain medication intake

Acute headache pain medication intake was pre-specified as a secondary efficacy outcome in Study 079, while it was not pre-specified as a primary or a secondary outcome in Study 080. At week 24, in Study 079, in both the onabotulinumtoxinA and placebo groups, the mean decrease from baseline in the frequency of acute headache pain medication intakes per 28-day period was –10.1 intakes for the onabotulinumtoxinA group versus –9.8 intakes for the placebo group. The mean decrease from baseline in the frequency of acute headache pain medication days per 28-day period was –5.8 days for the onabotulinumtoxinA group versus –5.8 days for placebo group. In addition, there was an overall reduction in the use and overuse of acute headache pain medications. None of the aforementioned between group comparisons was statistically significant, however.

In Study 080, in both the onabotulinumtoxinA and placebo groups, the mean decrease from baseline in the frequency of acute headache pain medication intakes per 28-day period was –9.7 intakes for the onabotulinumtoxinA group versus –8.1 intakes for placebo group (*P* = not statistically significant). The mean decrease from baseline in acute headache pain medication days per 28-day period was –6.4 days for the onabotulinumtoxinA group versus –4.8 days for placebo group ($P < 0.001$). In addition, in both the onabotulinumtoxinA and placebo groups, there was an overall reduction in the use of acute headache pain medications, with a larger reduction in the overuse of acute headache pain medications in the onabotulinumtoxinA group than in the placebo group by approximately 9%, with $P = 0.017$.

Detailed results are presented in Table 11, Figure 5, Figure 6, Figure 7, and Figure 8. Figure 5 to 8 present results of the mean change from baseline in acute headache pain medication intake, mean change from baseline in frequency of acute headache pain medications days, proportion of patients who used acute headache pain medications, and proportion of patients who overused acute headache pain medications per 28-day period at different time points, respectively. These figures indicate that improvements were observed after the first treatment, with smaller improvements noticed after the second treatment.

TABLE 11: ACUTE HEADACHE PAIN MEDICATION INTAKE

Outcome	Study 191622-079			Study 191622-080		
	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, LSMean (SD)	25.2 (19.27)	25.7 (22.29)		21.9 (18.76)	22.8 (18.87)	
Change From Baseline at Week 24, LSMean (SD)	–10.1 (18.67)	–9.8 (18.54)	0.795	–9.7 (15.53)	–8.1 (14.92)	0.132
Acute Headache Pain Medications Days per 28-day Period (Observed Data)[b]						
Baseline, LSMean (SD)	15.0 (6.32)	15.4 (6.38)		14.3 (6.42)	14.4 (6.30)	
Change From Baseline at Week 24, LSMean (SD)	–5.8 (6.63)	–5.8 (6.22)	0.996	–6.4 (5.73)	–4.8 (5.93)	<0.001
Acute Headache Pain Medications 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 Medications 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

CSR = Clinical Study Report; LSMean = Least squares mean; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.
Note: SD is for the mean. LSMean 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).
Source: Study 191622-079 CSR,[17] Study 191622-080 CSR.[18]

Subgroup Analyses

In both studies, in both the onabotulinumtoxinA and placebo groups, there was a decrease from baseline in the frequency of acute headache pain medication intakes for all subgroups of interest: patients who overused and did not overuse headache pain medication, males, females, and patients who had used three or more prior prophylactics. The effect size was greater for the subgroup of patients who overused headache pain medication compared with those who did not, and in females compared with males.

The between-group difference for the mean change from baseline in acute headache pain medication intake was statistically significant in Study 080 in the subgroup of patients who had used three or more prior prophylactics. All other between-group comparisons were not statistically significant. Detailed results are presented in Table 23.

3.6.4 Other efficacy outcomes

Reduction from baseline in headache days and migraine/probable migraine days per 28-day period, frequency of headache days and migraine/probable migraine days per 28-day period, number of moderate/severe headache days per 28-day period, total cumulative hours of headache occurring on headache days per 28-day period, reduction from baseline in headache episodes and migraine/probable migraine episodes per 28-day period, frequency of headache episodes and migraine/probable migraine episodes per 28-day period, emergency room (ER) visits and hospitalizations for migraine symptoms, and time lost due to migraine were reported in both studies.

a) Per cent reductions in headache days per 28-day period

In both studies, the reduction in the number of headache days per 28-day period was assessed using observed data (without imputation for missing values). In both studies, a greater proportion of patients in the onabotulinumtoxinA group had a 25% reduction, a 50% reduction, and a 75% reduction in headache days per 28-day period compared with the placebo group. The proportion of patients with a 100% reduction in headache days was similar in both treatment groups. Results are presented in Table 24. Figure 9 and Figure 10 present the proportion of patients with 25%, 50%, 75%, and 100% reduction in headache days per 28-day period at different time points in Studies 079 and 080, respectively.

Frequency of headache days per 28-day period

This was the primary end point for Study 080 (after the protocol change prior to unblinding) and a secondary end point for Study 079. The change in number of headache days per 28-day period was assessed using the ITT population, with missing values imputed using mLOCF. At week 24, patients treated with onabotulinumtoxinA had a greater decrease from baseline in frequency of headache days per 28-day period (LSMean = –7.8 in Study 079 and –9.2 in Study 080) than patients treated with placebo (LSMean = –6.4 in Study 079 and –6.9 in Study 080). *P* values for between-group differences were 0.006 and < 0.001 for Study 079 and Study 080, respectively. Detailed results are presented in Table 24 and Figure 13.

Results for subgroups of interest are presented in Table 25. At week 24, the between-group difference in the mean change from baseline in the frequency of headache days per 28-day period favoured onabotulinumtoxinA for all subgroups, including patients who overused headache medications and those who did not, males (except Study 079 where placebo was better), females, and patients who had used three or more prior prophylactics.

Per cent reductions in migraine/probable migraine days per 28-day period

In both studies, the reduction in the number of migraine/probable migraine days per 28-day period was assessed using observed data (without imputation for missing values). In both studies, a greater proportion of patients in onabotulinumtoxinA group had a 25% reduction, a 50% reduction, and a 75% reduction in migraine/probable migraine days per 28-day period compared with the placebo group. The proportion of patients with a 100% reduction in migraine/probable migraine days was approximately similar between both treatment groups at week 24. Results are presented in Table 24. Figure 11 and Figure 12 present the proportion of patients with 25%, 50, 75%, and 100% reduction in migraine/probable migraine days per 28-day period at different time points in Studies 079 and 080, respectively.

Frequency of migraine/probable migraine days per 28-day period

This was a secondary end point in both studies. The change in the number of migraine/probable migraine days per 28-day period was assessed using the ITT population with missing values imputed

using mLOCF. At week 24, patients treated with onabotulinumtoxinA had a greater decrease from baseline in frequency of migraine/probable migraine days per 28-day period (LSMean = –7.6 in Study 079 and –8.8 in Study 080) than patients treated with placebo (LSMean = –6.0 in Study 079 and –6.5 in Study 080). *P* values for between-treatment group differences were 0.006 and < 0.001 for Study 079 and Study 080 respectively. Detailed results are presented in Table 24 and Figure 16.

Results for the subgroups of interest are presented in Table 26. At week 24, the between-group difference in the mean change from baseline in the frequency of migraine/probable migraine days per 28-day period favoured onabotulinumtoxinA for all subgroups, including patients who overused headache medications and those who did not, males (except Study 079 where both treatment groups were similar), females, and patients who had used three or more prior prophylactics.

Frequency of moderate/severe headache days per 28-day period

This was a secondary end point in Study 080 and a post hoc analysis in Study 079. The change in number of moderate/severe headache days per 28-day period was assessed using the ITT population, with missing values imputed using mLOCF. At week 24, the between-group difference in the mean change from baseline in frequency moderate/severe headache days per 28-day period was –1.5 days in Study 079 and –2.4 days in Study 080 (*P* < 0.001), with fewer moderate/severe headache days with onabotulinumtoxinA. Detailed results are presented in Table 24 and Figure 14.

Results for the subgroups of patients with three or more prior prophylactics are presented in Table 25. At week 24, the between-group difference in the mean change from baseline in frequency moderate/severe headache days per 28-day period was –1.9 days in Study 079 and –3.8 days in Study 080, with fewer moderate/severe headache days with onabotulinumtoxinA.

Total Cumulative Hours of Headache Occurring on Headache Days per 28-day Period

This was a secondary end point in Study 080 and a post hoc analysis in Study 079. The change in total cumulative hours of headache occurring on headache days per 28-day period was assessed using the ITT population with missing values imputed using mLOCF. At week 24, the between-group difference in the mean change from baseline in the total cumulative hours of headache was approximately –30 hours in Study 079 and approximately –40 hours in Study 080 (*P* < 0.001), with fewer total cumulative hours of headache with onabotulinumtoxinA. Detailed results are presented in Table 24 and Figure 15.

Results for the subgroups of patients who had used three or more prior prophylactics are presented in Table 25. At week 24, the between-group difference in the mean change in total cumulative hours of headache occurring on headache days per 28-day period was approximately –52 hours in Study 079 and approximately –58 hours in Study 080, with fewer total cumulative hours of headache with onabotulinumtoxinA.

Frequency of headache episodes per 28-day period

This was the primary end point for Study 079 and a secondary end point in Study 080. The change in number of headache episodes per 28-day period was assessed using the ITT population with missing values imputed using mLOCF. 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 Study 079 (*P* = NS) and –1.0 episodes in Study 080 (*P* = 0.003), with fewer headache episodes with onabotulinumtoxinA. Detailed results are presented in Table 27.

Results for the subgroups of interest are presented in Table 28. The between-group difference in the mean change from baseline in frequency of headache episodes per 28-day period at week 24 was less than one point for all subgroups. There were statistically significant differences in favour of the onabotulinumtoxinA group in the subgroup of patients who overused headache medication, female patients, and patients who had used three or more prior prophylactics in Study 080 only. There was no statistically significant difference at week 24 for any subgroup of patients in Study 079.

Frequency of migraine/probable migraine episodes per 28-day period
This was a secondary end point in Study 079 and was not defined a priori as a parameter to be measured in the protocol for Study 080. The change in the number of migraine/probable migraine episodes per 28-day period was assessed using the ITT population, with missing values imputed using mLOCF. 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 Study 079 (*P* = NS) and –0.9 episodes in Study 080, with fewer migraine/probable migraine episodes with onabotulinumtoxinA. Detailed results are presented in Table 27.

Results for the subgroups of interest are presented in Table 28. At week 24, the between-group difference in the mean change from baseline in frequency migraine/probable migraine episodes per 28-day period was less than 2.0 points for all subgroups. There were statistically significant differences in favour of the onabotulinumtoxinA group in the subgroup of patients who overused headache medication and in the subgroup of patients who had used three or more prior prophylactics. In Study 079, the *P* value was less than 0.05 at week 24 for the subgroup of patients who overused headache medication.

Emergency room visits and hospitalizations due to migraine symptoms
The mean change in number of ER visits and hospitalizations due to migraine symptoms was assessed using observed data (Table 29). The baseline numbers of ER visits and hospitalizations 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. The frequency of visits and stays is too low to interpret these results.

Work Status and Productivity
The mean changes in number of hours worked, the days of work missed, the days of reduced work productivity, and the proportion of patients not working due to migraine were assessed using observed data. In some of the analyses, data from US patients were used. Results are presented in Table 30. Between-group differences were similar except for Study 080, in which the proportion of patients not working due to migraine at week 24 was 4.6% for the onabotulinumtoxinA group and 9.2% for the placebo group.

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol).

3.7.1 Adverse events

The proportion of patients who experienced at least one AE was higher in the onabotulinumtoxinA group (59.7% in Study 079 and 65.1% in Study 080) than in the placebo group (46.7% in Study 079 and 56.4% in Study 080) Table 12.

Overall, the most frequent AE associated with onabotulinumtoxinA was neck pain (8.2% in Study 079 and 9.8% in Study 080). In comparison, neck pain was reported in 3.3% and 2.2% of placebo-treated patients in Studies 079 and 080, respectively. Muscular weakness (5.9% and 5.2%) and headache (4.4% and 4.6%) were the next most frequently reported AEs in the onabotulinumtoxinA-treated patients (compared with 0% and 0.6% in Study 079, and with 3% and 3.4% in Study 080 in placebo-treated patients).

Other AEs that occurred with higher frequency in the onabotulinumtoxinA-treated patients when compared with placebo were eyelid ptosis, injection site pain, musculoskeletal pain, muscle spasms, musculoskeletal stiffness, myalgia, and migraine.

3.7.2 Serious adverse events

The proportion of patients with at least one SAE was higher in the onabotulinumtoxinA group (5.3% in Study 079 and 4.3% in Study 080) than in the placebo group (2.4% in Study 079 and 2.2% in Study 080) Table 12. In Study 080, SAEs reported by two or more patients in any treatment group were pneumonia (0.6% in the onabotulinumtoxinA group versus 0.3% in the placebo group), breast cancer (0.6% in the onabotulinumtoxinA group versus 0% in the placebo group), and migraine (0.9% in onabotulinumtoxinA group versus 0.3% in the placebo group); in Study 079, uterine leiomyoma was the only SAE reported by two or more patients (0.6% of patients in onabotulinumtoxinA group versus none in the placebo group).

3.7.3 Withdrawals due to adverse events

WDAEs occurred in 4.1% and in 3.5% of onabotulinumtoxinA-treated patients compared with 0.9% and 1.4% of placebo-treated patients in Study 079 and Study 080, respectively (Table 12). The most frequent reasons for withdrawals were headache in Study 079 and migraine in Study 080.

3.7.4 Mortality

No deaths were reported in either trial.

3.7.5 Adverse events of special interest

Drug hypersensitivity was reported by 0.3% and 0.6% of onabotulinumtoxinA-treated patients compared with 0% and 0.3% of placebo-treated patients in Study 079 and Study 080, respectively. Dysphagia was reported by 0.9% and 0.6% in the onabotulinumtoxinA-treated patients versus 0.3% and 0% in the placebo group for Study 079 and 080, respectively. Palpitations was only reported in Study 080 by 0.6% of patients in the onabotulinumtoxinA group. No other AEs of interest identified in the protocol were reported.

TABLE 12: HARMS

	Study 191622-079		Study 191622-080	
	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)

	Study 191622-079		Study 191622-080	
	Ona A (N = 340)	Placebo (N = 334)	Ona A (N = 347)	Placebo (N = 358)
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)
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)

	Study 191622-079		Study 191622-080	
	Ona A (N = 340)	Placebo (N = 334)	Ona A (N = 347)	Placebo (N = 358)
Dysphagia	3 (0.9)	1 (0.3)	2 (0.6)	0 (0.0)

AE = adverse event; CSR = Clinical Study Report; Ona A = onabotulinumtoxinA; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

4. DISCUSSION

4.1 Summary of Available Evidence

Two manufacturer-sponsored, multi-centre, randomized, DB, parallel-group, placebo-controlled, phase 3 superiority trials met the inclusion criteria for this systematic review. Study 079 (N = 679) and Study 080 (N = 705) were identical in design. Both trials enrolled patients between the ages of 18 and 65 years with a history of CM headache disorder. Patients were randomized to receive 155 U onabotulinumtoxinA or placebo administered IM at fixed sites on the head and neck at day 0 and week 12 during the DB phase. Additional doses of up to 40 U could be administered using a "follow-the-pain" method. The duration of the DB phase in both studies was 24 weeks. The primary efficacy outcome for Study 079 was the frequency of headache episodes per 28-day period ending with week 24, while the primary efficacy outcome for Study 080 was the frequency of headache days per 28-day period ending with week 24. At week 24, patients were offered to continue the trial for another 32 weeks, during which time they received open-label onabotulinumtoxinA. Results of the OLE phase for both trials are summarized in APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION PHASE OF STUDY 079 AND STUDY 080.

The key limitations of the available evidence included the lack of trials to assess the efficacy and safety of onabotulinumtoxinA compared with standard prophylactic CM treatments, the difficulty in maintaining blinding, and the baseline imbalance in some patient characteristics between the onabotulinumtoxinA and placebo groups in Study 079. Only two doses of onabotulinumtoxinA were administered in the DB phase, which may be too few to fully understand the long-term benefits of onabotulinumtoxinA. Furthermore, the total study duration (DB plus OLE phases) was relatively short (1 year) for both studies, and the long-term safety is unknown in this patient population. Adjustments for type 1 error were done for some, but not all, efficacy outcomes.

4.2 Interpretation of Results

4.2.1 Efficacy

In Study 079, a statistically significant difference was seen between onabotulinumtoxinA and placebo for the following secondary outcomes: frequency of headache days and frequency of migraine/probable migraine days. The effect sizes for Study 080 were greater than those for Study 079, and statistical significance was obtained for more outcomes. In Study 080, statistically significant differences between groups were obtained for the primary outcome (headache days) and the following secondary outcomes: severe HIT-6 category score, moderate/severe headache days, total cumulative hours of headache occurring on headache days, migraine/probable migraine days, and headache episodes. In both treatment groups, the main improvement for all efficacy end points was noticed at week 12, with a small additional improvement noticed at week 24, indicating that the main response was achieved after the first treatment with a small incremental benefit after the second onabotulinumtoxinA treatment. Statistical significance was also reached for other outcomes including all three domains of MSQ in both trials, and acute headache pain medication days and acute headache pain medication overuse in Study

080. However, it is unclear whether statistical adjustments were made to account for multiple testing. Hence, despite similar study protocols, there were important differences in the findings between Studies 079 and 080.

The reasons for the better results obtained in Study 080 are unclear, but were perhaps due to differences in baseline patient characteristics between onabotulinumtoxinA and placebo patients in Study 079. At baseline in Study 079, patients on onabotulinumtoxinA had fewer headache episodes and migraine episodes. Furthermore, in Study 080, the primary outcome was changed to headache days prior to unblinding when it became evident that there was no statistically significant difference between treatment groups in headache episodes in Study 079. This change in primary end point may limit the interpretation of results of Study 080.

HRQoL is an important outcome according to the patient group inputs provided for this review and following discussion with the clinical expert involved in the review; as such, it was chosen as a key efficacy outcome for the review. In the included trials, HRQoL was measured using MSQ. The mean changes from baseline for the three HRQoL domains measured by MSQ demonstrated clinically important and consistent results across both trials at week 12 and at the end of the DB phase in patients who received onabotulinumtoxinA treatment. In both studies, patients who received onabotulinumtoxinA treatment exceeded the established within-group MCIDs. The clinical expert consulted for this review concurred with this finding, as he noted that the improvement in change from baseline obtained with onabotulinumtoxinA was clinically important. Patients receiving placebo had an improvement in all three domains of MSQ; however, the changes did not exceed MCIDs. The between-group differences were statistically significant at weeks 12 and 24; however, the MCIDs for between-group differences in MSQ score are not available, and it is unclear whether the differences in MSQ between onabotulinumtoxinA and placebo were clinically important. Furthermore, from the range of domain scores reported, it would seem that some patients did not understand the MSQ or did not answer the questionnaire truthfully, because some patients reported scores of 100 points (highest function) at baseline, yet at week 12 and week 24, some reported a difference in score of 100 points.

Other patient-reported outcomes, which included HIT-6 scores, were also chosen as key efficacy outcomes. The between-group difference in HIT-6 at week 24 favoured the onabotulinumtoxinA group, and the difference was clinically important. The clinical expert involved in the review stated that HIT-6 is self-reported by patients and can be completed over the Internet. Some patients may have exaggerated their symptoms in order to be included in the clinical trial. This would have been reflected in a large proportion of patients (approximately 93%) reporting “severe” HIT-6 scores at baseline.

At baseline, there were 20 days of headache, of which, 19 days were migraine. The clinical expert involved in the review indicated that some patients may find it difficult to differentiate between headaches and migraines. The clinical expert also indicated that a decrease in 2 or more headache days per week is likely clinically important. In the included trials, headache days decreased by approximately eight to nine days (from 20 days) per 28-day period for onabotulinumtoxinA at the end of the DB phase. Placebo patients achieved a decrease of six to seven headache days per 28 days. The between-group difference was approximately one to two headache days, which is unlikely to be clinically important according to the clinical expert. The clinical expert further indicated that a treatment failure is considered a lack of return to EM, but treatment failure was not specifically measured in the trials. Potentially, patients could go back and forth between CM and EM with onabotulinumtoxinA. There are no data on how often a patient could stop/start onabotulinumtoxinA treatment if he or she fluctuates between the two subtypes of migraine because of onabotulinumtoxinA treatment.

In both studies, migraine-free status was evaluated in each of the trials as the proportion of patients with a 100% decrease in migraine days from baseline, with only a small proportion of patients (fewer than 5%) achieving migraine-free status.

The change in cumulative hours of headache favoured the onabotulinumtoxinA group. Compared with placebo, onabotulinumtoxinA patients had an additional 40 hours of headache-free time (and thus approximately one work week). However, the clinical expert believed that this outcome is not a useful measure and that it is unreliable, as it is difficult for patients to accurately report the number of hours with headache.

The greater reduction in headache and migraine days seen with onabotulinumtoxinA compared with placebo was not reflected in a greater reduction in acute headache pain medication intake. However, the analysis of acute headache pain medication intake was limited, because patients were not required to report medication dose. Nonetheless, both treatment groups decreased their medications by eight to 10 intakes (five to six days) without completely eliminating their need for medications. The clinical expert confirmed that, even with onabotulinumtoxinA treatment, the patients' need for acute pain headache medications would not likely be eliminated.

The baseline numbers of ER visits and hospitalizations were too small to draw conclusions about the impact of onabotulinumtoxinA on the use of these resources. There was no improvement in work productivity despite improvements in key outcomes for the review, such as HRQoL.

The outcomes were subject to variations in interpretation. For example, there may have been instances when a single episode of headache may have been counted as two episodes, as it may be difficult to distinguish between episodes especially if acute medications had been used with some temporary benefit. Similarly, it may have been difficult to distinguish between two or three shorter headaches occurring back to back, compared with one headache occurring over several days. This is underscored at baseline by the fact that some patients experienced more than one headache per day. The clinical expert indicated that this was surprising, and that it was more likely that the headaches experienced on the same day are in fact the same headache.

Blinding was difficult to maintain in light of the AEs expected with onabotulinumtoxinA; as such, placebo-treated patients who guessed that they had been randomized to placebo would have had no expectation of improvement. The other issue with improper blinding is that the effect of onabotulinumtoxinA could have been overestimated.

More than 60% of patients had a history of prophylactic medication use; conversely, less than 40% of patients had not used prior prophylactic treatment. This is surprising given, that the average duration of illness was 17 to 20 years and that the average age of patients was 40 years. The manufacturer's listing request is for use in patients who have failed (due to lack of efficacy, intolerance, or clinical contraindication) three or more prior oral prophylactic medications. The trials showed that patients who had a history of prophylactic use of three or more medications had a response similar to the overall patient population. However, this subgroup analysis was post hoc and the manufacture did not conduct a test for interaction. Furthermore, "failure of prophylactic treatment" was not clearly defined by the manufacturer. Hence, it is challenging to draw a conclusion for this subpopulation. Moreover, the manufacture did not conduct an analysis on the subpopulation of patients who did not use three or more prophylactic medication, and as such, we do not know if prophylactic treatment-naive patients or patients who used less than three prophylactics would benefit from onabotulinumtoxinA treatment.

Except for males, results from the subgroup analyses (females and patients with or without overuse of acute headache pain medications) were consistent with the overall patient population results for almost all of the outcomes. Results for males were not different between-treatment groups, possibly due to the small sample of males included in the trial. A subgroup analysis according to duration of illness was not conducted.

It is possible that some of the included patients suffered from MOH instead of CM, a type of migraine recognized as being distinct from CM according to ICHD-3.[1] These patients would likely have benefited from stopping all acute pain medications as a first step in the treatment of their CM, and by doing so, would have reverted to EM. Hence the response seen would have been due to acute headache pain medication discontinuation and not due to onabotulinumtoxinA treatment. However, the clinical expert involved in the review indicated that there is considerable overlap between the two types of migraine and in clinical practice it is difficult to distinguish between MOH and CM.

Other generalizability issues are worth noting. Patients had suffered from CM for an average of 17 to 20 years; stratifying the randomization of patients to treatment groups and/or pre-specified subgroups analysis according to duration of illness would have been informative. Results may only be applicable to patients with long-standing disease, as it is unknown if the duration of illness would affect a patient's response to treatment. Furthermore, the results may not be generalizable to patients with comorbid illnesses who require the use of drugs that are used in the prophylactic treatment of CM and other conditions, for example propranolol used in hypertension or amitriptyline used in depression. In the included trials, more than 90% of patients reported a HIT-6 score greater than 65. The trials results may not be applicable to patients with less severe headaches.

Very few patients required additional "follow-the pain" doses. It should be noted that the administration of onabotulinumtoxinA is a complicated procedure which requires proper training of clinicians. Hence, patients may be required to access specialized treatment centres.

In the OLE phase, patients received onabotulinumtoxinA treatment for 32 weeks (APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION PHASE OF STUDY 079 AND STUDY 080). Irrespective of group assignment in the DB phase, there were no between-group differences at the end of the study for the various outcomes measured. This is not surprising because, in the DB phase, when an improvement in an outcome was achieved with onabotulinumtoxinA, it occurred after the first dose. With the second dose, the incremental benefit was small. Therefore, patients who had been on placebo in the DB phase would have obtained relief immediately with onabotulinumtoxinA in the OLE phase.

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 Studies 079 and 080. Acute headache pain medications could not be completely stopped, with more than 70% of patients still requiring acute pain medications at week 56. However, fewer than 20% of patients overused acute pain medications at week 56. The frequency of headache days and migraine/probable migraine days decreased by 10 to 11 days per month at week 56, from approximately 19 to 20 days per month at baseline. This means that patients continued to experience on average eight to nine migraines per month, reverting back to a diagnosis of EM.

Results from the OLE phase should be interpreted with caution, given that all patients received open-label treatment and the outcomes measured were subjective. In addition, no large increase in efficacy was noticed at week 56 when compared with week 24. Finally, 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.

4.2.2 Harms

There were no deaths during the DB and OLE phases of the included trials.

The proportion of patients who experienced AEs, SAEs and WDAEs was higher in the onabotulinumtoxinA group. Overall, the most frequent AEs associated with onabotulinumtoxinA were neck pain, muscular/musculoskeletal AEs, and eyelid ptosis. SAEs reported by two or more patients in any treatment group were pneumonia, breast cancer, uterine leiomyoma, and migraine. However, the clinical expert involved in the review indicated that these SAEs were unlikely to be due to onabotulinumtoxinA treatment. The most frequent reasons for withdrawals were headache in Study 079 and migraine in Study 080. The injection may have caused neck pain, but it is unlikely that it caused headache or migraine, according to the clinical expert. It is more likely that these patients did not obtain improvement of their condition with onabotulinumtoxinA or experienced an increase in the severity of their headaches and reported them as AEs.

Results from the OLE phase (APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION PHASE OF STUDY 079 AND STUDY 080) howed that the pattern and frequency of AEs with onabotulinumtoxinA were similar to those observed in the DB phase.

Over the course of the entire trial, approximately 10% of patients reported neck pain. Few patients reported dysphagia or a cardiac event. Furthermore, there was no evidence of distant toxin spread, no report of anaphylaxis, and no report of autonomic dysreflexia.

5. CONCLUSIONS

Two manufacturer-sponsored, multi-centre, randomized, DB, parallel-group, placebo-controlled, phase 3 superiority trials evaluating the efficacy and safety of onabotulinumtoxinA in patients with CM were included in this systematic review. The results of Study 079 and Study 080 suggest that onabotulinumtoxinA was superior to placebo in improving patient-reported outcomes as measured with MSQ and HIT-6. Furthermore, onabotulinumtoxinA patients experienced fewer headache and migraine days than patients in the placebo group at the end of the DB phase; however, the absolute numerical difference between groups was approximately one to two days and is unlikely to be clinically important. Patients decreased the frequency of, but could not completely discontinue their intake of, acute headache pain medication. Improvement in both treatment groups was observed after the first dose, with a smaller improvement noticed after the second dose. There were no deaths, no evidence of toxin spread, and no anaphylactic reactions reported. OnabotulinumtoxinA was associated with a relatively low incidence of SAEs in the included trials. The trials are limited by their short duration, the lack of an active comparator, the imbalance of patient characteristics at baseline in Study 079, the use of subjective outcome measures, and the possibility that patients could have guessed the treatment they were receiving. The results of the trial may not be generalizable to male patients, to patients with migraines that are less severe, or in patients with comorbid illnesses.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

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

One patient group, Headache Network Canada (HNC), provided input. HNC is a Canadian registered charity whose mandate is to provide educational services to the headache sufferer and his/her family; raise the awareness level among the general public of the nature and impact of headache disorders; assist the medical profession and other health disciplines in the management of headache disorders; co-operate and work with governments at all levels to advance knowledge about all aspects of headache disorders and to encourage governmental assistance in this field; and to maintain and operate an educational website on the subject of headache disorders.

HNC receives unrestricted educational grants from Glaxo, Allergan, Tribute, Pfizer, Janssen, and Merck. HNC declared no conflict of interest in the preparation of the submission.

2. Condition and Current Therapy-related Information

Information to complete this section was gathered from various sources, including a survey distributed to the members of HNC (150 persons), to attendees at educational seminars and public forums (88 persons), and to caregivers (23 responses). Individual conversations took place with patients who had or had not previously used Botox.

CM is defined as follows: having a migraine headache on at least 15 days per month; on eight or more of these “migraine headache days,” having one-sided throbbing that is moderate or severe and that is aggravated by physical activity; and, at least one of nausea and/or vomiting, sensitivity to light, and/or sensitivity to sound.

Patients with CM are stigmatized by society, and even by family and friends at times. They often report that their lives are "ruined" by headaches that are "almost always" there. The pain interrupts every facet of their enjoyment of life. Along with the physical symptoms, sufferers report difficulty with mentally challenging tasks, feelings of hopelessness and helplessness, guilt, stress, and depression. Some people are forced to curtail schooling, employment, or having a family. They report having to cancel work and social and family activities and obligations when symptoms are severe. Furthermore, the unpredictability of attacks creates a natural resistance to committing to events, whether the events are personal, social, or vocational. When they are able to access partial relief or are experiencing a mild attack, they may be able to press on, but they underachieve, a condition coined "presenteeism."

Caregivers and loved ones report that living with or caring for someone with CM takes a lot of patience. It is an "invisible" disease. It is much easier to have sympathy for someone with a broken arm in a cast. CM is neither diagnosed by a blood test, nor does it show up on a radiographic image. People with migraine and their caregivers tell us they avoid making plans in case they have to cancel. They avoid hosting get-togethers, and fear the unpredictable nature of the attacks.

Patients report using medications that have not been approved for use in migraines. They may turn to controlled substances, illegal substances (such as marijuana), massage therapy, acupuncture, physiotherapy, chiropractic treatments, aromatherapy, and natural food store products. Some alternative treatments are advertised as "cures," and often are very expensive and have no scientific evidence of benefits. Some of these products may cause gastrointestinal side effects which may be embarrassing. In general, patients are dissatisfied with current treatments and there is a huge unmet need for safe, effective, and universally available relief from the symptoms of CM.

Accessing therapy is challenging in that there are not enough specialists. Some physicians are not adequately trained to treat CM. Patients with CM often have other comorbid illnesses making diagnosis difficult at times. The cost of medications is an issue. This may leave some patients untreated or poorly treated; consequently, they are sick for more than half a month, which makes employment difficult. The reality for some is poverty.

3. Related Information About the Drug Being Reviewed

Patients expect that their lives will be improved with Botox by decreasing the number of attacks. Currently, there are no approved medications specifically for CM. For many patients, having an option for this disabling problem is like a dream come true. Many patients cite 50% reduction in headache days as the marker of efficacy. Other patients state that if they could take a treatment with minimal side effects to prevent one attack of CM during an important event in their lives — for example, being able to reduce the fear of an attack during their or their child's wedding day — this would make a world of difference. Reduction in trips to the ER, functional attendance at work, becoming re-employed, or escaping poverty may finally be possible.

Survey respondents who have never used Botox report that they would be unwilling to experience possible SAEs (such as death) because while CM affects quality of life, it is not fatal, although suicides do occur.

Respondents with experience using Botox reported that this medication manages their CMs better than any other existing therapy, with fewer to no side effects; no respondents reported AEs. As the injections take place only once every three months at most, patients do not need to carry the medication or remember to take it daily. On the other hand, receiving injections could be an issue for some, although no patients reported that this was an actual deterrent to receiving Botox therapy.

Finally, Botox may enable patients to get back to all of the activities of daily living they used to enjoy. Those receiving disability benefits may be able to re-enter paid employment. Patients who have tried, are using, or who want access to Botox believe it an excellent option to fight the almost unimaginable yet invisible hardship of living with migraine.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 16, 2013
Alerts:	Weekly search updates until (date of CDEC meeting)
Study Types:	randomized controlled trials
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode 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
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt Publication type	
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Strategy**
1	exp Botulinum Toxin Type A/ or (botulinum* or botox or dysport* or oculinum or BTX-A or BTX or BTXA or BoNTA* or Botulin A or Botulin toxin A or Neuronox or Onaclostox or Xeomin or nabotulinumtoxinA or onabotulinum*).ti,ab,ot,sh,hw,rn,nm.
2	(93384-43-1 or EC 3-4-24-69).rn,nm.
3	1 or 2
4	exp Migraine Disorders/
5	(migraine or migraines or migrainous or (sick adj headach*) or migrainosus or migraineur* or antimigrain* or migraigne).ti,ab.
6	4 or 5
7	3 and 6
8	7 use pmez
9	exp *botulinum toxin A/ or (botulinum* or botox or dysport* or oculinum or BTX-A or BTX or BTXA or BoNTA* or Botulin A or Botulin toxin A or Neuronox or Onaclostox or Xeomin or nabotulinumtoxinA or onabotulinum*).ti,ab.
10	(migraine or migraines or migrainous or (sick adj headach*) or migrainosus or migraineur* or antimigrain* or migraigne).ti,ab.
11	exp migraine/
12	10 or 11
13	9 and 12
14	13 use oemezd
15	8 or 14
16	conference abstract.pt.
17	15 not 16
18	8 or 17
19	remove duplicates from 18
20	exp animals/
21	exp animal experimentation/ or exp animal experiment/
22	exp models animal/
23	nonhuman/
24	exp vertebrate/ or exp vertebrates/
25	animal.po.
26	or/20-25
27	exp humans/
28	exp human experimentation/ or exp human experiment/
29	human.po.
30	or/27-29
31	26 not 30
32	19 not 31
33	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
34	Randomized Controlled Trial/
35	Randomized Controlled Trials as Topic/
36	"Randomized Controlled Trial (topic)"/
37	Controlled Clinical Trial/
38	Controlled Clinical Trials as Topic/

MULTI-DATABASE STRATEGY	
Line #	**Strategy**
39	"Controlled Clinical Trial (topic)"/
40	Randomization/
41	Random Allocation/
42	Double-Blind Method/
43	Double-Blind Procedure/
44	Double-Blind Studies/
45	Single-Blind Method/
46	Single Blind Procedure/
47	Single-Blind Studies/
48	Placebos/
49	Placebo/
50	Control Groups/
51	Control Group/
52	(random* or sham or placebo*).ti,ab,hw.
53	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
54	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
55	(control* adj3 (study or studies or trial*)).ti,ab.
56	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
57	allocated.ti,ab,hw.
58	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
59	or/33-58
60	32 and 59

OTHER DATABASES	
PubMed	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:	To September 27, 2013
Keywords:	Botox, onabotulinumtoxinA, onabotulinumtoxin A, botulinum toxin A, botulinum toxin type A, migraine, headache
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 evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/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 13: EXCLUDED STUDIES

Reference	Reason for Exclusion
Dodick et al., 2010[30]	Pooled analysis
Aurora et al., 2011[31]	Pooled analysis
Lipton et al., 2011[32]	Pooled analysis
Silberstein et al., 2013[33]	Pooled analysis
Aurora et al., 2013[34]	Pooled analysis
Dodick et al., 2005[35]	Inappropriate population
Sandrini et al., 2011[36]	Inappropriate population
Ondo et al., 2004[37]	Inappropriate population
Vo et al., 2007[38]	Inappropriate population
Anand et al., 2006[39]	Inappropriate population
Conway et al., 2005[40]	Inappropriate study design
Silberstein et al., 2005[41]	Inappropriate dosage
Cady et al., 2011[25]	Inappropriate dosage
Mathew et al., 2009[24]	Inappropriate dosage
Magalhaes et al., 2010[27]	Inappropriate dosage
Freitag et al., 2008[42]	Inappropriate dosage
Blumenfeld et al., 2008[26]	Inappropriate dosage
Blumenkron et al., 2006[43]	Inappropriate dosage
Millan-Guerrero et al., 2009[44]	Inappropriate dosage
Cady et al., 2008[45]	Inappropriate dosage
Evers et al., 2004[46]	Inappropriate dosage
Silberstein et al., 2000[47]	Inappropriate dosage

APPENDIX 4: DETAILED OUTCOME DATA

Efficacy Outcomes

Health-Related Quality of Life Data

TABLE 14: BASELINE AND MEAN CHANGE FROM BASELINE AT WEEKS 12 AND 24 IN MSQ SCORES AND EQ-VAS SCORES (OBSERVED DATA WITHOUT IMPUTATION FOR MISSING VALUES)[A]

Outcome	Study 191622-079			Study 191622-080		
	Ona A (N = 341)	Placebo (N = 338)	*P* value	Ona A (N = 347)	Placebo (N = 358)	*P* value
MSQ Scores						
Role Function – Restrictive						
Baseline, n	337	335		347	358	
Baseline, Mean (SD)	61.3 (16.58)	63.1 (17.06)		61.7 (16.54)	59.7 (17.30)	
Median (Min, Max)	60.0 (9, 100)	62.9 (23, 100)		60.0 (14, 100)	60.0 (9, 100)	
Week 12, n	320	316		335	351	
Change From Baseline at Week 12, Mean (SD)	–16.0 (20.52)	–10.6 (19.07)	< 0.001	–16.4 (20.99)	–9.3 (18.44)	< 0.001
Median (Min, Max)	–11.4 (–94, 40)	–5.7 (–83, 34)		–14.3 (–89, 40)	–5.7 (–100, 49)	
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, max)	–11.4 (–83, 29)	–2.9 (–80, 40)		–14.3 (–91, 34)	–5.7 (–89, 49)	
Role Function – Preventive						
Baseline, n	337	335		347	358	
Baseline, Mean (SD)	43.2 (20.85)	46.0 (21.17)		44.7 (21.61)	42.0 (22.12)	
Median (Min, Max)	40.0 (0, 100)	45.0 (0, 100)		40.0 (0, 100)	40.0 (0, 100)	
Week 12, n	320	316		335	351	
Change From Baseline at Week 12, Mean (SD)	–11.9 (20.18)	–9.2 (18.38)	0.173	–14.0 (21.53)	–7.0 (18.77)	< 0.001
Median (Min, Max)	–10.0 (–90, 40)	–5.0 (–80, 45)		–10.0 (–75, 55)	–5.0 (–100, 40)	
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, Max)	–10.0 (–95, 45)	–5.0 (–80, 65)		–10.0 (–80, 40)	–2.5 (–95, 60)	
Role Function – Emotional Function						
Baseline, n	337	334		347	357	
Baseline, Mean (SD)	59.1 (23.54)	60.3 (24.61)		56.8 (24.61)	55.0 (25.03)	
Median (Min, Max)	60.0 (7, 100)	60.0 (0, 100)		53.3 (0, 100)	53.3 (0, 100)	
Week 12, n	320	315		332	350	
Change From Baseline at	–16.7	–11.0 (23.53)	0.002	–19.8	–10.9	< 0.001

Outcome	Study 191622-079			Study 191622-080		
	Ona A (N = 341)	Placebo (N = 338)	*P* value	Ona A (N = 347)	Placebo (N = 358)	*P* value
Week 12, Mean (SD)	(22.77)			(26.83)	(24.23)	
Median (Min, Max)	–13.3 (–87, 33)	–13.3 (–100, 53)		–13.3 (–93, 80)	–6.7 (–100, 73)	
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, Max)	–13.3 (–87, 60)	–6.7 (–100, 47)		–13.3 (–100, 53)	–6.7 (–100, 60)	
EQ-VAS[b] Scores						
Baseline, n	337	332		345	358	
Baseline, Mean (SD)	65.1 (22.43)	62.5 (23.42)		64.6 (21.62)	61.6 (23.44)	
Week 24, n	279	280		300	326	
Change From Baseline at Week 24, Mean (SD)	6.8 (22.41)	5.0 (25.29)	0.413	5.4 (20.10)	5.1 (23.69)	0.719

CSR = Clinical Study Report; EQ-VAS = Euro-Qol Visual Analog Scale; max = maximum; min = minimum; MSQ = Migraine-Specific Quality of Life Questionnaire; Ona A = onabotulinumtoxinA; SD = standard deviation.

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

[b] The scores of the EQ-5D Visual Analog Scale range from 0 to 100, with 100 being the best and 0 being the worst.

Source: Additional information from the manufacturer;[29] Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

TABLE 15: SUBGROUP ANALYSIS OF MEAN CHANGE FROM BASELINE AT WEEK 24 IN MSQ SCORES FOR PATIENTS WITH THREE OR MORE PRIOR PROPHYLACTICS (OBSERVED DATA WITHOUT IMPUTATION FOR MISSING VALUES)[A]

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* value	Ona A	Placebo	*P* value
MSQ Scores for Role Function – Restrictive						
Baseline, n	107	109		124	139	
Baseline, Mean (SD)	61.5 (15.80)	63.1 (16.95)		64.9 (15.65)	60.8 (17.58)	
Change From Baseline at Week 24, n	92	97		117	130	
Change From Baseline at Week 24, Mean (SD)	–11.1 (19.04)	–5.2 (18.66)	0.010	–16.3 (23.31)	–4.6 (16.30)	< 0.001
MSQ Scores for Role Function – Preventive						
Baseline, n	107	109		124	139	
Baseline, Mean (SD)	43.7 (20.56)	45.5 (20.32)		49.7 (19.57)	42.8 (22.22)	
Change From Baseline at Week 24, n	92	97		117	130	
Change From Baseline at Week 24, Mean (SD)	–7.1 (19.66)	–4.7 (17.84)	0.403	–13.5 (21.91)	–3.8 (17.30)	< 0.001
MSQ Scores for Role Function – Emotional Function						
Baseline, n	107	109		124	139	
Baseline, Mean (SD)	59.7 (23.17	61.8 (21.27)		61.3 (23.73)	56.4 (25.75)	
Change From Baseline at Week 24, n	91	97		117	130	
Change From Baseline at Week 24, Mean (SD)	–13.1 (25.96)	–6.1 (22.35)	0.024	–18.1 (29.27)	–7.7 (22.59)	0.007

MSQ = Migraine-Specific Quality of Life Questionnaire; Ona A = onabotulinumtoxinA; SD = standard deviation.
[a] *P* values for between-treatment comparisons were determined by the Wilcoxon rank-sum test.
Source: CADTH Common Drug Review submission binder.[10]

TABLE 16: BASELINE AND MEAN CHANGE FROM BASELINE AT WEEK 24 IN MSQ SCORES BY GENDER

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* value	Ona A	Placebo	*P* value
Gender: Male						
MSQ Scores for Role Function – Restrictive						
Baseline, n	36	48		48	55	
Baseline, Mean (SD)	60.0 (19.65)	57.2 (17.92)		59.2 (17.12)	55.3 (17.80)	
Change From Baseline at Week 24, n	31	40		44	52	
Change From Baseline at Week 24, Mean (SD)	–12.4 (22.79)	–8.9 (21.41)	0.529	–12.5 (19.22)	–8.5 (17.81)	0.146
MSQ Scores for Role Function – Preventive						
Baseline, n	36	48		48	55	
Baseline, Mean (SD)	41.9 (24.94)	40.1 (19.45)		41.4 (22.31)	34.9 (19.52)	
Change From Baseline at Week 24, n	31	40		44	52	
Change From Baseline at Week 24, Mean (SD)	–8.4 (19.21)	–10.4 (19.09)	0.689	–10.7 (18.57)	–4.2 (17.44)	0.061
MSQ Scores for Role Function – Emotional Function						
Baseline, n	36	48		48	55	
Baseline, Mean (SD)	55.4 (24.99)	56.0 (27.77)		46.7 (23.98)	49.3 (24.48)	
Change From Baseline at Week 24, n	31	40		44	52	
Change From Baseline at Week 24, Mean (SD)	–12.3 (24.89)	–12.5 (24.35)	0.821	–12.3 (20.38)	–9.2 (22.05)	0.419
Gender: Female						
Role Function – Restrictive						
Baseline, n	301	287		299	303	
Baseline, Mean (SD)	61.5 (16.21)	64.0 (16.74)		62.1 (16.45)	60.5 (17.12)	
Change From Baseline at Week 24, n	267	248		269	282	
Change From Baseline at Week 24, Mean (SD)	–17.2 (22.12)	–8.8 (20.22)	<0.001	–17.9 (22.69)	–8.4 (20.58)	< 0.001
MSQ Scores for Role Function – Preventive						
Baseline, n	301	287		299	303	
Baseline, Mean (SD)	43.3 (20.35)	46.9 (21.32)		45.3 (21.48)	43.3(22.35)	
Change From Baseline at Week 24, n	267	247		269	282	
Change From Baseline at Week 24, Mean (SD)	–13.1 (21.78)	–7.2 (19.74)	0.002	–14.0 (22.55)	–5.6 (20.53)	< 0.001
MSQ Scores for Role Function – Emotional Function						
Baseline, n	301	286		299	302	

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* value	Ona A	Placebo	*P* value
Baseline, Mean (SD)	59.6 (23.37)	61.0 (24.02)		58.4 (24.36)	56.1 (25.02)	
Change From Baseline at Week 24, n	266	245		269	281	
Change From Baseline at Week 24, Mean (SD)	–17.3 (27.25)	–9.6 (25.17)	<0.001	–20.1 (27.97)	–9.0 (24.91)	< 0.001

MSQ = Migraine-Specific Quality of Life Questionnaire; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Table completed by the manufacturer.[48]

TABLE 17: BASELINE AND MEAN CHANGE FROM BASELINE AT WEEK 24 IN MSQ SCORES BY MEDICATION OVERUSE

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Medication Overuse = Yes						
MSQ Scores for Role Function – Restrictive						
Baseline, n	223	234		219	224	
Baseline, Mean (SD)	63.0 (17.26)	63.9 (17.08)		63.7 (17.23)	60.5 (17.06)	
Change From Baseline at Week 24, n	202	204		200	210	
Change From Baseline at Week 24, Mean (SD)	–17.1 (21.90)	–8.3 (19.80)	< 0.001	–16.6 (21.90)	–6.9 (19.26)	< 0.001
MSQ Scores for Role Function – Preventive						
Baseline, n	223	234		219	224	
Baseline, Mean (SD)	44.3 (21.40)	46.7 (21.40)		47.5 (21.81)	43.4 (21.93)	
Change From Baseline at Week 24, n	202	204		200	210	
Change From Baseline at Week 24, Mean (SD)	–13.5 (21.12)	–7.0 (18.92)	0.003	–14.2 (21.79)	–4.6 (20.27)	< 0.001
MSQ Scores for Role Function – Emotional Function						
Baseline, n	223	234		219	223	
Baseline, Mean (SD)	61.0 (22.82)	61.8 (24.15)		58.7 (25.31)	57.0 (24.69)	
Change From Baseline at Week 24, n	201	202		200	209	
Change From Baseline at Week 24, Mean (SD)	–18.0 (26.14)	–9.5 (24.21)	< 0.001	–18.4 (26.62)	–8.0 (23.52)	< 0.001
Medication Overuse = No						
MSQ Scores for Role Function – Restrictive						
Baseline, n	114	101		128	134	
Baseline, Mean (SD)	58.0 (14.69)	61.1 (16.92)		58.2 (14.73)	58.3 (17.67)	
Change From Baseline at Week 24, n	96	84		113	124	

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Change From Baseline at Week 24, Mean (SD)	–15.9 (22.90)	–10.1 (21.71)	0.054	–18.3 (23.02)	–10.9 (21.42)	0.009
MSQ Scores for Role Function – Preventive						
Baseline, n	114	101		128	134	
Baseline, Mean (SD)	41.1 (19.65)	44.2 (20.61)		40.0 (20.47)	39.6 (22.32)	
Change From Baseline at Week 24, n	96	83		113	124	
Change From Baseline at Week 24, Mean (SD)	–10.7 (22.43)	–9.2 (21.38)	0.601	–12.4 (22.52)	–6.7 (19.73)	0.020
MSQ Scores for Role Function – Emotional Function						
Baseline, n	114	100		128	134	
Baseline, Mean (SD)	55.4 (24.58)	56.7 (25.40)		53.6 (23.12)	51.6 (25.31)	
Change From Baseline at Week 24, n	96	83		113	124	
Change From Baseline at Week 24, Mean (SD)	–14.2 (28.75)	–11.1 (27.06)	0.469	–20.0 (28.13)	–10.9 (25.96)	0.008

MSQ = Migraine-Specific Quality of Life Questionnaire; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Table filled by the manufacturer.[48]

Other Patient-Reported Outcomes

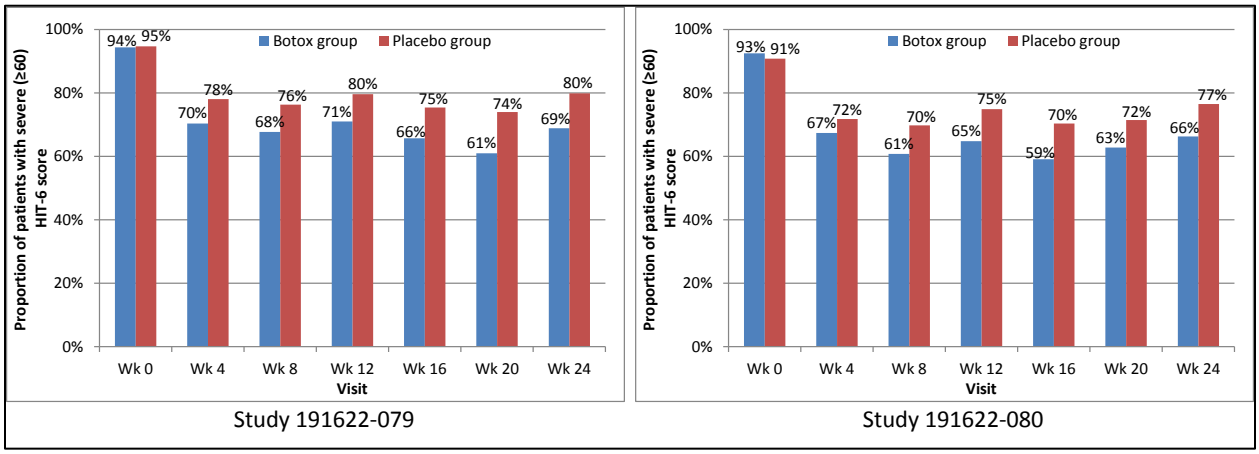
TABLE 18: BASELINE AND MEAN CHANGE FROM BASELINE AT WEEK 24 IN HIT-6 SCORES (MLOCF) AND HEADACHE IMPACT SCORES (OBSERVED DATA)

Outcome	Study 191622-079			Study 191622-080		
	Ona A (N = 341)	Placebo (N = 338)	*P* Value	Ona A (N = 347)	Placebo (N = 358)	*P* Value
HIT-6 Scores[a]						
Baseline Scores						
Little or No Impact (Total HIT-6 Score Range 36 to 49), n (%)	0 (0.0)	0 (0.0)		0 (0.0)	1 (0.3)	
Some Impact (Total HIT-6 Score Range 50 to 55), n (%)	4 (1.2)	3 (0.9)		6 (1.7)	12 (3.4)	
Substantial Impact (Total HIT-6 Score Range 56 to 59)	15 (4.4)	15 (4.4)		20 (5.8)	20 (5.6)	
Severe Impact (Total HIT-6 Score Range 60 to 78), n (%)	322 (94.4)	320 (94.7)		321 (92.5)	325 (90.8)	
HIT-6 Score, Mean (SD)	65.4 (3.82)	65.8 (4.14)		65.6 (4.26)	65.0 (4.46)	
At Week 24						
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	37 (10.9)	27 (8.0)		36 (10.4)	39 (10.9)	

Outcome	Study 191622-079			Study 191622-080		
	Ona A (N = 341)	Placebo (N = 338)	*P* Value	Ona A (N = 347)	Placebo (N = 358)	*P* Value
Score Range 56 to 59)						
Severe Impact (Total HIT-6 Score Range 60 to 78), n (%)	235 (68.9)	270 (79.9)		230 (66.3)	274 (76.5)	
Change From Baseline in HIT-6 Score, Mean (SD)	–4.7 (7.11)	–2.4 (5.63)	< 0.001[c]	–4.9 (6.97)	–2.4 (6.50)	< 0.001[c]
Headache Impact Scores[d]						
Baseline Score, LSMean (SD)	2.5 (0.50)	2.5 (0.53)		2.5 (0.50)	2.5 (0.56)	
Change From Baseline at Week 24, LSMean (SD)	–0.5 (0.63)	–0.4 (0.69)	0.002[e]	–0.7 (0.61)	–0.4 (0.61)	< 0.001[e]

CSR = Clinical Study Report; HIT-6 = Headache Impact Test; LSMean = Least squares means; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.
Note: SD is for the mean. LSMean and mean were close to each other.
[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.
[c] *P* values for between-treatment comparisons were determined by the Wilcoxon rank-sum test.
[d] Headache Impact scores: 1 = no impact, 2 = little impact, 3 = moderate impact, 4 = severe impact, 5 = unable to do anything.
[e] The data used are observed data. *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.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR;[18] Additional information from the manufacturer.[29]

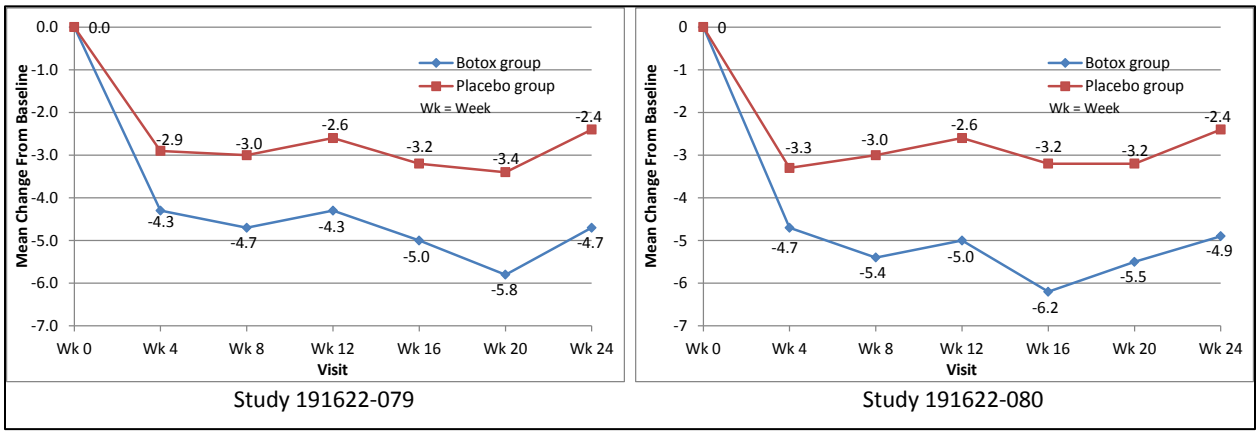
FIGURE 3: PROPORTION OF PATIENTS WITH SEVERE (≥ 60) HIT-6 SCORES AT DIFFERENT TIME PERIODS



CDR = CADTH Common Drug Review; CSR = Clinical Study Report; HIT-6 = Headache Impact Test; Wk = week.
[18]

Note: *P* values for total HIT-6 score categories (< 60 versus ≥ 60) were determined by Pearson's chi-square or Fisher's exact (f) tests (if ≥25% of the expected cell counts are less than 5.)
Source: Created by CDR reviewer using data from Study 191622-079 CSR,[17] Study 191622-080 CSR.

FIGURE 4: MEAN CHANGE FROM BASELINE IN HIT-6 SCORES AT DIFFERENT TIME POINTS



CDR = CADTH Common Drug Review; CSR = Clinical Study Report; HIT-6 = Headache Impact Test; Wk = week.
Note: *P* values for between-treatment comparisons were determined by the Wilcoxon rank-sum test.
Source: Created by CDR reviewer using data from Study 191622-079 CSR;[17] Study 191622-080 CSR.[18] Additional information from the manufacturer.[29]

TABLE 19: SUBGROUP ANALYSIS OF MEAN CHANGE FROM BASELINE AT WEEK 24 IN HIT-6 SCORES AND HEADACHE IMPACT SCORES (MLOCF)

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
HIT-6 Scores[a]						
Patients With 3 or More Prior Prophylactics[b]						
Baseline Scores, n	107	109		124	139	
Little or No Impact (Total HIT-6 Score Range 36 to 49), n (%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0%)	
Some Impact (Total HIT-6 Score Range 50 to 55), n (%)	2 (1.9)	0 (0.0)		2 (1.6)	5 (3.6%)	
Substantial Impact (Total HIT-6 Score Range 56 to 59)	5 (4.7)	4 (3.7)		3 (2.4)	10 (7.2%)	
Severe Impact (Total HIT-6 Score Range 60 to 78), n (%)	100 (93.5)	105 (96.3)		119 (96.0)	124 (89.2%)	
HIT-6 Score, Mean (SD)	65.3 (4.05)	66.0 (3.83)		66.2 (3.92)	65.3 (4.50)	
At Week 24, n	107	109		124	139	
Little or No Impact (Total HIT-6 Score Range 36 to 49), N (%)	4 (3.7)	3 (2.8)	0.389	10 (8.1)	5 (3.6)	0.065
Some Impact (Total HIT-6 Score Range 50 to 55), N (%)	9 (8.4)	4 (3.7)		14 (11.3)	4 (2.9)	
Substantial Impact (Total HIT-6 Score Range 56 to 59)	11 (10.3)	13 (11.9)		9 (7.3)	17 (12.2)	
Severe Impact (Total HIT-6 Score Range 60 to 78), N (%)	83 (77.6)	89 (81.7)		91 (73.4)	113 (81.3)	
Change From Baseline in HIT-6 Score, Mean (SD)	–3.0 (4.92)	–1.9 (5.27)	0.021	–4.5 (7.03)	–1.6 (6.53)	< 0.001

HIT-6 = Headache Impact Test; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; 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.

Source: CADTH Common Drug Review submission binder.[10]

TABLE 20: SUBGROUP ANALYSIS OF MEAN CHANGE FROM BASELINE AT WEEK 24 IN HIT-6 SCORES BY GENDER

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Gender: Male						
Baseline HIT-6 Scores, n						
Little or No Impact (Total HIT-6 Score Range 36 to 49), n (%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Some Impact (Total HIT-6 Score Range 50 to 55), n (%)	0 (0.0)	1 (2.1)		2 (4.2)	4 (7.3)	
Substantial Impact (Total HIT-6 Score Range 56 to 59)	3 (8.1)	1 (2.1)		1 (2.1)	9 (16.4)	
Severe Impact (Total HIT-6 Score Range 60 to 78), n (%)	34 (91.9)	46 (95.8)		45 (93.8)	42 (76.4)	
HIT-6 Score, Mean (SD)	65.7 (4.37)	64.4 (4.00)		65.3 (4.92)	63.4 (5.00)	
At Week 24, n						
Little or No Impact (Total HIT-6 Score Range 36 to 49), n (%)	2 (5.4)	3 (6.3)	0.973	6 (12.5)	3 (5.5)	0.075
Some Impact (Total HIT-6 Score Range 50 to 55), n (%)	4 (10.8)	7 (14.6)		4 (8.3)	7 (12.7)	
Substantial Impact (Total HIT-6 Score Range 56 to 59)	3 (8.1)	4 (8.3)		1 (2.1)	8 (14.6)	
Severe Impact (Total HIT-6 Score Range 60 to 78), n (%)	28 (75.7)	34 (70.8)		37 (77.1)	37 (67.3)	
Change From Baseline in HIT-6 Score, Mean (SD)	–3.6 (7.39)	–3.1 (6.33)	0.915	–3.7 (7.39)	–2.1 (7.33)	0.346
Gender: Female						
Baseline HIT-6 Scores, n						
Little or No Impact (Total HIT-6 Score Range 36 to 49), n (%)	0 (0.0)	0 (0.0)		0 (0.0)	1 (0.33)	
Some Impact (Total HIT-6 Score Range 50 to 55), n (%)	4 (1.3)	2 (0.7)		4 (1.3)	8 (2.64)	
Substantial Impact (Total HIT-6 Score Range 56 to 59)	12 (4.0)	14 (4.8)		19 (6.4)	11 (3.63)	
Severe Impact (Total HIT-6 Score Range 60 to 78), n (%)	288 (94.7)	274 (94.5)		276 (92.3)	283 (93.40)	
HIT-6 Score, Mean (SD)	65.4 (3.75)	66.0 (4.12)		65.7 (4.15)	65.3 (4.30)	
At Week 24, n						
Little or No Impact (Total HIT-6 Score Range 36 to 49), n (%)	31 (10.20)	8 (2.76)	< 0.001	25 (8.4)	13 (4.3)	< 0.001
Some Impact (Total HIT-6 Score Range 50 to 55), n (%)	32 (10.53)	23 (7.93)		46 (15.4)	22 (7.3)	
Substantial Impact (Total HIT-6 Score Range 56 to 59)	34 (11.18)	23 (7.93)		35 (11.7)	31 (10.2)	
Severe Impact (Total HIT-6 Score range 60 to 78), n (%)	207 (68.09)	236 (81.38)		193 (64.6)	237 (78.2)	
Change From Baseline in HIT-6 Score, Mean (SD)	–4.8 (7.08)	–2.3 (5.52)	< 0.001	–5.1 (6.99)	–2.4 (6.35)	< 0.001

HIT-6 = Headache Impact Test; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Table completed by the manufacturer.[48]

TABLE 21: SUBGROUP ANALYSIS OF MEAN CHANGE FROM BASELINE AT WEEK 24 IN HIT-6 SCORES BY MEDICATION OVERUSE

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Medication Overuse = Yes						
Baseline HIT-6 Scores, n						
Little or No Impact (Total HIT-6 Score Range 36 to 49), n (%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Some Impact (Total HIT-6 Score Range 50 to 55), n (%)	2 (0.9)	1 (0.4)		5 (2.3)	6 (2.7)	
Substantial Impact (Total HIT-6 Score Range 56 to 59)	9 (4.0)	5 (2.1)		7 (3.2)	13 (5.8)	
Severe Impact (Total HIT-6 Score Range 60 to 78), n (%)	215 (95.1)	229 (97.5)		207 (94.5)	205 (91.5)	
HIT-6 Score, Mean (SD)	65.6 (3.86)	66.3 (3.99)		66.1 (4.46)	65.3 (4.28)	
At Week 24, n						
Little or No Impact (Total HIT-6 Score Range 36 to 49), n (%)	22 (9.7)	6 (2.6)	0.005	19 (8.7)	9 (4.0)	0.018
Some Impact (Total HIT-6 Score Range 50 to 55), n (%)	18 (8.0)	16 (6.8)		26 (11.9)	13 (5.8)	
Substantial Impact (Total HIT-6 Score Range 56 to 59)	24 (10.6)	18 (7.7)		20 (9.1)	21 (9.4)	
Severe Impact (Total HIT-6 Score Range 60 to 78), n (%)	162 (71.7)	195 (83.0)		154 (70.3)	181 (80.8)	
Change From Baseline in HIT-6 Score, Mean (SD)	–4.5 (6.63)	–2.2 (5.50)	< 0.001	–4.8 (6.69)	–2.3 (6.72)	< 0.001
Medication Overuse = No						
Baseline HIT-6 Scores, n						
Little or No Impact (Total HIT-6 Score Range 36 to 49), n (%)	0 (0.0)	0 (0.0)		0 (0.0)	1 (0.8)	
Some Impact (Total HIT-6 Score Range 50 to 55), n (%)	2 (1.7)	2 (1.9)		1 (0.8)	6 (4.5)	
Substantial Impact (Total HIT-6 Score Range 56 to 59)	6 (5.2)	10 (9.7)		13 (10.2)	7 (5.2)	
Severe Impact (Total HIT-6 Score Range 60 to 78), n (%)	107 (93.0)	91 (88.4)		114 (89.1)	120 (89.6)	
HIT-6 Score, Mean (SD)	65.0 (3.71)	64.8 (4.30)		64.7 (3.74)	64.5 (4.71)	
At Week 24, n						
Little or No Impact (Total HIT-6 Score range 36 to 49), n (%)	11 (9.5)	5 (4.9)	0.415	12 (9.4)	7 (5.2)	0.203
Some Impact (Total HIT-6 Score Range 50 to 55), n (%)	18 (15.7)	14 (13.6)		24 (18.8)	16 (11.9)	
Substantial Impact (Total HIT-6 Score Range 56 to 59)	13 (11.3)	9 (8.7)		16 (12.5)	18 (13.4)	
Severe Impact (Total HIT-6 Score Range 60 to 78), n (%)	73 (63.5)	75 (72.8)		76 (59.4)	93 (69.4)	
Change From Baseline in HIT-6 Score, Mean (SD)	–5.0 (8.00)	–2.8 (5.94)	0.052	–5.2 (7.44)	–2.6 (6.14)	0.004

HIT = Headache Impact Test; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Table completed by the manufacturer.[48]

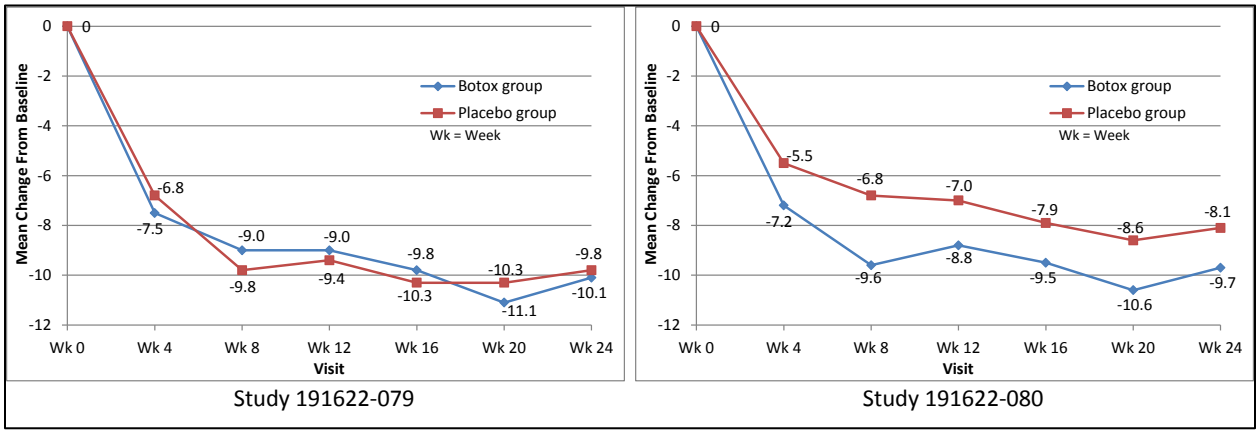
TABLE 22: SUBGROUP ANALYSIS OF HEADACHE IMPACT SCORES

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Patients Who Overuse Headache Pain Medication						
Baseline Score, Mean (SD)	65.6 (3.86)	66.3 (3.99)		66.1 (4.46)	65.3 (4.28)	
Change From Baseline at Week 24, Mean (SD)	–4.5 (6.63)	–2.2 (5.50)	< 0.001	–4.8 (6.69)	–2.3 (6.72)	< 0.001
Patients Who Did Not Overuse Headache Pain Medication						
Baseline Score, Mean (SD)	65.0 (3.71)	64.8 (4.30)		64.7 (3.74)	64.5 (4.71)	
Change from baseline at Week 24, Mean (SD)	–5.1 (8.00)	–2.84 (5.94)	0.052	–5.2 (7.44)	–2.6 (6.14)	0.004
Male Patients						
Baseline Score, Mean (SD)	65.7 (4.37)	64.4 (4.00)		65.3 (4.92)	63.4 (5.00)	
Change From Baseline at Week 24, Mean (SD)	–3.6 (7.39)	–3.1 (6.33)	0.915	–3.7 (7.39)	–2.13 (7.33)	0.346
Female Patients						
Baseline Score, Mean (SD)	65.4 (3.75)	66.0 (4.12)		65.7 (4.15)	65.3 (4.30)	
Change From Baseline at Week 24, Mean (SD)	–4.8 (7.08)	–2.3 (5.52)	< 0.001	–5.1 (6.90)	–2.4 (6.35)	< 0.001
Patients With 3 or More Prior Prophylactics						
Baseline Score, Mean (SD)	65.3 (4.05)	66.0 (3.83)		66.2 (3.92)	65.3 (4.50)	
Change from baseline at Week 24, Mean (SD)	–3.0 (4.92)	–1.9 (5.27)	0.021	–4.5 (7.03)	–1.6 (6.53)	< 0.001

Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Table completed by the manufacturer.[48]

Acute Headache Pain Medication Intakes

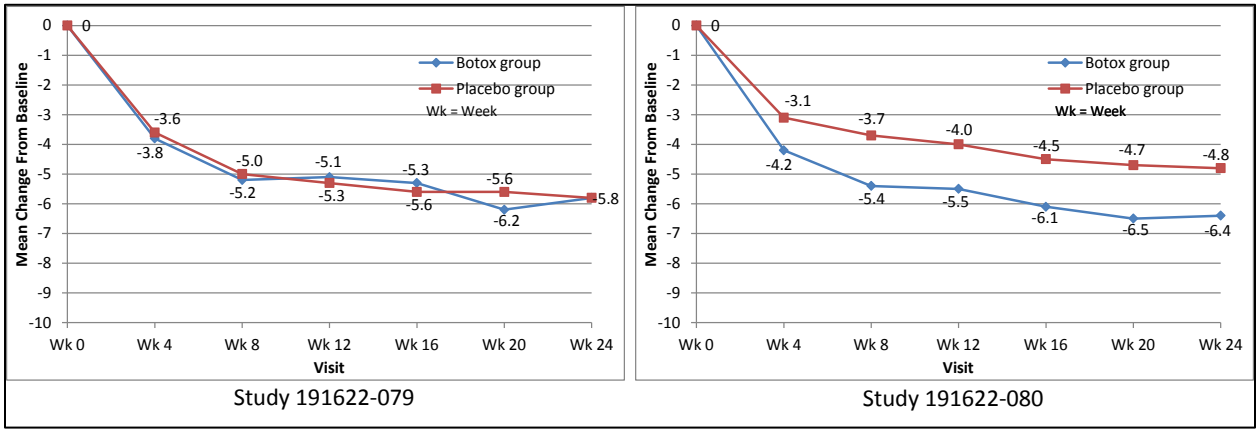
FIGURE 5: MEAN CHANGE FROM BASELINE IN ACUTE HEADACHE PAIN MEDICATION INTAKES PER 28-DAY PERIOD AT DIFFERENT TIME POINTS



Study 191622-079 Study 191622-080

ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; Wk = week.
Note: *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of acute headache pain medication intakes as covariate. The main effects in the ANCOVA included treatment and medication-overuse strata.
Source: Created by CDR reviewer using data from Study 191622-079 CSR,[17] Study 191622-080 CSR.[18]

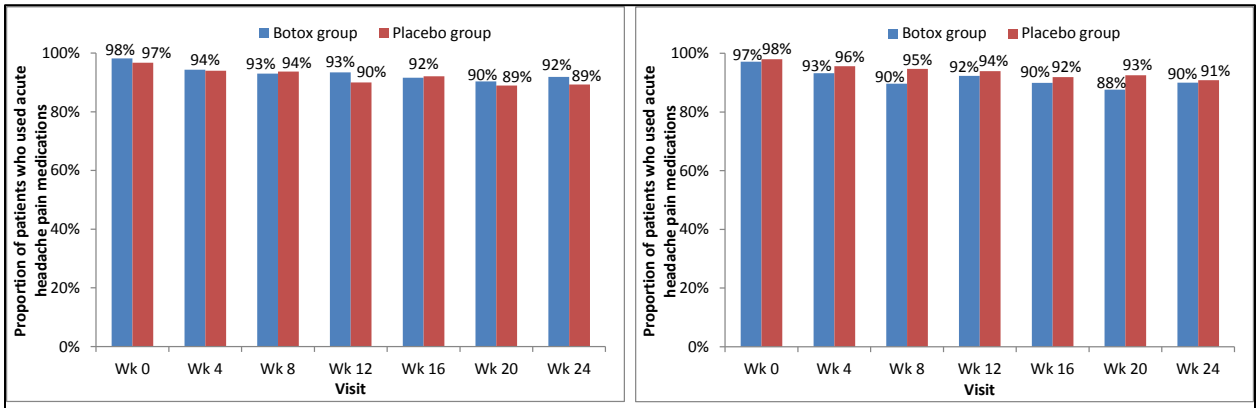
FIGURE 6: MEAN CHANGE FROM BASELINE IN FREQUENCY OF ACUTE HEADACHE PAIN MEDICATIONS DAYS PER 28-DAY PERIOD AT DIFFERENT TIME POINTS



Study 191622-079 Study 191622-080

ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; HIT-6 = Headache Impact Test; Wk = week.
Note: *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of acute headache pain medication days as covariate. The main effect in the ANCOVA was treatment.
Source: Created by CDR reviewer using data from Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

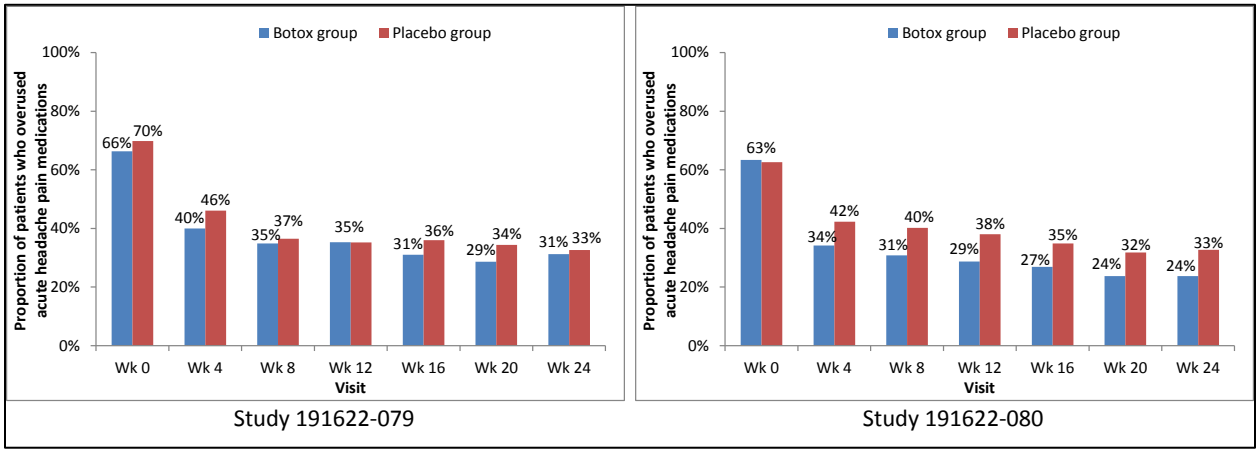
FIGURE 7: PROPORTION OF PATIENTS WHO USED ACUTE HEADACHE PAIN MEDICATIONS PER 28-DAY PERIOD AT DIFFERENT TIME POINTS



Study 191622-079 Study 191622-080

CDR = CADTH Common Drug Review; CSR = Clinical Study Report; Wk = week.
Note: *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 five).
Source: created by CDR reviewer using data from Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

FIGURE 8: PROPORTION OF PATIENTS WHO OVERUSED ACUTE HEADACHE PAIN MEDICATIONS PER 28-DAY PERIOD AT DIFFERENT TIME POINTS



CDR = CADTH Common Drug Review; CSR = Clinical Study Report; Wk = week.
Note: *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 five).
Source: created by CDR reviewer using data from Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

TABLE 23: SUBGROUP ANALYSIS OF ACUTE HEADACHE PAIN MEDICATION INTAKE (MLOCF)

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Acute Headache Pain Medication Intakes per 28-day Period						
Patients Who Overuse Headache Pain Medication (mLOCF)[a]						
N	226	235		219	224	
Baseline, LSMean (SD)	36.7 (17.38)	38.0 (21.91)		32.4 (18.73)	33.6 (18.72)	
Change From Baseline at Week 24, LSMean (SD)	–13.7 (19.65)	–12.7 (20.39)	0.571	–12.7 (18.15)	–10.6 (17.47)	0.210
Patients Who Did Not Overuse Headache Pain Medication[a]						
N	115	103		128	134	
Baseline, LSMean (SD)	14.1 (13.12)	12.9 (9.95)		11.4 (8.72)	11.9 (8.41)	
Change From Baseline at Week 24, LSMean (SD)	–3.8 (14.72)	–5.0 (11.64)	0.469	–5.4 (7.58)	–4.4 (7.86)	0.226
Male Patients[a]						
N	37	48		48	55	
Baseline, LSMean (SD)	31.3 (26.99)	27.0 (26.03)		24.6 (16.14)	22.8 (13.14)	
Change From Baseline at Week 24, LSMean (SD)	–7.0 (25.47)	–4.0 (13.77)	0.478	–8.4 (15.82)	–9.0 (13.10)	0.838
Female Patients[a]						
N	304	290		299	303	
Baseline, LSMean (SD)	28.8 (18.15)	30.9 (21.61)		24.7 (19.17)	25.9 (19.72)	
Change From Baseline at Week	–11.2	–11.0	0.868	–10.2	–8.2	0.093

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
24, LSMean (SD)	(17.67)	(19.05)		(15.50)	(15.25)	
Patients With 3 or More Prior Prophylactics[b]						
N	107	109		124	139	
Baseline, LSMean (SD)	25.2 (19.63)	26.8 (20.58)		23.1 (20.97)	23.4 (19.88)	
Change From Baseline at Week 24, LSMean (SD)	–7.4 (18.54)	–4.3 (19.46)	0.222	–9.1 (15.57)	–4.7 (15.57)	0.023

ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; LSMean = Least squares mean; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.
Note: SD is for the mean. LSMean 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.
Source: Study 191622-079 CSR,[17] Study 191622-080 CSR,[18] CDR submission binder.[10]

Improvement in Headache/Migraine Days

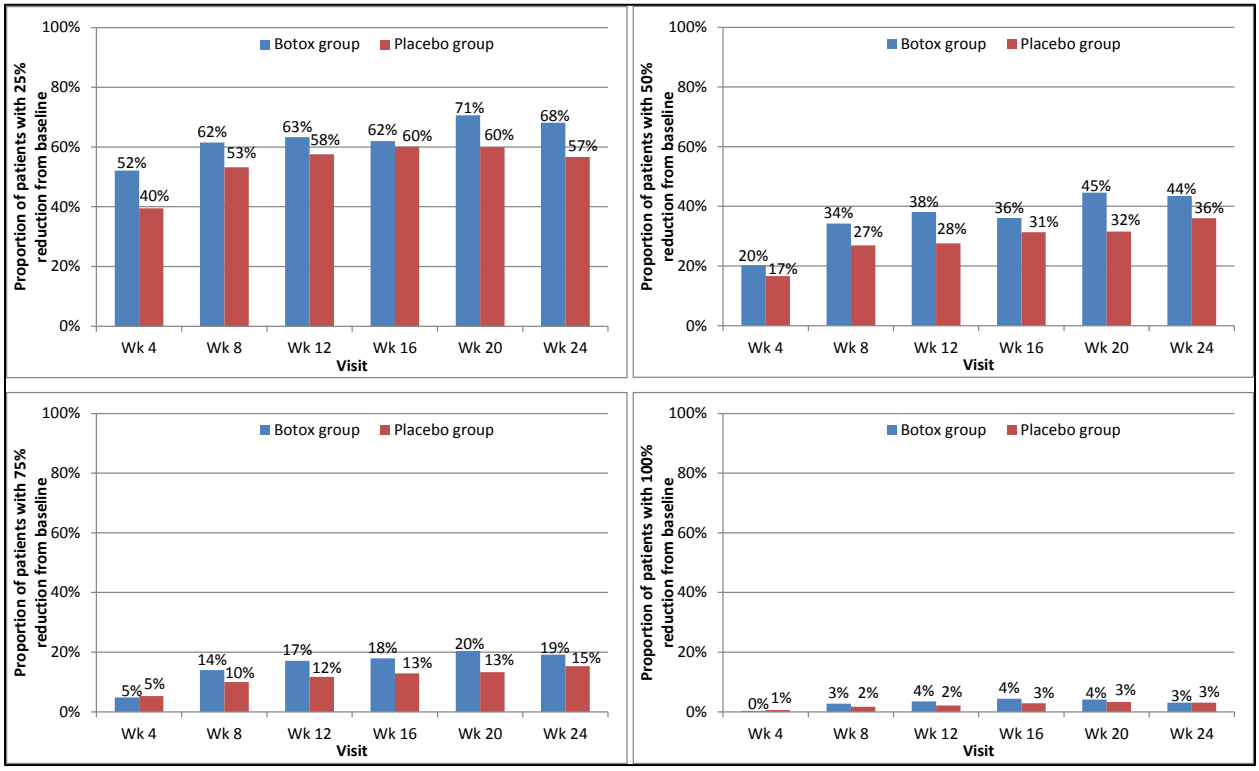
TABLE 24: IMPROVEMENT FROM BASELINE IN HEADACHE DAYS AND MIGRAINE DAYS

Outcome	Study 191622-079			Study 191622-080		
	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]						
25% reduction, n/total (%)	177/260 (68.1)	148/261 (56.7)	0.007	206/279 (73.8)	174/294 (59.2)	< 0.001
50% reduction, n/total (%)	113/260 (43.5)	94/261 (36.0)	0.082	141/279 (50.5)	101/294 (34.4)	< 0.001
75% reduction, n/total (%)	50/260 (19.2)	40/261 (15.3)	0.238	73/279 (26.2)	46/294 (15.6)	0.002
100% reduction, n/total (%)	8/260 (3.1)	8/261 (3.1)	0.994	12/279 (4.3)	9/294 (3.1)	0.430
Frequency of Headache Days per 28-day Period (mLOCF)[b]						
Baseline, LSMean (SD)	19.9 (3.73)	19.7 (3.71)		19.8 (3.63)	19.7 (3.65)	
Change From Baseline at Week 24, LSMean (SD)	–7.8 (6.57)	–6.4 (6.69)	0.006	–9.2 (6.54)	–6.9 (6.67)	< 0.001
Number of Moderate/Severe Headache Days per 28-day Period (mLOCF)[c]						
Baseline, LSMean (SD)	17.9 (4.22)	18.0 (4.23)		18.0 (4.03)	17.6 (4.26)	
Change From Baseline at Week 24, LSMean (SD)	–7.1 (6.32)	–5.6 (6.63)	0.004	–8.4 (6.37)	–6.0 (6.59)	< 0.001
Total Cumulative Hours of Headache Occurring on Headache Days per 28-day Period (mLOCF)[d]						
Baseline, LSMean (SD)	299.24 (116.81)	279.16 (110.90)		299.09 (121.04)	289.99 (118.90)	
Change From Baseline at Week 24, LSMean (SD)	–104.49 (134.03)	–73.62 (136.80)	0.003	–134.15 (130.22)	–94.54 (133.76)	< 0.001

Outcome	Study 191622-079			Study 191622-080		
	Ona A (N = 341)	Placebo (N = 338)	*P* Value	Ona A (N = 347)	Placebo (N = 358)	*P* Value
Results for Migraine/Probable Migraine Days						
Reduction From Baseline in Migraine/Probable Migraine Days per 28-day Period at Week 24 (observed data)[a]						
25% Reduction, n/total (%)	180/260 (69.2)	151/261 (57.9)	0.007	205/279 (73.5)	172/294 (58.5)	< 0.001
50% Reduction, n/total (%)	118/260 (45.4)	98/261 (37.5)	0.069	142/279 (50.9)	104/294 (35.4)	< 0.001
75% Reduction, n/total (%)	59/260 (22.7)	40/261 (15.3)	0.032	74/279 (26.5)	47/294 (16.0)	0.002
100% Reduction, n/total (%)	12/260 (4.6)	10/261 (3.8)	0.656	14/279 (5.0)	10/294 (3.4)	0.334
Frequency of Migraine/Probable Migraine Days per 28-day Period (mLOCF)[e]						
Baseline, LSMean (SD)	19.0 (4.04)	19.0 (4.05)		19.1 (3.94)	18.7 (4.05)	
Change From Baseline at Week 24, LSMean (SD)	–7.6 (6.51)	–6.0 (6.78)	0.002	–8.8 (6.64)	–6.5 (6.71)	< 0.001

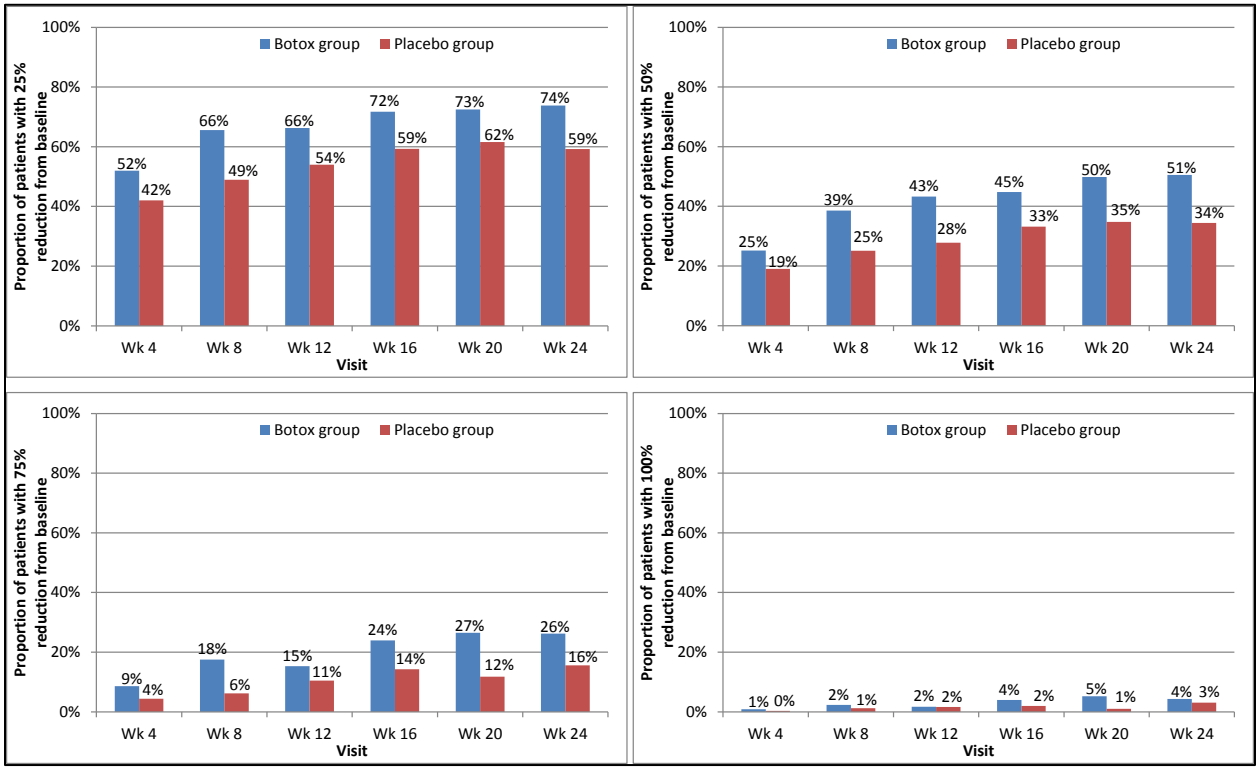
ANCOVA = analysis of covariance; CSR = Clinical Study Report; LSMean = Least squares mean; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.
Note: SD is for the mean. LSMean and mean were approximately the same. ANCOVA included treatment and medication-overuse strata.
[a] *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).
[b] *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of headache days as covariate.
[c] *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of moderate/severe headache days as covariate.
[d] *P* values for between-treatment comparisons are from ANCOVA, with baseline values as covariate.
[e] *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of migraine/probable migraine days as covariate.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

FIGURE 9: PROPORTION OF PATIENTS WITH REDUCTION FROM BASELINE IN HEADACHE DAYS PER 28-DAY PERIOD AT DIFFERENT TIME POINTS IN STUDY 191622-079



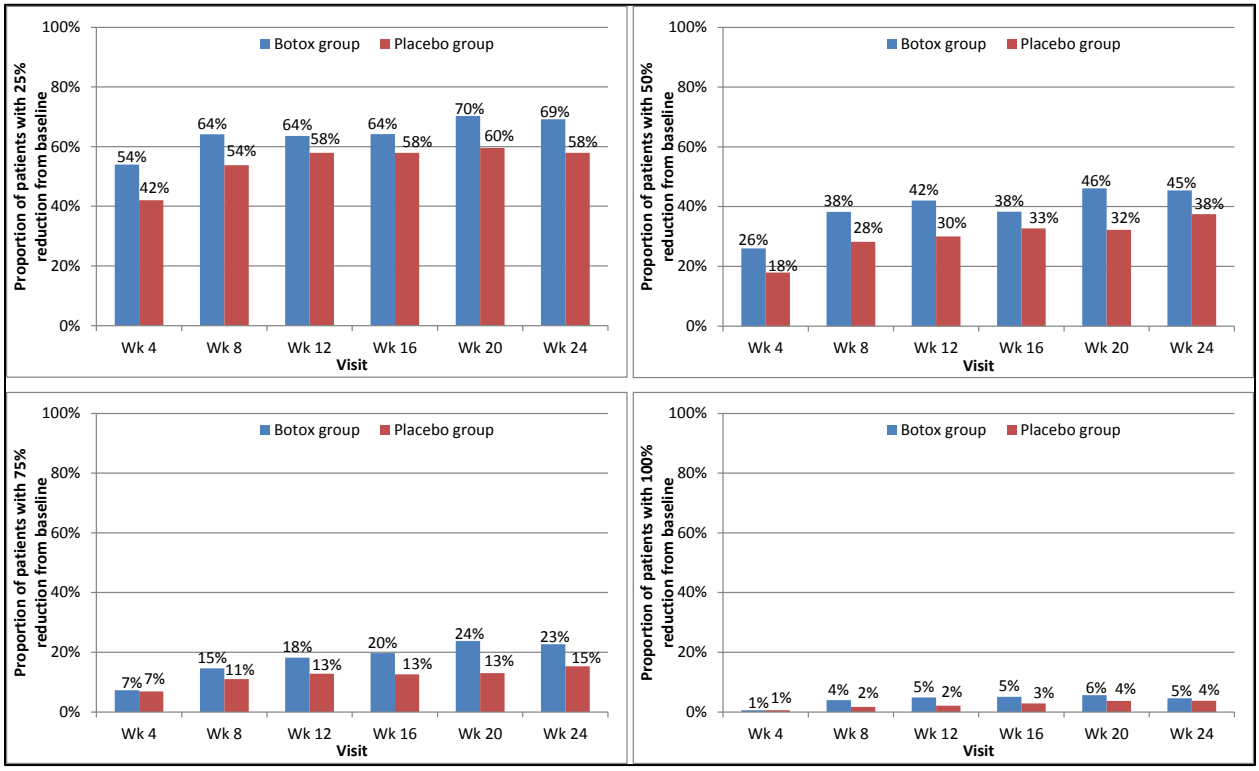
CDR = CADTH Common Drug Review; CSR = Clinical Study Report; Wk = week.
Note: *P* values for between-treatment comparisons were determined by Pearson's chi-square or Fisher's exact (f) tests (if ≥ 25% of the expected cell counts are less than five).
Source: Created by CDR reviewer using data from Study 191622-079 CSR.[17]

FIGURE 10: PROPORTION OF PATIENTS WITH REDUCTION FROM BASELINE IN HEADACHE DAYS PER 28-DAY PERIOD AT DIFFERENT TIME POINTS IN STUDY 191622-080



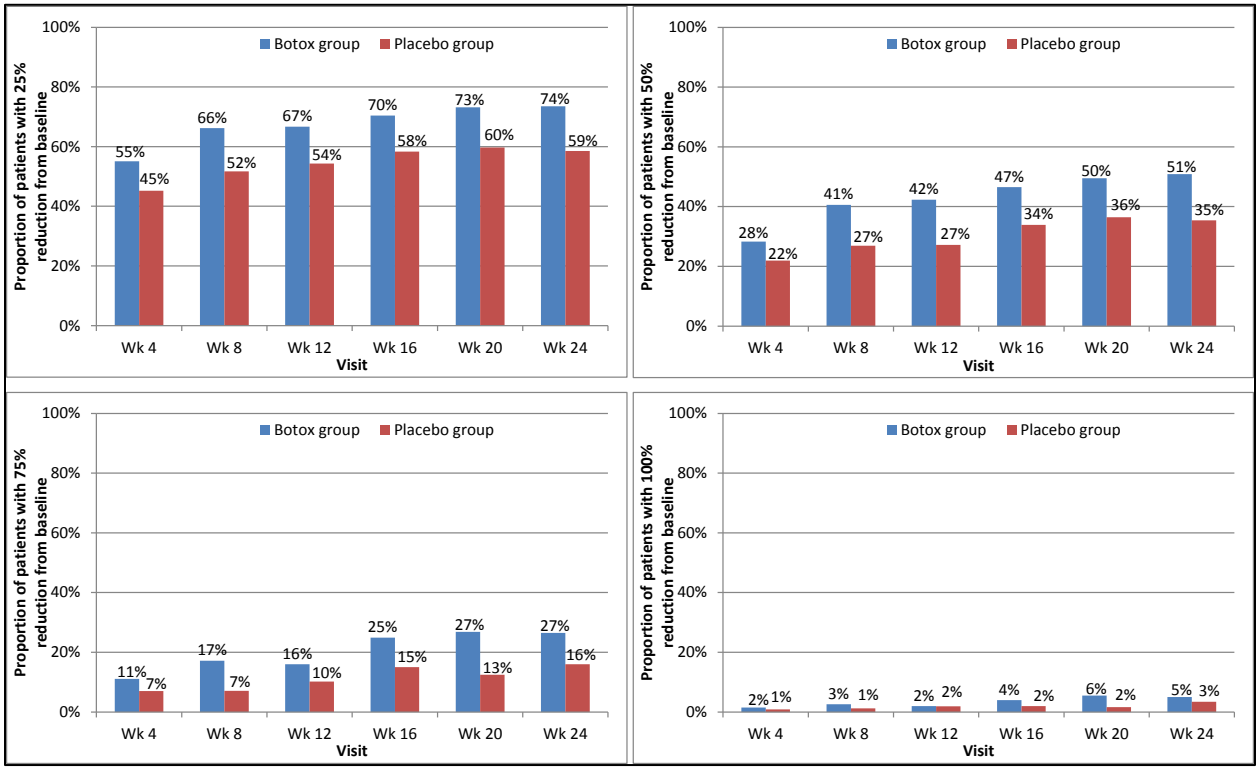
CDR = CADTH Common Drug Review; CSR = Clinical Study Report; Wk = week.
Note: *P* values for between-treatment comparisons were determined by Pearson's chi-square or Fisher's exact (f) tests (if ≥ 25% of the expected cell counts are less than five).
Source: Created by CDR reviewer using data from Study 191622-080 CSR.[18]

FIGURE 11: PROPORTION OF PATIENTS WITH REDUCTION FROM BASELINE IN MIGRAINE/PROBABLE MIGRAINE DAYS PER 28-DAY PERIOD AT DIFFERENT TIME POINTS IN STUDY 191622-079



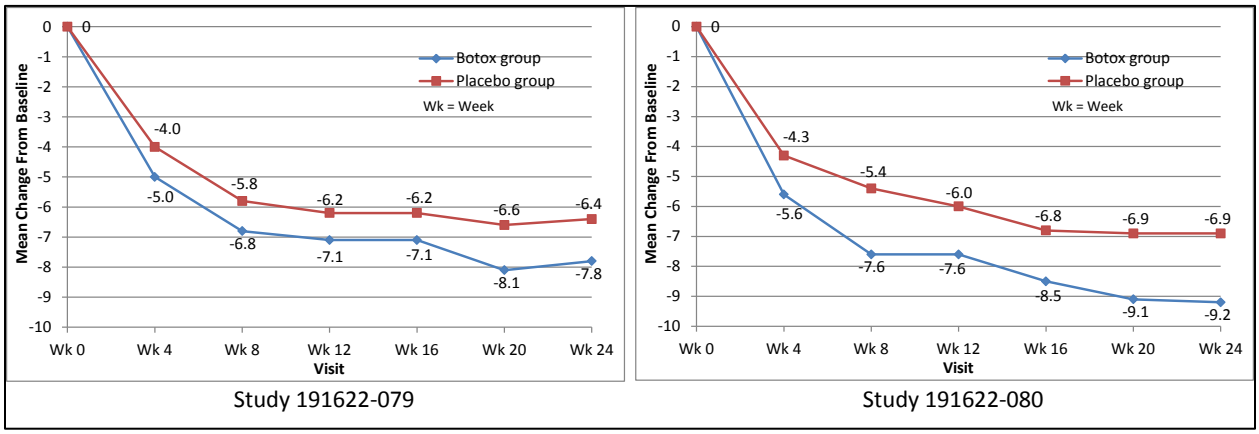
CDR = CADTH Common Drug Review; CSR = Clinical Study Report; Wk = week.
Note: *P* values for between-treatment comparisons were determined by Pearson's chi-square or Fisher's exact (f) tests (if ≥ 25% of the expected cell counts are less than five).
Source: Created by CDR reviewer using data from Study 191622-079 CSR.[17]

FIGURE 12: PROPORTION OF PATIENTS WITH REDUCTION FROM BASELINE IN MIGRAINE/PROBABLE MIGRAINE DAYS PER 28-DAY PERIOD AT DIFFERENT TIME POINTS IN STUDY 191622-080



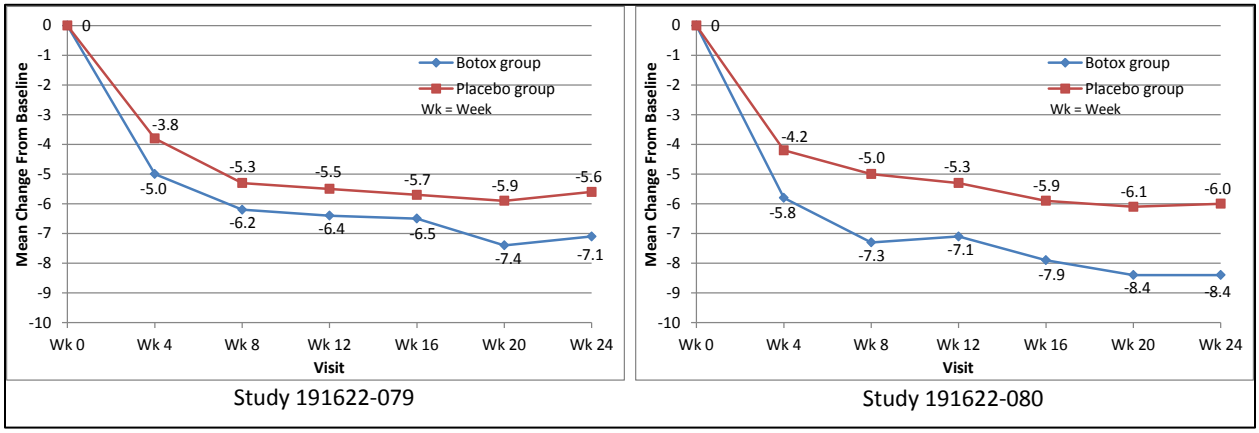
CDR = CADTH Common Drug Review; CSR = Clinical Study Report; Wk = week.
Note: *P* values for between-treatment comparisons were determined by Pearson's chi-square or Fisher's exact (f) tests (if ≥ 25% of the expected cell counts are less than five).
Source: Created by CDR reviewer using data from Study 191622-080 CSR.[18]

FIGURE 13: MEAN CHANGE FROM BASELINE IN FREQUENCY OF HEADACHE DAYS PER 28-DAY PERIOD AT DIFFERENT TIME POINTS



ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; Wk = week.
Note: *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of headache days as covariate. The main effects in the ANCOVA included treatment and medication-overuse strata.
Source: Created by CDR reviewer using data from Study 191622-079 CSR,[17] Study 191622-080 CSR.[18]

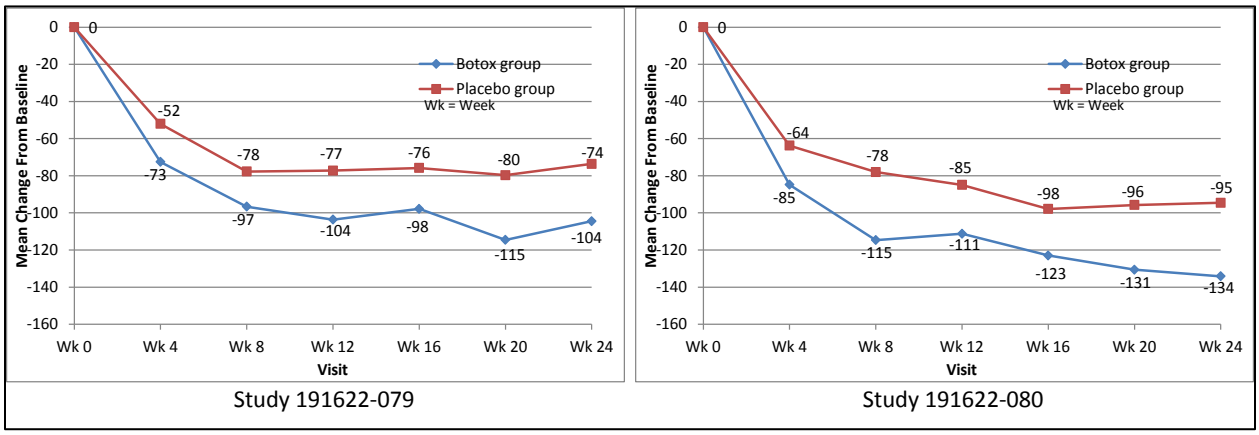
FIGURE 14: MEAN CHANGE FROM BASELINE IN NUMBER OF MODERATE/SEVERE HEADACHE DAYS PER 28-DAY PERIOD AT DIFFERENT TIME POINTS



Study 191622-079 Study 191622-080

CDR = CADTH Common Drug Review; CSR = Clinical Study Report; Wk = week.
Note: *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of moderate/severe headache days as covariate. The main effects in the ANCOVA included treatment and medication-overuse strata.
P values for between-treatment comparisons are from ANCOVA, with baseline values as covariate.
Source: Created by CDR reviewer using data from Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

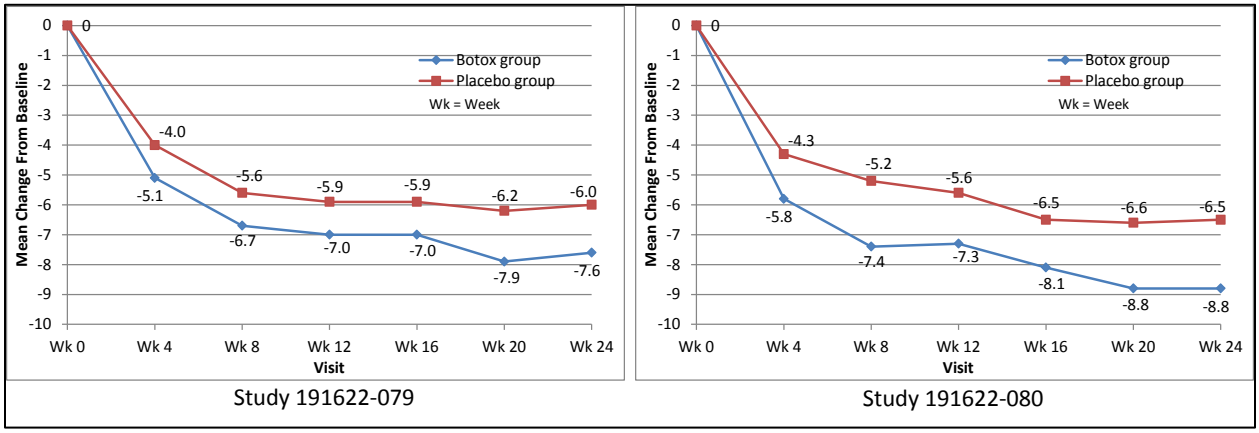
FIGURE 15: MEAN CHANGE FROM BASELINE IN TOTAL CUMULATIVE HOURS OF HEADACHE OCCURRING ON HEADACHE DAYS PER 28-DAY PERIOD AT DIFFERENT TIME POINTS



Study 191622-079 Study 191622-080

ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; Wk = week.
Note: *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.
Source: Created by CDR reviewer using data from Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

FIGURE 16: MEAN CHANGE FROM BASELINE IN FREQUENCY OF MIGRAINE/PROBABLE MIGRAINE DAYS PER 28-DAY PERIOD AT DIFFERENT TIME POINTS



Study 191622-079 Study 191622-080

ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; Wk = week.
Note: *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of migraine/probable migraine days as covariate. The main effects in the ANCOVA included treatment and medication-overuse strata.
Source: Created by CDR reviewer using data from Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

TABLE 25: SUBGROUP ANALYSIS OF HEADACHE DAYS (MLOCF)

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Results for Headache Days						
Frequency of Headache Days per 28-day Period						
Patients Who Overuse Headache Pain Medication[a]						
N	226	235		219	224	
Baseline, LSMean (SD)	20.3 (3.77)	19.8 (3.60)		19.9 (3.67)	19.8 (3.60)	
Change From Baseline at Week 24, LSMean (SD)	–7.8 (6.42)	–6.5 (6.70)	0.028	–8.6 (6.42)	–5.9 (6.48)	< 0.001
Patients Who Did Not Overuse Headache Pain Medication[a]						
N	115	103		124	134	
Baseline, LSMean (SD)	19.3 (3.56)	19.9 (3.96)		19.9 (3.57)	19.6 (3.73)	
Change From Baseline at Week 24, LSMean (SD)	–7.9 (6.87)	–6.2 (6.70)	0.074	–9.7 (6.70)	–8.1 (6.77)	0.059
Male Patients[a]						
N	37	48		48	55	
Baseline, LSMean (SD)	20.0 (3.40)	20.0 (3.63)		20.8 (3.42)	20.7 (3.86)	
Change From Baseline at Week 24, LSMean (SD)	–6.5 (6.35)	–6.7 (6.72)	0.901	–9.0 (6.75)	–7.7 (6.77)	0.326
Female Patients[a]						
N	304	290		299	303	
Baseline, LSMean (SD)	20.0 (3.77)	19.8 (3.73)		19.7 (3.65)	19.6 (3.59)	
Change From Baseline at Week 24, LSMean (SD)	–8.0 (6.59)	–6.4 (6.69)	0.003	–9.0 (6.51)	–6.5 (6.65)	< 0.001

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Patients With 3 or More Prior Prophylactics[b]						
N	107	109		124	139	
Baseline, LSMean (SD)	20.2 (3.46)	20.5 (3.74)		20.0 (3.62)	20.1 (3.98)	
Change From Baseline at Week 24, LSMean (SD)	–6.3 (6.92)	–4.4 (6.43)	0.033	–8.3 (6.26)	–4.9 (6.40)	< 0.001
Number of Moderate/Severe Headache Days per 28-day Period						
Patients With 3 or More Prior Prophylactics[b]						
N	107	109		124	139	
Baseline, LSMean (SD)	18.0 (4.00)	18.7 (4.33)		18.2 (4.12)	18.1 (4.60)	
Change From Baseline at Week 24, LSMean (SD)	–5.6 (6.65)	–3.7 (6.03)	0.028	–7.7 (6.22)	–3.9 (6.50)	< 0.001
Total Cumulative Hours of Headache Occurring on Headache Days per 28-day Period						
Patients With 3 or More Prior Prophylactics[b]						
N	107	109		124	139	
Baseline, LSMean (SD)	300.20 (101.47)	283.62 (110.75)		282.36 (126.77)	286.08 (124.75)	
Change From Baseline at Week 24, LSMean (SD)	–83.16 (128.96)	–31.20 (138.13)	0.004	–109.00 (115.17)	–51.30 (118.33)	< 0.001

ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; LSMean = Least squares mean; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.
Note: SD is for the mean. LSMean and mean were approximately the same.
[a] *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of headache days 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.
Note: *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of migraine/probable migraine days as covariate. The main effect in the ANCOVA was treatment.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR;[18] CDR submission binder.[10]

TABLE 26: SUBGROUP ANALYSIS OF MIGRAINE/PROBABLE MIGRAINE DAYS (MLOCF)

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Frequency of Migraine/Probable Migraine Days per 28-day Period						
Patients Who Overuse Headache Pain Medication[c]						
N	226	235		219	224	
Baseline, LSMean (SD)	19.4 (4.02)	19.2(3.85)		19.2 (3.96)	19.0 (4.00)	
Change From Baseline at Week 24, LSMean (SD)	–7.7 (6.33)	–6.3 (6.79)	0.017	–8.4 (6.48)	–5.7 (6.54)	< 0.001
Patients Who Did Not Overuse Headache Pain Medication[c]						
N	115	103		128	134	
Baseline, LSMean (SD)	18.3 (4.01)	18.8 (4.47)		19.1 (3.92)	18.3 (4.12)	
Change From Baseline at Week 24, LSMean (SD)	–7.5 (6.88)	–5.6 (6.78)	0.038	–9.1 (6.89)	–7.4 (6.88)	0.045
Male Patients[c]						
N	37	48		48	55	
Baseline, LSMean (SD)	19.1 (3.59)	19.2 (4.25)		20.2 (3.64)	19.6 (4.56)	
Change From Baseline at Week 24, LSMean (SD)	–6.1 (6.39)	–6.1 (6.69)	0.978	–8.8 (6.76)	–7.3 (6.61)	0.249
Female Patients[c]						
N	304	290		299	303	
Baseline, LSMean (SD)	19.1 (4.10)	19.1 (4.02)		19.0 (3.96)	18.6 (3.94)	
Change From Baseline at Week 24, LSMean (SD)	–7.8 (6.51)	–6.1 (6.81)	0.001	–8.7 (6.63)	–6.2 (6.72)	< 0.001
Patients With 3 or More Prior Prophylactics[b]						
N	107	109		124	139	
Baseline, LSMean (SD)	19.5 (4.03)	19.7 (4.05)		19.3 (3.80)	19.2 (4.30)	
Change From Baseline at Week 24, LSMean (SD)	–6.1 (6.87)	–4.0 (6.56)	0.025	–8.0 (6.28)	–4.5 (6.46)	< 0.001

ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; LSMean = Least squares mean; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.
Note: SD is for the mean. LSMean and mean were approximately the same.
[a] *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of headache days 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.
[c] *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of migraine/probable migraine days as covariate. The main effect in the ANCOVA was treatment.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR;[18] CDR submission binder.[10]

Improvement in Headache/Migraine Episodes

TABLE 27: IMPROVEMENT FROM BASELINE IN HEADACHE EPISODES AND MIGRAINE EPISODES

Outcome	Study 191622-079			Study 191622-080		
	Ona A (N = 341)	Placebo (N = 338)	*P* Value	Ona A (N = 347)	Placebo (N = 358)	*P* Value
Results for Headache Episodes						
Reduction From Baseline in Headache Episodes per 28-day Period at Week 24 (Observed Data)[a]						
25% Reduction, n/total (%)	195/260 (75.0)	186/261 (71.3)	0.347	208/279 (74.6)	200/294 (68.0)	0.085
50% Reduction, n/total (%)	122/260 (46.9)	124/261 (47.5)	0.905	140/279 (50.2)	115/294 (39.1)	0.008
75% Reduction, n/total (%)	52/260 (20.0)	39/261 (14.9)	0.119	65/279 (23.3)	46/294 (15.6)	0.021
100% Reduction, n/total (%)	8/260 (3.1)	8/261 (3.1)	0.955	12/279 (4.3)	9/294 (3.1)	0.430
Frequency of Headache Episodes per 28-day Period (mLOCF)[b]						
Baseline, LSMean (SD)	11.9 (5.23)	12.8 (5.71)		11.7 (5.27)	12.4 (5.29)	
Change From Baseline at Week 24, LSMean (SD)	–5.4 (5.27)	–5.0 (5.85)	0.344	–5.6 (5.12)	–4.6 (4.84)	0.003
Results for Migraine/Probable Migraine Episodes						
Reduction From Baseline in Migraine/Probable Migraine Episodes per 28-day Period at Week 24 (Observed Data)[a]						
25% Reduction, n/total (%)	194/260 (74.6)	182/261 (69.7)	0.202	203/279 (72.8)	196/294 (66.7)	0.113
50% Reduction, n/total (%)	120/260 (46.2)	127/261 (48.7)	0.598	139/279 (49.8)	114/294 (38.8)	0.008
75% Reduction, n/total (%)	58/260 (22.3)	40/261 (15.3)	0.041	65/279 (23.3)	43/294 (14.6)	0.008
100% Reduction, n/total (%)	12/260 (4.6)	10/261 (3.8)	0.808	14/279 (5.0)	10/294 (3.4)	0.334
Frequency of Migraine/Probable Migraine Episodes per 28-day Period (mLOCF)[c]						
Baseline, LSMean (SD)	11.0 (5.06)	12.1 (5.72)		11.0 (4.99)	11.5 (5.08)	
Change From Baseline at Week 24, LSMean (SD)	–5.0 (5.06)	–4.5 (5.74)	0.206	–5.1 (5.00)	–4.2 (4.68)	0.003

ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; LSMean = Least squares mean; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.
Note: SD is for the mean. LSMean and mean were close to each other.
[a] *P* values for between-treatment comparisons were determined by logistic regression with the unranked baseline frequency as covariate.
[b] *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of headache episodes as covariate.
[c] *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of migraine/probable migraine episodes as covariate.
The main effects in the ANCOVA included treatment and medication-overuse strata.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

TABLE 28: SUBGROUP ANALYSIS OF HEADACHE AND MIGRAINE EPISODES (MLOCF)

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Results for headache episodes						
Frequency of Headache Episodes per 28-day Period						
Patients Who Overuse Headache Pain Medication[a]						
N	226	235		219	224	
Baseline, LSMean (SD)	13.0 (5.33)	14.3 (5.63)		12.6 (5.38)	13.3 (5.29)	
Change From Baseline at Week 24, LSMean (SD)	–5.7 (5.55)	–5.5 (5.65)	0.705	–5.5 (5.48)	–4.2 (5.00)	0.004
Patients Who Did Not Overuse Headache Pain Medication[a]						
N	115	103		128	134	
Baseline, LSMean (SD)	11.0 (4.76)	11.1 (5.26)		10.8 (4.88)	11.6 (5.13)	
Change From Baseline at Week 24, LSMean (SD)	–4.7 (4.64)	–3.8 (6.07)	0.219	–5.4 (4.44)	–4.9 (4.54)	0.320
Male Patients[a]						
N	37	48		48	55	
Baseline, LSMean (SD)	12.8 (5.04)	14.0 (5.54)		13.7 (6.26)	13.1 (6.34)	
Change From Baseline at Week 24, LSMean (SD)	–4.2 (4.57)	–5.4 (5.37)	0.250	–6.0 (5.08)	–5.0 (4.48)	0.264
Female patients[a]						
N	304	290		299	303	
Baseline, LSMean (SD)	12.3 (5.26)	13.3 (5.74)		11.7 (5.05)	12.6 (5.08)	
Change From Baseline at Week 24, LSMean (SD)	–5.5 (5.33)	–5.0 (5.93)	0.180	–5.4 (5.12)	–4.4 (4.91)	0.006
Patients with 3 or More Prior Prophylactics[b]						
N	107	109		124	139	
Baseline, LSMean (SD)	12.4 (5.56)	14.0 (5.38)		12.9 (5.16)	13.6 (5.94)	
Change From Baseline at Week 24, LSMean (SD)	–4.5 (5.39)	–4.7 (5.31)	0.680	–5.7 (5.67)	–3.9 (5.13)	0.004
Results for Migraine/Probable Migraine episodes						
Frequency of Migraine/Probable Migraine Episodes per 28-day Period						
Patients Who Overuse Headache Pain Medication[c]						
N	226	235		219	224	
Baseline, LSMean (SD)	12.2 (5.21)	13.7 (5.58)		11.9 (5.08)	12.5 (5.21)	
Change From Baseline at Week 24, LSMean (SD)	–5.5 (5.36)	–5.2 (5.54)	0.490	–5.2 (5.36)	–3.9 (4.91)	0.006
Patients Who Did Not Overuse Headache Pain Medication[c]						
N	115	103		128	134	
Baseline, LSMean (SD)	10.0 (4.41)	10.3 (5.33)		10.1 (4.61)	10.4 (4.61)	
Change From Baseline at Week 24, LSMean (SD)	–4.2 (4.36)	–3.3 (5.92)	0.161	–4.8 (4.34)	–4.3 (4.28)	0.267
Male patients[c]						
N	37	48		48	55	
Baseline, LSMean (SD)	11.8 (4.35)	13.3 (5.81)		13.0 (5.98)	12.0 (5.99)	
Change From Baseline at	–3.7 (4.43)	–4.9 (5.40)	0.242	–5.6 (5.01)	–4.5 (4.16)	0.155

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Week 24, LSMean (SD)						
Female patients [c]						
N	304	290		299	303	
Baseline, LSMean (SD)	11.4 (5.14)	12.6 (5.71)		11.0 (4.76)	11.7 (4.91)	
Change From Baseline at Week 24, LSMean (SD)	–5.2 (5.11)	–4.6 (5.81)	0.092	–4.9 (5.00)	–4.0 (4.77)	0.008
Patients with 3 or more prior prophylactics [b]						
N	107	109		124	139	
Baseline, LSMean (SD)	11.7 (5.46)	13.3 (5.43)		12.2 (5.05)	12.7 (5.83)	
Change From Baseline at Week 24, LSMean (SD)	–4.2 (5.21)	–4.4 (5.07)	0.761	–5.2 (5.53)	–3.5 (4.91)	0.004

ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; LSMean = Least squares means; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR;[18] CDR submission binder.[10]
Note: SD is for the mean. LSMean and mean were approximately the same.
[a] *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of headache episodes 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.
[c] *P* values for between-treatment comparisons are from ANCOVA, with baseline frequency of migraine/probable migraine episodes as covariate. The main effect in the ANCOVA was treatment.

Other Outcomes

TABLE 29: EMERGENCY ROOM VISITS, HOSPITALIZATIONS FOR MIGRAINE SYMPTOMS IN THE PAST THREE MONTHS (OBSERVED DATA WITHOUT IMPUTATION FOR MISSING VALUES)

Outcome	Study 191622-079			Study 191622-080		
	Ona A (N = 341)	Placebo (N = 338)	*P* Value	Ona A (N = 347)	Placebo (N = 358)	*P* Value
Baseline						
N	337	334		346	358	
ER visits, Mean (SD)	0.4 (1.05)	0.4 (1.46)		0.4 (1.87)	0.3 (1.20)	
Hospitalizations, Mean (SD)	0.0 (0.29)	0.0 (0.20)		0.0 (0.17)	0.0 (0.54)	
Total Overall Hospital Visits, Mean (SD)	0.4 (1.17)	0.4 (1.50)		0.5 (1.90)	0.4 (1.33)	
Change From Baseline at Week 12						
N	318	315		331	348	
ER visits, Mean (SD)	–0.1 (0.84)	–0.2 (1.16)	0.654	–0.3 (1.61)	–0.1 (0.97)	0.315
Hospitalizations, Mean (SD)	–0.0 (0.32)	–0.0 (0.26)	0.824	–0.0 (0.20)	–0.0 (0.55)	0.359
Total Overall Hospital Visits, Mean (SD)	–0.1 (0.99)	–0.2 (1.23)	0.916	–0.3 (1.64)	–0.2 (1.14)	0.293
Change from Baseline at Week 24						
N	297	287		311	331	
ER visits, Mean (SD)	–0.1 (1.11)	–0.1 (0.81)	0.804	–0.2 (1.78)	–0.2 (1.13)	0.543
Hospitalizations, Mean (SD)	–0.0 (0.35)	–0.0 (0.18)	0.460	–0.0 (0.18)	–0.0 (0.57)	0.961
Total Overall Hospital Visits, Mean (SD)	–0.2 (1.27)	–0.1 (0.87)	0.627	–0.3 (1.80)	–0.2 (1.28)	0.391

CSR = Clinical Study Report; ER = emergency room; Ona A = onabotulinumtoxinA; SD = standard deviation.
Note: *P* values for between-treatment comparisons were determined by the Wilcoxon rank-sum test.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

TABLE 30: WORK STATUS AND PRODUCTIVITY (OBSERVED DATA WITHOUT IMPUTATION FOR MISSING VALUES)

Outcome	Study 191622-079			Study 191622-080		
	Ona A	Placebo	*P* Value	Ona A	Placebo	*P* Value
Number of Hours Worked in the Past 4 Weeks[a,b]						
Baseline, n	241	232		205	198	
Baseline, Mean (SD)	37.2 (12.01)	36.9 (14.13)		38.2 (12.62)	39.3 (14.56)	
Week 12, n	218	209		183	178	
Change From Baseline at Week 12, Mean (SD)	0.9 (9.24)	–0.5 (10.18)	0.216	1.0 (7.47)	1.2 (12.67)	0.592
Week 24, n	202	182		170	168	
Change From Baseline at Week 24, Mean (SD)	0.4 (10.02)	0.2 (11.23)	0.952	1.0 (10.43)	0.8 (11.81)	0.587
Days of Work Missed in the Past 4 Weeks[b]						
Baseline, n	232	224		274	270	
Baseline, Mean (SD)	2.1 (3.00)	2.2 (2.57)		2.5 (3.75)	2.5 (4.23)	
Week 12, n	209	201		248	244	
Change From Baseline at Week 12, Mean (SD)	–0.4 (3.00)	–0.4 (2.67)	0.566	–0.8 (3.12)	–0.3 (3.46)	0.017
Week 24, n	195	181		231	230	
Change From Baseline at Week 24, Mean (SD)	–0.5 (2.68)	–0.5 (2.28)	0.411	–0.4 (3.93)	–0.2 (3.41)	0.093
Days of Reduced Work Productivity in the Past 4 Weeks[b]						
Baseline, n	260	248		275	269	
Baseline, Mean (SD)	10.3 (6.92)	10.1 (8.19)		10.3 (6.54)	10.1 (6.62)	
Week 12, n	234	224		248	245	
Change From Baseline at Week 12, Mean (SD)	–3.5(6.96)	–2.2 (8.60)	0.012	–3.1 (8.21)	–2.2 (6.55)	0.077
Week 24, n	218	194		232	230	
Change From Baseline at Week 24, Mean (SD)	–3.7 (7.20)	–2.9 (9.33)	0.075	–3.3 (7.00)	–2.1 (7.10)	0.126
Job Status in the Past 4 Weeks[a,c]						
Baseline, n	315	313		266	274	
Not working Due to Migraine at Baseline, n (%)	24 (7.6)	36 (11.5)		16 (6.0)	27 (9.9)	
Week 12, n	300	296		254	267	
Not Working Due to Migraine at Week 12, n (%)	22 (7.3)	28 (9.5)	0.349	14 (5.5)	22 (8.2)	0.220
Week 24, n	280	271		238	249	
Not Working Due to Migraine at Week 24, n (%)	21 (7.5)	29 (10.7)	0.191	11 (4.6)	23 (9.2)	0.046

CSR = Clinical Study Report; Ona A = onabotulinumtoxinA; SD = standard deviation.

[a] Only US patients are included in this analysis.

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

[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 five).

Source: Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To assess the validity of patient-related outcome measures used in clinical trials of chronic migraines (CM), specifically the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) and the Headache Impact Test-6 (HIT-6), and to define the minimal clinically important difference (MCID).

Findings

Migraine-Specific Quality of Life Questionnaire

The Migraine-Specific Quality of Life Questionnaire (MSQ) is a disease-specific instrument which 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.[49] MSQ version 2.1 is a 14-item instrument developed from MSQ v1.0. MSQ content was improved by rewording different items for greater clarification and by shortening the questionnaire for easier administration.

Health-related quality of life (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, 4 items assessing how migraines prevent these activities), and emotional function (EF, three items assessing the emotions associated with migraines).[50] 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*, which are 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. A higher score indicates better HRQoL.[50] MSQ can also be scored in the reverse fashion, with a lower score indicating higher function, as per the CDR submission.[10]

A study by Bagley et al. provided evidence of the validity and reliability of MSQ v2.1 in CM patients.[50] The study was a Web-based, cross-sectional survey conducted in 8,726 patients with EM (< 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). *Reliability*: Internal consistency for the overall sample for RR, RP, and EF was Cronbach's alpha 0.96, 0.90, and 0.87 respectively. Internal consistency for the CM sample for RR, RP, and EF was Cronbach's alpha 0.95, 0.90, and 0.85 respectively. *Construct validity*: Low to moderate correlation between MSQ scores and scores for HIT-6 (r = –0.60 to –0.71), Migraine Disability Assessment Scale (MIDAS, r = –0.38 to –0.39), and Patient Health Questionnaire (PHQ-4, r = –0.21 to –0.42) were observed in CM.[50]

Rendas-Baum et al. provided further validation of MSQ v2.1 in CM patients undergoing prophylactic treatment.[51] Data were pooled from the two trials, 079 and 080, and included 1,376 patients. *Reliability*: Internal consistency at baseline ranged from Cronbach's alpha 0.80 for all three scales, varying between 0.80 for EF and 0.93 for RR. At 24 weeks, Cronbach's alpha ranged from 0.90 to 0.97 across the three domains and the two studies. *Construct validity*: MSQ and HIT-6 scores were moderately to 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. *Responsiveness*: MSQ change scores indicated large and moderate effect sizes for patients who experienced ≥ 50% improvement and improvement between 30% and 50%, respectively.[51]

Minimally Clinically Important Difference: MCID in MSQ v2.1 score was determined from a multi-centre, DB, placebo-controlled randomized trial of 328 patients with CM.[52] 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 9 years and reported 20 HDPM at baseline. Outcomes measured included MIDAS, MSQ v2.1, Subject's Global Impression of Change (SGIC), and Physician's Global Impression of Change (PGIC). SGIC and PGIC, completed at the end of the study, used a seven-point scale with 1 = very much improved and 7 = being very much worse.[52]

MCID was established using an anchor-based approach, with a patient global rating of change (SGIC) as the anchor. For change from baseline in MSQ-RR versus SGIC, there was an improvement in MSQ-RR, with a regression-estimated MCID of 10.9. For change from baseline in MSQ-RP versus SGIC, there was an improvement in MSQ-RP, with a regression-estimated MCID of 8.3. For change from baseline in MSQ-EF versus SGIC, there was an improvement in MSQ-EF, with a regression-estimated MCID of 12.2 (Table 31).[52]

TABLE 31: MCID FOR EACH MSQ DOMAIN — WITHIN-GROUP DIFFERENCES

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

CI = confidence interval; MCID = minimally clinically important difference; MSQ = Migraine-Specific Quality of Life Questionnaire.
Source: Dodick et al.[52]

Headache Impact Test

The HIT is a Web-based, multi-question health assessment that quantifies the impact of headache on a patient's life.[53] The HIT uses computerized adaptive testing technology to select and ask only survey questions that are relevant to the respondent. A total of 84 possible questions covers topics such functional health and well-being. Optional questions may be used to obtain information on pain, medications, and treatment satisfaction.[53]

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

HIT-6 measures pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress.[22] 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*.[22]

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).[54] A follow-up survey of 540 of the original adults was conducted 14 days after the first survey. *Reliability:* The instrument showed good internal consistency (Cronbach's alpha 0.89 and 0.90 for the first and second survey respectively) and test-retest reliability (0.78, n = 540). *Construct validity*: Correlation between HIT-6 and the Short-Form 8 Health Survey (SF-8) scales and summaries were obtained. The highest correlations were observed between HIT-6 and role-physical and social functioning (r = –0.36 and r = –0.37, respectively) and the lowest correlations with bodily pain and mental health (r = –0.25 and r = –0.27., respectively). HIT-6 correlated better with physical summary (r = –0.35) than mental summary (r = –0.31). *Responsiveness*: The instrument was responsive to self-reported changes in headache impact. Score improved with respondents who self-reported improved headache impact, whereas score declined with respondents who self-reported worsening headache impact.[54]

A study by Kawata et al. was conducted in patients with chronic daily headaches (≥ 15 HDPM).[22] 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. *Reliability*: The instrument showed good internal consistency (Cronbach's alpha 0.87). *Construct validity*: Correlation between HIT-6 scores and the Short-Form 36 Health Survey (SF-36) health domain subscales were obtained. The highest correlation was observed between HIT-6 scores and role-physical (r = –0.52) and social functioning subscales(r = –0.57). Correlation was lowest with mental health (r = –0.22) and general health (r = –0.29) subscales of SF-36.[22]

Further testing of HIT-6 was completed by Yang et al. in 2,049 patients with EM or CM.[55] 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 applicable 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 EM 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). *Reliability*: The instrument showed good internal consistency (Cronbach's alpha 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). *Construct validity*: Correlation between HIT-6 scores and other scores (MIDAS, headache pain severity, and number of HDPM) were also obtained. The highest correlation was observed between HIT-6 scores and total MIDAS scores (r = 0.56). Correlation was moderate (r = 0.46) and low (r = 0.29) with headache pain intensity and number of HDPM respectively. *Discriminant validity*: HIT-6 scores differed significantly between subgroups of CM, EM, and non-migraine headaches ($P < 0.0001$). CM patients were more likely to report substantial or severe headache impact compared with the patients of EM and non-migraine headaches.[55]

Minimally Clinically Important Difference: The MCID in HIT-6 score was determined by Coeytaux et al. from on a study involving 71 patients who suffered from chronic daily headaches (≥ 15 HDPM).[56] Patients were randomly assigned to 10 acupuncture sessions administered over six weeks and 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.[56]

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 to define a meaningful or important 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."[56]

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.[56]

Baseline HIT-6 scores were 64.9 (95 % 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.[56] 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 = Headache Impact Test; MCID = minimally clinically important difference.
Source: Coeytaux et al.[56]

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

Summary

MSQ v2.1 is a 14-item instrument that assesses the impact of migraine on a patient's HRQoL across three domains: RR (how migraines limit one's daily social and work-related activities); RP (how migraines prevent these activities); and EF (emotions associated with migraines). Scores range from 0 to 100; in the CDR submission, a lower score indicates better HRQoL. Validation of MSQ v2.1has been conducted in patients with CMs. The instrument showed good internal consistency and construct validity. One study determined an MCID of 10.9, 8.3, and 12.2 for RR, RP, and EF, respectively, for within-group differences. There is no MCID for between-group differences in CM.

The HIT-6 is a short-form version of the HIT, a Web-based, multi-question health assessment that quantifies the impact of headache on a patient's life. HIT-6 is comprised of six questions which measures pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress in patients suffering from headaches. Scores range from 36 to 78; a higher score indicates a greater impact of the disease on the daily life of the respondent. Validation of HIT-6 was completed in patients with

chronic daily headaches and in patients with EM or CM. It showed good to moderate internal consistency and moderate to poor construct validity. One study conducted in chronic daily headache patients suggested that a between-group difference in HIT change scores of 2.3 units was thought to be clinically important. Recall bias was an issue with this trial.

APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION PHASE OF STUDY 079 AND STUDY 080

Aim

To review the efficacy and harms data reported from the open-label extension (OLE) phase of the included trials, Study 079 and Study 080.

Findings

Study/Phase design

The 24-week, double-blind (DB), randomized, placebo-controlled, parallel-group phase of Studies 079 and 080 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 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 onabotulinumtoxinA in the DB phase are referred to as the onabotulinumtoxinA/onabotulinumtoxinA group in the OLE phase, while patients who had previously received placebo in the DB phase are referred to as the placebo/onabotulinumtoxinA 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 Study 079, 71.1% of patients completed the OLE phase. In Study 080, 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 due to "other" causes, which were undefined (Table 33). Few patients (2% to 4%) discontinued the study due to a lack of efficacy.

TABLE 33: PATIENT DISPOSITION

	Study 079		Study 080	
	Ona A/ Ona A	Placebo/ Ona A	Ona A/ Ona A	Placebo/ Ona A
Enrolled	341	338	347	358
Completed OLE 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)
AEs	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)
AEs	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)

	Study 079		Study 080	
	Ona A/ Ona A	Placebo/ Ona A	Ona A/ Ona A	Placebo/ Ona A
Pregnancy	2 (0.6)	4 (1.2)	4 (1.2)	2 (0.6)
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)

AE = adverse event; CSR = Clinical Study Report; OLE = open-label extension; Ona A = onabotulinumtoxinA.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

Drug Exposure

In the OLE phase, patients received three doses of onabotulinumtoxinA of approximately 164 U each at 33 injection sites at weeks 24, 36, and 48 (Table 34). The mean dose of onabotulinumtoxinA across all five cycles was 164 U (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 34: DRUG EXPOSURE IN THE OLE PHASE AND ACROSS ALL FIVE CYCLES

	Studies 079 and 080 Combined			
Drug Exposure	Week 24 Treatment Cycle 3	Week 36 Treatment Cycle 4	Week 48 Treatment Cycle 5	Week 0 to Week 48 Treatment Cycles 1 to 5
n	1,092	558	518	1,300
Units, Mean (SD)	164.5 (13.3)	164.9 (13.5)	164.4 (14.6)	164.0 (12.9)
Units, Median (Min, Max)	155 (130, 195)	155.0 (130, 195)	155.0 (65, 195)	158.3 (15, 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; OLE = open-label extension; SD = standard deviation.
Source: CADTH Common Drug Review submission.[10]

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 Studies 079 and 080 for both the onabotulinumtoxinA/onabotulinumtoxinA group and the placebo/onabotulinumtoxinA group (Table 35). 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 onabotulinumtoxinA/onabotulinumtoxinA and placebo/onabotulinumtoxinA for any of the domains (role function – restrictive [RR], role function – preventive [RP], and emotional function [EF]) at week 56.

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 Studies 079 and 080 for the onabotulinumtoxinA/onabotulinumtoxinA group and the placebo/onabotulinumtoxinA group (Table 36). Whether this finding is clinically important is unknown because the MCID for within-group 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 onabotulinumtoxinA/onabotulinumtoxinA and placebo/onabotulinumtoxinA 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 37). 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 was 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 onabotulinumtoxinA/onabotulinumtoxinA group had a greater improvement in medication days and medication overuse compared with the placebo/onabotulinumtoxinA 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 to 12 days per month at week 56, from approximately 20 days per month at baseline (Table 38). Similarly, the frequency of migraine/probable migraine days decreased by 10 to 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 EM.

Between-group comparison: In Study 079, there were no statistically significant differences between the onabotulinumtoxinA/onabotulinumtoxinA group and the placebo/onabotulinumtoxinA group for any of the measures related to headache/migraine days, whereas in Study 080 all between-group differences were statistically significant.

TABLE 35: BASELINE AND MEAN CHANGE FROM BASELINE AT WEEK 56 IN MSQ SCORES

	Study 079			Study 080		
	Ona A/ Ona A	Placebo/ Ona A	*P* value	Ona A/ Ona A	Placebo/ Ona A	*P* value
MSQ Scores						
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, Max)	60.0 (9, 100)	62.9 (23, 100)		60 (14, 100)	60.0 (9, 100)	
Week 56, n	266	258		292	310	

	Study 079			Study 080		
	Ona A/ Ona A	Placebo/ Ona A	*P* value	Ona A/ Ona A	Placebo/ Ona A	*P* value
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, Max)	–25.7 (–91, 37)	–20.00 (–100, 49)		–22.9 (–100, 40)	–18.8 (–100, 46)	
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, 100)	45 (0, 100)		40.0 (0, 100)	40.0 (0, 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, Max)	–20.0 (–95, 40)	–17.5 (–90, 55)		–15.0 (–100, 55)	–15.0 (–100, 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, 100)	60.0 (0, 100)		53.3 (0,100)	53.3 (0, 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, 47)	–20 (–93, 47)		–20 (–100, 53)	–20, (–100, 73)	

CSR = Clinical Study Report; max = maximum; min = minimum; MSQ = Migraine-Specific Quality of Life Questionnaire; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

TABLE 36: BASELINE AND MEAN CHANGE FROM BASELINE AT WEEK 56 IN HIT-6 AND HEADACHE IMPACT SCORES

	Study 079			Study 080		
	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, Max)	65.0 (51, 78)	66.0 (53, 78)		66.0 (50, 78)	65.0 (46, 78)	
Change From Baseline at Week 56, Median (Min, Max)	–6.0 (–32, 14)	–6.0 (–30, 10)		–7.0 (–42, 15)	–5.5 (–42, 11)	

CSR = Clinical Study Report; max = maximum; min = minimum; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

TABLE 37: ACUTE HEADACHE PAIN MEDICATION INTAKE

	Study 079			Study 080		
	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, LSMean (SD)	25.2 (19.3)	25.7 (22.3)		21.9 (18.8)	22.8 (18.9)	
Change From Baseline at Week 56, LSMean (SD)	–16.0 (20.0)	–17.1 (19.9)	0.400	–15.1 (15.7)	–13.6 (16.4)	0.097
Acute Headache Pain Medications Days per 28-day Period (Observed Data)						
Baseline, LSMean (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, LSMean (SD)	–8.6 (7.1)	–9.1 (7.0)	0.420	–8.7 (6.2)	–7.6 (6.3)	0.027
Acute Headache Pain Medications Use per 28-day Period (Observed Data)						
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 Medications Overuse per 28-day Period (Observed Data)						
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

CSR = Clinical Study Report; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

TABLE 38: IMPROVEMENT FROM BASELINE IN HEADACHE DAYS AND MIGRAINE DAYS

	Study 079			Study 080		
	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, LSMean (SD)	19.9 (3.7)	19.7 (3.7)		19.8 (3.6)	19.7 (3.7)	
Change From Baseline at Week 56, LSMean (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, LSMean (SD)	17.9 (4.2)	18.0 (4.2)		18.0 (4.0)	17.6 (4.3)	
Change From Baseline at Week 56, LSMean (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, LSMean (SD)	299.2 (116.8)	279.2 (110.9)		299.1 (121.0)	290.0 (118.9)	
Change From Baseline at Week 56, LSMean (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, LSMean (SD)	19.0 (4.0)	19.0 (4.0)		19.1 (3.9)	18.7 (4.1)	
Change From Baseline at Week 56, LSMean (SD)	–11.0 (7.0)	–10.6 (6.7)	0.405	–11.5 (6.4)	–10.3 (7.0)	0.015

CSR = Clinical Study Report; mLOCF = modified last observation carried forward; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Study 191622-079 CSR;[17] Study 191622-080 CSR.[18]

Harm: An event occurring during the DB phase and continuing into the OLE phase was only counted in the DB phase. In addition, an event occurring during the DB phase and continuing into the OLE phase and whose severity increased in the OLE phase was only counted in the DB phase.

The number and percentage of patients with AEs, SAEs, and WDAEs are presented in Table 39 and Table 40. A patient was counted once for each AE when multiple occurrences of the same AEs were reported.

There were no deaths. In the OLE phases of Studies 079 and 080, 58% of patients experienced an AE with onabotulinumtoxinA. Over the course of the five treatment cycles, 74% of patients exposed to onabotulinumtoxinA reported an AE.

In the OLE phases of Studies 079 and 080, the most common AEs were neck pain, sinusitis, and nasopharyngitis (Table 40). 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 39). 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 were no reports of anaphylaxis reactions.
- Antibody formation: Serum samples for toxin-neutralizing antibody titer analysis were not collected in Studies 079 and 080. However, the sponsor indicates that "there is no heightened risk for immunogenicity in this patient population" (Clinical Summary Module 2.7.4, page 118).
- Autonomic dysreflexia: There were no reports of autonomic dysreflexia.

TABLE 39: OVERALL HARMS

	Study 079		Study 080	
	Ona A/Ona A	Placebo/ Ona A	Ona A/Ona A	Placebo/ Ona A
OLE Phase, n	287	284	305	329
All AEs, n (%)	155 (54.0)	165 (58.1)	174 (57.0)	209 (63.5)
SAEs, n (%)	20 (7.0)	8 (2.8)	7 (2.3)	11 (3.3)
Discontinuation Due to AEs, n (%)	4 (1.4)	5 (1.8)	9 (3.0)	13 (4.0)
Death, n	0	0	0	0
Entire Study, n	340	334	347	358
All AEs, n (%)	254 (74.7)	220 (65.9)	268 (77.2)	280 (78.2)
SAEs, n (%)	34 (10.0)	15 (4.5)	22 (6.3)	19 (5.3)
Discontinuation Due to AEs, n (%)	18 (5.3)	8 (2.4)	20 (5.8)	18 (5.0)
Death, n	0	0	0	0
AEs 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)	

AE = adverse event; OLE = open-label extension; Ona A = onabotulinumtoxinA;
SAE = serious adverse event.
Source: CADTH Common Drug Review submission.[10]

TABLE 40: DETAILED HARMS, OPEN-LABEL EXTENSION PHASE

	Studies 079 and 080 Combined		
	Ona A/Ona A (N = 592)	Placebo/Ona A (N = 613)	Total (N = 1205)
AEs 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)
Depression	3 (0.5)	13 (2.1)	16 (1.3)
SAEs 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)
WDAEs 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)

AE = adverse event; CDR = CADTH Common Drug Review; Ona A = onabotulinumtoxinA; SAE = serious adverse event; WDAR = withdrawal due to adverse event.
Source: CDR submission.[10]

Summary

The 32-week OLE phase began at the week-24 visit. Patients received on average 164 U of onabotulinumtoxinA at 33 injection sites every 12 weeks (weeks 24, 36, and 48). Patients completed study visits every four weeks, with the last visit recorded at week 56. The overall treatment duration was a mean 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 Studies 079 and 080. Acute headache pain medications could not be completely stopped, with more than 70% of patients still requiring acute pain medications at week 56. However, fewer than 20% of patients overused acute pain medications at week 56. The frequency of headache days and migraine/probable migraine days decreased by 10 to 11 days per month at week 56, from approximately 19 to 20 days per month at baseline. This means that patients experienced on average eight to nine migraines per month, reverting back to a diagnosis of EM. There were no deaths reported in either Study 079 or Study 080. SAEs were infrequent. Fewer 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 were no reports of anaphylaxis reactions.

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