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Monoclonal Antibodies to Prevent Migraine Headaches

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Summary

- Migraine is a common, chronic, neurological disorder. To prevent chronic migraine headaches, botulinum toxin has received regulatory approval. This medication requires multiple injections into specific head and neck sites. Other drugs are used in migraine prevention but patient adherence and efficacy are issues.
- Anti-calcitonin gene-related peptide (anti-CGRP) monoclonal antibodies belong to a novel class of drugs that target CGRP — a potent vasodilator — which plays a role in pain and migraines.
- Four anti-CGRP monoclonal antibodies are currently in development for use in the prevention of episodic and chronic migraines: eptinezumab, erenumab, fremanezumab, and galcanezumab. They have not yet been approved in any country.
- Phase II and phase III trial results are available for all four drugs. The evidence available to date demonstrated a statistically significant decrease in the frequency of migraines. Episodic migraine sufferers experienced one to two fewer migraine days each month. Patients with chronic migraine experienced two to two-and-one-half fewer migraine days each month. There were no safety concerns identified with these drugs.
- Although the cost of these drugs has not been determined, these drugs will potentially have a significant budget impact because of the high cost of biologics and the prevalence of episodic and chronic migraines.

Background

A migraine is characterized as a headache, with at least two of the following pain attributes: moderate or severe, throbbing, localized to one area, and avoidance of routine physical activity because of the pain.[1,2] The headache must be accompanied by at least one of the following symptoms: nausea or vomiting, or photophobia (light sensitivity) and phonophobia (sensitivity to noise).[1] Up to 20% of patients with migraines may experience a visual or auditory disturbance (aura); a migraine attack can last from four hours to 72 hours.[3,4]

Migraines are classified, based on the frequency of attacks, into episodic migraine (headaches that occur less than 15 days per month) and chronic migraine (headaches for 15 days or more per month).[5,6] In Western countries, episodic migraines affect approximately 12% of the adult population, while chronic migraines affect approximately 1% of the adult population.[2,4,5] Chronic migraines affect three times more women than men and are associated with an increased societal burden, an increased number of comorbidities, and a negative impact on quality of life.[2,4,5]

Research is in progress to develop drugs specifically for the prevention of episodic and chronic migraines. It is reported that migraines are the third most-prevalent and the seventh most-disabling condition worldwide.[7] Therefore, these medications will potentially be important in improving the quality of life and reducing the disease burden of patients who suffer from chronic or episodic migraines.

The Technology

Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide present in the peripheral and central nervous systems.[6,8] A release of CGRP has been shown to induce migraine attacks.[9] Anti-CGRP monoclonal antibodies act to weaken the migraine signalling pathway.[9]

Previous studies conducted on small molecules targeting the CGRP receptors demonstrated efficacy in treating and preventing migraines. However, these trials were stopped prematurely because of serious concerns of liver toxicity and other reasons (Appendix 1).[6,8]

Monoclonal antibodies (mAbs) targeting the CGRP signalling pathway are currently being developed as preventive therapy for episodic and chronic migraines.[3,6,8] Clinical trials are in progress for three mAbs targeting CGRP and one targeting the CGRP receptor.[3,6,8] Anti-CGRP mAbs remove excess CGRP molecules, while anti-CGRP receptor mAbs block signalling at the receptor.[6] This prevents the activation of CGRP signalling pathways, which may decrease headache frequency over time.[3,6]

The three mAbs targeting CGRP are eptinezumab (ALD403; Alder Biopharmaceuticals), fremanezumab (TEV-48215 or LBR-101; Teva Canada Innovation), and galcanezumab (LY2951742; Eli Lilly Canada Inc.), while erenumab (AMG 334; Amgen Canada) is targeting the CGRP receptor.[3,6,8]

Table 1: Administration of Anti-CGRP Monoclonal Antibodies[10,16-23]

Drug	Dose(s)	Route of Administration	Dosing Interval
Eptinezumab	100 mg or 300 mg	Intravenous infusion	Every 3 months
Erenumab	70 mg or 140 mg	Subcutaneous injection	Every month
Fremanezumab	225 mg[a]	Subcutaneous injection	Every month
	675 mg	Subcutaneous injection	Every 3 months
Galcanezumab	120 mg or 240 mg	Subcutaneous injection	Every month

anti-CGRP = anti-calcitonin gene-related peptide.

[a] 675 mg initial dose followed by 225 mg monthly dose in chronic migraines.

Regulatory Status

These drugs have not yet been approved to be marketed in any country.

Eptinezumab: Alder Biopharmaceuticals will be making a Biologics License Application (BLA) to the FDA for eptinezumab in the second half of 2018.[10]

Erenumab: Erenumab is currently under review by Health Canada.[11] On June 21, 2017, the European Medicines Agency accepted a marketing authorization application from Novartis for erenumab.[12] The FDA accepted a BLA for erenumab on July 20, 2017.[13] Of note, Amgen is transitioning the Canadian commercialization rights of erenumab to Novartis (Geoff Sprang, Executive Director, Value & Access, Amgen Canada, Mississauga, ON: personal communication, 2017 Sep 11).

Fremanezumab: Teva announced the submission of a BLA to the FDA for fremanezumab on October 17, 2017.[14] Submissions to other regulatory agencies will follow at a later date. (Christine Poulin, General Manager, Teva Canada Innovation, Montreal, QC: personal communication, 2017 Sep 13).

Galcanezumab: Eli Lilly has submitted a BLA for galcanezumab to the FDA;[15] submissions to other regulatory agencies will occur at a later date (Doron Sagman, Senior Medical Director, Eli Lilly Canada Inc., Toronto, ON: personal communication, 2017 Sep 13).

Cost and Administration

The costs for erenumab, fremanezumab, and galcanezumab are currently unavailable (Doron Sagman : personal communication, 2017 Sep 13; Christine Poulin: personal communication, 2017 Sep 13; Geoff Sprang: personal communication, 2017 Sep 11). We have no information on eptinezumab.

All four drugs are administered parenterally; dosage information obtained from the clinical trials is available in Table 1, although these may change based on Health Canada's regulatory reviews.

Target Population

The intended use of these anti-CGRP mAbs is for migraine prevention in patients suffering from episodic or chronic migraines.[1,24] Patients who have failed other preventive migraine therapies may be a target population for the use of anti-CGRP therapy.[8,25]

Current Practice

Existing therapies for migraine management focus on both the acute and the preventive management of symptoms.[1,24] 5HT1B/1D agonists, known as triptans, are the mainstay for the treatment of acute migraine episodes and are available in a number of formulations.[1,24] Other pharmacologic options for treating acute migraines include analgesics (acetaminophen) and nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, and ASA).[24]

Methods

These bulletins summarize information available about a new or emerging technology. Industry is invited to review the information, and drafts are reviewed by at least one clinical expert.

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and the Cochrane Library. Grey literature was identified by searching relevant sections of the Grey Matters checklist (cadth.ca/grey-matters). No methodological filters were applied. The search was not limited by language or publication date. Regular alerts updated the search until project completion; only citations retrieved before 18 December 2017 were incorporated into the analysis. Conference abstracts were included from the search results.

Table 2: Characteristics of Randomized, Double-Blind, Placebo-Controlled Trials — Episodic Migraine

Author (Year) Name of Study, Country, Funding	Study Phase, Study Duration, Sample Size	Population	Intervention(s), Comparator	Primary Outcome
Episodic Migraine				
Eptinezumab				
Alder Biopharmaceuticals Press Release (2017)[10] ClinicalTrials.gov (NCT02559895)[29] Keller (2017)[30] PROMISE-1 Multi-centre, US Alder Biopharmaceuticals	Phase III 24 weeks N = 888	Patients 18- to 65-years-old with episodic migraines	Eptinezumab[a] 100 mg IV every 3 months (n = 222) Eptinezumab 300 mg IV every 3 months (n = 222) Placebo (n = 222)	Change from baseline over weeks 1 to12 in monthly migraine days
Dodick et al. (2014)[7] Multi-centre, US Alder Biopharmaceuticals	Phase II 12 weeks N = 174	Patients 18- to 55-year-old with 5 to 14 migraine days per month	Eptinezumab 1,000 mg IV one dose (n = 86) Matching placebo (n = 88)	Change from baseline in weeks 5 to 8 in the frequency of migraine days
Erenumab				
Dodick et al. (2017)[16] ClinicalTrials.gov (NCT02483585)[31] Brauser (2017)[32] ARISE North America and Europe Amgen	Phase III 12 weeks N = 577	Patients 18- to 65-years-old with 4 to 14 migraine days per month	Erenumab 70 mg SC monthly (n = 289) Placebo (n = 291)	Change from baseline to weeks 9 to12 in monthly migraine days
Goadsby et al. (2017)[17,18,33] ClinicalTrials.gov (NCT02456740)[34] Brauser (2017)[32] STRIVE North America and Europe Amgen	Phase III 24 weeks N = 955	Patients 18- to 65-years-old with 4 to 14 migraine days per month	Erenumab 70 mg SC monthly (n = 317) Erenumab 140 mg SC monthly (n = 319) Placebo (n = 319)	Change from baseline in monthly migraine days over weeks 13 to 24
Sun et al. (2016)[35] North America and Europe Amgen	Phase II 12 weeks N = 483	Patients 18- to 60-years-old with 4 to 14 migraine days per month	Erenumab[b] 70 mg SC monthly (n = 107) Matching placebo (n = 160)	Change from baseline in monthly migraine days between weeks 9 to 12

Author (Year) Name of Study, Country, Funding	Study Phase, Study Duration, Sample Size	Population	Intervention(s), Comparator	Primary Outcome
Fremanezumab				
Teva Press Release (2017)[20,21] Keller (2017)[30] HALO-EM Multi-centre (global) Teva Pharmaceutical Industries	Phase III 12 weeks N = 875	Patients 18- to 70-years-old with 6 to 14 days per month	Fremanezumab 225 mg SC for 3 months (monthly dose regimen) (n = 290) Fremanezumab 675 mg at initiation, followed by placebo for 2 months (quarterly dose regimen) (n = 291) Matching placebo, 3 monthly doses (n = 294)	Change from baseline in the monthly migraine days during the 12-week period
Bigal et al. (2015)[22] Multi-centre, US Teva Pharmaceutical Industries	Phase IIb 12 weeks N = 297	Patients 18- to 65-years-old with 8 to 14 migraine days per month	Fremanezumab 225 mg SC monthly (n = 96) Fremanezumab 675 mg SC monthly (n = 97) Matching placebo (n = 104)	Change from baseline in the number of migraine days during weeks 9 to 12
Galcanezumab				
Eli Lilly Press Release (2017)[19] ClinicalTrials.gov (NCT02614183)[36] Keller (2017)[30] EVOLVE-1 US, Canada Eli Lilly	Phase III 24 weeks N = 825	Patients 18- to 65-years-old with migraines 8 to 14 days per month	Galcanezumab 120 mg SC monthly (n = NR) Galcanezumab 240 mg SC monthly (n = NR) Matching placebo (n = NR)	Change from baseline in monthly migraine days over 24 weeks
Eli Lilly Press Release (2017)[19] ClinicalTrials.gov (NCT02614196)[37] EVOLVE-2 Multi-centre (global) Eli Lilly	Phase III 24 weeks N = 825	Patients 18- to 65-years-old with migraines 8 to 14 days per month	Galcanezumab 120 mg SC monthly (n=NR) Galcanezumab 240 mg SC monthly (n=NR) Matching placebo (n=NR)	Change from baseline in monthly migraine days over 24 weeks

Author (Year) Name of Study, Country, Funding	Study Phase, Study Duration, Sample Size	Population	Intervention(s), Comparator	Primary Outcome
Dodick et al. (2014)[38] Multi-centre, US Arteaus Therapeutics	Phase II 12 weeks N = 218	Patients 18- to 65-years-old with 4 to14 migraine days per month	Galcanezumab 150 mg SC injection every 2 weeks (n = 108) Placebo (n = 110)	Change from baseline to weeks 9 to12 in monthly migraine days

IV = intravenous; NR = not reported; SC = subcutaneous.

[a] A dose of 30 mg (n = 222) was also tested in the trial.

[b] Doses of 7 mg (n = 108) and 21 mg (n = 108) were also tested in the trial.

Patients who suffer from recurrent attacks may benefit from prophylactic therapy.[26] Botulinum toxin has received regulatory approval for the prevention of chronic migraine headaches. This medication requires multiple injections into specific head and neck sites. [1,6,24] Topiramate is used for the prophylaxis of migraine headaches in adults experiencing four or more migraine attacks per month. [27] Other drugs used for migraine prevention are anti-epileptics (divalproex sodium, lamotrigine, gabapentin), antidepressants (amitriptyline, nortriptyline, fluoxetine, venlafaxine, duloxetine), beta blockers (metoprolol, propranolol), calcium channel blockers (verapamil, flunarizine), and magnesium. These drugs have not been approved for use in migraine prevention and are associated with low adherence because of side effects or efficacy.[1,5,8,24,26,28]

Summary of the Evidence

Episodic Migraine

A total of 10 randomized, double-blind, placebo-controlled trials have been conducted in adult patients: three of these trials were phase II trials, one was a phase IIb trial, and six were phase III trials. All trials involved multiple testing centres and all were industry-sponsored (Table 2). The sample sizes ranged from 174 patients to 955 patients. The patient population included adult patients experiencing episodic migraines for 12 months or longer before screening. Patients were randomly assigned to receive either the treatment drug or placebo. The primary outcome measured for these drugs was the change in the frequency of migraines. The trial durations were 24 weeks for the PROMISE-1, STRIVE, EVOLVE-1, and EVOLVE-2 studies; and 12 weeks for the other trials.

Chronic Migraine

A total of five randomized, double-blind, placebo-controlled trials have been conducted in adult patients: two were phase II trials, one was a phase IIb trial, and two were phase III trials. All trials involved multiple testing centres and all were industry-sponsored (Table 3). The sample sizes ranged from 264 patients to 1,130 patients. The patient population included adult patients with a history of chronic migraine. Patients were randomized to receive either the treatment drug or placebo. The drugs were tested over a 12-week period. The primary outcome included the change in frequency of migraines or headaches.

Results

Efficacy

The results of the primary outcomes of the phase II/IIb and phase III trials are depicted in Tables 4 and 5. Of note, except for the STRIVE and HALO-CM studies, the results of the phase III trials have not yet been fully published; the data were obtained from conference abstracts and press releases.

Overall, there was a statistically significant decrease in the frequency of migraines compared with placebo. Episodic migraine sufferers experienced one to two fewer migraine days each month. Patients with chronic migraines experienced two to two-and-one-half fewer migraine days each month.

Episodic Migraine: The primary outcome measured in the trials for episodic migraine was the change from baseline in monthly migraine days.

Eptinezumab: In the PROMISE-1 study, the mean differences in monthly migraine days for eptinezumab 100 mg and eptinezumab 300 mg were −0.7 days (P = 0.0179) and −1.1 days (P = 0.0001) compared with placebo, respectively.

In a phase II trial, a single dose of eptinezumab 1,000 mg resulted in a mean difference of −1 day (95% confidence interval [CI], −2.1 to 0.1, P = 0.0306), with migraine in weeks 5 to weeks 8 compared with placebo.

Table 3: Characteristics of Randomized, Double-Blind, Placebo-Controlled Trials — Chronic Migraine

Author (Year) Name of Study, Country, Funding	Study Phase, Study Duration, Sample Size	Population	Intervention(s), Comparator	Primary Outcome
Chronic Migraine				
Eptinezumab				
Smith et al. (2017)[39] ClinicalTrials.gov (NCT02275117)[40] US, Australia, New Zealand, Georgia Alder Biopharmaceuticals	Phase II 12 weeks N = 665	Patients 18- to 55-years-old with 15 to 28 headache days per month (at least 8 migraine days)	Eptinezumab[a] 100 mg IV one dose (n = NR) Eptinezumab 300 mg IV once (n = NR) Matching placebo (n = NR)	% patients achieving ≥ 75% reduction from baseline in migraine days over weeks 1 to 12
Erenumab				
Tepper et al. (2017)[41] North America and Europe Amgen	Phase II 12 weeks N = 667	Patients 18- to 65-years-old with 15 or more headache days per month (at least 8 migraine days)	Erenumab 70 mg SC monthly (n = 191) Erenumab 140 mg SC monthly (n = 190) Matching placebo (n = 286)	Change from baseline to weeks 9 to 12 in monthly migraine days
Fremanezumab				
Silberstein et al. (2017)[42] Teva Press Release (2017)[20,21] ClinicalTrials.gov (NCT02621931)[43] HALO-CM Multi-centre Teva Pharmaceutical Industries	Phase III 12 weeks N = 1,130	Patients 18- to 70-years-old with a history of chronic migraine	Fremanezumab 675 mg SC followed by monthly 225 mg for two months (monthly dosing regimen) (n = 379) Fremanezumab 675 mg SC at initiation followed by placebo for two months (quarterly dosing regimen) (n = 376) Matching placebo (n = 375)	Change from baseline in monthly average number of headache days of at least moderate severity over 3 months after the first dose of study drug
Bigal et al. (2015)[23] Multi-centre, US Teva Pharmaceutical Industries	Phase IIb 12 weeks N = 264	Patients 18- to 65-years-old with chronic migraine	Fremanezumab 675 mg first dose, then 225 mg[b] SC monthly (n = 88) Fremanezumab 900 mg SC monthly (n = 87) Matching placebo (n = 89)	Change from baseline in headache-hours during weeks 9 to12

Author (Year) Name of Study, Country, Funding	Study Phase, Study Duration, Sample Size	Population	Intervention(s), Comparator	Primary Outcome
Galcanezumab				
Eli Lilly Press Release (2017)[19] ClinicalTrials.gov (NCT02614261)[44] Keller (2017)[30] REGAIN Multi-centre Eli Lilly	Phase III 12 weeks N = 825	Patients 18- to 65-years-old with at least 15 migraine headaches days per month	Galcanezumab 120 mg SC monthly[c] (n = 278) Galcanezumab 240 mg SC once monthly[c] (n = 277) Matching placebo (n = 558)	Change from baseline in monthly migraine days over 12 weeks

IV = intravenous; NR = not reported; SC = subcutaneous.

[a] Doses of 10 mg and 30 mg were also tested in the trial.

[b] Patients in this trial arm received an initial dose of 675 mg, followed by monthly doses of 225 mg.

[c] Participants received an initial dose of 240 mg.

Erenumab: In ARISE and in STRIVE, the mean differences in monthly migraine days for erenumab 70 mg were −1.1 days ($P < 0.001$) and −1.4 days ($P < 0.001$) compared with placebo, respectively. At the 140 mg dose, the mean difference was −1.9 days ($P < 0.001$) in the STRIVE study.

In a phase II trial, the mean difference in monthly migraine days was −1.1 days (95% CI, −2.1 to −0.2, $P = 0.021$) when comparing erenumab 70 mg with placebo.

Fremanezumab: The mean difference in monthly migraine days for fremanezumab 225 mg compared with placebo was −1.5 days ($P < 0.0001$) in the HALO-EM study. The mean difference in the number of migraine days during weeks 9 to 12 was −2.81 days (95% CI, −4.07 to −1.55, $P < 0.0001$) in the phase IIb trial.

Comparing a single dose of fremanezumab 675 mg with a placebo quarterly dose regimen, the mean difference in monthly migraine days was −1.2 days ($P < 0.0001$) in HALO-EM. The mean difference in the number of migraine days during weeks 9 to 12 was −2.64 days (95% CI, −3.90 to −1.38, $P < 0.0001$) for fremanezumab 675 mg compared with placebo in the phase IIb trial.

Galcanezumab: In EVOLVE-1 and in EVOLVE-2, the mean differences in monthly migraine days for galcanezumab 120 mg were −1.9 days ($P < 0.001$) and −2.0 days ($P < 0.001$) compared with placebo, respectively. At the 240 mg dose, the mean differences were −1.8 days ($P < 0.001$) and −1.9 days ($P < 0.001$) compared with placebo, respectively.

In a phase II trial, the mean difference in monthly migraine days was −1.2 days (95% CI, −1.9 to −0.6, $P = 0.003$) when comparing galcanezumab 150 mg with placebo.

Chronic Migraine: Various primary outcomes were measured in the trials for chronic migraine.

Eptinezumab: With eptinezumab 100 mg and eptinezumab 300 mg, 31% and 33% of patients achieved a 75% reduction or more in migraine days over the course of the 12-week trial, respectively, compared with 21% of placebo patients ($P < 0.05$ for both comparisons).

Erenumab: In a phase II trial, the mean difference in monthly migraine days was −2.5 days (95% CI, −3.5 to −1.4, $P < 0.0001$) for both erenumab 70 mg and erenumab 140 mg compared with placebo.

Fremanezumab: In HALO-CM, the mean difference in monthly headache days was −2.1 days (SE 0.3) for the fremanezumab 675 mg initial dose followed by 225 mg group and −1.8 days (SE 0.3) for fremanezumab 675 mg single dose, compared with placebo ($P < 0.001$ for both comparisons).

In a phase III trial, the mean difference in headache-hours during weeks 9 to 12 was −22.74 hours (95% CI, −44.28 to −1.21, $P = 0.0386$) for fremanezumab 675 mg initial dose followed by 225 mg group and −30.41 hours (95% CI: −55.88 to −8.95, $P = 0.0057$) for fremanezumab 900 mg, compared with placebo.

Table 4: Change in Frequency of Migraines[a] — Episodic Migraine

Eptinezumab	Phase III Trial (PROMISE-1)[10,30]		
Change from baseline over weeks 1 to12 in monthly migraine days			
Dose	100 mg (n = 222)	300 mg (n = 222)	Placebo (n = 222)
Days (SD or SE)	−3.9 (NR)	−4.3 (NR)	−3.2 (NR)
Difference vs. PL, days (95% CI)	NR	NR	
P value	0.0179	0.0001	
Eptinezumab	**Phase II Trial[7]**		
Change from baseline to weeks 5 to 8 in the frequency of migraine days			
Dose		1,000 mg (n = 73)	Placebo (n = 78)
Days (SD)		−5.6 (3.0)	−4.6 (3.6)
Difference vs. PL, days (95% CI)		−1.0 (−2.1 to 0.1)	
P value		0.0306	
Erenumab	**Phase III Trial (ARISE)[16,32]**		
Change from baseline to weeks 9 to 12 in monthly migraine days			
Dose	70 mg (n = 289)		Placebo (n = 291)
Days (SD or SE)	−2.9 (NR)		−1.8 (NR)
Difference vs. PL, days (95% CI)	NR		
P value	< 0.001		
Erenumab	**Phase III Trial (STRIVE)[17,18,32,33]**		
Change from baseline in monthly migraine days between weeks 13 to 24			
Dose	70 mg (n = 312)	140 mg (n = 318)	Placebo (n = 316)
Days (SE)	−3.2 (0.2)	−3.7 (0.2)	−1.8 (0.2)
Difference vs. PL, days (95% CI)	−1.4 (−1.9 to −0.9)	−1.9 (−2.3 to −1.4)	
P value	< 0.001	< 0.001	
Erenumab	**Phase II Trial[35]**		
Change from baseline in monthly migraine days between weeks 9 to12			
Dose	70 mg (n = 107)		Placebo (n = 160)
Days (SE)	−3.4 (0.4)		−2.28 (0.3)
Difference vs. PL, days (95% CI)	−1.1 (−2.1 to −0.2)		
P value	0.021		
Fremanezumab	**Phase III Trial (HALO EM)[21]**		
Change from baseline in the monthly migraine days during the 12-week period			
Dose	225 mg (n = NR)	675 mg (n = NR)	Placebo (n = NR)
Days (SD or SE)	−3.7 (NR)	−3.4 (NR)	−2.2 (NR)
Difference vs. PL, days (95% CI)	NR	NR	
P value	< 0.0001	< 0.0001	
Fremanezumab	**Phase IIb Trial[22]**		
Change from baseline in the number of migraine days during weeks 9 to 12			
Dose	225 mg (n = 95)	675 mg (n = 95)	Placebo (n = 104)
Days (SD)	−6.27 (5.38)	−6.09 (5.22)	−3.46 (5.4)
Difference vs. PL, days (95% CI)	−2.81 (−4.07 to −1.55)	−2.64 (−3.90 to −1.38)	
P value	< 0.0001	< 0.0001	

Galcanezumab	Phase III (EVOLVE-1)[19]		
Change from baseline in monthly migraine days over 24 weeks			
Dose	120 mg (n = NR)	240 mg (n = NR)	Placebo (n = NR)
Days (SD or SE)	−4.7 (NR)	−4.6 (NR)	−2.8 (NR)
Difference vs. PL, days (95% CI)	NR	NR	
P value	< 0.001	< 0.001	
Galcanezumab	**Phase III (EVOLVE-2)[19]**		
Change from baseline in monthly migraine days over 24 weeks			
Dose	120 mg (n = NR)	240 mg (n = NR)	Placebo (n = NR)
Days (SD or SE)	−4.3 (NR)	−4.2 (NR)	−2.3
Difference vs. PL, days (95% CI)	NR	NR	
P value	< 0.001	< 0.001	
Galcanezumab	**Phase II[38]**		
Change from baseline to weeks 9 to 12 in monthly migraine days			
Dose	150 mg (n = 108)		Placebo (n = 110)
Days (SD)	−4.2 (3.1)		−3.0 (3.0)
Difference vs. PL, days (90% CI)	−1.2 (−1.9 to −0.6)		
P value	0.003		

CI = confidence interval; NR = not reported; PL = placebo; SD = standard deviation; SE = standard error.

[a] For detailed dosing information, please consult Table 2.

Table 5: Change in Frequency of Migraines or Headaches [a] — Chronic Migraine

Eptinezumab	Phase II Trial[39]		
% patients achieving ≥ 75% reduction from baseline in migraine days over weeks 1 to 12			
Dose	100 mg (n = NR)	300 mg (n = NR)	Placebo (n = NR)
% patients (n/N)	31 (NR)	33 (NR)	21 (NR)
Odds Ratio (95% CI)	NR	NR	
P value	< 0.05	< 0.05	
Erenumab	**Phase II Trial[41]**		
Change from baseline to weeks 9 to 12 in monthly migraine days			
Dose	70 mg (n = 188)	140 mg (n = 187)	Placebo (n = 281)
Days (SE)	−6.6 (0.4)	−6.6 (0.4)	−4.2 (0.4)
Difference vs. PL, days (95% CI)	−2.5 (−3.5 to −1.4)	−2.5 (−3.5 to −1.4)	
P value	< 0.0001	< 0.0001	
Fremanezumab	**Phase III Trial (HALO-CM)[42,45]**		
Change from baseline in monthly headache days over 3 months			
Dose	675 mg/ 225 mg (n = 375)	675 mg/placebo (n = 375)	Placebo (n = 371)
Days (SE)	−4.6 (0.3)	−4.3 (0.3)	−2.5 (0.3)
Difference vs. PL, days (95% CI)	−2.1 (0.3)	−1.8 (0.3)	
P value	< 0.001	< 0.001	

Fremanezumab	Phase II Trial[23]		
Change from baseline in headache-hours during weeks 9 to 12			
Dose	675 mg/ 225 mg (n = 88)	900 mg (n = 87)	Placebo (n = 89)
Hours (SD)	−59.84 (80.38)	−67.51 (79.37)	−37.10 (79.44)
Difference vs. PL, hours (95% CI)	−22.74 (−44.28 to −1.21)	−30.41 (−51.88 to −8.95)	
P value	0.0386	0.0057	
Galcanezumab	**Phase III (REGAIN)[19,30]**		
Change from baseline in monthly migraine days over 12 weeks			
Dose	120 mg (n = 278)	240 mg (n = 277)	Placebo (n = 558)
Days (SD or SE)	−4.8 (NR)	−4.6 (NR)	−2.7 (NR)
Difference vs. PL, days (95% CI)	NR	NR	
P value	0.001	0.001	

CI = confidence interval; NR = not reported; PL = placebo; SD = standard deviation; SE = standard error.

[a] For detailed dosing information, please consult Table 3.

Galcanezumab: In REGAIN, the mean differences in monthly migraine days compared with placebo were −2.1 days (*P* = 0.001) and −1.9 days (*P* = 0.001) for galcanezumab 120 mg and galcanezumab 240 mg, respectively.

Safety

There was insufficient safety information in the phase III randomized controlled trials reported as conference abstracts or press releases and, therefore, only the safety results for published phase II and phase IIb trials are reported in Table 5.

No deaths were reported in the phase II and phase IIb trials.

The frequency of adverse events ranged from 44% to 72% with the anti-CGRP mAbs and from 39% to 67% with placebo. Adverse events most frequently reported included upper respiratory tract infection, nasopharyngitis, urinary tract infection, fatigue, back pain, muscle spasm, arthralgia, and abdominal pain, with similar frequencies across active and placebo arms. Injection site pain and injection site reactions were more frequent in the active groups compared with placebo.

A total of 1% to 2% of patients in the active treatment arms experienced a serious adverse event. These included:

- With eptinezumab 1,000 mg, one patient experienced chest pain, transient ischemic attack, conversion disorder, and dyspnea, and one patient had pyelonephritis requiring hospitalization, compared with one patient fracturing a fibula in the placebo group.
- With erenumab 70 mg, six patients experienced vertigo and migraine, intervertebral disc protrusion, appendicitis, costochondritis, fibroma, non-cardiac chest pain, and a fracture of the radius, whereas with erenumab 140 mg, two patients reported abdominal adhesions, abdominal pain, or cartilage injury. With placebo, seven patients experienced a serious adverse event, which included intervertebral disc protrusion, cholecystitis, migraine, pancreatitis, parotitis, urinary tract infection, and vomiting.
- With fremanezumab 225 mg, one patient fractured a fibula and one patient had a migraine associated with a hypertensive crisis, whereas with the 675 mg dose, one patient reported tremor and another reported antiphospholipid syndrome. In the group receiving an initial dose of 675 mg followed by fremanezumab 225 mg, one patient had pneumonia. At the higher dose of 900 mg, depression with suicide attempt, suicide attempt, and severe irritable bowel syndrome were reported in two patients. In the placebo group, one patient had nephrolithiasis.
- Details regarding the serious adverse events experienced with galcanezumab were not provided in the publications.

Withdrawals due to adverse events were infrequent. Reasons for stopping treatment because of adverse events included temperature intolerance, headache and migraine (erenumab 70 mg, all in one patient), fibula fracture and migraine associated with hypertensive crisis (fremanezumab 225 mg, one patient), and antiphospholipid syndrome and tremor (fremanezumab 675 mg, one patient). Two patients stopped erenumab 140 mg because of adverse events (constipation, fatigue, and metrorrhagia). Withdrawals because of an adverse event were reported in four patients and three patients administered with initial dose of 675 mg followed by fremanezumab 225 mg, and fremanezumab 900 mg, respectively; no reasons were provided in the publication.

Table 6: Harms from Published Phase II and Phase II/b Randomized Controlled Trials — Number of Patients With Events

EPTINEZUMAB						
	Episodic[7]					
	1,000 mg (n = 81)	Placebo (n = 82)				
NoP (%): Adverse Events	46 (57)	43 (52)				
NoP(%): Serious Adverse Events	2 (2)	1(1)				
NoP (%): Withdrawals Due to Adverse Events	0	0				
ERENUMAB						
	Episodic[35]			*Chronic*[41]		
	70 mg (n =106)	Placebo (n =153)		140 mg (n = 188)	70 mg (n = 190)	Placebo (n = 282)
NoP (%): Adverse Events	54 (51)	80 (53)		88 (47)	83 (44)	110 (39)
NoP (%): Serious Adverse Events	1(1)	0		2(1)	6 (3)	7 (2)
NoP (%): Withdrawals Due to Adverse Events	1(1)	1 (< 1)		2(1)	0	2 (< 1)
FREMANEZUMAB						
	Episodic[22]			*Chronic*[23]		
	225 mg (n = 96)	675 mg (n = 96)	Placebo (n = 104)	675/225 mg (n = 88)	900 mg (n = 86)	Placebo (n = 89)
NoP (%): Adverse Events	44 (46)	57 (59)	58 (56)	47 (53)	41 (48)	36 (40)
NoP (%): Serious Adverse Events	2 (2)	2 (2)	0	1 (1)	2 (2)	1 (1)
NoP (%): Withdrawals Due to Adverse Events	1 (1)	1 (1)	0	4 (5)	3 (3)	1 (1)
GALCANEZUMAB						
	Episodic[38]					
	150 mg (n = 107)	Placebo (n = 110)				
NoP (%): Adverse Events	77 (72)	74 (67)				
NoP (%): Serious Adverse Events	2 (2)	4 (4)				
NoP (%): Withdrawals Due to Adverse Events	0	1 (1)				

NoP= number of patients.

Of note, CGRP neuropeptides, which are widely distributed in the body, are potent vasodilators. Thus, inhibiting CGRPs could potentially cause serious adverse events, including ischemic events.[3,30] So far, the trials showed no evidence of serious cardiovascular adverse events.

Study Limitations

A common theme for all the trials is that the study population included a high proportion of women compared with men. This is expected considering that migraine headaches affect three times more women than men.[2,4,5] This raises concerns about the generalizability of the results to the male population. The majority of the study population was white, which also raises the concern about the generalizability of these study results in patients of other ethnic origins as medication efficacy and side effects can vary with ethnicity.[46]

The evidence on efficacy obtained so far for all four drugs is from placebo-controlled trials. There is a need to assess the efficacy of these drugs in comparison to standard of care in head-to-head trials in order to better determine their place in therapy.

Finally, some of the data were obtained from conference abstracts and press releases. There may be gaps in the results.

Concurrent Developments

PROMISE-2 is a phase III, randomized, double-blind, placebo-controlled trial of eptinezumab currently being conducted in the prevention of chronic migraines. The final data collection date for the primary outcomes measure (change in number of migraine days) is set for June 2018.[47]

Galcanezumab and fremanezumab are currently in phase III trials for the management of cluster headaches.[48-53]

Atogepant (AGN-241689, formerly MK-8031; Allergan) is currently being studied for episodic migraine prevention.[54,55]

Ubrogepant (MK-1602-006; Allergan) and rimegepant (BHV-3000; Biohaven Pharmaceuticals) are currently in phase III trials to evaluate their efficacy in the treatment of acute migraines.[54]

Lasmiditan (COL-144 or LY573144; Eli Lilly.), a 5-HT1F receptor agonist (commonly known as a "ditan ") is currently in phase III clinical trials for the treatment of acute migraine.[54,56,57 58]

Implementation Issues

Access to anti-CGRP mAbs is currently limited, as they have not been approved in any country. Therefore none of the drugs are currently marketed in Canada. Although the cost of these drugs has not been determined, they will potentially have a significant budget impact because of the high cost of biologics and the prevalence of episodic and chronic migraines.

Eptinezumab is the only drug administered intravenously. Intravenous administration could pose a challenge depending on the accessibility and availability of treatment centres. Eptinezumab and fremanezumab are administered every three months; this administration schedule could be desirable to patients who prefer less-frequent dosing regimens.

The appropriate duration of treatment and whether these drugs can eventually be tapered down or discontinued still needs to be clarified. Information on how these drugs will be used with other preventive migraine therapies is lacking.[30]

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Appendix 1: Small-Molecule CGRP Receptor Antagonists to Treat Acute Migraine No Longer in Development

Drug	Development Name	Development Status
Olcegepant	BIBN4096BS	Did not proceed beyond phase II because of modest efficacy
Telcagepant	MK-0974	Six completed phase III trials; sponsor has stopped clinical development because of liver toxicity
NA	BI 44370 TA	Development phase discontinued; reasons unknown
NA	MK-3207	Development discontinued because of liver toxicity

NA = not applicable.