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Small Molecule Calcitonin Gene-Related Peptide Receptor Antagonists for the Acute Treatment of Migraine

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CADTH

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Methods

These bulletins are not systematic reviews and do not involve critical appraisal or include a detailed summary of study findings. Rather, they present an overview of the technology and available evidence. They are not intended to provide recommendations for or against a particular technology.

Literature Search Strategy

A limited literature search was conducted by an information specialist on key resources including MEDLINE All (1946-) through Ovid, Embase (1974-) through OVID, PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were rimegepant and ubrogepant. The initial search was completed on September 26, 2019. Regular alerts updated the search until project completion; only citations retrieved before February 3, 2020 were incorporated into the analysis. No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Where possible, retrieval was limited to the human population.

Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention was rimegepant and ubrogepant and if the studies were a phase III randomized controlled trial (RCTs). Conference abstracts and grey literature were included when they provided additional information to that available in the published studies.

Peer Review

A draft version of this bulletin was reviewed by one clinical expert. The manufacturers of the drugs were also given the opportunity to comment on an earlier draft.

Summary

- Migraine is a common neurological disease and one of the leading causes of disability. The majority of adults with migraine use medications for their migraine attacks. Triptans are the most commonly used medication for moderate to severe attacks. However, for one-third of people with migraine, triptans are not effective, have decreased response over time, or are contraindicated.
- Small molecule calcitonin gene-related peptide (CGRP) receptor antagonists, also known as gepants, belong to a novel class of drugs that target CGRP receptors, which are thought to play a role in pain and migraines.
- Six gepants have gone through clinical development for the acute treatment of migraine. However, four of these had their development halted. Two gepants, rimegepant and ubrogepant, have completed phase III trials for the acute treatment of migraine. Ubrogepant was approved for marketing by the US FDA in December 2019. Rimegepant is currently under review by the US FDA.
- Evidence from phase III RCTs showed that rimegepant and ubrogepant were better than placebo for two key outcomes — freedom from pain and freedom from the most bothersome symptom (from among the migraine-associated symptoms: photophobia, phonophobia, or nausea) — at two-hours post-dose. There were no safety concerns identified with these drugs in the RCTs and in a one-year extension trial; however, increases in serum alanine aminotransferase (ALT) and aspartate transaminase (AST) above the upper limit of normal range (ULN) were reported in all the studies for rimegepant and ubrogepant.
- No studies comparing the gepants to other acute treatment of migraine were identified and thus their relative efficacy and safety to the triptans and their place in therapy are unknown. The studies evaluated the gepants on a single episode of a migraine attack which did not permit the assessment of the consistency of the effects of the drugs over time.
- Although the cost of the drugs in Canada is not available, it is likely to have a significant budget impact due to the high prevalence of migraine and the unmet need of migraine treatments in up to one-third of migraine sufferers.

Background

Migraine is a common, debilitating neurological disease.[1,2] Migraine is typically episodic, and recurrent attacks are characterized by headache that are often one-sided and described as pulsatile or throbbing. Migraine is clinically diagnosed based on the frequency and nature of the headache and the presence or absence of aura. Aura refers to a gradual onset of sensory or visual symptoms either before the onset of headache or as part of the headache.[3] Migraine without aura, the most common type of migraine, is characterized by headache attacks lasting four to 72 hours. Attacks are usually accompanied by photophobia (light sensitivity), phonophobia (sensitivity to noise), and nausea, with or without vomiting. In addition to these symptoms, migraine with aura is also characterized by reversible focal neurological symptoms that usually precede the headache and last up to 60 minutes, or occasionally longer.[2]

According to the 2016 Global Burden of Disease Study, migraine is the second leading cause of years lived with disability globally.[4] Studies have shown the prevalence of migraine to be up to 26% in women, and up to 10% in men, in Canada.[2] In 2010-2011, an estimated 8.3% of Canadians (2.7 million) were diagnosed with migraine. Among them, 42% took prescription medication for their condition. Migraine affects many aspects of daily life including education, work, sleep, and driving.[5] As such, migraines are costly,

both in terms of direct and indirect costs. Given the prevalence, and social and economic impact of migraine, new therapies under clinical development including those targeting CGRP, could be important to reduce the disease burden and improve the quality of life.

The Technology

The CGRP is a 37-amino acid neuropeptide with vasodilator properties. It is present in the peripheral and central nervous systems and is considered to play a role in the pathophysiology of migraine pain. Hence, therapies targeting CGRP may be effective in the management of migraines. To date, two drug classes of CGRP antagonists have been developed: monoclonal antibodies (mAbs) targeting either CGRP or CGRP receptors, and small molecule CGRP receptor antagonists, also called gepants. The latter are the focus of this Emerging Health Technology Bulletin.[6-9] Of note, a CADTH Emerging Health Technology Bulletin on anti-CGRP mAbs was published in February 2018.[10]

Small molecule CGRP receptor antagonists, gepants, are in clinical development for the acute relief of migraine headache.[8] To date, six gepant compounds went through clinical development for the acute treatment of migraine. However, four of these had their development halted due to difficulties in developing an oral formulation (olcegepant [BIBN4096BS]), safety concerns (namely hepatotoxicity) (telcagepant [MK-0974] and [MK-3207]), or for unknown reasons (BI 44370 TA). Currently there are three second generation gepants in clinical development.[11] Two second generation gepants, rimegepant (BHV-3000; formerly BMS-927711; Biohaven Pharmaceuticals) and ubrogepant (MK-1602; Allergan), have completed phase III trials for the acute treatment of migraine.[7,8,12] Ubrogepant was approved for marketing by the US FDA in December 2019.[13] Another second generation gepant, atogepant (MK-8031) has a completed phase II/III trial for the prevention of migraine.[12] This bulletin focuses on rimegepant and ubrogepant.

Regulatory Status

Ubrogepant was approved for marketing by the US FDA in December 2019.[13] Rimegepant has not yet been approved to be marketed in any country.

Rimegepant (Zydis ODT [orally dissolving tablet], formerly BHV-3000; BMS-927711; Biohaven Pharmaceuticals): Biohaven Pharmaceuticals submitted a new drug application (NDA) to the US FDA in the second quarter of 2019. The company purchased an FDA priority review voucher (PRV) to use with the NDA submission of rimegepant. The PRV entitles the holder to designate an NDA for priority review and provides for an expedited six-month review.[14]

Ubrogepant (Ubrelvy, previously MK-1602; Allergan): Ubrogepant received FDA approval in December 2019, for the acute treatment of migraine with or without aura in adults.[15]

Cost and Administration

The Canadian cost of rimegepant and ubrogepant is currently not available. In the US, ubrogepant costs $85 per dose.[3]

The phase III RCTs evaluated 75 mg of rimegepant, given orally.[16-18] Rimegepant is formulated with the ODT technology, that is, a fast-dissolve formulation. Zydis ODT is a unique, oral solid dosage form that disperses almost instantly in the mouth — no water required. [14,19,20]

The recommended dose of ubrogepant (Ubrelvy) is 50 mg or 100 mg taken orally with or without food. If needed, a second dose may be taken at least two hours after the initial dose. The maximum dose in a 24-hour period is 200 mg.[15]

Target Population

Rimegepant and ubrogepant are intended for the acute treatment of migraine.[14,15] These drugs may potentially be an option for patients who do not respond to triptans, for those with triptan-induced medication overuse headache, or for those with cardiovascular risk factors.[12] Of note, rimegepant is also being studied for the prevention of migraine and treatment of refractory trigeminal neuralgia.[21,22]

Current Practice

In Canada, it is estimated that the majority of adults with migraine (90%) use medications for their migraine attacks. Acute (symptomatic) pharmacological migraine therapy refers to the use of medication to treat individual migraine attacks.[2] Acute attacks of mild-to-moderate severity are treated with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ASA, ibuprofen, or naproxen. 5-$HT_{1B/1D}$ receptor agonists — commonly known as triptans — are the most commonly used medication for moderate to severe attacks.[1-3,9] However, for one-third of people with migraine, triptans are not effective, have decreased response over time, or are contraindicated.[3,12]Opioids should not be used routinely.[1-3,9]

Summary of the Evidence

Description of the Included Studies

Rimegepant: Three randomized, double-blind, placebo-controlled phase III trials have been completed in adult patients with migraine. All trials involved multiple testing centres in the US and were industry-sponsored (Table 1). The sample sizes ranged from 1,072 patients to 1,351 patients.[16-18]

The patient population included adults aged 18 years or older with history of migraine (with or without aura) of at least one year, with two to eight migraine attacks of moderate or severe intensity per month, and fewer than 15 monthly headache days (migraine or non-migraine) over the last three months. Patients had to be able to distinguish tension-type headaches and cluster headaches from migraine headaches. Those on preventive medicine for migraine had to be on a stable dose for at least three months before entry into the study. Participants with contraindication to triptans were included if they met all other inclusion criteria. One of the key exclusion criteria was a history of a clinically significant or an unstable medical condition that would interfere with the study assessment of efficacy and safety, or expose participants to undue risk of a significant adverse event. These medical conditions included uncontrolled, unstable or recently diagnosed cardiovascular disease, history of alcohol or drug abuse, and major depression, among others.[16-18]

Patients were randomly assigned to receive one dose of either the treatment drug (rimegepant 75 mg) or placebo. Patients were allowed to take rescue medication (e.g., NSAIDs) two-hours post-dose. Trial duration was 48 hours post-dose. Patients reported symptoms at fixed time points: at the onset of the treated attack; at 15, 30, 45, 60, and 90 minutes; and at hours 2, 3, 4, 6, 8, 24, and 48 post-dose (Table 1). Primary outcome measures for these trials were freedom from pain at two-hours post-dose and freedom from the most bothersome symptom (from among the migraine-associated symptoms: photophobia, phonophobia, or nausea) at two-hour post-dose. [16-18]

Randomized patients who did not have a qualifying migraine attack during the trial period, and hence did not receive the medication or placebo, were excluded from the analysis. Efficacy was assessed on the basis of data recorded by the patients in an electronic diary. The safety follow-up period for rimegepant trials was seven days.[16-18]

Ubrogepant: There were two randomized, double-blind, placebo-controlled phase III trials conducted in adult patients with migraine. All trials involved multiple testing centres in the US, and all were industry-sponsored (Table 2). ACHIEVE I and ACHIEVE II included 1,327 patients and 1,355 patients, respectively. [26,27]

The patient population in ACHIEVE I and ACHIEVE II included adults 18 to 75 years old with at least a one-year history of migraine, with or without aura, with two to eight migraine attacks of moderate or severe intensity per month over the last three months. Participants who had taken acute treatment for migraine on 10 or more days in any of the three months before screening were excluded. Patients were excluded if the investigator had difficulty distinguishing their migraine headache from tension-type headache or other headaches, or if the patient had a history of 15 or more headache days per month (on average) during the six months before screening. Participants with current diagnosis of chronic migraine were excluded unless the investigator was of the opinion that the participant had fewer than 15 headache days per month because of concomitant preventive treatment. In both RCTs, patients with clinically significant cardiovascular diseases were excluded. In both RCTs, patients with ALT/AST levels > 1.5 times the ULN, a total bilirubin level of > 26 µmol per liter, or a serum albumin level of < 2.8 g per deciliter at screening were excluded. [26,27]

Patients were randomly assigned to receive one dose of either the treatment drug (ubrogepant 25 mg, 50 mg or 100 mg) or placebo. Patients were allowed to take an optional second dose of the study drug or their own rescue medication (e.g., triptans, ergots, and NSAIDs) two hours to 48 hours after the initial dose. Trial duration was 48 hours post-dose. Patients reported symptoms at fixed time points: before the initial dose; at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 hours after the initial dose; at the time of the second dose; and two hours after the second dose. Primary outcome measures for these trials were freedom from pain at two-hour post-dose and freedom from the most bothersome symptom (from among the migraine-associated symptoms: photophobia, phonophobia, or nausea) at two-hour post-dose.[26,27]

Randomized patients who did not have a qualifying migraine attack during the trial period, and hence did not receive the medication or placebo, were excluded from the analysis. Efficacy was assessed on the basis of data recorded by the participants in an electronic diary. The safety follow-up period for ubrogepant trials was 30 days.[26,27]

Of note, there is also one completed extension study on the long-term safety and tolerability of ubrogepant.[28]

Table 1: Characteristics of Phase III, Multi-centre, RCTs on Rimegepant

Author (year), name of study, funding	Study duration, sample size	Population	Intervention(s), comparator	Co-primary outcomes
Croop 2019[16] Study 303 ClinicalTrials.gov (NCT03461757)[23] Biohaven Pharmaceuticals	48 hours post-dose N = 1,351	Adults aged 18 years or older with history of migraine (with or without aura) of at least 1 year, with two to eight migraine attacks of moderate or severe intensity per month, and fewer than 15 monthly headache days (migraine or non-migraine) over the last 3 months	placebo (n = 682) one dose of rimegepant 75 mg ODT (n = 669)	Freedom from pain at 2 h post-dose Freedom from the most bothersome symptom (photophobia, phonophobia or nausea) at 2 h post-dose
Lipton 2019[18] Study 302 ClinicalTrials.gov (NCT03237845)[24] Biohaven Pharmaceuticals, Inc.	48 hours post-dose N = 1,072		placebo (n = 535) one dose of rimegepant 75 mg ODT (n = 537)	
Lipton 2019 [Poster][17] Study 301 ClinicalTrials.gov (NCT03235479)[25] Biohaven Pharmaceuticals, Inc.	48 hours post-dose N = 1,084		placebo (n = 541) one dose of rimegepant 75 mg ODT (n = 543)	

ODT = orally disintegrating tablet.

Table 2: Characteristics of Phase III, Multi-centre, RCTs on Ubrogepant

Author (Year), name of study, funding	Study duration, sample size	Population	Intervention(s), comparator	Primary outcome
Dodick 2019[26] ACHIEVE I ClinicalTrials.gov (NCT02828020)[29] Allergan	48 hours after initial dose N = 1,327	Adults and older adults, 18-75 years of age with migraine (with or without aura), with 2 to 8 migraine attacks of moderate or severe intensity per month during the previous 3 months, and fewer than 15 monthly headache days over the last 6 months	placebo (n = 456) ubrogepant 50 mg (n = 423) ubrogepant 100 mg (n = 448)	Freedom from pain and freedom from the most bothersome symptom (photophobia, phonophobia or nausea) at 2 h post-dose
Lipton 2019 [27] ACHIEVE II ClinicalTrials.gov (NCT02867709)[30] Allergan	48 hours after initial dose N = 1,355		placebo (n = 456) ubrogepant 25 mg (n = 435) ubrogepant 50 mg (n = 464)	

Results

Efficacy

Phase III multicenter, placebo-controlled RCTs for rimegepant: Data for two studies were published (Study 302 and 303), and data for the third study (Study 301) were obtained from a conference poster. In all three studies, the majority of the participants were female (85% to 87%), and the mean age was 40.2 (standard deviation [SD] 12.0) to 41.6 (SD 12.2) years. In both the published trials, the majority of the participants were white (74% to 75%).[16-18]

Patients reported a history of a mean of 4.6 (SD 1.8) to 4.7 (SD 1.8) migraine attacks per month, each of which lasted a mean of 29.5 (SD 21.6) to 32.5 (SD 22.1) hours if left untreated. The most commonly reported, most bothersome symptom was photophobia (51.9% to 57%), followed by nausea (23% to 29.6 %), and phonophobia (15.3% to 19%).[16-18]

In all three trials, rimegepant 75 mg ODT was better than placebo for both co-primary outcome measures, that is, freedom from pain and freedom from the most bothersome symptom at two-hours post-dose (Table 3).[16-18]

Phase III multicenter, placebo-controlled RCTs for ubrogepant: Both ACHIEVE I and ACHIEVE II were available as full publications. The majority of the participants were female (88.2% and 90%), and the mean age was 40.5 (SD 11.8) and 41.5 (SD 12.3) years. In both the trials, the majority of the participants were white (82.5% and 82%). Immediately before treating their migraine attack, 62.9 % and 59% described their migraine attack as moderate and 37.1% and 41% as severe. The most commonly reported, most bothersome symptoms were photophobia (56.4% and 57%), followed by phonophobia (22.3% and 26%), and nausea (20.9% and 17%). A mean of 98.2% and 96.8% of the participants were using concurrent preventive treatment at screening.[26,27]

In ACHIEVE II, patients reported a history of a mean of 4.6 (SD 1.8) migraine attacks per month 41.8%, 42.3% and 41.9% were triptan-naive in ubrogepant 50 mg, ubrogepant 25 mg, and placebo groups respectively. [27]

In the ACHIEVE I study, both ubrogepant 50 mg and ubrogepant 100 mg showed a greater percentage of patients achieving freedom from pain and freedom from the most bothersome symptom at two-hours post-dose (Table 3). In the pooled ubrogepant group, 38.6% (336/871) took the optional second dose of the study medication. The percentage of patients with rescue medication used after the first dose of the study medication were 16.3% (69/423) in the 50 mg ubrogepant group, 15.2% (68/448) in the 100 mg ubrogepant group and 28.7% (131/456) in the placebo group. The frequencies of rescue medication use after an optional second dose of the study medication were 9.0% (38/423) in the 50 mg ubrogepant group, 10.0% (45/448) in the 100 mg ubrogepant group and 21.1% (96/456) in the placebo group. [12,26,29]

In the ACHIEVE II study both ubrogepant 25 mg and ubrogepant 50 mg showed a greater percentage of patients achieving freedom from pain at two-hours post-dose. Only the ubrogepant 50 mg dose showed a greater percentage of patients achieving freedom from the most bothersome symptom (Table 3). In the pooled ubrogepant group, 37.6% (338 of 899) of patients received an optional second dose of the study medication. The frequencies of rescue medication use after the first dose of the study medication were 16.4% for the 50 mg group, 20.5% for the 25-mg group, and 25.7% for the placebo group. The frequency of rescue medication use after an optional second dose of study medication were 9.7% for the 50 mg group, 10.1% for the 25 mg group, and 19.5% for the placebo group.[12,27,30]

Safety

The safety analyses for both rimegepant and ubrogepant trials were conducted on all patients who underwent randomization and took a dose of placebo or the drug (rimegepant or ubrogepant).[16-18,26,27]

No deaths were reported in the phase III trials for rimegepant or ubrogepant. Serious adverse events were reported in two out of three phase III studies for rimegepant and in both phase III studies for ubrogepant (Table 4). [16-18,26,27]

Common adverse events (> 1% of patients) reported with rimegepant included nausea, dizziness, and urinary tract infection. Common adverse events (> 2% of patients) reported with ubrogepant included nausea, dizziness, somnolence, dry mouth, upper respiratory tract infection, and nasopharyngitis (Table 5). Increases in alanine aminotransferase (ALT) or aspartate transaminase (AST) up to three times (but, not higher than five times) the upper limit for normal range were reported in all phase III studies (Table 6). There were no reports of increases in total bilirubin or hepatotoxicity.[16-18,26,27]

Long-Term Extension Study– Ubrogepant

There is one completed phase III, multicenter, randomized, open-label, 52-week extension trial evaluating the long-term safety and tolerability of ubrogepant 50 mg and 100 mg in the treatment of migraine. Data from the study are published (Table 7). Participants entered the trial after completing one of the two phase III RCTs (ACHIEVE I and ACHIEVE II). Participants

were randomized 1:1:1 to usual care, ubrogepant 50 mg or ubrogepant 100 mg. Usual care was defined as a standard of care treatment for migraine attacks, prescribed by the physician and administered for up to one year. The usual care population was mainly included to contextualize background rates of ALT/AST elevations. The usual care population included participants who were non-naive, non-contraindicated, and had tolerated their (usual care) medication prior to enrolment and use in the trial. Although an open-label trial, randomization to ubrogepant dose was blinded. Primary outcome measures were safety and tolerability. The safety population for the ubrogepant arms included all randomized participants who received at least one dose of treatment. Participants randomized to ubrogepant could treat up to eight migraine attacks per four-week interval during the one-year trial period. A qualifying migraine attack had to meet the following conditions: at least 48 hours had passed since the last dose of ubrogepant, the participant had at least 48 hours pain free, less than four hours had passed since the headache started, the headache was not resolving on its own, and prohibited medications were not taken. Safety assessments were taken at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 weeks relative to the randomization visit. An additional follow-up visit occurred four weeks after the 52-week visit or after early termination. Participants who did not treat a single migraine attack in the first six months of the trial were discontinued. An optional second dose of ubrogepant or rescue medication, including analgesics, antiemetics, or triptans, was allowed at least two hours after the initial dose if the participant had a nonresponding migraine or migraine recurrence.[28]

A total of 1,230 participants were included in the safety population; 665 participants from the ACHIEVE I lead-in trial and 565 from the ACHIEVE II lead-in trial. Participants were on average 42 years of age, 90% (1,106 of 1,230) female and 85% (1,043 of 1,230) white. Over the course of the one-year trial, an average of 13.2 and 14.8 migraine attacks were treated with one dose of ubrogepant 50 mg and 100 mg, respectively. An average of 12.3 and 12.4 migraine attacks were treated with two or more doses of ubrogepant 50 mg and 100 mg, respectively. The average number of doses taken per participant over the one-year extension period was 38.5 doses for ubrogepant 50 mg and 40.2 doses for ubrogepant 100 mg. No deaths occurred during the trial. Discontinuation due to adverse events were reported by 2.2% (9 of 404) in ubrogepant 50 mg, 2.7% (11 of 409) in the ubrogepant 100 mg, and by 1% (4 of 417) is the usual care group. The most common treatment-emergent adverse events (reported by > 5% of patients) included: upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, and influenza (Table 8).[28]

Study Limitations

In all the trials, the study populations included a high proportion of women compared with men, which is expected considering that migraine affects three times more women than men. The study populations were predominantly white.[16-18,26,27]

The evidence on efficacy obtained so far for both drugs are from placebo-controlled trials[16-18,26,27] 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. Given that these are single-attack design studies, (assessment of treatment effect on a single episode of a condition) it does not permit assessment of the consistency of the efficacy of the drugs from attack to attack over time in the same patient.[16-18,26,27]

In the ubrogepant trials, patients were excluded if the investigator had difficulty distinguishing the participant's migraine headache from tension-type headache or other headaches. In the rimegepant trials, the patients had to be able to distinguish tension-type headache and cluster headache from migraine headache. There may have been variability across trials on how patients and investigators classified headaches.

Clinical trials on rimegepant excluded patients with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease.[16-18] Clinical trials on ubrogepant excluded patients with clinically significant cardiovascular diseases.[26,27] This raises concerns about the use of these drug in patients with cardiovascular diseases which is an unmet need in migraine therapy, as triptans are contraindicated in patients with cardiovascular diseases.[12] Further, clinical trials on rimegepant also excluded patients with current diagnosis of major depression, a condition that is commonly comorbid with migraine.[16-18]

Finally, some of the data on rimegepant (Study 301) were obtained from a conference poster. There may be gaps in the results for this trial.

Table 3: Results for Co-primary Outcomes

Author (year), name of study		Freedom from pain at 2-hours post-dose	Freedom from the most bothersome symptom at 2-hours post-dose
Rimegepant			
Croop 2019[16] Study 303	Placebo	10.9% (74/682)	26.8% (183/682)
	Rimegepant 75 mg ODT	21.2% (142/669)	35.1% (235/669)
	P value	< 0.0001	0.0009
	Risk difference (95% CI)	10.4 (6.5 to 14.2)	8.3 (3.4 to 13.2)
Lipton 2019[18] Study 302	Placebo	12.0% (64/535)	25.2% (135/535)
	Rimegepant 75 mg ODT	19.6% (105/537)	37.6% (202/537)
	P value	< 0.001	< 0.001
	Absolute difference (95% CI)	7.6 (3.3 to 11.9)	12.4 (6.9 to 17.9)
Lipton 2019 [Poster][17] Study 301	Placebo	14.2% (77/541)	27.7% (150/541)
	Rimegepant 75 mg ODT	19.2% (104/543)	36.6% (199/543)
	P value	0.0298	0.0016
Ubrogepant			
Dodick, 2019[26] ACHIEVE I	Placebo	11.8% (54/456)	27.8% (126/454)
	Ubrogepant 50 mg	19.2% (81/442)	38.6% (162/420)
	P value	0.002	0.002
	OR (95% CI)	1.83 (1.25 to 2.66)	1.70 (1.27 to 2.28)
	Ubrogepant 100 mg	21.2% (95/448)	37.7% (169/448)
	P value	< 0.001	0.002
	OR (95% CI)	2.04 (1.41 to 2.95)	1.63 (1.22 to 2.17)
Lipton, 2019[27] ACHIEVE II	Placebo	14.3% (65/ 456)	27.4% (125/456)
	Ubrogepant 25 mg	20.7% (90/435)	34.1% (148/434)
	P value	0.03	0.07
	OR (95% CI)	1.56 (1.09 to 2.22)	1.37 (1.02 to 1.83)
	Ubrogepant 50 mg	21.8% (101/464)	38.9% (180/463)
	P value	0.01	0.01
	OR (95% CI)	1.62 (1.14 to 2.29)	1.65 (1.25 to 2.20)

CI = confidence interval; ODT=orally disintegrating tablet; OR = odds ratio.

Table 4: Serious Adverse Events

Author (year), name of study	Number of SAEs, n/N (%)	Description of events
Croop 2019[16] Study 303	rimegepant = 0/682 placebo = 0/693	NA
Lipton 2019[18] Study 302	rimegepant = 1/543 (0.2) placebo = 2 /543 (0.4)	Rimegepant: back pain Placebo: chest pain and urinary tract infection (1 participant each)
Lipton 2019 [Poster][17] Study 301	rimegepant = 2/546 (0.4) placebo = 1/549 (0.2)	Details not available. Both participants in the rimegepant group had not been dosed before the onset of the serious adverse events.
Dodick, 2019[26] ACHIEVE I	Ubrogepant 50 mg = 3/466[a] (0.6) Ubrogepant 100 mg = 2/485[a] (0.4) Placebo = 0/485	Ubrogepant 50 mg: appendicitis, spontaneous abortion, pericardial effusion (1 participant each) Ubrogepant 100 mg: appendicitis and seizure (1 participant each)
Lipton 2019[27] ACHIEVE II	Ubrogepant 25 mg = 1/478[a] (0.2) Ubrogepant 50 mg = 0/488 Placebo = 0/499	Ubrogepant 25 mg: One participant reported 7 SAEs related to a bicycling accident (ligament sprain, loss of consciousness, renal hematoma, road traffic accident, splenic rupture, syncope, and traumatic renal injury)

NA = not applicable; SAE= serious adverse events.

[a] Reported after 48 hours, but within 30 days after any dose.

Table 5: Treatment-Emergent Adverse Events

Author (year), name of study	Number of treatment-emergent adverse events, n/N (%)
Croop 2019[16] Study 303	rimegepant = 90/682 (13.0) placebo = 73/693 (11.0)
Lipton 2019[18] Study 302	rimegepant = 93/543 (17.1) placebo = 77/543 (14.2)
Lipton 2019 [Poster][17] Study 301	rimegepant = 69/546 (12.6) placebo = 59/549 (10.7)
Dodick 2019[26] ACHIEVE I	within 48 hours of any dosing ubrogepant 50 mg = 44/466 (9.4) ubrogepant 100 mg = 79/485 (16.3) placebo = 62/485 (12.8)
	within 30 days of any dosing ubrogepant 50 mg = 126/466 (27) ubrogepant 100 mg = 139/485 (28.7) placebo = 113/485 (23.3)
Lipton 2019[27] ACHIEVE II	within 48 hours of any dosing ubrogepant 25 mg = 44/478 (9.2) ubrogepant 50 mg = 63/488 (12.9) placebo = 51/499 (10.2)
	within 30 days of any dosing ubrogepant 25 mg = 105/478 (22.0) ubrogepant 50 mg = 133/488 (27.3) placebo = 112/499 (22.4)

Concurrent Developments

Rimegepant is also being studied for the prevention of episodic or chronic migraine and for treatment of refractory trigeminal neuralgia.[21,22]

Atogepant (MK-8031; Allergan), another gepant, is currently in development (one completed phase II/III trial) for the prevention of migraine.[12]

Lasmiditan (Reyvow; Eli Lilly), a 5-HT_{1F} receptor agonist (commonly known as a *ditan*) was approved by FDA in October 2019 for the acute treatment of migraine with or without aura in adults. [32]

There are four injectable monoclonal antibodies (mAbs) targeting the CGRP signalling pathway that are either approved by the FDA or are currently being developed as preventive therapy for episodic and chronic migraines. Erenumab (Aimovig ; Amgen Canada) and galcanezumab (Emgality; Eli Lilly Canada Inc.) have been approved by Health Canada and the FDA. [10,33-35] Fremanezumab (Ajovy; Teva Canada Innovation) has been approved by the FDA and is under review by Health Canada. These three mAbs target the CGRP. Eptinezumab (ALD403; Alder Biopharmaceuticals), is the fourth mAbs that targets the CGRP receptor. Eptinezumab has not yet received regulatory approval in US or Canada. [10,35]

Implementation Issues

Access to small molecule CGRP receptor antagonists (gepants) are currently limited in Canada as the drugs have not yet received regulatory approval in Canada.

The Canadian cost of the drug is unknown. However, these drugs will likely have a significant budget impact due to the high prevalence of migraine and the unmet need of migraine treatments in up to one-third of migraine sufferers; they have the potential to displace cheaper alternatives that are available as generics or available without a prescription.

Similar to many medications currently used for the acute treatment of migraine, both rimegepant and ubrogepant will offer oral dosage convenience. Additionally, rimegepant is formulated as a ODT, which could further aid its administration.

Given that the development of earlier generation gepants (for example telcagepant) were halted due to hepatotoxicity, it would be important to assess the clinical significance of the increased ALT/AST levels in the clinical trials for both of the gepants, which were comparable to that of placebo.

The clinical trials on both rimegepant and ubrogepant are conducted for single-attack migraine; hence, their long-term efficacy is unknown, including whether or not they will have reduced efficacy overtime. Further it is unknown if these drugs can meet the gap in treatment with triptans, that is, in patients with cardiovascular diseases, as these drugs have not been studied in that population.

Table 6: Hepatic Events — Liver Function Test

Author (year), name of study	Description	Number of events, n/N (%)
Croop 2019[16] Study 303	Serum AST or ALT > 3× ULN	rimegepant = 1/682 (0.1) placebo = 1/693 (0.1)
Lipton 2019[18] Study 302	Serum AST or ALT above ULN	rimegepant = 13/543 (2.4) placebo = 12/543 (2.2)
Lipton 2019 [Poster][17] Study 301	Serum AST or ALT above ULN	rimegepant = 11/546 (2.0) placebo = 20/549 (3.6)
	Serum AST or ALT > 3× ULN	rimegepant = 1/546 (0.2) placebo = 1/549 (0.2)
Dodick 2019[26] ACHIEVE I	Serum AST or ALT > 3× ULN	ubrogepant 50 mg = 2/456 (0.4) ubrogepant 100 mg = 3/479 (0.6) placebo = 1/478 (0.2)
Lipton 2019[27] ACHIEVE II	Serum AST or ALT > 3× ULN	ubrogepant 25 mg = 0/474 (0) ubrogepant 50 mg = 3/485 (0.6) placebo = 1/493 (0.2)

ALT = alanine aminotransferase; AST= aspartate transaminase; ULN=upper limit of normal range.

Table 7: Study Characteristics of the Phase III Long-term Extension Trial

Author (year), name of study, country, funding	Study duration, sample size	Population	Intervention(s), comparator	Primary outcome
Ailani 2020[28] ClinicalTrials.gov (NCT02873221)[31] Multi-centre, US Allergan	56 Weeks N = 1,230	Adults aged 18-76 years with migraine (with or without aura) who had participated in ACHIEVE I or ACHIEVE II	usual care (n = 417) ubrogepant 50 mg (n = 404) ubrogepant 100 mg (n = 409)	Percentage of participants with at least 1 treatment-emergent adverse event

Table 8: Study Results of the Phase III Long-term Extension Trial[28]

Types of events	Number of events, n/N (%)	Description of serious adverse events
Serious adverse events	ubrogepant 50 mg = 9/404(2) ubrogepant 100 mg = 12/409(3) usual care = 17/417 (4.1)	ubrogepant 50 mg: sinus tachycardia, intestinal obstruction, gait disturbance, cholelithiasis, cholecystitis acute, device allergy, pneumonia, pelvic inflammatory disease, post procedural infection, substance-induced mood disorder, hypertensive crisis ubrogepant 100 mg: colitis, hiatus hernia, pancreatitis acute, non-cardiac chest pain, cholelithiasis, cholecystitis acute, gastroenteritis norovirus, pneumonia, sepsis, subdural hematoma, diabetic ketoacidosis, hemiparesis , abortion, abortion spontaneous, ectopic pregnancy, suicidal ideation, acute respiratory failure. usual care[a]: anemia, myocardial infraction, constipation, diverticulum, femoral hernia, cholelithiasis, pneumonia, appendicitis, post procedural infection, pyelonephritis, muscle strain, pulmonary contusion, rib fracture, dehydration, hypokalemia, pancreatic carcinoma, migraine, syncope, abortion, abortion spontaneous, suicidal ideation.
Treatment-emergent adverse events	ubrogepant 50 mg = 268/404 (66) ubrogepant 100 mg = 297/409 (73) usual care = 271/417 (65.5)	
Hepatic events	Serum AST or ALT > 3× ULN ubrogepant 50 mg = 5/399 (1.3) ubrogepant 100 mg = 11/406 (2.7) usual care = 4/398 (1.0%) (No concurrent bilirubin elevation reported)	

ALT = alanine aminotransferase; AST = aspartate transaminase; ULN = upper limit of normal range.

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