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Qulipta® (Atogepant): Taking the Headache Out of Migraine Prevention

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Migraine is a common disorder that affects approximately one out of every six people, over a billion people worldwide, and is commonly among the top five reasons cited for emergency room visits due to severe, unresolved symptoms and the fear that the symptoms may be a sign of another serious health condition.[1,2,3] According to the Bureau of Labor Statistics, the total indirect cost associated with migraine in the United States has been estimated at $19.3 billion, mostly due to employees missing work.[4] While migraine is a subtype of headache, it differs from a tension or cluster headache in symptom onset and duration. A migraine is defined as a headache lasting 4 to 72 hours when untreated or unsuccessfully treated with at least two of the following characteristics: unilateral location, pulsating quality, moderate to severe pain, and is aggravated by or leads to the avoidance of routine physical activity. Additionally, during the headache, one of the following must also occur to be classified as a migraine: nausea and/or vomiting, photophobia and phonophobia.[5] Migraine sufferers experience significant disruption in social and leisure activities, physical and emotional functioning, as well as reduction in health-related quality of life.[6]

Migraine can be further subdivided into chronic or episodic migraine treatment categories. Chronic migraine is defined as headaches occurring 15 or more days a month for more than three months, and meeting all the diagnostic criteria of migraine at least 8 of those days of the month.[7] In contrast, episodic migraines occur fewer than 15 days a month.[7] Current medications available for use as first-line acute treatment options for migraine include acetaminophen, non-steroidal anti-inflammatory (NSAID), triptans, acetaminophen/aspirin/caffeine and sumatriptan/naproxen.[8]

While significant impacts on society are noted for migraine sufferers, the exact mechanism of migraine development is still not well understood. Historically, there have been two main theories regarding migraine origin: the vascular theory and the central neuronal theory. The vascular theory suggests that vasodilation of the intracranial blood vessels leads to activation of the trigeminal nerves, in turn causing nociceptor activation which signaling pain. The central neuronal theory is more widely accepted as the likely pathogenesis of migraine and states that a primary neuronal dysfunction, like in amyotrophic lateral sclerosis (ALS), leads to a sequence of changes that account for migraine and its associated symptoms.[9]

To determine the dysfunction occurring, clinical models have investigated signaling molecules thought to be important in the genesis of migraine attacks related to calcitonin gene-related peptide (CGRP). This has led to the development of drugs targeting CGRP and its associated receptor, with an emphasis on migraine prevention. Several injectables, like Aimovig® (erenumab) and Emgality® (galcanezumab), are currently on the market and used as subcutaneous injections for migraine prevention. These are monoclonal antibodies that work by binding to CGRP or its receptor to block its function.[10,11] Currently, injectable monoclonal antibodies are available for migraine prevention, but oral options specifically for migraine prevention are lacking.[12]

Qulipta® (atogepant) is the first and only oral CGRP receptor antagonist specifically developed for the preventive treatment of episodic migraine, approved by the Food and Drug Administration (FDA) in September 2021.[13] Similar to the injectable CGRP medications, atogepant works to block CGRP receptors and can be administered orally due to the small molecule size (molecular weight 603.5 vs approximately 150,000 for the monoclonal antibodies).[10,11,14] This review will discuss the pharmacology and important features of atogepant as well as the clinical trials that led to the approval of this groundbreaking new drug.

Pharmacology

Mechanism of Action

Atogepant is a CGRP receptor antagonist.[14] A 37-amino acid long peptide, CGRP, is produced by neurons in both the CNS and the peripheral nervous system and acts as a potent vasodilator.[15] It is concentrated at anatomical sites, such as the trigeminovascular system, which are involved in migraine pathophysiology. Studies have suggested that CGRP neurons are a primary relay for pain signals and may encode stimulus intensity.[16] CGRP concentrations are elevated during acute migraine attacks and may be chronically elevated in chronic migraineurs, thus blocking CGRP from binding to its receptor is thought to reduce

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migraine frequency.[9,15,16]

Pharmacokinetics

When administered orally, atogepant achieves peak concentrations in 1-2 hours. Atogepant is highly protein bound at 95.3% and has an approximate volume of distribution of 292 liters. The half-life is 11 hours and is metabolized mainly by CYP3A4. The clearance of atogepant is approximately 19 liters per hour and approximately 42% and 5% of the dose if found unchanged in the feces and urine, respectively. A summary of these pharmacokinetics parameters is found in **Table 1**.

As previously stated, the renal route of elimination plays a minor role in the clearance of atogepant.[14] In patients with severe renal impairment (creatinine clearance (CrCl) 15-29 mL/min), and in patients with end-stage renal disease (ESRD) (CrCl <15mL/min), the recommended dosage of atogepant is 10 mg once daily.[14] For patients with ESRD undergoing intermittent dialysis, atogepant should preferably be taken after the dialysis session.[14]

Pharmacokinetic models suggest no clinically significant difference between elderly and younger subjects, however clinical studies of atogepant did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients.[14] Generally, dose selection should be cautious with elderly patients, starting at the lowest dose.[14]

Table 1 | Select Atogepant Pharmacokinetics[14]

Absorption	
T_{max}[a]	1 - 2 hours
Distribution	
V_{ss}[b]	292 L
Protein Binding	95.3%
Metabolism	
	CYP3A4
Elimination	
Plasma Clearance	19 L/hour
$T_{1/2}$[c]	11 hours
Fecal	42%
Urine	5%

[a]Time to maximum concentration; [b]Steady state volume of distribution; [c]Half-life

Clinical Trials

The efficacy of atogepant for the preventive treatment of episodic migraine in adults was demonstrated in two randomized, multicenter, double-blind, placebo-controlled studies. Both studies enrolled patients with at least a one-year history of migraine, with or without aura, according to the International Classification of Headache Disorders (ICHD-3) diagnostic criteria.[14] This section will review both trials conducted by Joel Trugman et al. leading to the FDA-approval of atogepant for episodic migraine prevention.

NCT02848326 Joel Trugman, et al.[17]

A phase II/III, multicenter, randomized, double-blind, placebo controlled, parallel-group study was conducted to evaluate the efficacy, safety, and tolerability of multiple dosing regimens of oral AGN-241689 (atogepant) in episodic migraine prevention.[17] The trial included adults ages 18-75 with a one year or longer history of migraine with 4 –14 migraine days per month.[17] Subjects were excluded for the following: experienced 15 or more migraine days per month, had inadequate response to three or more medications (including at least two different classes) used for migraine prevention, had used opioids or barbiturates more than 2 days per month, had used triptans or ergots 10 days or more per month, or had used simple analgesics 15 days or more per month in the 3 months prior to initial visit or during the baseline period.[17] Before administration of study treatment, women of childbearing potential were required to have a negative urine pregnancy test and all participants were required to have been using a reliable means of contraception.[17]

A total of 825 patients were randomly assigned 2:1:2:2:1:1 ratio to received either placebo or atogepant 10mg daily, 30mg daily, 60mg daily, 30mg twice daily or 60mg twice daily, respectively.[17] The study anticipated efficacy of once-daily dosing, however the pharmacokinetic characteristics of atogepant suggested twice-daily dosing might provide better CGRP inhibition than a once-daily regimen, so twice-daily dosing was also included.[17]

The primary endpoint measured drug efficacy with change from baseline in mean monthly migraine days across the 12-week treatment period, with baseline defined as the 4 weeks prior to treatment.[17] Participants kept an electronic diary (eDiary) during the pretreatment and treatment periods to provide information about headache duration and characteristics, symptoms, and acute medication use, and an algorithm was used to identify migraine days and probable migraine days, headache days, and acute medication use days.[17] Migraine and probable migraine days were thereafter combined for simplicity, headache days were defined as any calendar day on which headache pain lasted at least two hours or required acute medication use after headache onset.

Results included a statistically significant decrease in the mean number of migraine days compared to placebo over the 12-week treatment period for all atogepant dosage groups.[17] The atogepant 10mg daily group saw a mean decrease of 4.0 days (adjusted p value=0.024), the atogepant 30mg once daily group saw a mean decrease of 3.8 days (adjusted p value=0.039) and the atogepant 60mg once daily group saw a mean decrease of 3.6 days (adjusted p value=0.039).[17] Based on these results, researchers concluded atogepant demonstrated efficacy for migraine prevention.

Secondary outcomes studied included reduction in monthly headache days, ≥50% reduction in monthly migraine days, and reduction in acute medication use days. The only secondary outcome that showed statistical significance for all atogepant doses versus placebo was the reduction in monthly headache days, while the other two outcomes were insignificant for all doses compared to placebo. Adverse effects (ADE) observed were minor.[17] Moreover, no hepatic safety issues related to atogepant were identified, which was a concern in earlier efforts to develop oral CGRP receptor antagonists for migraine prevention as shown by alanine aminotransferase elevation at least three times the upper limit of normal in the study of chronic telcagepant use for migraine prevention.[17,18] Overall, the study showed atogepant to be fairly well tolerated and efficacious for migraine prevention.

NCT03777059 Joel Trugman, et al.[19]

This phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study aimed to evaluate the efficacy, safety, and tolerability of oral atogepant for the prevention of

Table 2 | Summary of Primary Outcomes[17,19]

Trial	Treatment Arms	Endpoint	Results (95% CI)	P-Value
NCT02848326[17]	Atogepant 10mg daily (n=92)	Change in mean number of migraine days per month from baseline	-1.2 (-1.9 to –0.4)	0.024
	Atogepant 30mg daily (n=182)		-0.9 (-1.6 to –0.3)	0.039
	Atogepant 60mg daily (n=177)		-0.7 (-1.4 to –0.1)	0.039
	Atogepant 30mg BID (n=79)		-1.4 (-2.2 to –0.6)	0.0034
	Atogepant 60mg BID (n=87)		-1.3 (-2.1 to –0.5)	0.0031
NCT03777059[19]	Atogepant 10mg daily (n=214)		-1.2 (-1.8 to –0.6)	<0.001
	Atogepant 30mg daily (n=223)		-1.4 (-1.9 to –0.8)	<0.001
	Atogepant 60mg daily (n=222)		-1.7 (-2.3 to –1.2)	<0.001

migraine in participants with episodic migraine.

This study looked at the efficacy of three different daily doses of atogepant versus placebo. A total of 873 participants were included in the efficacy analysis. Patients were randomly assigned 1:1:1:1 to once daily atogepant 10mg, 30mg, 60mg or placebo, respectively.[19] Similar to the previous trial, this study included a 4-week screening and baseline period that served as the comparator group for atogepant efficacy. Participants were included if they were age 18-80 years, had 4 to 14 migraine days in the three months prior to screening, or had a one-year history of migraine with or without aura.[19] Subjects were excluded if they had a current diagnosis of chronic migraine, new daily persistent headache, cluster headache, painful cranial neuropathy, or if they averaged 15 or more headache days per month in the three months prior to enrollment or during the baseline period.[19] Similar to the previous trial, patients were also excluded if they used opioids or barbiturates on more than two days per month, triptans or ergots on more than 10 days per month, or NSAIDs or acetaminophen on more than 15 days per month in the three months prior to, or during the baseline period.[19] Females who were pregnant, planning to become pregnant, or lactating were excluded, and like the other trial, those of childbearing age had to use effective birth control to take part in the trial.[19]

The primary efficacy endpoint included mean change in number of migraine days per month across the 12-week study period.[19] Trial participants recorded data about headache occurrences in an eDiary daily, or on a tablet at the trial site during trial visits.[19] Primary outcome results conclude the average change from baseline in the mean number of migraine days per month across the 12-week treatment period was −3.7 with atogepant 10mg, −3.9 with atogepant 30mg, −4.2 with atogepant 60mg, and −2.5 with placebo.[19] The mean difference from placebo was statistically significant for each dose and was reported to be −1.2 days with 10 mg atogepant (95% confidence interval [CI], −1.8 to −0.6), −1.4 days with 30 mg atogepant (95% CI, −1.9 to −0.8), and −1.7 days with 60 mg atogepant (95% CI, −2.3 to −1.2).[19] A summary of the primary outcomes across both trials can be found in **Table 2**.

Three secondary outcomes studied were similar to the previous study: reduction in number of monthly headache days, ≥50% reduction in monthly migraine days and decrease in number of days requiring acute migraine medication use.[19] Secondary outcomes for each of these were found to be statistically significant and are summarized in **Table 3**.[19]

Additional secondary outcomes studied were the change from baseline in the score on the Role Function–Restrictive (RFR) domain of the MSQ (The Migraine-Specific Quality of Life Questionnaire), the change from baseline in the mean monthly score on the Performance of Daily Activities domain of the AIM-D (The Activity Impairment in Migraine–Diary) across the 12-week treatment period; and the change from baseline in the mean monthly score on the Physical Impairment domain of the AIM-D across the 12-week treatment period.[19] The MSQ and AIM-D are tools to assess the impact of migraine on quality of life. Both tools

Table 3 | Summary of Secondary Outcomes[16,26]

Trial	Outcome		Atogepant 10mg daily (n=92,214)	Atogepant 30mg daily (n=182,223)	Atogepant 60mg daily (n=177,222)	Atogepant 30mg BID (n=79)	Atogepant 60mg BID (n=87)
NCT02848326[17]	Reduction in monthly headache days vs. placebo	Mean (95% CI)	1.4 (0.5 to 2.2)	1.2 (0.6 to 1.9)	0.9 (0.2 to 1.6)	1.3 (0.4 to 2.2)	1.4 (0.5 to 2.3)
		Adjusted P value	0.024	0.039	0.039	0.013	0.0083
NCT03777059[19]		Mean (95% CI)	1.4 (0.8 to 2.0)	1.5 (0.9 to 2.1)	1.7 (1.1 to 2.3)	—	—
		Adjusted P value	<0.001	<0.001	<0.001	—	—
NCT02848326[17]	≥50% reduction in monthly migraine days vs. placebo	Odds Ratio (95% CI)	1.5 (1.0 to 2.3)	1.5 (1.0 to 2.1)	1.4 (1.0 to 2.0)	1.8 (1.2 to 2.9)	2.0 (1.3 to 3.2)
		Adjusted P value	0.11	0.11	0.15	0.034	0.0097
NCT03777059[19]		Odds Ratio (95% CI)	3.1 (2.0 to 4.6)	3.5 (2.4 to 5.3)	3.8 (2.6 to 5.7)	—	—
		Adjusted P value	<0.001	<0.001	<0.001	—	—
NCT02848326[17]	Reduction in acute medication use days vs. placebo	Mean (95% CI)	1.3 (0.6 to 2.0)	1.4 (0.9 to 2.0)	1.1 (0.5 to 1.7)	1.4 (0.6 to 2.1)	1.2 (0.5 to 1.9)
		Adjusted P value	0.11	0.11	0.15	0.034	0.0097
NCT03777059[19]		Mean (95% CI)	1.3 (0.8 to 1.8)	1.3 (0.8 to 1.8)	1.5 (1.0 to 2.0)	—	—
		Adjusted P value	<0.001	<0.001	<0.001	—	—

are split into various sections, or domains, that focus on different quality measures. The RFR domain of the MSQ measures the functional impact of migraine through limitations on daily social and work activities. In the AIM-D, the performance of daily activities includes things like difficulty with everyday activities like concentrating, errands, or leisure activities and the physical impairment domain focuses on movements like walking or moving one's head. The outcomes for two AIM-D scores for the 10mg dose showed improvement versus placebo, but were not shown to be statistically significant.[19] The improvements to the MSQ scores for the 10mg, 30mg and 60mg daily doses of atogepant were 30.3+/-1.6, 30.5+/-1.6, and 31.2+/-1.6 respectively with each p-value statistically significant at <0.001.[19] Placebo showed an improvement in the MSQ score of 20.4+/-1.6.[19] Score on the daily activities domain of the AIM-D improved by 7.3+/-0.5, 8.6+/-0.5, and 9.4+/-0.5 for the atogepant 10mg, 30mg and 60mg doses respectively, while placebo scores improved by 6.1+/-0.5.[19] P-values included p=0.09 for the atogepant 10mg daily dose and p<0.001 for both the atogepant 30mg daily and 60mg daily doses.[19] Finally, scores on the physical impairment domain of AIM-D improved by 5.1+/-0.4, 6.0+/-0.4, and 6.5+/-0.4 for the atogepant 10mg, 30mg, and 60mg daily doses, respectively.[19] Placebo showed an improvement of 4.0+/-0.4 and the p-values included 0.09, 0.002, and <0.001 for atogepant 10mg, 30mg, and 60mg daily, respectively.[19]

Adverse effects observed in trial participants were minor overall and similar between both studies. In addition, the frequency of events was similar between treatment and placebo groups. The most common ADEs were constipation, nausea, and upper respiratory tract infection which are summarized in Table 4.[19]

Dosage and Administration

Atogepant is available in the recommended doses of 10mg, 30mg, and 60mg strength tablets. Each dose is to be taken by mouth once daily with or without food (max: 60mg/day). Dosage should be adjusted for patient specific drug-drug interaction concerns, age, and renal function.[14]

Drug Interactions

Significant drug interactions exist when taken in combination with atogepant that may require dose or frequency adjustment or avoidance. Use of strong CYP3A4 *inhibitors* (e.g., ketoconazole, itraconazole, clarithromycin) requires dose reduction of 10 mg once daily.[14] No dosage adjustment of atogepant is needed with concomitant use of moderate or weak CYP3A4 inhibitors.[14] Dosage adjustment of atogepant with concomitant use of strong or moderate CYP3A4 *inducers* (e.g., rifampin, carbamazepine, phenytoin, St. John's wort, efavirenz, etravirine) is 30 mg or 60 mg once daily (dependent on medication) with no dosage adjustment needed with concomitant use of weak CYP3A4 inducers.[14] Consultation with a pharmacist or use of drug interaction database is advised prior to starting treatment.

Special Populations

Pediatrics & Geriatrics

The safety and efficacy of atogepant has yet to be established in the pediatric population, including children and adolescence less than 18 years of age. There should remain caution of use in this population. Meanwhile, elderly patients do not require any dose adjustments of atogepant, though recommendations still suggest starting at the lowest dose.[14]

Table 4 | Common Adverse Effects with Atogepant[17,19]

Adverse Effect	Incidence Rate
Constipation	3 - 8%
Nausea	4.1 - 12%
Upper Respiratory Tract Infection	3.9 - 8%
Urinary Tract Infection	1.4 - 6%

Pregnancy & Breastfeeding

There is no data available regarding the use of atogepant in pregnant women. Similarly, there are no adequate data on the presence of atogepant in human breast milk, the effects on the breastfed infant, or the effects on milk production.[14] Pregnancy tests should be performed to verify the pregnancy status in women prior to atogepant initiation. Additionally, females of reproductive potential should be advised to use effective contraception during treatment.[14]

Renal & Hepatic Impairment

Atogepant requires renal adjustment to 10mg once daily with CrCl <30 ml/min. For patient with ESRD on dialysis, dosing is recommended at 10mg once daily to be administered after dialysis.[14] Additionally, while there is no dose adjustment needed in patients with mild to moderate hepatic impairment, atogepant is not recommended in patients with severe hepatic impairment.[14] Baseline kidney and liver function tests should be performed, with repeat testing as clinically indicated.

Cost and Availability

Atogepant is estimated to cost $981.17 for a 30-day supply, making it more cost effective than Nurtec® for migraine prevention, which has an estimate cost of $1707.69 for a 30-day supply.[20] The estimated costs for a 30-day supply of the injectable agents (Aimovig®, Ajovy®, Emgality®, and Vyepti®) range from $220.39 to $635.41, but many patients may prefer an oral option.[20] Of note, the estimated average cost of $516.73 of a 30-day supply of Vyepti® does not include costs associated with intravenous infusion administration.[20] Patients with commercial insurance may be eligible for a manufacturer savings card enabling acquisition of the medication at little to no out-of-pocket costs.[21]

Clinical Implications

The American Headache Society (AHS) 2021 guidelines recommend that patients having to use acute migraine treatments more than twice weekly should be offered preventive therapy, and those still exceeding acute treatment twice weekly while on preventive therapy may require a second preventive agent.[22] These guidelines also state that patients should be considered for preventive treatment if the attacks interfere significantly with daily routines despite acute treatment, if the patient experiences adverse events with acute treatments, or if the patient prefers to use preventive treatment.[22] At the time of publication of the 2021 guidelines, there were no oral preventive treatment options on the market. A summary of the medications available for migraine prevention as of the 2021 AHS guidelines is seen in Table 5.

Conclusion

Atogepant is an orally administered CGRP receptor antagonist that has been shown to be both safe and effective in preventing migraines. Safety and efficacy were shown in approval trials to

Table 5 | 2021 American Headache Society Guideline Medication Recommendations for Migraine Prevention[22]

Oral	Parenteral
Candesartan	Eptinezumab
Divalproex / Valproate	Erenumab
Frovatriptan	Fremanezumab
Metoprolol / Propranolol	Galcanezumab
Topiramate	Onabotulinumtoxin A

be an option for chronic migraine sufferers as a daily oral episodic migraine prevention option. The oral once daily administration makes atogepant an attractive alternative to the current selection of migraine prevention treatments dominated by parenterally administered monoclonal antibodies. As always, the clinician should review all options available and patient factors before determining which treatment option is best for the patient.

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Drug Update:
New Indications and Dosage Forms
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Vabysmo® (faricimab-svoa) Intravitreal Injection
New Molecular Entity: Vascular endothelial growth factor and angiopoietin-2 inhibitor indicated for the treatment of age-related macular degeneration and diabetic macular edema in adults; dosing specific to indication for use

Enjaymo® (sutimlimab-jome) Injection
New Molecular Entity: Immunomodulatory classical complement inhibitor used to decrease the need for red blood cell transfusion due to hemolysis for adults with cold agglutinin disease; dosing based on total body weight

Pyrukynd® (mitapivat) Tablet
New Molecular Entity: Pyruvate kinase activator used to treat hemolytic anemia in pyruvate kinase deficiency for adults; administered with dose titration schedule provided via package insert and continued based on hemoglobin response

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