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Ubrelvy® (ubrogepant): Adding to the Abortive Therapy Arsenal for Migraine Treatment

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Migraine is a disorder that affects roughly one in six Americans and is among the top five reasons for visits to the emergency room.[1] It is characterized by severe pain, nausea/vomiting, and sensory-sensitivity.[2,3] Migraines are further classified as those with or without aura. The exact pathophysiology is unknown, however proposed theories include a genetic component, dilation of cranial blood vessels, and the role of calcitonin gene-related peptide (CGRP).[3] Diagnostic criteria for migraine is multifactorial and based on the presence of aura, headache characteristics, and the time course of symptoms.[2]

Treatment of acute migraine headache is the same regardless of type with the main goal of resolving symptoms as quickly as possible or preventing them from occurring. The current guidelines suggest initiating abortive therapy within one hour of headache onset for an acute attack.[4] Options for abortive therapy include over-the-counter (OTC) therapies such as acetaminophen, ibuprofen, naproxen, or combination products containing aspirin and caffeine. Prescription-only abortive therapies include triptans, ergotamines, and barbiturate-containing combination products. Per the American Academy of Family Physicians (AAFP) Guidelines for Treatment of Acute Migraine Headache, triptans and combination analgesics have the best evidence for rapid relief of acute attacks with neither opiates nor barbiturates recommended for acute attacks.[4] Triptans work by binding to serotonergic receptors, and are considered first-line in moderate to severe migraine attacks.[4]

Unfortunately for some patients, triptans and OTC abortives are not effective, driving development of alternative agents. Ubrelvy® (ubrogepant) was approved in December of 2019 for the acute treatment of migraine with or without aura in adults.[5] This manuscript will review the clinical pharmacology of ubrogepant as well as the clinical trials leading to its approval.

Clinical Pharmacology

In migraine, activation of the trigeminal sensory nerves causes a release of CGRP from the nerve endings. This induces vessel dilation and plasma extravasation, which triggers pain sensory fibers.[3] Ubrogepant is a calcitonin gene-related peptide receptor antagonist. By blocking the CGRP receptor, it interrupts the blood vessel dilation and plasma leakage that can cause pain.[6] This is believed to be a major mechanism of migraine and therefore the source of ubrogepant's use as an abortive therapy option.

Clinical Trials

There were two phase III clinical trials that examined the efficacy and safety of Ubrogepant in th ACHIEVE series. The results of these trials are summarized in **Table 2** and **Table 3**.

ACHIEVE I[7]

The ACHIEVE I study was a phase III clinical trial that tested the efficacy, safety, and tolerability of oral ubrogepant in the treatment of acute migraine attack.[7] This trial was a multicenter, randomized, double-blind, placebo-controlled study that ran from July 2016 to December 2017.

Table 1 | Select Ubrogepant Pharmacokinetics[3]

Absorption	
T_{max}[a]	1.5 hours
Distribution	
Vd[b]	350 L
Protein Binding	87%
Metabolism	
CYP3A4	
Elimination	
Cl[c]	87 L/hr
T1/2[d]	5-7 hours
Fecal Excretion	42%
Renal Excretion	6%

[a]Time to maximum plasma concentration; [b]Volume of distribution; [c]Clearance; [d]Half-life

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Table 2 | Primary Efficacy Endpoints for ACHIEVE I & II[7,8]

	ACHIEVE I[7]			ACHIEVE II[8]		
	Ubrogepant 50 mg	Ubrogepant 100 mg	Placebo	Ubrogepant 25 mg	Ubrogepant 50 mg	Placebo
Pain free at two hours						
% Responders	19.2	21.2	11.8	20.7	21.8	14.3
p-value	0.002	<0.001	-	0.03	0.01	-
Most bothersome symptom free at two hours						
% Responders	38.6	37.7	27.8	34.1	38.9	27.4
p-value	<0.001	<0.001	-	0.07	0.01	-

To be included, participants had to have at least a one year history of migraine (with or without aura) consistent with the diagnostic criteria provided by the International Classification of Headache Disorders (ICHD), migraine onset before the age of 50, history of migraines that typically last from 4-72 hours if untreated or treated unsuccessfully with at least 48 pain-free hours between episodes, and a history of two to eight migraine attacks per month with moderate to severe pain in each of the previous three months. Patients were excluded if they had difficulty distinguishing migraine headaches from other types of headache, had taken an abortive therapy on ten or more days per month in the previous three months, had a history of migraine aura with diplopia or impaired level of consciousness, had a diagnosis of cluster headaches or painful cranial neuropathy, required hospital treatment for migraine three or more times in the previous six months, required daily pain medications for another chronic non-headache condition, had a history of malignancy in the last five years, or had a history of GI conditions that could potentially affect the absorption or metabolism of the drug.

The trial included 1,672 participants, randomized in a 1:1:1 ratio to receive placebo (n=559), ubrogepant 50 mg (n=556), or ubrogepant 100 mg (n=557). There were 2 primary endpoints for this trial. The first primary endpoint of this trial was the percentage of participants with pain freedom at 2 hours after initial dose. This was defined as a reduction in headache severity from moderate/severe at baseline to no pain two hours after the initial dose. The other primary endpoint was the percentage of participants with absence of most bothersome migraine-associated symptom identified at baseline at two hours after the initial dose. These symptoms included photophobia, phonophobia, or nausea. Both of these primary endpoints were recorded directly by the patient in the patient's diary. Patients were also told to record the presence or absence of migraine-associated symptoms in the provided diary.

The secondary endpoints were the percentage of participants with pain relief at two hours after the initial dose (a reduction of pain from moderate/severe to mild or no headache), percentage of participants with sustained pain relief from two to 24 hours after the initial dose, percentage of participants with sustained pain freedom from two to 24 hours after the initial dose, percentage of patients with absence of photophobia, phonophobia, and nausea at two hours after the initial dose. For each secondary endpoint, statistical testing was only performed if significance was shown for both primary endpoints. Within each dose, the secondary endpoints were tested in the order in which they are listed above. If statistical significance was not shown higher up in the hierarchy, additional statistical testing was not performed.

Patients were provided with two tablets of either active therapy or placebo, the first to be taken at the time of a qualifying migraine attack (i.e., an attack of moderate or severe pain intensity). If the headache persisted beyond the initial dose, patients could take the second dose between two and 48 hours after the first. For the first primary endpoint, 19.2% of patients in the ubrogepant 50 mg group (p=0.002) and 21.2% of patients in the ubrogepant 100 mg group (p<0.001)), compared to the 11.8% of the placebo group, achieved freedom from migraine pain after two hours, compared to the 11.8% of the placebo group. For the second primary endpoint, 38.6% of patients in the ubrogepant 50 mg group (p=0.002) and 37.7% of the ubrogepant 100 mg group (p=0.002) had an absence of migraine symptoms after two hours compared to 27.8% in the placebo group. The trial did not assess the differences in efficacy of 100 mg vs 50 mg, and instead reported only each dose vs. placebo.

The percentage of patients who had pain relief at two hours was 60.7% in the 50 mg group (p=0.002), 61.4% in the 100 mg group (p=0.002), and 49.1% in the placebo group. No statistical difference was found between ubrogepant 50 mg and placebo at the level of sustained pain relief from two to 24 hours, so no inferences could be made about the subsequent secondary outcomes due to the hierarchical nature of the study design. A summary of the results for the secondary endpoints of the ACHIEVE I and II trials can be found in **Table 3**.

The type of adverse effects were similar across all groups, with the 100 mg dose having slightly higher frequencies. The most commonly reported adverse effects were nausea (1.7-4.1% in the first 48 hours), somnolence (0.6%-2.5% in the first 48 hours), and dry mouth (0.6%-2.1% in the first 48 hours). These were reported during the first 48 hours after treatment and appeared to be dose dependent. A summary of the safety data can be found in **Table 4**.

ACHIEVE II[8]

The ACHIEVE II trial sought to evaluate the efficacy, safety, and tolerability of two doses of ubropegant (25 mg and 50 mg) compared to placebo for the acute treatment of a single migraine attack.[8] This trial was a phase III, multicenter, randomized, double-blind, placebo controlledplacebo-controlled study. This study was performed nearly identically to the ACHIEVE I trial (described above). The main difference between ACHIEVE I and

ACHIEVE II was the doses used in the treatment arms: ubrogepant 25 mg, ubrogepant 50 mg, and placebo.

As in the ACHIEVE I trial, there were two primary endpoints. The first was the percentage of participants with pain freedom at two hours after initial dose, and the second was the percentage of participants with absence of most bothersome migraine-associated symptom identified at baseline at two hours after the initial dose. These symptoms included photophobia, phonophobia, or nausea). Again, patients were provided a diary to record the presence or absence of migraine-associated symptoms. The secondary endpoints also remained the same as in ACHIEVE I.

Patients were randomized 1:1:1 to receive either ubrogepant 25 mg (n=435), ubrogepant 50 mg (n=464), and placebo (n=456). Like the previous trial, patients were provided with two tablets of their assigned dose of ubrogepant or placebo. An optional second dose was allowed in the event of persistent symptoms 2-48 hours after the initial dose. For those who opted for the second dose, participants were further randomized to receive either a placebo or their assigned dose for the second dose.

Pain freedom after two hours was reported in 21.8% of the ubrogepant 50 mg group (p=0.01) and 20.7% in the ubrogepant 25 mg group (p=0.03) compared to 14.3% in the placebo group. Absence of bothersome symptoms was reported by 38.9% of patients in the ubrogepant 50 mg group (p=0.01) and 34.1% of patients in the ubrogepant 25 mg group (p=0.07) compared to 27.4% in the placebo group.

Rates of pain freedom two hours after the optional second dose were higher in participants who took the second dose of ubrogepant 50 mg (36.1%) over those who took placebo as their second dose (19%). No significant difference was found for the patients who took the second dose of ubrogepant 25 mg.

The ubrogepant 50 mg group was found to have significant results for most of the secondary endpoints including pain relief from two to 24 hours (OR, 1.77 [95% CI, 1.35-2.32]; adjusted p=0.01), sustained pain relief from two to 24 hours (OR, 2.16 [95% CI, 1.59-2.92]; adjusted p=0.01), sustained pain freedom from two to 24 hours (OR, 1.85 [95% CI, 1.20-2.83]; adjusted p=0.01), absence of photophobia (OR, 1.52 [95% CI, 1.14-2.02]; adjusted p=0.02), and absence of phonophobia (OR, 1.39 [95% CI, 1.05-1.84]; adjusted p=0.04). Responder rates were not found to be statistically significant for the absence of nausea.

Safety results were similar between placebo and both ubrogepant groups. Nausea was the most commonly reported side effect, at ~2% incidence. There were no deaths or discontinuations due to an adverse event.

Adverse Effects and Precautions

Specific clinical trial data for adverse reactions is presented in

Table 3 | Secondary Efficacy Endpoints for ACHIEVE I & II[7,8]

	ACHIEVE I[7]			ACHIEVE II[8]		
	Ubrogepant 50 mg	Ubrogepant 100 mg	Placebo	Ubrogepant 25 mg	Ubrogepant 50 mg	Placebo
Sustained pain relief at 2 hours						
% Responders	60.7	61.4	49.1	62.7	60.5	48.2
p-value	0.002	0.002	-	0.01	NE[a]	-
Sustained pain relief 2-24 hours						
% Responders	36.3	38.0	20.8	36.7	32.5	21.0
p-value	0.002	0.002	-	0.01	NE	-
Sustained freedom from pain 2-24 hours						
% Responders	12.7	15.4	8.6	14.4	12.7	8.2
p-value	NE	0.004	-	0.01	NE	-
Absence of photophobia at 2 hours						
% Responders	40.7	45.8	31.4	43.8	39.3	35.5
p-value	NE	0.004	-	0.02	NE	-
Absence of phonophobia at 2 hours						
% Responders	57.9	54.5	47.1	54.1	53.6	46.3
p-value	NE	NE	-	0.04	NE	-
Absence of nausea at 2 hours						
% Responders	70.2	69.2	62.3	71.3	70.6	70.0
p-value	NE	NE	-	0.95	NE	-

[a]Not evaluated in accordance with hierarchical plan

Table 4. The most frequently reported side effects with ubrogepant were nausea, somnolence, and dry mouth[6-8] There were no reported serious adverse effects within the first 48 hours of administration. There were two cases of appendicitis, one case of pericardial effusion, one seizure, and one spontaneous abortion within 30 days after any dose.[7] There have been no reports of death thought to be related to use of ubrogepant.

Ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, clarithromycin).[6] Using ubrogepant with strong CYP3A4 inhibitors can result in increased exposure to ubrogepant. For patients taking moderate CYP3A4 inhibitors (such as grapefruit juice, verapamil, ciprofloxacin, fluconazole, or fluvoxamine), a dose reduction is recommended. There is no data available for the use of ubrogepant with mild CYP3A4 inhibitors, although the package insert recommends a dose reduction. Ubrogepant should not be used with CYP3A4 inducers, as the drug will be metabolized before the patient can have adequate exposure. Lastly, a dose reduction is also recommended when ubrogepant is used with a BCRP and/or P-gp inhibitor (e.g., quinidine, carvedilol, eltrombopag, curcumin).

There is no data available for the use of ubrogepant in human pregnancies or lactation.[6] Ubrogepant was detected in the plasma of a breastfeeding rat. There is not enough human data available to make a recommendation.

Dosing and Administration

Ubrogepant comes as a 50 mg and 100 mg tablet. The recommended dose is 50 mg or 100 mg taken orally as needed. A second dose may be administered at least two hours after the initial dose if symptoms do not improve. Patient should not take more than two doses in one day with a maximum dose of 200 mg with in a 24 hour period.[6]

There is limited information available about dose adjustments outside of what is provided in the package insert. Dose adjustments are recommended for patients with CrCl 15-29 mL/min, but a dose is not specified.[6] Similarly, a dose reduction is recommended in patients with hepatic impairment however a specific dose recommendation was not included in the package insert.[6]

Cost and Availability

The manufacturer of ubrogepant provides a cost-savings program called "U-Save" that is compatible with commercial insurance. With this Rx card, patients can get the prescription starting at $10/month ($1/dose).[9] According to GoodRx, the cash price for ten 50 mg tablets is $1,026, which can be brought down to $846 with the coupon.[10] As of the writing of this article, public insurance plans (medicare, medicaid, tricare) have not come to a decision on price for ubrogepant.[13] For uninsured patients, access may prove to be difficult. Migraine impacts unemployed and lower socioeconomic individuals at higher rates, making access to new drugs like ubrogepant even more unlikely.[1]

Clinical Implications

The ACHIEVE II trial study found that only the 50 mg dose of ubrogepant was significantly more effective than placebo for achieving the absence of most bothersome migraine symptoms. Therefore, doses below 50 mg were not approved for use.[8] The ACHIEVE I trial established the efficacy of both 50 mg and 100 mg dosing.[7]

Table 4 | Adverse Drug Reactions[7,8]

Event	Incidence
Nausea	1.7-4.7%
Somnolence	0.6-2.5%
Dry Mouth	0.6-2.1%
URTI[a]	1.1-2.1%

[a]Upper respiratory tract infection

When using the ACHIEVE trials to decide on changes to clinical practice, several limitations should be evaluated. The first limitation worth mentioning is that both studies only looked at one acute attack. There is no data provided in regards to efficacy and safety of ubrogepant in multiple migraine attacks over a long period of time (beyond the 30 days that were accounted for in the study). These trials only focused on one headache episode per patient, rather than including information from multiple headaches from the same patient. Migraine is a chronic condition, and most patients require repeated abortive therapies over the course of their lives. Additionally, these trials had patients take the medication when their headache pain was considered moderate or severe. This treatment strategy is at odds with the recommendations of the American Headache Society to treat migraine at the first sign of headache (usually before the pain escalates to a moderate or severe level).[4,7]

Another weakness in the available data is the lack of an active comparator. There are multiple drug options available for use in treatment of acute migraine, it is important to know where ubrogepant stands in comparison to triptans and other combination analgesics. Additionally, in traditional abortive regimens, it is commonplace to use triptans and combination analgesics together.[3] A study that looks at use of ubrogepant in combination with other therapies could be performed. This would also allow the clinician to determine when ubrogepant's place in therapy among the other options available.

Ubrogepant has a reasonable safety profile which may be even better than that of triptans, however as mentioned, there were no direct comparisons to any active therapies therefore it is difficult to draw any conclusions.[11] Triptans have a long list of side effects including dizziness, nausea, drowsiness, tingling of the skin, flushing, chest pain, and weakness.[11] Ubrogepant adverse effects include only nausea, somnolence, and dry mouth, which may be more tolerable than those associated with triptans. However, safety data for ubrogepant has only been provided in these short-term clinical trials.

Rimegepant ODT, another CGRP receptor antagonist, is currently undergoing a phase III clinical trial.[12] There is no data associated with this study available for review at the time of this article. Having an orally disintegrating formulation will create a shorter onset of action, which is imperative for treating acute migraines.

Conclusion

The new CGRP receptor antagonist Ubrelvy® (ubrogepant), FDA-approved for acute migraine therapy, has been shown to have a significant effect on pain levels and migraine symptoms at two hours after the dose is taken. Ubrogepant has a mild safety

profile with the most common side effects being nausea, somnolence, and dry mouth. At this time, the data for Ubrelvy (ubrogepant) is not sufficient to replace triptans as a first-line agent in abortive therapy for migraines. It can be included as a possible alternative agent in patients who are intolerable to or without relief from triptan use.

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