NAME OF THE MEDICINAL PRODUCT

AQUIPTA Tablet 10 mg
AQUIPTA Tablet 60 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

AQUIPTA Tablet 10 mg

Each tablet contains 10 mg of atogepant.

AQUIPTA Tablet 60 mg

Each tablet contains 60 mg of atogepant.

Excipient with known effect

Each 60 mg tablet contains 31.5 mg sodium.

For the full list of excipients, see section **List of excipients**.

PHARMACEUTICAL FORM

Tablet

AQUIPTA Tablet 10 mg

White to off-white, round biconvex tablet, diameter 6 mm, and debossed with "A" and "10" on one side.

AQUIPTA Tablet 60 mg

White to off-white, oval biconvex tablet, 16 mm x 9 mm, and debossed with "A60" on one side.

CLINICAL PARTICULARS

Therapeutic indications

AQUIPTA is indicated for:
- Acute treatment of migraine with or without aura in adults
- Prophylaxis of migraine in adults who have at least 4 migraine days per month.

Posology and method of administration

Posology

The maximum dose per day for AQUIPTA is 60 mg.

For acute treatment of migraine as needed, the recommended dose for AQUIPTA is 60 mg.

For prophylaxis of migraine, the recommended dose is 60 mg atogepant once daily.

The tablets can be taken with or without meals.

Missed dose

For migraine prophylaxis, a missed dose should be taken as soon as it is remembered. If it is forgotten for an entire day, the missed dose should be skipped and the next dose taken as scheduled.

Dose modifications

Dosing modifications for concomitant use of specific medicinal products are provided in Table 1 (see section **Interaction with other medicinal products and other forms of interaction**).

Table 1: Dose modifications for interactions

Dose modifications	Recommended once daily dose
Strong CYP3A4 inhibitors	10 mg
Strong OATP inhibitors	10 mg

Special populations

Elderly
Population pharmacokinetic modelling suggests no clinically significant pharmacokinetic differences between elderly and younger subjects. No dose adjustment is needed in elderly patients.

Renal impairment
No dose adjustment is recommended for patients with mild or moderate renal impairment (see section **Pharmacokinetic properties**). In patients with severe renal impairment (creatinine clearance [CLcr] 15-29 mL/min), and in patients with end-stage renal disease (ESRD) (CLcr < 15 mL/min), the recommended dose is 10 mg once daily. For patients with ESRD undergoing intermittent dialysis, AQUIPTA should preferably be taken after dialysis.

Hepatic impairment
No dose adjustment is recommended for patients with mild or moderate hepatic impairment (see section **Pharmacokinetic properties**). Atogepant should be avoided in patients with severe hepatic impairment.

Paediatric population
The safety and efficacy of atogepant in children (< 18 years of age) have not yet been established. No data are available.

Method of administration

AQUIPTA is for oral use. Tablets should be swallowed whole and should not be split, crushed, or chewed.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section **List of excipients.**

Special warnings and precautions for use

Serious hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, dyspnoea, rash, pruritus, urticaria, and facial oedema, have been reported with use of AQUIPTA (see section **Undesirable effects**). Most serious reactions have occurred within 24 hours of first use, however, some hypersensitivity reactions can occur days after administration. Patients should be warned about the symptoms associated with

hypersensitivity. If a hypersensitivity reaction occurs, discontinue AQUIPTA and institute appropriate therapy.

Hepatic impairment

Atogepant is not recommended in patients with severe hepatic impairment (**Posology and method of administration**).

Excipients with known effect

AQUIPTA Tablet 10 mg contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

AQUIPTA Tablet 60 mg contain 31.5 mg sodium per tablet, equivalent to 1.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interaction with other medicinal products and other forms of interaction

CYP3A4 inhibitors

Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir) can significantly increase systemic exposure to atogepant. Co-administration of atogepant with itraconazole resulted in increased exposure (C_{max} by 2.15-fold and AUC by 5.5-fold) of atogepant in healthy subjects (see section **Posology and method of administration)**. Changes in atogepant exposure when co-administered with weak or moderate CYP3A4 inhibitors are not expected to be clinically significant.

Transporter inhibitors

Organic anion transporting polypeptide (OATP) inhibitors (e.g., rifampicin, ciclosporin, ritonavir) can significantly increase systemic exposure to atogepant. Co-administration of atogepant with single dose rifampicin resulted in increased exposure (C_{max} by 2.23-fold and AUC by 2.85-fold) of atogepant in healthy subjects (see section **Posology and method of administration)**.

Frequently co-administered medicinal products

Co-administration of atogepant with oral contraceptive components ethinyl estradiol and levonorgestrel, paracetamol, naproxen, sumatriptan, or ubrogepant did not result in significant pharmacokinetic interactions for either atogepant or co-administered medicinal products. Co-administration with famotidine or esomeprazole did not result in clinically relevant changes of atogepant exposure.

Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of atogepant in pregnant women. Studies in animals have shown reproductive toxicity (see section **Preclinical safety data**). Atogepant is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Pharmacokinetic data after single-dose administration showed minimal transfer of atogepant into breast milk (see section **Pharmacokinetic properties**).

There are no data on the effects of atogepant on the breastfed infant or the effects of atogepant on milk production.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for atogepant and any potential adverse effects on the breastfed infant from atogepant or from the underlying maternal condition.

Fertility

No human data on the effect of atogepant on fertility are available. Animal studies showed no impact on female and male fertility with atogepant treatment (see section **Preclinical safety data**).

Effects on ability to drive and use machines

Atogepant has no or negligible influence on the ability to drive and use machines. However, it may cause somnolence in some patients. Patients should exercise caution before driving or using machinery until they are reasonably certain that atogepant does not adversely affect performance.

Undesirable effects

Summary of the safety profile

The safety of AQUIPTA was evaluated in 3 852 patients with migraine who received at least one dose of AQUIPTA. Of these, 1 225 patients were exposed to AQUIPTA for prophylaxis daily for at least 6 months and 826 patients were exposed for 12 months. 895 patients were exposed during 24 weeks on an as-needed basis for treatment of acute migraine attacks.

In 12-week, placebo-controlled prophylaxis clinical studies, 678 patients received at least one dose of atogepant 60 mg once daily, and 663 patients received placebo. In the placebo-controlled clinical study for acute treatment of migraine, 1 195 patients received at least one dose of AQUIPTA 60 mg, and 1 177 patients received placebo; patients received both AQUIPTA and placebo to treat qualifying migraines.

In placebo-controlled prophylaxis studies, the most commonly reported adverse reactions were nausea (9%), constipation (8%), and fatigue/somnolence (5%). Most of the reactions were mild or moderate in severity. The adverse reaction that most commonly led to discontinuation for prophylaxis was nausea (0.4%). Nausea (1.3%) was the most commonly reported adverse reaction for acute treatment.

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials and from post-marketing experience are listed below by system organ class and frequency, most frequent reactions first. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Given the lower exposure in the setting of acute treatment of migraine, adverse drug reactions may not occur or may not be as frequent as when used for the prophylaxis of migraine.

Table 2. Adverse drug reactions identified with AQUIPTA*

System organ class	Frequency	Adverse reaction
Immune system disorders	Not known	Hypersensitivity (e.g., anaphylaxis, dyspnoea, rash, pruritus, urticaria, facial oedema)
Metabolism and nutrition disorders	Common	Decreased appetite

Gastrointestinal disorders	Common	Nausea, Constipation
General disorders and administration site conditions	Common	Fatigue/somnolence
Investigations	Common	Weight decreased**
	Uncommon	ALT/AST increased †**

* Frequency categories are based on once daily administration. Given the lower exposure in the setting of acute treatment of migraine, adverse drug reactions may not occur or may not be as frequent as when used for the prophylaxis of migraine.
** Defined in clinical trials as weight decrease of at least 7% at any point.
†** Cases of ALT/AST elevations (defined as ≥ 3× upper limit of normal) temporally associated with atogepant were observed in clinical trials, including cases with a potential positive dechallenge history that resolved within 8 weeks of discontinuation. However, the overall frequency of liver enzyme elevations was similar in the atogepant and placebo groups.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Overdose

In clinical studies, atogepant was administered as single doses up to 300 mg and as multiple doses up to 170 mg once daily. Adverse reactions were comparable to those seen at lower doses, and no specific toxicities were identified. There is no known antidote for atogepant. Treatment of an overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, calcitonin gene-related peptide (CGRP) antagonists, ATC code: N02CD07

Mechanism of action

Non-clinical receptor binding studies and *in vitro* functional studies point to an involvement of more than one receptor type in the pharmacological effects of atogepant. Atogepant shows affinity to several receptors of the calcitonin/CGRP-receptor family. In view of the clinically relevant free plasma concentrations of atogepant (C_{max} > 20 nM for a 60 mg dose) and the fact that CGRP and amylin-1 receptors are considered to be involved in the pathophysiology of migraine, inhibitory effects of atogepant at these receptors (K_i-value 26 pM and 2.4 nM, respectively) could be of clinical relevance.

However, the precise mechanism of action of atogepant in the prophylaxis of migraine remains to be established.

Clinical efficacy and safety

Acute treatment of migraine

The efficacy of AQUIPTA for the acute treatment of migraine with or without aura in adults was studied in a randomized, double-blind, placebo-controlled study (ECLIPSE). In the 16-week blinded treatment period, 1 328 subjects were randomized to 1 of 4 sequence groups to treat 4 qualifying migraine attacks of moderate or severe headache pain intensity with either AQUIPTA 60 mg (3 attacks) or placebo (1 attack)

in a prespecified order. Subjects who completed the blinded period of the study treated subsequent attacks with open-label AQUIPTA 60 mg until the end of week 24. Approximately 22% of subjects were using concomitant migraine-prophylaxis medication (e.g., topiramate, amitriptyline, propranolol). Rescue medication was permitted beginning 2 hours after taking study drug. The use of a concomitant medicinal product that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine.

Approximately 84% subjects who received study drug treated 4 qualifying migraine attacks during the double-blind study period. Patients had a mean age of 42 years (range: 18 to 74 years), 2% were 65 years or older, 85% were female, 59% were white, and 40% were Asian. Mean migraine frequency was approximately 4 moderate to severe migraine attacks per month over the 3 months prior to enrolment.

The primary efficacy endpoint was pain freedom (defined as reduction in headache severity from moderate/severe to no pain) at 2 hours during Attack 1 (Table 3). Secondary endpoints included absence of patient-identified most bothersome symptom at 2 hours, pain relief (defined as reduction in headache severity from moderate/severe to mild/no pain) at 2 hours, sustained pain relief from 2 hours to 48 hours, use of rescue medication within 24 hours, ability to function normally at 2 hours, and sustained pain freedom from 2 hours to 48 hours. AQUIPTA demonstrated statistically significant improvement for these endpoints compared to placebo.

Table 3: Efficacy endpoints during Attack 1 in ECLIPSE

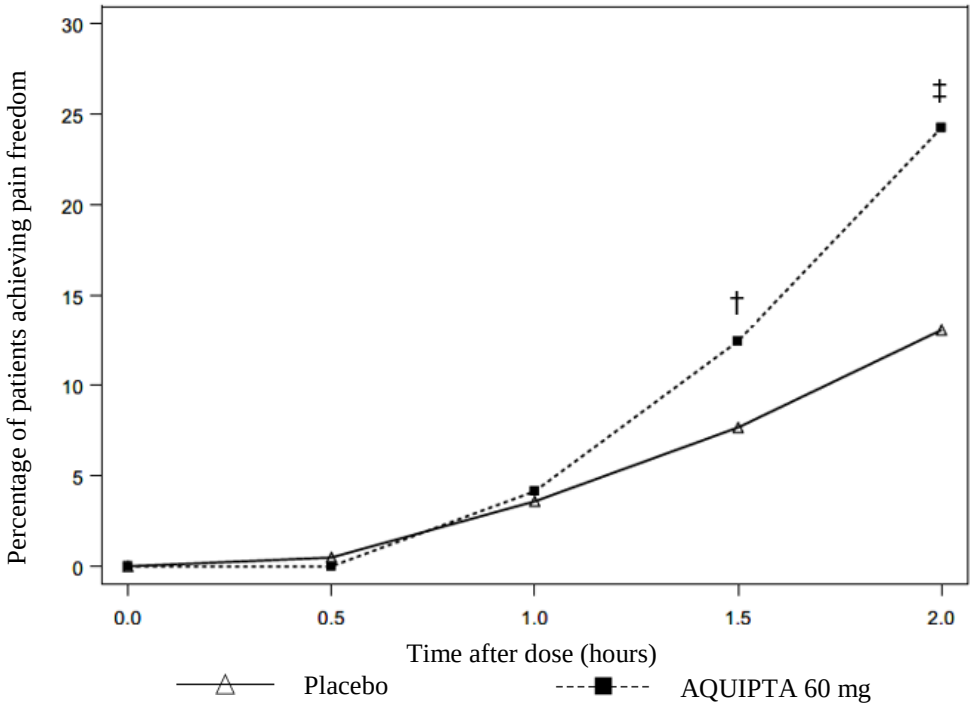
	AQUIPTA 60 mg	**Placebo**
Pain-free at 2 hours		
Responders, n/N (%)	146/602 (24.3)	80/612 (13.1)
Model-based Response Rate[a], %	24.5	12.1
Risk Difference, % (95% CI)	12.42 (8.31, 16.52)	
Relative Risk (95% CI)	2.02 (1.53, 2.52)	
Odds ratio (95% CI)	2.36 (1.76, 3.15)	
p-value	<0.0001[b]	
Freedom from most bothersome symptom[c] at 2 hours		
Responders, n/N (%)	263/602 (43.7)	200/612 (32.7)
Model-based Response Rate[a], %	43.7	30.5
Risk Difference, % (95% CI)	13.25 (7.95, 18.56)	
Relative Risk (95% CI)	1.44 (1.22, 1.65)	
Odds ratio (95% CI)	1.77 (1.41, 2.24)	
p-value	<0.0001[b]	
Pain relief at 2 hours		
Responders, n/N (%)	434/602 (72.1)	333/612 (54.4)
Model-based Response Rate[a], %	73.0	53.6
Risk Difference, % (95% CI)	19.47 (14.18, 24.76)	
Relative Risk (95% CI)	1.36 (1.24, 1.48)	
Odds ratio (95% CI)	2.35 (1.85, 2.98)	
p-value	<0.0001[b]	
Sustained pain relief from 2 to 48 hours		
Responders, n/N (%)	311/602 (51.7)	142/612 (23.2)
Model-based Response Rate[a], %	51.9	22.3
Risk Difference, % (95% CI)	29.63 (24.51, 34.75)	
Relative Risk (95% CI)	2.33 (1.95, 2.71)	
Odds ratio (95% CI)	3.77 (2.95, 4.82)	
p-value	<0.0001[b]	
Use of rescue medication within 24 hours		
Responders, n/N (%)	91/602 (15.1)	327/613 (53.3)
Model-based Response Rate[a], %	14.1	53.1
Risk Difference, % (95% CI)	-39.04 (-43.98, -34.10)	
Relative Risk (95% CI)	0.27 (0.21, 0.32)	
Odds ratio (95% CI)	0.14 (0.11, 0.19)	

p-value	<0.0001[b]	
Normal function at 2 hours		
Responders, n/N (%)	288/602 (47.8)	245/613 (40.0)
Model-based Response Rate[a], %	47.1	34.7
Risk Difference, % (95% CI)	12.40 (6.18, 18.62)	
Relative Risk (95% CI)	1.36 (1.15, 1.57)	
Odds ratio (95% CI)	1.68 (1.29, 2.18)	
p-value	<0.0001[b]	
Sustained pain freedom from 2 to 48 hours		
Responders, n/N (%)	100/602 (16.6)	35/612 (5.7)
Model-based Response Rate[a], %	16.7	5.2
Risk Difference, % (95% CI)	11.43 (8.09, 14.76)	
Relative Risk (95% CI)	3.18 (2.02, 4.35)	
Odds ratio (95% CI)	3.62 (2.43, 5.39)	
p-value	<0.0001[b]	

n=number of responders/N=number of subjects for Attack 1 in the efficacy analysis population
[a] Model-based response rates were calculated from a generalized linear mixed model with a logit link function to analyse primary and key secondary endpoints
[b] p-values were calculated for model-based odds ratios and adjusted for multiple comparisons
[c] Patient-identified as nausea (31%), photophobia (44%), or phonophobia (25%)

A greater percentage of patients treated with AQUIPTA 60 mg achieved pain freedom beginning at 1.5 hours during Attack 1 compared to patients who received placebo (Figure 1). AQUIPTA also demonstrated consistent effect with 26.3% of patients achieving pain freedom at 2 hours in at least 2 of 3 migraine attacks.

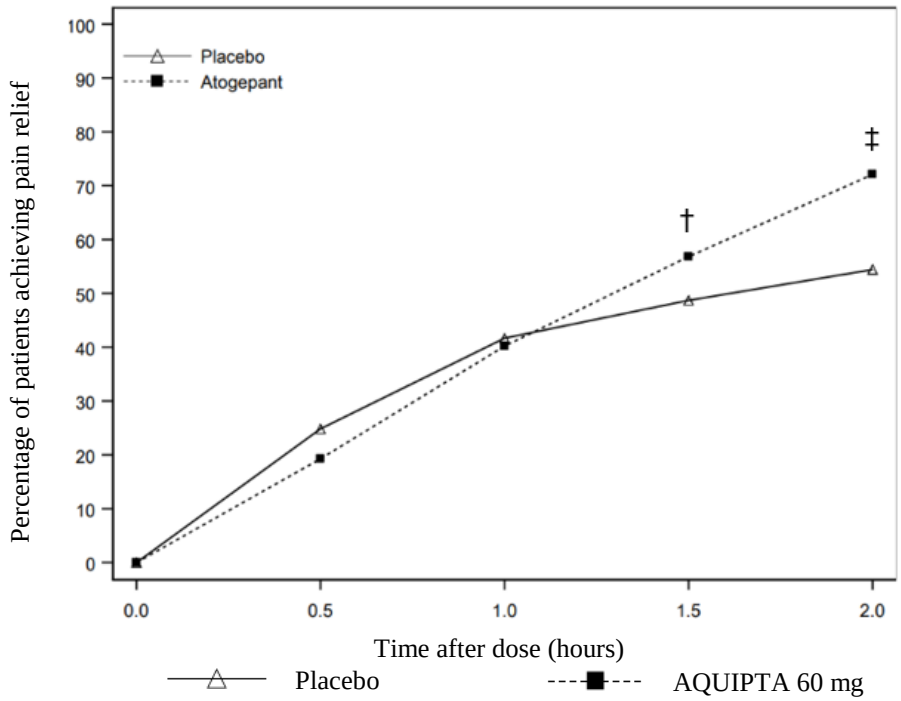
Figure 1: Percentage of patients achieving pain freedom within 2 hours for Attack 1 in ECLIPSE



† p < 0.001 (not adjusted for multiple comparisons)
‡ p < 0.0001 (adjusted for multiple comparisons)

A greater percentage of patients treated with AQUIPTA 60 mg achieved pain relief beginning at 1.5 hours during Attack 1 compared to patients who received placebo (Figure 2). AQUIPTA also demonstrated consistent effect with 79.3% of patients achieving pain relief at 2 hours in at least 2 of 3 migraine attacks.

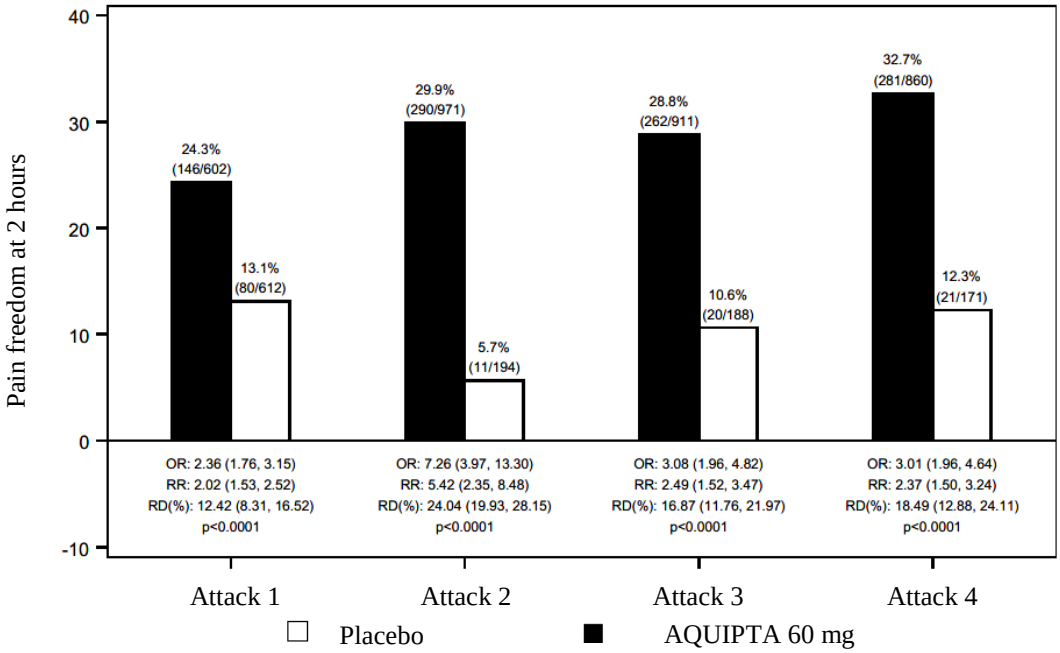
Figure 2: Percentage of patients achieving pain relief within 2 hours during Attack 1 in ECLIPSE



† p < 0.001 (not adjusted for multiple comparisons)
‡ p < 0.0001 (adjusted for multiple comparisons)

AQUIPTA 60 mg showed higher response rates than placebo for pain freedom at 2 hours for each of the 4 single attacks during the double-blind period (nominal p-value < 0.0001 for Attacks 2 to 4) as shown in Figure 3. The AQUIPTA response rates for Attacks 2 to 4 were similar to Attack 1.

Figure 3: Percentage of patients achieving pain freedom at 2 hours for Attacks 1 to 4 in ECLIPSE



Prophylaxis of migraine

Atogepant was evaluated for the prophylaxis of migraine in two pivotal studies across the migraine spectrum in chronic and episodic migraine. The episodic migraine study (ADVANCE) enrolled patients

who met International Classification of Headache Disorders (ICHD) criteria for a diagnosis of migraine with or without aura. The chronic migraine study (PROGRESS) enrolled patients who also met ICHD criteria for chronic migraine. Both studies excluded patients with myocardial infarction, stroke, or transient ischemic attacks within six months prior to screening.

Episodic migraine

Atogepant was evaluated for the prophylaxis of episodic migraine (4 to 14 migraine days per month) in a randomised, multicentre, double-blind, placebo-controlled study (ADVANCE). Patients were randomised to AQUIPTA 60 mg (N = 235) or placebo (N = 223) once daily for 12 weeks. Patients were allowed to use acute headache treatments (i.e., triptans, ergotamine derivatives, NSAIDs, paracetamol and opioids) as needed. The use of a concomitant medicinal product that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine.

A total of 88% patients completed the 12-week double-blind study period. Patients had a mean age of 42 years (range: 18 to 73 years), 4% were 65 years or older, 89% were female, and 83% were white. The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) across the 12-week treatment period. Secondary endpoints controlled for multiplicity included the change from baseline in mean monthly headache days, the change from baseline in mean monthly acute medication use days, the proportion of patients achieving at least a 50% reduction from baseline in mean MMD (3 month average), and several patient-reported outcome measures assessing functioning. Statistically significant findings were demonstrated for AQUIPTA versus placebo for the primary and secondary efficacy endpoints in ADVANCE, as summarized in Table 4.

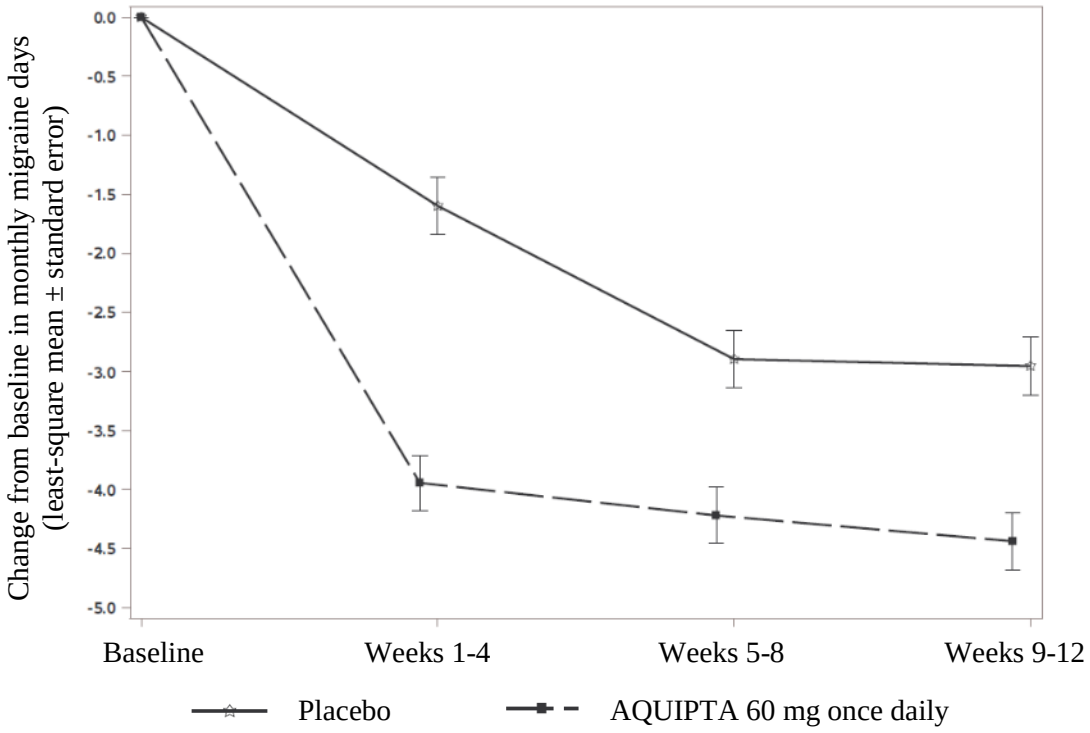
Table 4: Efficacy endpoints in ADVANCE

	AQUIPTA 60 mg N=226	**Placebo N=216**
Monthly migraine days (MMD) across 12 weeks		
Baseline	7.8	7.5
Mean change from baseline	-4.1	-2.5
Difference from placebo	-1.7	
p-value	<0.001	
Monthly headache days across 12 weeks		
Baseline	9.0	8.5
Mean change from baseline	-4.2	-2.5
Difference from placebo	-1.7	
p-value	<0.001	
Monthly acute medication use days across 12 weeks		
Baseline	6.9	6.5
Mean change from baseline	-3.8	-2.3
Difference from placebo	-1.4	
p-value	<0.001	
≥ 50% MMD responders across 12 weeks		
% Responders	59	29
Odds ratio (95% CI)	3.55 (2.39, 5.28)	
p-value	<0.001	

Figure 4 shows the mean change from baseline in MMD in ADVANCE. Patients treated with AQUIPTA 60 mg once daily had greater mean decreases from baseline in MMD across the 12-week treatment period compared to patients who received placebo. AQUIPTA 60 mg once daily resulted in significant decreases

from baseline in mean monthly migraine days within the first 4-week interval compared to placebo-treated patients.

Figure 4: Change from baseline in monthly migraine days in ADVANCE



Long-term efficacy

Efficacy was sustained for up to one year in an open-label study in which 546 patients with episodic migraine were randomised to receive AQUIPTA 60 mg once daily. 68% (373/546) of patients completed the treatment period. The reduction in the least-squares mean number of monthly migraine days in the first month (weeks 1-4) was -3.8 days and improved to a least-squares mean reduction of -5.2 days in the last month (weeks 49-52). Approximately 84%, 70%, and 48% of patients reported ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine days at weeks 49-52, respectively.

Patients with previous failure to 2 to 4 classes of oral prophylactic treatments

In the ELEVATE study, 315 adult patients with episodic migraine who previously failed 2 to 4 classes of oral prophylactic treatments (e.g., topiramate, tricyclic antidepressants, beta-blockers) based on efficacy and/or tolerability were randomised 1:1 to receive either atogepant 60 mg (N = 157) or placebo (N = 158) for 12 weeks. Results in this study were consistent with the main findings of previous episodic migraine efficacy studies and statistically significant for primary and secondary efficacy endpoints including several patient-reported outcome measures assessing functioning. Atogepant treatment led to a reduction of 4.2 days in mean MMD compared to 1.9 days in the placebo group ($p<0.001$). 50.6% (78/154) of patients in the atogepant group achieved at least a 50% reduction from baseline in MMD compared to 18.1% (28/155) in the placebo group (odds ratio [95% CI]: 4.82 [2.85, 8.14], $p<0.001$).

Chronic migraine

Atogepant was evaluated for the prophylaxis of chronic migraine (15 or more headache days per month with at least 8 migraine days) in a randomised, multicentre, double-blind, placebo-controlled study (PROGRESS). Patients were randomised to AQUIPTA 60 mg (N = 262) or placebo (N = 259) once daily for 12 weeks. A subset of patients (11%) was allowed to use one concomitant migraine prophylaxis medicinal product (e.g., amitriptyline, propranolol, topiramate). Patients were allowed to use acute headache treatments (i.e., triptans, ergotamine derivatives, NSAIDs, paracetamol and opioids) as needed. Patients with acute medication overuse and medication overuse headache also were enrolled. The use of a concomitant medicinal product that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine.

A total of 463 (89%) patients completed the 12-week double-blind study. Patients had a mean age of 42 years (range: 18 to 74 years), 3% were 65 years or older, 87% were female, and 59% were white. The mean migraine frequency at baseline was approximately 19 migraine days per month and was similar across treatment groups.

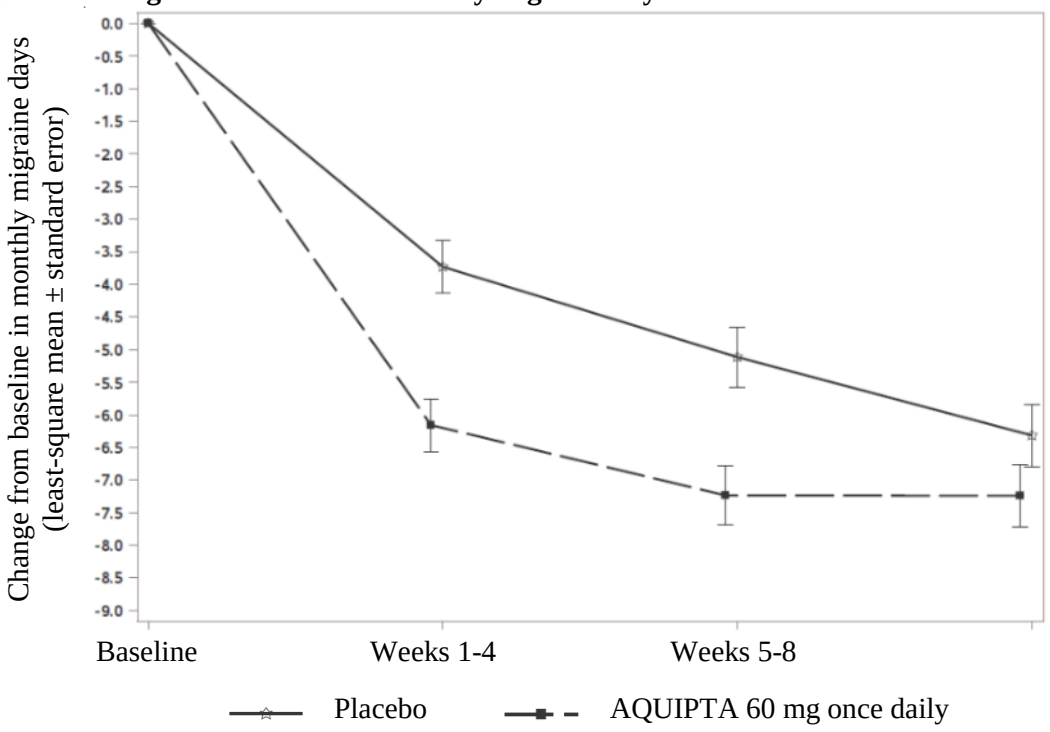
The primary efficacy endpoint was the change from baseline in mean MMD across the 12-week treatment period. Secondary endpoints controlled for multiplicity included the change from baseline in mean monthly headache days, the change from baseline in mean monthly acute medication use days, the proportion of patients achieving at least a 50% reduction from baseline in mean MMD (3-month average), and several patient-reported outcome measures assessing functioning. Statistically significant findings were demonstrated for AQUIPTA versus placebo for the primary and secondary efficacy endpoints for PROGRESS, as summarized in Table 5.

Table 5: Efficacy endpoints in PROGRESS

	AQUIPTA 60 mg N=257	**Placebo N=249**
Monthly migraine days (MMD) across 12 weeks		
Baseline	19.2	19.0
Mean change from baseline	-6.8	-5.1
Difference from placebo	-1.7	
p-value	0.002	
Monthly headache days across 12 weeks		
Baseline	21.5	21.4
Mean change from baseline	-6.9	-5.2
Difference from placebo	-1.7	
p-value	0.002	
Monthly acute medication use days across 12 weeks		
Baseline	15.5	15.3
Mean change from baseline	-6.2	-4.1
Difference from placebo	-2.1	
p-value	0.002	
≥ 50% MMD responders across 12 weeks		
% Responders	40	27
Odds ratio (95% CI)	1.90 (1.29, 2.79)	
p-value	0.002	

Figure 5 shows the mean change from baseline in MMD in PROGRESS. Patients treated with AQUIPTA 60 mg once daily had a greater mean decrease from baseline in MMD across the 12-week treatment period compared to patients who received placebo

Figure 5: Change from baseline in monthly migraine days in PROGRESS



Pharmacokinetic properties

Absorption

Following oral administration, atogepant is absorbed with peak plasma concentrations at approximately 1 to 2 hours. Following once daily dosing, atogepant displays dose-proportional pharmacokinetics up to 170 mg (approximately 3 times the highest recommended dose), with no accumulation.

Effect of food

When atogepant was administered with a high-fat meal, AUC and C_{max} were reduced by approximately 18% and 22%, respectively, with no effect on median time to maximum atogepant plasma concentration. Atogepant was administered without regard to food in clinical efficacy studies.

Distribution

Plasma protein binding of atogepant was not concentration-dependent in the range of 0.1 to 10 µM; the unbound fraction of atogepant was approximately 4.7% in human plasma. The mean apparent volume of distribution of atogepant (V_z/F) after oral administration is approximately 292 L.

Biotransformation

Atogepant is eliminated mainly through metabolism, primarily by CYP3A4. The parent compound (atogepant), and a glucuronide conjugate metabolite (M23) were the most prevalent circulating components in human plasma.

CYP3A4 inducers

Co-administration of atogepant with steady state rifampicin, a strong CYP3A4 inducer, resulted in a significant decrease in exposure (Cmax by 30% and AUC by 60%) of atogepant in healthy subjects.

Co-administration of atogepant with steady-state topiramate, a mild CYP3A4 inducer, resulted in a decrease in exposure (Cmax by 24% and AUC by 25%) of atogepant.

In vitro, atogepant is not an inhibitor for CYP3A4, 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, MAO-A, or UGT1A1 at clinically relevant concentrations. Atogepant also is not an inducer of CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.

Elimination

The elimination half-life of atogepant is approximately 11 hours. The mean apparent oral clearance (CL/F) of atogepant is approximately 19 L/h. Following single oral dose of 50 mg ^{14}C-atogepant to healthy male subjects, 42% and 5% of the dose was recovered as unchanged atogepant in faeces and urine, respectively.

Transporters

Atogepant is a substrate of P-gp, BCRP, OATP1B1, OATP1B3, and OAT1. Dose adjustment for concomitant use with strong inhibitors of OATP is recommended based on a clinical interaction study with a strong OATP inhibitor. Atogepant is not a substrate of OAT3, OCT2, or MATE1.

Atogepant is not an inhibitor of P-gp, BCRP, OAT1, OAT3, NTCP, BSEP, MRP3, or MRP4 at clinically relevant concentrations. Atogepant is a weak inhibitor of OATP1B1, OATP1B3, OCT1, and MATE1, but no clinically relevant interactions are expected.

Special populations

Renal impairment

The renal route of elimination plays a minor role in the clearance of atogepant. Based on population pharmacokinetic analysis, there is no significant difference in the pharmacokinetics of atogepant in patients with mild or moderate renal impairment (CLcr 30-89 mL/min) relative to those with normal renal function (CLcr ≥ 90 mL/min). As patients with severe renal impairment or end-stage renal disease (ESRD; CLcr < 30 mL/min) have not been studied, use of atogepant 10 mg is recommended in those patients.

Hepatic impairment

In patients with pre-existing mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe hepatic impairment (Child-Pugh Class C), total atogepant exposure was increased by 24%, 15% and 38%, respectively. However, unbound atogepant exposure was approximately 3-fold higher in patients with severe hepatic impairment. The use of AQUIPTA in patients with severe hepatic impairment should be avoided.

Transfer into breast milk

In a study of 12 healthy lactating women administered a single oral dose of atogepant 60 mg between 1 to 6 months postpartum, peak levels of atogepant in breast milk occurred between 1 to 3 hours after administration. The C_{max} and AUC of atogepant in breast milk were significantly lower by approximately 93% compared to women's plasma. The mean relative infant dose was approximately 0.19% (range 0.06 to 0.33%) of the maternal weight-adjusted dose with a mean milk-to-plasma ratio of 0.08 (0.02 to 0.10). The cumulative amount of atogepant excreted in breast milk over 24 hours was minimal, at less than 0.01 mg.

Other special populations

Based on a population pharmacokinetic analysis, sex, race, and body weight did not have a significant effect on the pharmacokinetics (C_{max} and AUC) of atogepant. Therefore, no dose adjustments are warranted based on these factors.

Preclinical safety data

Notwithstanding marked interspecies differences in CGRP-receptor affinity of atogepant, non-clinical data reveal no special hazard for atogepant in humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, phototoxicity or carcinogenic potential.

Impairment of fertility

Oral administration of atogepant to male and female rats prior to and during mating and continuing in females to gestation day 7 resulted in no adverse effects on fertility or reproductive performance. Plasma exposures (AUC) are up to approximately 15 times that in humans at the maximum recommended human dose (MRHD).

Reproductive and developmental toxicology

Oral administration of atogepant to pregnant rats and rabbits during the period of organogenesis resulted in decreased foetal body weight in rats and an increased incidence of foetal visceral and skeletal variations at doses associated with minimal maternal toxicity. At the no-effect dose for adverse effects on embryofoetal development, plasma exposure (AUC) was approximately 4 times in rats and 3 times in rabbits that in humans at the MRHD of 60 mg/day.

Oral administration of atogepant to rats throughout gestation and lactation resulted in non-adverse significant decreased pup body weight which persisted into adulthood. Plasma exposure (AUC) at the no-effect dose for pre- and postnatal development were approximately 5-times that in humans at the MRHD. In lactating rats, oral dosing with atogepant resulted in levels of atogepant in milk approximately 2-fold higher than those in maternal plasma.

PHARMACEUTICAL PARTICULARS

List of excipients

Polyvinylpyrrolidone/ Vinyl acetate copolymer
Vitamin E polyethylene glycol succinate
Mannitol
Microcrystalline cellulose
Sodium chloride
Croscarmellose sodium
Colloidal silicon dioxide
Sodium stearyl fumarate

Incompatibilities

Not applicable.

Shelf life

3 years

Storage
Store at or below 30°C.

Nature and contents of container

AQUIPTA Tablet 10 mg

Aluminium foil and PVC/PE/PCTFE blisters, each containing 7 tablets.
Packs containing 28 tablets.

AQUIPTA Tablet 60 mg

Aluminium foil and PVC/PE/PCTFE blisters, each containing 7 tablets.
Packs containing 7 and 28 tablets.

Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufacturer:
Forest Laboratories Ireland, Limited

Clonshaugh Business and Technology Park Clonshaugh, Dublin 17, Ireland

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