Summary Report of Benefit-Risk Assessment

AQUIPTA TABLET 10MG AND 60MG

NEW DRUG APPLICATION

Active Ingredient(s)	Atogepant monohydrate eqv atogepant
Product Registrant	AbbVie Pte. Ltd.
Product Registration Number	SIN17145P, SIN17146P
Application Route	Abridged evaluation
Date of Approval	29 November 2024

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A INTRODUCTION

Aquipta is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.

The active substance, atogepant, is a small molecule, selective calcitonin gene-related peptide (CGRP) receptor antagonist that blocks the binding of the CGRP to the receptor and antagonises CGRP receptor function. CGRP is a neuropeptide that has been associated with migraine pathophysiology.

Aquipta is available as tablets containing 10 mg or 60 mg of atogepant. Other ingredients in the tablet are polyvinylpyrrolidone/vinyl acetate copolymer, vitamin E polyethylene glycol succinate, mannitol, microcrystalline cellulose, sodium chloride, croscarmellose sodium, colloidal silicon dioxide and sodium stearyl fumarate.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, atogepant, is manufactured at Changzhou SynTheAll Pharmaceutical Co, Ltd, Changzhou, China. The drug product, Aquipta, is manufactured at Forest Laboratories Ireland Limited, Dublin, Ireland.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline and the impurity limits have been appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The packaging is double lined low-density polyethylene (LDPE) bags, sealed with a cable tie and placed in a closed drum. The stability data presented was adequate to support the storage of the drug substance at 25ºC with a re-test period of 48 months.

Drug product:

The tablets are manufactured using a hot-melt extrusion followed by dry blending approach.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A guideline and impurity limits were considered adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline with information on the reference standards used for identity and assay presented.

The container closure system is a unit-dose blister composed of aluminium foil lidding with heat sealable to the thermoforming film laminated with polyvinylchloride/ polyethylene/ polychlorotrifluoroethylene (PVC/PE/PCTFE) Aclar® laminated blister forming film. Each pack contains 28 tablets, comprising of 4 blisters of 7 tablets. The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30ºC.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of atogepant in the prophylaxis of episodic migraine (EM) and chronic migraine (CM) was based primarily on two pivotal Phase III studies 3101-301-002 (study 301, referred to as ADVANCE) and 3101-303-002 (study 303, referred to as PROGRESS) in patients with EM and CM, respectively. The application was further supported by one supportive study, CGP-MD-01, and a long-term study, 3101-302-002 (study 302), both conducted in subjects with EM.

Study CGP-MD-01

Study CGP-MD-01 was a Phase II/III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose-finding study of atogepant compared with placebo for the prevention of EM.

Patients with EM, defined as 4 to 14 migraine/probable migraine days per month were randomised in a 1:2:1:2:1:2 ratio to receive oral atogepant 10 mg once daily, atogepant 30 mg once daily, atogepant 30 mg twice daily, atogepant 60 mg once daily, atogepant 60 mg twice daily, or placebo. The primary efficacy endpoint was the change from baseline in mean monthly migraine days across the 12-week treatment period and the secondary endpoints included the change from baseline in mean monthly headache days across the 12-week treatment period.

Efficacy evaluations were based on the modified intent-to-treat (mITT) population, which excluded patients never receiving treatment or not having baseline or any post-baseline diary data. A total of 834 patients were randomised in the study and 795 patients were included in the mITT population: 92, 182, 79, 177, 87 and 178 patients in the atogepant 10 mg once daily, atogepant 30 mg once daily, atogepant 30 mg twice daily, atogepant 60 mg once daily, atogepant 60 mg twice daily, and placebo arms, respectively.

Patients reported an average of 7.4 migraine days per month and 9.5 headache days per month in the 3 months prior to screening. At screening, nearly all patients (97.6%) reported current treatment for acute migraine. Only 28.1% of patients reported previous migraine prophylactic treatment.

Statistically significantly higher response rates were observed for all treatment arms of atogepant compared with placebo for both change from baseline in mean monthly migraine and headache days after multiplicity adjustment, with no clear dose response relationship.

Table 1 Change from baseline in mean monthly migraine days

Parameter	Statistic	Placebo (N=178)	Atogepant 10 mg once daily (N=92)	Atogepant 30 mg once daily (N=182)	Atogepant 60 mg once daily (N=177)	Atogepant 30 mg twice daily (N=79)	Atogepant 60 mg twice daily (N=87)
Baseline	Mean (SD)	7.81 (2.51)	7.63 (2.51)	7.64 (2.37)	7.74 (2.59)	7.38 (2.43)	7.62 (2.56)
Change from baseline	LS mean (SE)	-2.85 (0.23)	-4.00 (0.32)	-3.76 (0.23)	-3.55 (0.23)	-4.23 (0.35)	-4.14 (0.33)
Atogepant versus placebo							
LSMD			-1.15	-0.91	-0.70	-1.39	-1.29
95% CI			-1.93, -0.37	-1.55, -0.27	-1.35, -0.06	-2.21, -0.56	-2.09, -0.49
Nominal p-value			0.0039	0.0056	0.0325	0.0010	0.0016
Multiplicity-adjusted p-value			0.0236	0.0390	0.0390	0.0034	0.0031

SD = standard deviation, SE = standard error of the least squares, CI = confidence interval, LSMD = least squares mean difference

Table 2 Change from baseline in mean monthly headache days

Parameter	Statistic	Placebo (N=178)	Atogepant 10 mg once daily (N=92)	Atogepant 30 mg once daily (N=182)	Atogepant 60 mg once daily (N=177)	Atogepant 30 mg twice daily (N=79)	Atogepant 60 mg twice daily (N=87)
Baseline	Mean (SD)	9.07 (2.70)	8.89 (2.70)	8.74 (2.51)	8.86 (2.76)	8.71 (2.73)	8.80 (3.12)
Change from baseline	LS mean (SE)	-2.93 (0.25)	-4.31 (0.35)	-4.17 (0.25)	-3.86 (0.25)	-4.23 (0.38)	-4.32 (0.36)
Atogepant versus placebo							
LSMD			-1.38	-1.24	-0.94	-1.30	-1.39
95% CI			-2.23, -0.54	-1.94, -0.55	-1.64, -0.24	-2.20, -0.41	-2.26, -0.53
Nominal p-value			0.0014	0.0005	0.0087	0.0044	0.0017
Multiplicity-adjusted p-value			0.0236	0.0390	0.0390	0.0131	0.0083

Study 301 (ADVANCE)

Study 301 was a Phase III, multicentre, randomised, double-blind study of atogepant compared to placebo for the prevention of migraine in patients with EM who had at least a 1-year history of migraine with or without aura and who experienced 4 to 14 migraine days per month.

Patients were randomised in a 1:1:1:1 ratio to receive oral atogepant 10 mg once daily, atogepant 30 mg once daily, atogepant 60 mg once daily or placebo once daily for 12 weeks. The use of a concomitant medication that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine. Patients were allowed to use acute headache treatments (i.e., triptans, ergotamine derivatives, NSAIDs, paracetamol, and opioids) as needed.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days across the 12-week treatment period. Secondary clinical efficacy endpoints included change

from baseline in mean monthly headache days across the 12-week treatment period, change from baseline in mean monthly acute medication use days across the 12-week treatment period, and a ≥ 50% reduction in 3-month average of monthly migraine days. Secondary endpoints related to health outcomes were change from baseline in Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) Role Function-Restrictive (RFR) domain score at Week 12, change from baseline in mean monthly Performance of Daily Activities domain score of the Activity Impairment in Migraine – Diary (AIM-D) across the 12-week treatment period, and change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period.

A total of 910 patients were randomised in the study and 873 patients were included in the mITT population: 214, 223, 222 and 214 patients in the atogepant 10 mg once daily, atogepant 30 mg once daily, atogepant 60 mg once daily and placebo arms, respectively. The mITT population consisted of all randomised participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data and at least 1 evaluable postbaseline 4-week period of eDiary data during the double-blind treatment period. A total of 882 patients were included in the Off-treatment Hypothetical Estimand (OTHE) population: 216, 224, 226 and 216 patients in the atogepant 10 mg once daily, atogepant 30 mg once daily, atogepant 60 mg once daily and placebo arms, respectively. The OTHE population is similar to the mITT population, except that it includes patients who had at least 1 evaluable postbaseline 4-week period of eDiary data, regardless of whether on study treatment or off study treatment.

The median age was 41 years (range 18 to 73 years), the majority of subjects were female (88.8%) and White (83.4%), and 1.3% of subjects were Asian. In total, 16.2% of patients had solely migraine with aura, 45.0% of patients had migraine without aura, and 38.8% had migraine both with and without aura. The mean duration of migraine was 21.2 years. At screening, 99.3% of patients reported use of medications for the acute treatment of migraine. Overall, 70.3% of patients reported having used migraine prevention medication in the past. The average number of monthly migraine days over the last 3 months prior to screening was similar between the atogepant treatment groups (7.2 to 7.3 days) and the placebo treatment group (7.7 days), as was the average number of monthly headache days (9.1 to 9.3 days across the atogepant treatment groups and 9.5 days in the placebo treatment group).

The primary analysis of change from baseline in mean monthly migraine days across 12 weeks demonstrated statistically significant improvements for subjects in the three atogepant dose arms compared to placebo ($p<0.0001$) in the mITT population. A numerical dose-response relationship was observed in the least squares (LS) mean difference versus placebo of -1.21, -1.38 and -1.72 days in the atogepant 10 mg, 30 mg and 60 mg once daily dose groups, respectively. The majority of reduction in monthly migraine days was attained within the first 4 weeks of the 12-week double-blind treatment period in all atogepant dose groups. Significant reductions were also observed in all other secondary endpoints for the 30 mg and 60 mg once daily dose groups (Table 3), while changes in the performance of daily activities and physical impairment domain scores of AIM-D were not significant in the atogepant 10 mg daily group. A numerical dose-response relationship was evident for the change from baseline in mean monthly migraine and headache days across the 12-week treatment period. The primary endpoint results were consistent in sensitivity analyses performed, including analysis using the OTHE population (Table 4), demonstrating robustness of the data.

Table 3 Summary of efficacy endpoints, mITT population

	Placebo (N=214)	Atogepant 10 mg once daily	Atogepant 30 mg once daily	Atogepant 60 mg once daily

		(N=214)	(N=223)	(N=222)
Primary efficacy endpoint				
Change in mean monthly migraine days across 12-week Mean baseline no of days (SD) LS Mean change from baseline (SE) **Atogepant vs placebo** (95% CI) Nominal p-value Adjusted p-value[a]	 7.51 (2.39) -2.48 (0.21)	 7.45 (2.46) -3.69 (0.21) -1.21 (-1.78, -0.64) <0.0001 <0.0001	 7.86 (2.32) -3.86 (0.21) -1.38 (-1.94, -0.82) <0.0001 <0.0001	 7.75 (2.31) -4.20 (0.21) -1.72 (-2.28, -1.15) <0.0001 <0.0001
Secondary efficacy endpoints				
Change in mean monthly headache days across 12-week Mean baseline no of days (SD) LS Mean change from baseline (SE) **Atogepant vs placebo** (95% CI) Nominal p-value Adjusted p-value[a]	 8.43 (2.55) -2.52 (0.23)	 8.41 (2.75) -3.94 (0.23) -1.42 (-2.03, -0.81) <0.0001 <0.0001	 8.78 (2.62) -4.04 (0.22) -1.53 (-2.13, -0.92) <0.0001 <0.0001	 9.00 (2.56) -4.23 (0.22) -1.71 (-2.32, -1.10) <0.0001 <0.0001
Change in mean monthly acute medication use days across 12-week Mean baseline no of days (SD) LS Mean change from baseline (SE) **Atogepant vs placebo** (95% CI) Nominal p-value Adjusted p-value[a]	 6.48 (3.15) -2.35 (0.18)	 6.57 (2.99) -3.66 (0.18) -1.31 (-1.81, -0.82) <0.0001 <0.0001	 6.69 (3.02) -3.68 (0.18) -1.33 (-1.82, -0.83) <0.0001 <0.0001	 6.89 (3.17) -3.85 (0.18) -1.50 (-2.00, -1.01) <0.0001 <0.0001
≥50% reduction in 3-month average of monthly migraine days Responders, n (%) **Atogepant vs placebo** Odds ratio (95% CI) Nominal p-value Adjusted p-value[a]	 62 (29.0)	 119 (55.6) 3.06 (2.05, 4.56) <0.0001 <0.0001	 131 (58.7) 3.53 (2.37, 5.26) <0.0001 <0.0001	 135 (60.8) 3.82 (2.56, 5.71) <0.0001 <0.0001
Health outcome measures				
Change in MSQ v2.1 RFR domain score at Week 12 Mean baseline (SD) LS Mean change from baseline (SE) **Atogepant vs placebo** (95% CI) Nominal p-value Adjusted p-value[a]	 46.78 (19.88) 20.45 (1.62)	 44.79 (21.85) 30.35 (1.64) 9.90 (5.45, 14.36) <0.0001 <0.0001	 44.24 (19.70) 30.53 (1.59) 10.08 (5.71, 14.46) <0.0001 <0.0001	 47.48 (20.55) 31.25 (1.59) 10.80 (6.42, 15.18) <0.0001 <0.0001
Change in mean monthly performance of daily activities domain score of the AIM-D across 12-week Mean baseline (SD) LS Mean change from baseline (SE) **Atogepant vs placebo** (95% CI) Nominal p-value Adjusted p-value[a]	 15.06 (8.32) -6.09 (0.50)	 15.59 (8.89) -7.28 (0.50) -1.19 (-2.56, 0.17) 0.0856[b] 0.0856[b]	 16.89 (8.09) -8.63 (0.50) -2.54 (-3.91, -1.18) 0.0003 0.0005	 15.74 (8.34) -9.41 (0.50) -3.32 (-4.68, -1.96) <0.0001 <0.0001
Change in mean monthly physical impairment domain score of the AIM-D across 12-week Mean baseline (SD) LS Mean change from baseline (SE) **Atogepant vs placebo** (95% CI) Nominal p-value Adjusted p-value[a]	 10.99 (8.03) -4.03 (0.44)	 11.78 (8.60) -5.11 (0.44) -1.08 (-2.27, 0.11) 0.0743[b] 0.0856[b]	 12.96 (8.07) -6.02 (0.44) -1.99 (-3.18, -0.80) 0.0011 0.0021	 11.48 (7.77) -6.49 (0.44) -2.46 (-3.65, -1.28) <0.0001 0.0002

[a] Adjusted p-values: using graphical approach to control the overall type I error rate for multiple comparisons.
[b] Not statistically or nominally significant.

Table 4 Summary of efficacy endpoints, OTHE population

	Placebo (N=216)	Atogepant 10 mg once daily (N=216)	Atogepant 30 mg once daily (N=224)	Atogepant 60 mg once daily (N=226)
Primary efficacy endpoint				
Change in mean monthly migraine days across 12-week Mean baseline no of days (SD)	 7.53 (2.39)	 7.46 (2.47)	 7.86 (2.31)	 7.75 (2.33)

LS Mean change from baseline (SE) **Atogepant vs placebo** (95% CI) Nominal p-value Adjusted p-value[a]	-2.47 (0.21)	-3.69 (0.21) -1.22 (-1.79, -0.65) <0.0001 <0.0001	-3.85 (0.21) -1.38 (-1.94, -0.81) <0.0001 <0.0001	-4.14 (0.21) -1.66 (-2.23, -1.10) <0.0001 <0.0001
Secondary efficacy endpoints				
Change in mean monthly headache days across 12-week Mean baseline no of days (SD) LS Mean change from baseline (SE) **Atogepant vs placebo** (95% CI) Nominal p-value Adjusted p-value[a]	8.45 (2.55) -2.52 (0.23)	8.43 (2.75) -3.94 (0.22) -1.42 (-2.03, -0.81) <0.0001 <0.0001	8.78 (2.62) -4.03 (0.22) -1.51 (-2.11, -0.91) <0.0001 <0.0001	8.99 (2.58) -4.17 (0.22) -1.65 (-2.25, -1.04) <0.0001 <0.0001
Change in mean monthly acute medication use days across 12-week Mean baseline no of days (SD) LS Mean change from baseline (SE) **Atogepant vs placebo** (95% CI) Nominal p-value Adjusted p-value[a]	6.50 (3.15) -2.34 (0.18)	6.58 (2.99) -3.68 (0.18) -1.34 (-1.84, -0.84) <0.0001 <0.0001	6.66 (3.05) -3.65 (0.18) -1.31 (-1.81, -0.82) <0.0001 <0.0001	6.88 (3.15) -3.78 (0.18) -1.44 (-1.93, -0.94) <0.0001 <0.0001
≥50% reduction in 3-month average of monthly migraine days Responders, n (%) **Atogepant vs placebo** Odds ratio (95% CI) Nominal p-value Adjusted p-value[a]	63 (29.2)	118 (54.6) 2.91 (1.95, 4.33) <0.0001 <0.0001	131 (58.5) 3.46 (2.32, 5.14) <0.0001 <0.0001	134 (59.3) 3.55 (2.39, 5.28) <0.0001 <0.0001

[a] Adjusted p-values: using graphical approach to control the overall type I error rate for multiple comparisons.

Study 303 (PROGRESS)

Study 303 was a Phase III, multicentre, randomised, double-blind study of atogepant compared to placebo for the prevention of migraine in patients who had at least a 1-year history of CM and had ≥ 15 headache days per month with at least 8 migraine days.

Patients were randomised in a 1:1:1 ratio to receive oral atogepant 30 mg twice daily, atogepant 60 mg once daily or placebo once daily for 12 weeks. Patients were allowed to use acute headache treatments (i.e., triptans, ergotamine derivatives, NSAIDs, paracetamol, and opioids) as needed. A subset of patients (11%) was allowed to use one concomitant migraine preventive medication (e.g., amitriptyline, propranolol, topiramate). The use of a concomitant medicinal product that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine.

The primary efficacy endpoint and secondary clinical efficacy endpoints were identical to that in Study 301. Secondary efficacy endpoints related to health outcomes also included change from baseline in the Headache Impact Test (HIT)-6 total score at Week 12 in Study 303.

A total of 778 patients were randomised in the study and 755 patients were included in the mITT population: 253, 256 and 246 patients in the atogepant 30 mg twice daily, atogepant 60 mg once daily and placebo arms, respectively. A total of 760 patients were included in the OTHE population: 254, 257 and 249 patients in the atogepant 30 mg twice daily, atogepant 60 mg once daily and placebo arms, respectively. The mITT and OTHE populations were similarly defined as in Study 301.

The median age was 43 years (range 18 to 74 years), the majority of subjects were female (87.6%) and White (59.4%), and 36.4% of subjects were Asian. In total, 13.3% of patients had solely migraine with aura, 59.8% of patients had migraine without aura, and 26.9% had migraine both with and without aura. The mean duration of migraine was 21.4 years. At

screening, 98.3% of patients reported use of medications for the acute treatment of migraine. Overall, 82.9% of the patients reported having used migraine prevention medication in the past. The average number of monthly migraine days over the last 3 months prior to screening was similar between the atogepant treatment groups (15.9 to 16.6 days) and the placebo treatment group (15.7 days), as was the average number of monthly headache days (20.8 to 21.7 days across the atogepant treatment groups and 20.8 days in the placebo treatment group).

The primary analysis of change from baseline in mean monthly migraine days across 12 weeks demonstrated statistically significant improvements for subjects in the two atogepant dose arms compared to placebo (p≤0.0009) in the mITT population. The LS mean difference versus placebo was numerically higher in the atogepant 30 mg twice daily arm compared to the 60 mg once daily arm: -2.41 vs -1.82 days. The majority of reduction in monthly migraine days was attained within the first 4 weeks of the 12-week double-blind treatment period. Significant reductions were also observed in all other secondary endpoints for both 30 mg twice daily and 60 mg once daily groups (Table 5). The primary endpoint results were consistent in sensitivity analyses performed, including analysis using the OTHE population (Table 6), demonstrating robustness of the data.

Table 5 Summary of efficacy endpoints, mITT population

	Placebo (N=246)	**Atogepant 30 mg twice daily (N=253)**	**Atogepant 60 mg once daily (N=256)**
Primary efficacy endpoint			
Change in mean monthly migraine days across 12-week			
Mean baseline no of days (SD)	18.95 (4.78)	18.56 (5.07)	19.16 (5.28)
LS Mean change from baseline (SE)	-5.05 (0.41)	-7.46 (0.41)	-6.88 (0.41)
Atogepant vs placebo (95% CI)		-2.41 (-3.48, -1.33)	-1.82 (-2.89, -0.75)
Nominal p-value		<0.0001	0.0009
Adjusted p-value[a]		<0.0001	0.0009
Secondary efficacy endpoints			
Change in mean monthly headache days across 12-week			
Mean baseline no of days (SD)	21.40 (4.10)	21.14 (4.13)	21.52 (4.32)
LS Mean change from baseline (SE)	-5.13 (0.41)	-7.44 (0.40)	-7.00 (0.40)
Atogepant vs placebo (95% CI)		-2.32 (-3.38, -1.26)	-1.87 (-2.93, -0.81)
Nominal p-value		<0.0001	0.0005
Adjusted p-value[a]		<0.0001	0.0009
Change in mean monthly acute medication use days across 12-week			
Mean baseline no of days (SD)	15.42 (6.99)	14.47 (7.19)	15.46 (7.38)
LS Mean change from baseline (SE)	-4.10 (0.39)	-6.73 (0.39)	-6.23 (0.39)
Atogepant vs placebo (95% CI)		-2.63 (-3.63, -1.63)	-2.13 (-3.13, -1.13)
Nominal p-value		<0.0001	<0.0001
Adjusted p-value[a]		<0.0001	0.0009
≥50% reduction in 3-month average of monthly migraine days			
Responders, n (%)	64 (26.0)	108 (42.7)	105 (41.0)
Atogepant vs placebo Odds ratio (95% CI)		2.13 (1.45, 3.14)	2.04 (1.38, 3.00)
Nominal p-value		0.0001	0.0003
Adjusted p-value[a]		0.0003	0.0009
Health outcome measures			
Change from baseline in MSQ v2.1 RFR domain score at Week 12			
Mean baseline (SD)	43.55 (19.05)	44.00 (19.03)	43.56 (18.91)
LS Mean change from baseline (SE)	17.18 (1.38)	25.15 (1.37)	23.33 (1.37)

Atogepant vs. Placebo Nominal p-value Adjusted p-value[a]		7.96 (4.30, 11.63) <0.0001 0.0003	6.15 (2.51, 9.79) 0.0009 0.0009
Change in mean monthly performance of daily activities domain score of the AIM-D across 12-week Mean baseline (SD) LS Mean change from baseline (SE) **Atogepant vs. Placebo** Nominal p-value Adjusted p-value[a]	29.50 (13.73) -9.44 (0.72)	29.28 (15.06) -14.29 (0.72) -4.85 (-6.75, -2.95) <0.0001 0.0003	31.18 (16.47) -12.82 (0.72) -3.38 (-5.27, -1.49) 0.0005 0.0009
Change in mean monthly physical impairment domain score of the AIM-D across 12-week Mean baseline (SD) LS Mean change from baseline (SE) **Atogepant vs. Placebo** Nominal p-value Adjusted p-value[a]	25.24 (13.52) -7.92 (0.67)	25.36 (15.42) -12.11 (0.67) -4.19 (-5.95, -2.43) <0.0001 0.0003	27.11 (16.63) -10.63 (0.67) -2.71 (-4.47, -0.96) 0.0025 0.0025
Change from baseline in the HIT-6 total score at Week 12 Mean baseline (SD) LS Mean change from baseline (SE) **Atogepant vs. Placebo** Nominal p-value Adjusted p-value[a]	64.08 (4.77) -5.17 (0.52)	64.22 (5.19) -8.66 (0.52) -3.49 (-4.87, -2.11) <0.0001 0.0003	64.26 (5.01) -7.94 (0.51) -2.77 (-4.14, -1.40) <0.0001 0.0009

[a] Adjusted p-values: using graphical approach to control the overall type I error rate for multiple comparisons.

Table 6 Summary of efficacy endpoints, OTHE population

	Placebo (N=249)	**Atogepant 30 mg twice daily (N=254)**	**Atogepant 60 mg once daily (N=257)**
Primary efficacy endpoint			
Change in mean monthly migraine days across the 12-week Mean baseline no of days (SD) LS Mean change from baseline (SE) **Atogepant vs placebo** (95% CI) Nominal p-value Adjusted p-value[a]	18.95 (4.80) -5.09 (0.41)	18.60 (5.09) -7.33 (0.41) -2.24 (-3.31, -1.16) <0.0001 0.0001	19.19 (5.29) -6.75 (0.41) -1.66 (-2.72, -0.59) 0.0024 0.0024
Secondary efficacy endpoints			
Change in mean monthly headache days across 12-week Mean baseline no of days (SD) LS Mean change from baseline (SE) **Atogepant vs placebo** (95% CI) Nominal p-value Adjusted p-value[a]	21.42 (4.11) -5.17 (0.40)	21.17 (4.15) -7.32 (0.40) -2.14 (-3.20, -1.09) <0.0001 0.0002	21.54 (4.32) -6.90 (0.40) -1.72 (-2.78, -0.67) 0.0014 0.0024
Change in mean monthly acute medication use days across 12-week Mean baseline no of days (SD) LS Mean change from baseline (SE) **Atogepant vs placebo** (95% CI) Nominal p-value Adjusted p-value[a]	15.31 (7.05) -4.09 (0.39)	14.53 (7.22) -6.61 (0.39) -2.52 (-3.52, -1.53) <0.0001 0.0002	15.45 (7.36) -6.19 (0.38) -2.09 (-3.09, -1.10) <0.0001 0.0024
≥50% reduction in 3-month average of monthly migraine days Responders, n (%) **Atogepant vs placebo Odds ratio** (95% CI) Nominal p-value Adjusted p-value[a]	66 (26.5)	107 (42.1) 2.03 (1.38, 2.98) 0.0003 0.0006	103 (40.1) 1.90 (1.29, 2.79) 0.0011 0.0024

[a] Adjusted p-values: using graphical approach to control the overall type I error rate for multiple comparisons.

Study 302

Study 302 was a Phase III, multicentre, randomised, open-label, 52-week study to evaluate long-term safety and tolerability of atogepant for the prevention of migraine in patients with EM, defined as 4 to 14 migraine days per month. The study enrolled both de novo participants (85.6%) with no previous exposure to atogepant, and Study CGP-MD-01 completers (14.4%) without significant protocol deviations.

Patients were randomised in a 5:2 ratio to receive oral atogepant 60 mg once daily or SOC migraine preventive medication for 52 weeks. Efficacy variables included frequency of migraine days, headache days, acute medication use days, and health outcomes assessments. No clinical efficacy measurements were collected from participants in the SOC migraine preventive medication arm, which was included in the study for safety evaluation only.

Efficacy analyses were performed using the mITT population, consisting of all randomised participants who received at least 1 dose of atogepant, had an evaluable baseline period of eDiary data and had at least 1 evaluable postbaseline 4-week period of eDiary data. A total of 744 patients were randomised in the study: 546 and 198 patients in the atogepant 60 mg once daily and SOC arms, respectively. Among the randomised patients, 521 from the atogepant arm were included in the mITT population.

The LS mean change from baseline in the number of monthly migraine days in the first month (Weeks 1-4) was -3.84 days and continued to improve to -5.19 days in the last month (Weeks 49-52).

Table 7 Change from baseline in number of monthly migraine days

Visit Parameter	Statistics	Atogepant 60 mg (N=521)
Weeks 1-4	n	513
Baseline	Mean (SD)	7.30 (2.62)
Postbaseline	Mean (SD)	3.47 (3.35)
Change from baseline	LS Mean (SE)	-3.84 (0.14)
	95% CI	-4.10, -3.57
Weeks 9-12	n	466
Baseline	Mean (SD)	7.29 (2.62)
Postbaseline	Mean (SD)	2.85 (3.25)
Change from baseline	LS Mean (SE)	-4.38 (0.14)
	95% CI	-4.65, -4.11
Weeks 21-24	n	417
Baseline	Mean (SD)	7.27 (2.58)
Postbaseline	Mean (SD)	2.37 (3.21)
Change from baseline	LS Mean (SE)	-4.72 (0.15)
	95% CI	-5.00, -4.43
Weeks 33-36	n	379
Baseline	Mean (SD)	7.28 (2.62)
Postbaseline	Mean (SD)	2.06 (3.03)
Change from baseline	LS Mean (SE)	-4.95 (0.14)
	95% CI	-5.23, -4.67
Weeks 49-52	n	335
Baseline	Mean (SD)	7.28 (2.70)
Postbaseline	Mean (SD)	1.84 (3.28)
Change from baseline	LS Mean (SE)	-5.19 (0.16)
	95% CI	-5.50, -4.87

Across the two pivotal studies, 301 and 303, conducted patients with EM and CM, respectively, all atogepant treatment arms demonstrated superiority over placebo in the primary endpoint of change in mean monthly migraine days across 12 weeks. In study 301, a numerical dose-response relationship was observed for the change from baseline in mean monthly migraine days across the 12-week treatment period in EM patients, with the largest reduction observed in the 60 mg once daily group. The efficacy of atogepant 60 mg once daily dose was also supported by secondary efficacy endpoints in both studies 301 and 303. Furthermore, the open-label study 302 demonstrated that the efficacy of atogepant 60 mg once daily was maintained for up to one year in patients with EM. Although the 30 mg twice daily treatment arm performed numerically better than the 60 mg once daily treatment arm in the CM study 303, the 60 mg once daily dose was considered acceptable to provide a consistent dosing regimen for both EM and CM and for improved convenience and compliance.

Overall, the submitted efficacy data adequately supported the use of atogepant 60 mg once daily for prophylaxis of migraine in adults who have at least 4 migraine days per month.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of atogepant was based primarily on the placebo-controlled analysis set derived from the two pivotal Phase III studies (studies 301 and 303) and the dose ranging study CGP-MD-01, comprising a total of 2500 patients who received at least one dose of study treatment: 314, 411, 678, 343, 91 and 663 subjects in the atogepant 10 mg once daily, atogepant 30 mg once daily, atogepant 60 mg once daily, atogepant 30 mg twice daily, atogepant 60 mg twice daily and placebo arms, respectively. The median duration of exposure was 85 days in both overall atogepant and placebo arms.

In addition, safety data from 4 atogepant open-label, long-term safety studies up to 104 weeks duration (studies 302 and 309 in participants with EM, and studies 306 and 312 in participants with CM) provided supportive safety data. The long-term safety analysis set comprised a total of 1858 patients: 1662 in the atogepant 60 mg once daily arm and 196 in the SOC arm. The median duration of exposure was 280 days in the atogepant arm and 365 days in the SOC arm.

Table 8 Overview of safety profile in the placebo-controlled analysis set, n (%)

AE	Placebo (N=663)	Atogepant					
		10 mg once daily (N=314)	30 mg once daily (N=411)	60 mg once daily (N=678)	30 mg twice daily (N=343)	60 mg twice daily (N=91)	Overall atogepant (N=1837)
Any AE	334 (51.9)	178 (56.7)	234 (56.9)	396 (58.4)	197 (57.4)	53 (58.2)	1058 (57.6)
Treatment-related AE	84 (12.7)	68 (21.7)	73 (17.8)	132 (19.5)	70 (20.4)	24 (26.4)	367 (20.0)
SAE	7 (1.1)	3 (1.0)	2 (0.5)	9 (1.3)	4 (1.2)	0	18 (1.0)
Treatment-related SAE	0	1 (0.3)	0	0	0	0	1 (0.1)
Discontinuations due to AE	21 (3.2)	13 (4.1)	14 (3.4)	21 (3.1)	18 (5.2)	6 (6.6)	72 (3.9)
Deaths due to AE	0	0	0	0	0	0	0

Table 9 Overview of safety profile in the long-term safety analysis set, n (%)

AE	SOC (N=196)	Atogepant 60 mg once daily (N=1662)

Any AE	154 (78.6%)	1056 (63.5%)
Treatment-related AE	71 (36.2%)	221 (13.3%)
SAE	7 (3.6%)	56 (3.4%)
Treatment-related SAE	0	0
Discontinuations due to AE	5 (2.6%)	76 (4.6%)
Deaths due to AE	0	3 (0.2%)

In the placebo-controlled analysis set, the incidence of adverse events (AEs) was similar across all atogepant dose groups. Common AEs reported in the overall atogepant group (and their incidences vs placebo) include nausea (7.5% vs 3.3%), constipation (7.2% vs 2.0%), fatigue (3.2% vs 2.6%), and decreased appetite (2.1% vs 0.2%). The common gastrointestinal-related AEs have similarly been reported with other CGRP antagonists. A trend of dose-related nausea was observed (5.1%, 5.6%, 9.0% and 3.3% in the atogepant 10 mg, 30 mg, 60 mg once daily and placebo arms, respectively). Nausea AEs were mostly mild or moderate, and did not translate to dose-related rates of discontinuation due to nausea.

Serious AEs (SAEs) were reported with low and comparable incidences in the overall atogepant (1.0%) and placebo (1.1%) groups. Except for one SAE of optic neuritis reported in the atogepant 10 mg once daily group, none of the SAEs was considered by the investigator to be related to study drug. AEs leading to treatment discontinuation were also low and comparable between the overall atogepant (3.9%) and placebo (3.2%) groups. The most common AEs leading to treatment discontinuation were nausea (0.6% vs 0.3%) and constipation (0.5% vs 0.3%). There were no deaths reported in the placebo-controlled studies.

In the long-term safety analysis set, AEs were reported for 63.5% of patients in the atogepant 60 mg once daily group and 78.6% of patients in the SOC group. Most AEs were mild or moderate in severity, with few severe AEs in either treatment group. Treatment-related AEs were reported for 13.3% of patients in the atogepant 60 mg once daily group and 36.2% of patients in the SOC group. The most common AEs in the atogepant 60 mg once daily arm (and their incidences vs SOC) were constipation (6.0% vs 3.1%) and upper respiratory tract infection (6.0% vs 12.2%). SAEs were reported with low and comparable incidence in the atogepant and SOC groups (3.4% vs 3.6%), and none were considered to be treatment-related by the investigator. Three fatal AEs were reported in the atogepant 60 mg once daily group (toxic shock syndrome, homicide, and asphyxia), none of which were considered by the investigator to be related to study drug.

Potential AEs of special interest known to be associated with CGRP antagonists include cardiovascular events, hepatic AEs, suicidal ideation, and abuse, but no major safety signals have been identified in the atogepant studies. A warning statement recommending against use in severe hepatic impairment has been included in the package insert. The rate of aminotransferase elevations ≥ 3 × ULN was similar between atogepant-treated participants (0.9%) and placebo-treated participants (1.2%) and there were no potential Hy's law cases and no cases of severe liver injury.

The safety profile of atogepant was consistent with that of other CGRP antagonists used for the prevention of migraine. Overall, the safety profile of atogepant in migraine prevention was considered manageable and no major safety concerns were raised.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Migraine is a serious, chronic, disabling neurologic disease characterised by attacks of moderate to severe headache associated with other symptoms such as nausea, vomiting, photophobia, and phonophobia. Currently, there are limited oral CGRP antagonists available for prevention of migraine and none are approved for the prevention treatment of CM.

Superiority over placebo in the primary endpoint of change from baseline in mean monthly migraine days across 12 weeks was demonstrated for all atogepant treatment arms across the two pivotal Phase III studies (301 and 303), conducted patients with EM and CM, respectively. A numerical dose-response relationship was observed for the change from baseline in mean monthly migraine days across the 12-week treatment period in EM patients in study 301, with greater reductions observed with increasing atogepant dose (LS mean difference versus placebo: -1.22 for 10 mg once daily, -1.38 for 30 mg once daily, and -1.66 for 60 mg once daily). The observed effect size based on LS mean difference versus placebo of -1.72 days and -1.82 days in the atogepant 60 mg once daily dose groups in studies 301 and 303, respectively, is comparable to other CGRP antagonists for migraine prevention. The onset of overall treatment effect was apparent during the first 4 weeks in both pivotal studies. The efficacy of atogepant 60 mg once daily dose was further supported by the secondary efficacy endpoints. In addition, the efficacy of atogepant 60 mg once daily in EM patients was sustained for up to one year in the open-label study 302.

A common dose of 60 mg once daily is considered appropriate to provide a consistent posology for both EM and CM, which represents the continuum of the migraine disease spectrum and has potential compliance advantage over 30 mg twice daily dose in CM patients.

The safety profile of atogepant was consistent with that of other CGRP antagonists used for the prevention of migraine and was manageable. The most common AEs reported with atogepant in the clinical studies were nausea (7.5%), constipation (7.2%), fatigue (3.2%), and decreased appetite (2.1%). The adverse events have been adequately addressed in the product label.

Overall, the benefit-risk profile of atogepant for prophylaxis of migraine who have at least 4 migraine days per month was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Aquipta for the prophylaxis of migraine who have at least 4 migraine days per month was deemed favourable and approval of the product registration was granted on 29 November 2024.

APPROVED PACKAGE INSERT AT REGISTRATION

AQUIPTA TABLET 10MG

AQUIPTA TABLET 60MG

Atogepant

1. PRODUCT NAME

1.1 Generic name

Atogepant

1.2 Trade name

AQUIPTA™

2. INDICATIONS

AQUIPTA™ is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.

3. DOSAGE AND ADMINISTRATION

3.1 Recommended dosage

The recommended dose for AQUIPTA™ is 60 mg taken orally once daily with or without food.

There is no data that the 60 mg tablet can be divided into equal halves.

3.2 Missed dose

A missed dose should be taken right away. If it is almost time for the next dose, patients should be instructed to skip the missed dose and take the next dose as scheduled.

3.3 Dose modification

Dosing modifications for concomitant use of specific drugs (*see* **DRUG INTERACTIONS**) and for patients with renal impairment are provided in Table 1.

Table 1: Dose Modifications for Drug Interactions and for Specific Populations

Dose Modifications	Recommended Once Daily Dose of AQUIPTA™
Concomitant Drug Class	
Strong CYP3A4 Inhibitors	10 mg
Strong OATP Inhibitors	10 mg
Renal Impairment	
Severe Renal Impairment (CLcr 15-29 mL/min) and End-Stage Renal Disease (ESRD; CLcr <15 mL/min)	10 mg

3.4 Dosing in special populations

3.4.1 Pediatrics

Safety and effectiveness of AQUIPTA™ in pediatric patients have not been established.

3.4.2 Geriatric

Population pharmacokinetic modeling suggests no clinically significant pharmacokinetic differences between elderly and younger subjects. No dose adjustment of AQUIPTA™ is needed in elderly patients.

3.4.3 Renal impairment

For patients with severe renal impairment and ESRD, see dose adjustment in Table 1. No dose adjustment is recommended for patients with mild or moderate renal impairment.

For patients with ESRD undergoing intermittent dialysis, AQUIPTA™ should preferably be taken after dialysis.

3.4.4 Hepatic impairment

Avoid use of AQUIPTA™ in patients with severe hepatic impairment (Child-Pugh Class C) (*see* **PHARMACOLOGIC PROPERTIES**). No dose adjustment is recommended for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

4. CONTRAINDICATIONS

AQUIPTA™ is contraindicated in patients with a history of hypersensitivity to atogepant or any of the components of AQUIPTA™. Reactions have included anaphylaxis and dyspnea (*see* **WARNINGS AND PRECAUTIONS**).

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, dyspnea, rash, pruritus, urticaria, and facial edema, have been reported with use of AQUIPTA™ (*see* **ADVERSE REACTIONS**). Some hypersensitivity reactions can occur days after administration. If a hypersensitivity reaction occurs, discontinue AQUIPTA™ and institute appropriate therapy (*see* **CONTRAINDICATIONS**).

5.2 Hepatic impairment

Atogepant is not recommended in patients with severe hepatic impairment (see section 3.4).

6. DRUG INTERACTIONS

6.1 CYP3A4 Inhibitors

Co-administration of AQUIPTA™ with itraconazole, a strong CYP3A4 inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects (*see* **PHARMACOLOGIC PROPERTIES**). The recommended dosage of AQUIPTA™ with concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) is 10 mg once daily. No dose adjustment of AQUIPTA™ is needed with concomitant use of moderate or weak CYP3A4 inhibitors.

6.2 Organic anion transporting polypeptide (OATP) Inhibitors

Co-administration of AQUIPTA™ with single dose rifampicin [rifampin], an OATP inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects (*see* **PHARMACOLOGIC PROPERTIES**). The recommended dosage of AQUIPTA™ with concomitant use of strong OATP inhibitors (e.g., cyclosporine [ciclosporin]) is 10 mg.

7. PREGNANCY AND LACTATION

7.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of AQUIPTA™ in pregnant women. In animal studies, oral administration of atogepant during the period of organogenesis (rats and rabbits) or throughout pregnancy and lactation (rats) resulted in adverse developmental effects (decreased fetal and offspring body weight in rats; increased incidence of fetal structural variations in rabbits) at exposures greater than those used clinically. Atogepant is not recommended during pregnancy and in women of childbearing potential not using contraception.

7.1.1 Data (animal and/or human)

Animal Data

Oral administration of atogepant (0, 5, 15, 125, or 750 mg/kg/day) to pregnant rats during the period of organogenesis resulted in decreased fetal body weight and an increased incidence of fetal variations at the two highest doses tested (125 and 750 mg/kg) which was associated with maternal toxicity. At the no-effect dose (15 mg/kg/day) for adverse effects on embryofetal development, plasma exposure (AUC) was approximately 4 times that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

Oral administration of atogepant (0, 30, 90, or 130 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in an increase in fetal visceral and skeletal variations at the highest dose tested (130 mg/kg/day), which was associated with minimal maternal toxicity. At the no-effect dose (90 mg/kg/day) for adverse effects on embryofetal development, plasma exposure (AUC) was approximately 3 times that in humans at the MRHD.

Oral administration of atogepant (0, 15, 45, or 125 mg/kg/day) to rats throughout gestation and lactation resulted in decreased pup body weight at the highest dose tested (125 mg/kg/day), which persisted into adulthood. At the no-effect dose (45 mg/kg/day) for adverse effects on pre- and postnatal development, plasma exposure (AUC) was approximately 5 times that in humans at the MRHD.

7.2 Lactation

There are no data on the presence of atogepant in human milk, the effects of atogepant on the breastfed infant, or the effects of atogepant on milk production. In lactating rats, oral dosing with atogepant resulted in levels of atogepant in milk approximately 2-fold higher than those in maternal plasma. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AQUIPTA™ and any potential adverse effects on the breastfed infant from AQUIPTA™ or from the underlying maternal condition.

8. 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.

9. ADVERSE REACTIONS

9.1 Clinical trials experience

The safety of AQUIPTA™ was evaluated in 2657 patients with migraine who received at least one dose of AQUIPTA™. Of these, 1225 patients were exposed to AQUIPTA™ daily for at least 6 months, and 826 patients were exposed for 12 months.

In 12-week, placebo-controlled clinical studies, 314 patients received at least one dose of AQUIPTA™ 10 mg once daily, 411 patients received at least one dose of AQUIPTA™ 30 mg

once daily, 343 patients received at least one dose of AQUIPTA™ 30 mg twice daily, 678 patients received at least one dose of AQUIPTA™ 60 mg once daily, 91 patients received at least one dose of AQUIPTA™ 60 mg twice daily, and 663 patients received placebo.

Table 2 summarizes the adverse reactions that occurred during placebo-controlled studies.

Table 2. Adverse drug reactions identified with AQUIPTA™

System Organ Class	Frequency	Adverse Reaction
Metabolism and nutrition disorders	Common	Decreased appetite
Gastrointestinal disorders	Common	Nausea, constipation
General disorders and administration site conditions	Common	Fatigue/somnolence

The adverse reaction that most commonly led to discontinuation was nausea (0.6%).

Liver Enzyme Elevations

In placebo-controlled studies, the rate of transaminase elevations over 3 times the upper limit of normal was similar between patients treated with AQUIPTA™ (0.9%) and those treated with placebo (1.2%). There were cases with transaminase elevations over 3 times the upper limit of normal that were temporally associated with AQUIPTA™ treatment; these were asymptomatic, and resolved within 8 weeks of discontinuation. There were no cases of severe liver injury or jaundice.

Decreases in Body Weight

In placebo-controlled studies, the proportion of patients with a weight decrease of at least 7% at any point was 3.8% for patients treated with AQUIPTA™ 10 mg QD, 3.2% for AQUIPTA™ 30 mg QD, 5.3% for AQUIPTA™ 30 mg BID, 5.3% for AQUIPTA™ 60 mg QD, 6.8% for AQUIPTA™ 60 mg BID, and 2.5% for placebo.

9.2 Post marketing experience

The following adverse reactions have been identified during post-approval use of AQUIPTA™. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity (e.g., anaphylaxis, dyspnea, rash, pruritus, urticaria, facial edema)

10. DRUG ABUSE AND DEPENDENCY

No studies on the abuse liability of AQUIPTA™ have been performed in humans.

11. OVERDOSE

No specific antidote for the treatment of AQUIPTA™ overdose is available. Treatment of an overdose of AQUIPTA™ should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

12. PHARMACOLOGIC PROPERTIES

12.1 Mechanism of action

Atogepant (ATC code: N02CD07) is an orally administered, small molecule, selective calcitonin gene-related peptide (CGRP) receptor antagonist that blocks the binding of the CGRP to the receptor and antagonizes CGRP receptor function. CGRP is a neuropeptide that has been associated with migraine pathophysiology. In the trigeminovascular system, CGRP modulates nociceptive signaling and inflammation, and also functions as a vasodilator.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose 5 times the maximum recommended daily dose, AQUIPTA™ does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

12.3.1 Absorption

Following oral administration of AQUIPTA™, atogepant is rapidly absorbed with plasma concentrations >14 nM (EC_{90} based on capsaicin induced dermal vasodilation model [CIDV]) within 0.5 hours and median T_{max} values ranging from 1 to 2 hours. Atogepant displays dose-proportional pharmacokinetics through 300 mg single dose with no accumulation upon once daily dosing.

When AQUIPTA™ was administered with a high-fat meal, the food effect was not significant (AUC and C_{max} were reduced by approximately 18% and 22%, respectively, with no effect on median time to maximum atogepant plasma concentration). AQUIPTA™ was administered without regard to food in clinical efficacy studies.

12.3.2 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 (Vz/F) after oral administration is approximately 292 L.

12.3.3 Metabolism

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.

12.3.4 Excretion

The elimination half-life of atogepant is approximately 11 hours. The mean apparent oral clearance (CL/F) of atogepant is approximately 19 L/hr. 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 feces and urine, respectively.

12.4 Pharmacokinetics in special populations

Based on a population pharmacokinetic analysis, age, 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.

12.4.1 Pediatric

Data not available.

12.4.2 Geriatric

Population pharmacokinetic modeling suggests no clinically significant pharmacokinetic differences between elderly and younger subjects.

12.4.3 Renal impairment

The renal route of elimination plays a minor role in the clearance of atogepant. Based on physiologically based pharmacokinetic (PBPK) and 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 (CLcr 15-29 mL/min) or end-stage renal disease (ESRD; CLcr <15 mL/min) have not been studied, use of the lowest effective dose of atogepant (10 mg) is recommended in those patients. No dose adjustment is recommended for patients with mild or moderate renal impairment.

12.4.4 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. Avoid use of AQUIPTA™ in patients with severe hepatic impairment. No dose adjustment is recommended for patients with mild or moderate hepatic impairment.

12.4.5 Drug interactions

In Vitro Studies

Enzymes:

In vitro, atogepant is not an inhibitor for CYPs 3A4, 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 at clinically relevant concentrations. Atogepant does not inhibit MAO-A or UGT1A1 at clinically relevant concentrations. Atogepant is not anticipated to be a clinically significant perpetrator of drug-drug interactions through CYP450s, MAO-A, or UGT1A1 inhibition.

Atogepant is not an inducer of CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.

Transporters:

Atogepant is a substrate of P-gp, BCRP, OATP1B1, OATP1B3, and OAT1. Dose adjustment for concomitant use of AQUIPTA™ with inhibitors of OATP is recommended based on a clinical interaction study with an OATP inhibitor (*see* **DOSAGE AND ADMINISTRATION**).

Coadministration of atogepant with BCRP and/or P-gp inhibitors is not expected to increase the exposure of atogepant. 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. No clinical drug interactions are expected for atogepant as a perpetrator with these transporters.

In Vivo Studies

CYP3A4 Inhibitors:

Co-administration of AQUIPTA™ with itraconazole, a strong CYP3A4 inhibitor, resulted in a clinically significant increase (C_{max} by 2.15-fold and AUC by 5.5-fold) in the exposure of atogepant in healthy subjects (*see* **DRUG INTERACTIONS**).

PBPK modeling suggested co-administration of AQUIPTA™ with moderate (e.g., cyclosporine [ciclosporin], ciprofloxacin, fluconazole, fluvoxamine, grapefruit juice) or weak (e.g., cimetidine, esomeprazole) CYP3A4 inhibitors increase atogepant AUC by 1.7- and 1.1-fold, respectively. The changes in atogepant exposure when coadministered with weak or moderate CYP3A4 inhibitors are not expected to be clinically significant.

CYP3A4 Inducers:

Co-administration of AQUIPTA™ with rifampicin [rifampin], a strong CYP3A4 inducer, decreased atogepant AUC by 60% and C_{max} by 30% in healthy subjects (*see* **DRUG INTERACTIONS**). No dedicated drug interaction studies were conducted to assess concomitant use with moderate CYP3A4 inducers. Moderate inducers of CYP3A4 can decrease atogepant exposure (*see* **DRUG INTERACTIONS**). Clinically significant interaction was not observed with concomitant administration of topiramate, a weak inducer of CYP3A4 and AQUIPTA™.

BCRP/OATP/P-gp Inhibitors:

Co-administration of AQUIPTA™ with single dose rifampicin [rifampin], an OATP inhibitor, increased atogepant AUC by 2.85-fold and C_{max} by 2.23-fold in healthy subjects (*see* **DRUG INTERACTIONS**).

Co-administration of AQUIPTA™ with quinidine, a P-gp inhibitor, increased atogepant AUC by 26% and C_{max} by 4% in healthy subjects. The changes in atogepant exposure when co-administered with P-gp inhibitors are not expected to be clinically significant.

PBPK modeling suggests that co-administration of AQUIPTA™ with BCRP inhibitors increases atogepant exposure by 1.2-fold. This increase is not expected to be clinically significant.

Other Drug Interaction Evaluations:

Co-administration of AQUIPTA™ with oral contraceptive components ethinyl estradiol and levonorgestrel, famotidine, esomeprazole, acetaminophen, naproxen, sumatriptan, topiramate, or ubrogepant did not result in significant pharmacokinetic interactions for either atogepant or co-administered drugs.

13. CLINICAL STUDIES

13.1 Episodic Migraine

The efficacy of AQUIPTA™ for the preventive treatment of episodic migraine (4 to 14 migraine days per month) in adults was demonstrated in one randomized, multicenter, double-blind, placebo-controlled study (Study 1 [ADVANCE]). The study enrolled patients with at least a 1-year history of migraine with or without aura, according to the International Classification of Headache Disorders (ICHD-3) diagnostic criteria.

In Study 1 (NCT03777059), 910 patients were randomized 1:1:1:1 to receive AQUIPTA™ 10 mg (N = 222), AQUIPTA™ 30 mg (N = 230), 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 medication that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine. The study excluded patients with myocardial infarction, stroke, or transient ischemic attacks within six months prior to screening.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) across the 12-week treatment period. Additional endpoints 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% and 75% reduction from baseline in mean MMD (3-month average); the change from baseline at week 12 for Headache Impact Test (HIT-6) total score; Migraine Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) Role Function-Restrictive (RFR) domain score; and the change from baseline across the 12-week treatment period in mean monthly Activity Impairment in Migraine-Diary (AIM-D) Performance of Daily Activities (PDA) domain scores and mean monthly AIM-D Physical Impairment (PI) domain scores.

The HIT-6 measures the impact of headache on participants' ability to function at work, school, home, and in social situations. The AIM-D evaluates difficulty with performance of daily activities (PDA domain) and physical impairment (PI domain) due to migraine. A reduction in scores from baseline indicates improvement. The MSQ v2.1 RFR domain score assesses how

often migraine impacts function related to daily social and work-related activities. An increase in scores from baseline indicates improvement.

A total of 805 (88%) patients completed the 12-week double-blind study period. Patients had a mean age of 42 years (range: 18 to 73 years), 89% were female, 83% were White, 14% were Black and 9% were of Hispanic or Latino ethnicity. The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups.

AQUIPTA™ treatment demonstrated statistically significant improvements for key efficacy endpoints compared to placebo in Study 1, as summarized in Table 3.

Table 3: Efficacy Endpoints in Study 1

Endpoint	AQUIPTA™ 10 mg N=214	AQUIPTA™ 30 mg N=223	AQUIPTA™ 60 mg N=222	Placebo N=214
Monthly Migraine Days (MMD) across 12 weeks				
Baseline	7.5	7.9	7.8	7.5
Mean change from baseline	-3.7	-3.9	-4.2	-2.5
Difference from placebo	-1.2	-1.4	-1.7	
p-value	<0.001	<0.001	<0.001	
Monthly Headache Days across 12 weeks				
Baseline	8.4	8.8	9.0	8.4
Mean change from baseline	-3.9	-4.0	-4.2	-2.5
Difference from placebo	-1.4	-1.5	-1.7	
p-value	<0.001	<0.001	<0.001	
Monthly Acute Medication Use Days across 12 weeks				
Baseline	6.6	6.7	6.9	6.5
Mean change from baseline	-3.7	-3.7	-3.9	-2.4
Difference from placebo	-1.3	-1.3	-1.5	
p-value	<0.001	<0.001	<0.001	
≥ 50% MMD Responders across 12 weeks				
% Responders	56	59	61	29
Difference from placebo (%)	27	30	32	
p-value	<0.001	<0.001	<0.001	
MSQ v2.1 RFR Domain[a] at week 12				
Baseline	44.9	44.0	46.8	46.8
Mean change from baseline	30.4	30.5	31.3	20.5
Difference from placebo	9.9	10.1	10.8	
p-value	<0.001	<0.001	<0.001	
AIM-D PDA Domain[b] across 12 weeks				
Baseline	15.5	16.9	15.9	15.2
Mean change from baseline	-7.3	-8.6	-9.4	-6.1
Difference from placebo	-1.2	-2.5	-3.3	
p-value	NS[c]	<0.001	<0.001	

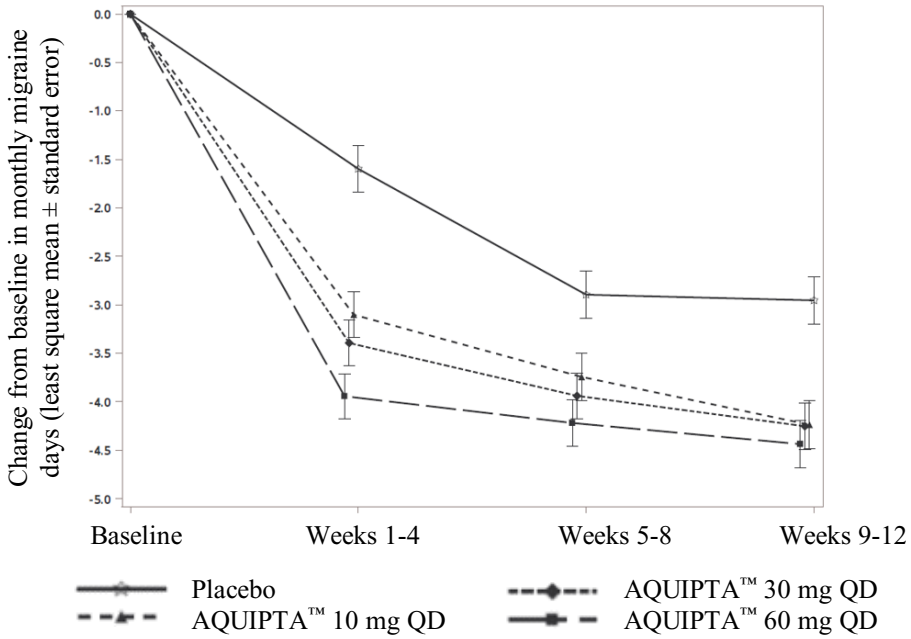
AIM-D PI Domain[b] across 12 weeks				
Baseline	11.7	13.0	11.6	11.2
Mean change from baseline	-5.1	-6.0	-6.5	-4.0
Difference from placebo	-1.1	-2.0	-2.5	
p-value	NS[c]	0.002	<0.001	
HIT-6[d] at week 12				
Baseline	64.2	64.3	63.8	64.5
Mean change from baseline	-8.4	-8.1	-9.2	-5.2
Difference from placebo	-3.2	-2.9	-4.0	
p-value	<0.001[e]	<0.001[e]	<0.001[e]	
≥ 75% MMD Responders across 12 weeks				
% Responders	30	30	38	11
Difference from placebo (%)	20	19	27	
p-value	<0.001[e]	<0.001[e]	<0.001[e]	

[a] Migraine Specific Quality of Life Questionnaire version 2.1 Role Function-Restrictive (RFR) domain scores
[b] Activity Impairment in Migraine-Diary domain scores: Performance of Daily Activities (PDA) and Physical Impairment (PI)
[c] Not statistically significant (NS)
[d] Headache Impact Test total score
[e] Not adjusted for multiple comparisons

Additional pre-specified endpoints included the MSQ v2.1 Role Function-Preventive (RFP) and Emotional Function (EF) domains. MSQ v2.1 assesses how migraine prevents daily social and work-related activities (RFP domain) and the emotions associated with migraine (EF domain). An increase in scores from baseline indicates improvement. At week 12, the mean change from baseline for the MSQ v2.1 RFP domain (placebo: 17.0, 10 mg: 22.8, 30 mg: 23.9, 60 mg: 24.1) and EF domain (placebo: 18.4, 10 mg: 26.7, 30 mg: 28.1, 60 mg: 29.0) demonstrated greater improvements with AQUIPTA™ (not controlled for multiple comparisons).

Figure 1 shows the mean change from baseline in MMD in Study 1. Patients treated with AQUIPTA™ had greater mean decreases from baseline in MMD across the 12-week treatment period compared to patients who received placebo. During the first month of treatment (starting the first day after the initial dose), AQUIPTA™ had greater mean decreases from baseline in weekly migraine days compared to placebo-treated patients.

Figure 1: Change from baseline in monthly migraine days in Study 1



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In patients failing one or more prophylactic medications, the treatment difference for the change from baseline in MMD observed as compared to placebo across the 12-week treatment period was -1.5 (95% CI: -2.4, -0.6), -1.5 (95% CI: -2.3, -0.7), and -2.2 (95% CI: -3.1, -1.4) for AQUIPTA™ 10 mg, 30 mg and 60 mg, respectively.

In Study 1, the proportions of participants with ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine days was greater for atogepant compared with placebo in each of the 4-week intervals assessed (Weeks 1-4, 5-8, and 9-12), and the percentage of responders at each threshold generally increased over time.

Table 4: Reduction of ≥ 50%, ≥ 75%, and 100% from baseline in MMD by 4-week interval[a]

	AQUIPTA™ 10 mg (%)	**AQUIPTA™ 30 mg (%)**	**AQUIPTA™ 60 mg (%)**	**Placebo (%)**
≥ 50% MMD Responders				
Weeks 1-4	49	49	61	27
Weeks 5-8	61[b]	62[b]	66	47
Weeks 9-12	64	61	71	44
≥ 75% MMD Responders				
Weeks 1-4	27	27	39	10
Weeks 5-8	39	36	41	17
Weeks 9-12	43	43	50	21

100% MMD Responders				
Weeks 1-4	14	12[b]	19	4
Weeks 5-8	22	18[b]	24	8
Weeks 9-12	21[b]	27	28	11

[a] $p < 0.001$ for all comparisons between AQUIPTA™ and placebo except as noted (not adjusted for multiple comparisons)

[b] $p < 0.009$ for comparison between AQUIPTA™ and placebo (not adjusted for multiple comparisons)

Results of Long-Term Study

Results from a multicenter, randomized, open-label, 52-week clinical study evaluating atogepant 60 mg safety and tolerability in 546 randomized patients with episodic migraine, demonstrated that efficacy was sustained over the 1-year treatment period. 68.4% of patients completed the treatment period. Atogepant treatment was associated with reduction in the least squares (LS) mean number of monthly migraine days in the first month (Weeks 1-4) of -3.84 days and continued to improve during the remainder of the 52-week treatment period to an LS mean reduction of -5.19 days in the last month (Weeks 49-52).

The proportion of participants who responded with ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine days at Weeks 1-4 was 60.4%, 37.2%, and 20.7%, respectively and the proportion of participants at Weeks 49-52 was 84.2%, 69.9%, and 48.4%, respectively.

13.2 Chronic Migraine

The efficacy of AQUIPTA™ for the preventive treatment of chronic migraine (15 or more headache days per month with at least 8 migraine days) in adults was demonstrated in one randomized, multicenter, double-blind, placebo-controlled study (Study 2 [PROGRESS]). The study enrolled patients with at least a 1-year history of chronic migraine, according to the ICHD-3 diagnostic criteria.

In Study 2 (NCT03855137), 778 patients were randomized 1:1:1 to receive AQUIPTA™ 30 mg twice daily (N = 257), AQUIPTA™ 60 mg once daily (N = 262), or placebo (N = 259) for 12 weeks. 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. A subset of patients (11%) was allowed to use one concomitant migraine preventive medication (e.g., amitriptyline, propranolol, topiramate). The use of a concomitant medicinal product that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine. The study excluded patients with myocardial infarction, stroke, or transient ischemic attacks within six months prior to screening.

The primary efficacy endpoint was the change from baseline in mean MMD across the 12-week treatment period. Additional endpoints 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% and 75% reduction from baseline in mean MMD (3-month average); the change from baseline at week 12 for Headache Impact Test (HIT-6) total score and MSQ v2.1 RFR domain score; and the change from baseline across the 12-week treatment period in mean monthly AIM-D PDA domain scores and mean monthly AIM-D PI domain scores.

Patients had a mean age of 42 years (range 18 to 74 years), 88% were female, 59% were White, 3% were Black, 36% were Asian, and 4% were of Hispanic or Latino ethnicity. The mean migraine frequency at baseline was approximately 19 migraine days per month and was similar across treatment groups. A total of 694 (89%) patients completed the 12-week double-blind study period.

Key efficacy results of Study 2 are summarized in Table 5.

Table 5: Efficacy Endpoints in Study 2

	AQUIPTA™ 30 mg BID N=253	**AQUIPTA™ 60 mg QD N=256**	**Placebo N=246**
Monthly Migraine Days (MMD) across 12 weeks			
Baseline	18.6	19.2	19.0
Mean change from baseline	-7.5	-6.9	-5.1
Difference from placebo	-2.4	-1.8	
p-value	<0.001	<0.001	
Monthly Headache Days across 12 weeks			
Baseline	21.2	21.5	21.4
Mean change from baseline	-7.4	-7.0	-5.1
Difference from placebo	-2.3	-1.9	
p-value	<0.001	<0.001	
Monthly Acute Medication Use Days across 12 weeks			
Baseline	14.5	15.5	15.4
Mean change from baseline	-6.7	-6.2	-4.1
Difference from placebo	-2.6	-2.1	
p-value	<0.001	<0.001	
≥ 50% MMD Responders across 12 weeks			
% Responders	43	41	26
Difference from placebo (%)	17	15	
p-value	<0.001	<0.001	
MSQ v2.1 RFR Domain[a] at week 12			
Baseline	44.0	43.4	43.9
Mean change from baseline	25.2	23.3	17.2

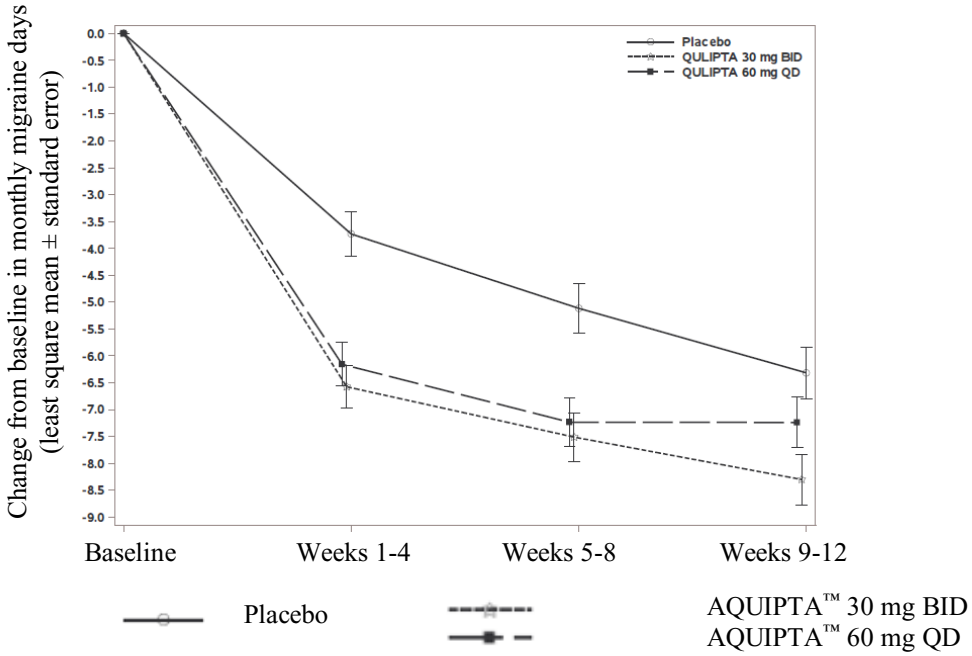
Difference from placebo	8.0	6.2	
p-value	<0.001	<0.001	
AIM-D PDA Domain[b] across 12 weeks			
Baseline	29.6	31.1	29.4
Mean change from baseline	-14.3	-12.8	-9.4
Difference from placebo	-4.9	-3.4	
p-value	<0.001[d]	<0.001[d]	
AIM-D PI Domain[b] across 12 weeks			
Baseline	25.7	27.0	25.2
Mean change from baseline	-12.1	-10.6	-7.9
Difference from placebo	-4.2	-2.7	
p-value	<0.001[d]	0.003[d]	
HIT-6[c] at week 12			
Baseline	64.3	64.4	63.8
Mean change from baseline	-8.7	-7.9	-5.2
Difference from placebo	-3.5	-2.8	
p-value	<0.001[d]	<0.001[d]	
≥ 75% MMD Responders across 12 weeks			
% Responders	21	19	6
Difference from placebo (%)	16	13	
p-value	<0.001[d]	<0.001[d]	

[a] Migraine Specific Quality of Life Questionnaire version 2.1 Role Function-Restrictive domain score
[b] Activity Impairment in Migraine-Diary domain scores: Performance of Daily Activities (PDA) and Physical Impairment (PI)
[c] Headache Impact Test total score
[d] Not adjusted for multiple comparisons

Additional pre-specified endpoints included the MSQ v2.1 RFP and EF domains. The mean change from baseline for the MSQ v2.1 RFP domain (placebo: 13.4, 30 mg BID: 21.4, 60 mg QD: 20.2) and EF domain (placebo: 15.6, 30 mg BID: 22.0, 60 mg QD: 22.4) demonstrated greater improvements with AQUIPTA™ at week 12 (not controlled for multiple comparisons).

Figure 2 shows the mean change from baseline in MMD in Study 2. Patients treated with AQUIPTA™ had greater mean decreases from baseline in MMD across the 12-week treatment period compared to patients who received placebo.

Figure 2: Change from Baseline in Monthly Migraine Days in Study 2



In patients failing one or more prophylactic pharmacotherapies, the treatment difference for the change from baseline in MMD observed between AQUIPTA™ and placebo across the 12-week treatment period was -2.0 (95% CI: -3.9, -0.2) for 30 mg BID and -1.8 (95% CI: -3.6, 0.1) for 60 mg QD. In patients failing two or more prophylactic pharmacotherapies, the treatment difference was -2.9 (95% CI: -4.7, -1.1) for 30 mg BID and -2.5 (95% CI: -4.2, -0.7) for 60 mg QD.

The proportions of participants with ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine days was greater in the atogepant treatment group than in the placebo treatment group for each of the 4-week intervals assessed (Weeks 1 to 4, 5 to 8, and 9 to 12), and the percentage of responders at each threshold increased over time.

Table 6: Reduction of ≥ 50%, ≥ 75%, and 100% from baseline in MMD by 4-week interval

	AQUIPTA™ 30 mg BID (%)	**AQUIPTA™ 60 mg QD (%)**	**Placebo (%)**
≥ 50% MMD Responders			
Weeks 1-4	40	40[a]	18
Weeks 5-8	48	44[a]	32

Weeks 9-12	52[a]	45	38
≥ 75% MMD Responders			
Weeks 1-4	21	17[a]	5
Weeks 5-8	23	25[a]	10
Weeks 9-12	27[a]	28[a]	15
100% MMD Responders			
Weeks 1-4	3[b]	4[b]	0
Weeks 5-8	5[b]	7[a]	<1
Weeks 9-12	8[b]	7[b]	3

[a] $p<0.01$ for comparison between AQUIPTA™ and placebo (not adjusted for multiple comparisons)
[b] $p<0.05$ for comparison between AQUIPTA™ and placebo (not adjusted for multiple comparisons)

14. PRE-CLINICAL SAFETY DATA

14.1 Carcinogenicity

Atogepant was administered orally to mice (0, 5, 20, or 75 mg/kg/day in males; 0, 5, 30, 160 mg/kg/day in females) and rats (0, 10, 20, or 100 mg/kg in males; 0, 25, 65, or 200 mg/kg in females) for up to 2 years. There was no evidence of drug-related tumors in either species. Plasma exposures at the highest doses tested in mice and rats were approximately 8 and 20-35 times, respectively, that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

14.2 Mutagenicity

Atogepant was negative in in vitro (Ames, chromosomal aberration test in Chinese Hamster Ovary cells) and in vivo (rat bone marrow micronucleus) assays.

14.3 Impairment of fertility

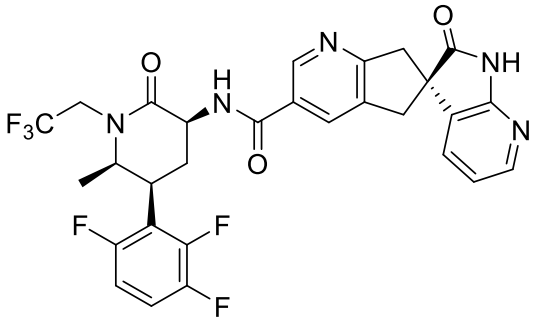
Oral administration of atogepant (0, 5, 20, or 125 mg/kg/day) to male and female rats prior to and during mating and continuing in females to Gestation Day 7 resulted in no adverse effects on fertility or reproductive performance. Plasma exposures (AUC) at the highest dose tested are approximately 15 times that in humans at the MRHD.

15. PHARMACEUTICAL PROPERTIES

15.1 Description

The active ingredient of AQUIPTA™ is atogepant, a calcitonin gene-related peptide (CGRP) receptor antagonist. The chemical name of atogepant is (3'*S*)-*N*- [(3*S*,5*S*,6*R*)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl]-2'-oxo-1',2',5,7-

tetrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide, and it has the following structural formula:



The molecular formula is $C_{29}H_{23}F_6N_5O_3$ and molecular weight is 603.5. Atogepant is a white to off-white powder. It is freely soluble in ethanol, soluble in methanol, sparingly soluble in acetone, slightly soluble in acetonitrile and practically insoluble in water.

AQUIPTA™ is available as tablets for oral administration containing 10 mg or 60 mg atogepant.

15.2 List of excipients

Colloidal silicon dioxide, croscarmellose sodium, mannitol, microcrystalline cellulose, polyvinylpyrrolidone/vinyl acetate copolymer, sodium chloride, sodium stearyl fumarate, vitamin E polyethylene glycol succinate

15.3 Storage

Store at or below 30°C.

15.4 How Supplied

AQUIPTA™ 10 mg is supplied as white to off-white, round biconvex tablets debossed with “A” and “10” on one side.

- PVC/PE/PCTFE Aclar- Aluminum blisters
    - 28-tablet packs

AQUIPTA™ 60 mg is supplied as white to off-white, oval biconvex tablets debossed with “A60” on one side.

- PVC/PE/PCTFE Aclar- Aluminum blisters
    - 28-tablet packs

Product Registrant:
AbbVie Pte. Ltd.
9 North Buona Vista Drive
The Metropolis #19-01
Singapore 138588

CCDSv4
Date of issue: DD MMM YYYY