23 April 2026
EMADOC-1700519818-3039313
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AQUIPTA

International non-proprietary name: Atogepant

Procedure No. EMA/VR/0000310717

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ASMA	anti-smooth muscle antibody
AST	aspartate aminotransferase
Ato	atogepant
CFS	Cognitive Function Scale
CGRP	calcitonin gene-related peptide
CI	confidence interval
CRF	case report form
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DB	double-blind
DSMB	Data and Safety Monitoring Board
DSS	Data and Statistical Sciences
ECG	electrocardiogram
eDiary	electronic diary
ePRO	electronic patient-reported outcome
EQ-5D-5L	European Quality of Life - 5 Dimension - 5 Level
EQ VAS	European Quality of Life Visual Analog Scale
FDS	Functional Disability Scale
GLMM	generalized linear mixed effects model
GCP	Good Clinical Practice
HEAC	Hepatic Event Adjudication Committee
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IHS	International Headache Society
IMP	investigational medicinal product
IRB	institutional review board
IRT	Interactive Response Technology
ITT	intent to treat
MBS	most bothersome migraine-associated symptom
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MQoLQ	Migraine Quality of Life Questionnaire
NSAID	nonsteroidal anti-inflammatory drug
NRI	nonresponse imputation
OL	open label
OR	odds ratio
Pbo	placebo
PCS	potentially clinically significant
PEP	Primary endpoint
PGIC	Patient Global Impression of Change
PRO	patient-reported outcome
PSSM	Patient Satisfaction with Study Medication

PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SEP	Secondary endpoint
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
USA	United States of America

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Abbvie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 6 November 2025 an application for a group of variations.

The following variations were requested in the group.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II
B.II.e.5.a.2	B.II.e.5.a.2 Change outside the range of the currently approved pack sizes	Variation type IB
B.II.e.5.a.2	B.II.e.5.a.2 Change outside the range of the currently approved pack sizes	Variation type IB
B.II.e.5.a.1	B.II.e.5.a.1 Change within the range of the currently approved pack sizes	Variation type IA_IN

A grouped application comprised of 1 Type II Variation and 3 Type I Variations, as follows: Type II (C.I.6): Extension of indication to include acute treatment of migraine with or without aura in adults, based on interim results from study M24-305; this is a 24-week, global, Phase 3, multicenter, randomized, double blind, placebo-controlled, multiple-migraine attack study with an open label period to evaluate the safety and efficacy of atogepant in adult participants for the acute treatment of migraine (ECLIPSE). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.2 of the RMP has also been submitted. Type IB (B.II.e.5.a.2): Addition of pack size of 7 tablets for 10mg strength tablets. Type IB (B.II.e.5.a.2): Addition of pack size of 2 tablets for 60mg strength tablets. Type IAIN (B.II.e.5.a.1): Addition of pack size of 7 tablets for 60mg strength tablets.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMA/PE/0000241150 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 25 May 2023 (EMA/SA/0000130143). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Janet Koenig

Timetable	Actual dates
Submission date:	12 November 2025
Start of procedure:	29 November 2025
CHMP Rapporteur's preliminary assessment report circulated on:	23 January 2026
CHMP Co-Rapporteur's preliminary assessment report circulated on:	26 January 2026
PRAC Rapporteur's preliminary assessment report circulated on:	30 January 2026
PRAC RMP advice and assessment overview adopted by PRAC:	12 February 2026
Joint Rapporteur's updated assessment report circulated on:	19 February 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 February 2026
MAH's responses submitted to the CHMP on:	23 March 2026
CHMP and PRAC Rapporteur's joint preliminary assessment report on the MAH's responses circulated on:	2 April 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	7 April 2026
PRAC RMP advice and assessment overview adopted by PRAC:	10 April 2026
CHMP opinion:	23 April 2026

2. Scientific discussion

2.1. Introduction

Atogepant is a potent, selective, orally administered, calcitonin gene-related peptide (CGRP) receptor antagonist that has been approved in the EU under the trade name AQUIPTA® on 11 August 2023 for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

The present Variation procedure EMA/VR/0000310717 is intended to expand the indication for atogepant to include the acute treatment of migraine with or without aura in adults, based on the results of Study M24-305 (ECLIPSE).

2.1.1. The development programme/compliance with CHMP guidance/scientific advice

On 25 May 2023, AbbVie received European Medicines Agency (EMA) Scientific Advice (EMA/SA/0000130143) regarding the proposed Study M24-305 to support a potential indication of acute treatment of migraine with or without aura in adults.

To align with the scientific advice and current clinical guidance, AbbVie made significant changes to the original study design. Study M24-305 was updated from a single-migraine attack study to the current 24-week DB, placebo-controlled, multiple-migraine attack study with an OL period, and the triptan-unsuitable substudy was added to support HTA requirements. It was originally planned to test for consistency under OL conditions and to include approx. 55% of participants categorized as "triptan unsuitable" in the main study (instead of examining triptan unsuitable patients in a substudy, after enrolment for the main study was complete).

In addition, a sensitivity analysis for the primary endpoint in the safety population was added to evaluate the robustness of primary analysis results, and as recommended, AbbVie provided relative risk and risk difference in addition to the primary measure of odds ratios (ORs) for the primary and key secondary efficacy endpoints. The Committee for Medicinal Products for Human Use (CHMP) recognized that extensive long-term data on daily use of atogepant 60 mg was available as part of the EU MAA for the prophylactic treatment of migraine and agreed that the proposed 24-week duration of the OL period was acceptable.

The Agency also recommended that the applicant consider using the coprimary efficacy endpoints defined for China in the European submission. While an application in China requires the 2 coprimary endpoints (freedom at 2 hours post-dose of pain and most bothersome symptom [MBS]), the implementation of the single primary efficacy endpoint (2 hours pain freedom) for Europe and other regions is aligned with current guidance. The primary efficacy endpoint specified for Study M24-305 (for applications in all regions other than China), pain freedom (defined as a reduction in headache severity from moderate/severe at baseline [predose] to no pain) at 2 hours after the DB dose for the first qualifying migraine attack, is per the EMA guideline (CPMP/EWP/788/01 Rev. 1). Absence of the most bothersome migraine-associated symptom (MBS) (to be identified at baseline [predose] for each subject) at 2 hours after the DB dose for the first qualifying migraine attack is ranked as the first key secondary efficacy endpoint to reflect the importance of the endpoint and the Agency's opinion regarding its clinical value and relevance.

2.2. Non-clinical aspects

An updated ERA has been submitted. No new non-clinical data has been submitted which is acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

The ERA Phase II Tier A and B provided for atogepant is considered acceptable.

Table 1. Summary of main study results: Phase I

Substance (INN/Invented Name):	Atogepant		
CAS-number (if available):	1374248-81-3		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD107	3.33 at pH 7	Potential PBT: *N*
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion

Bioaccumulation	log Kow	3.33 at pH 7	potentially B
	BCF (kinetic, lipid and growth corrected)	0.806 L/kg-1	Not B
Persistence	Ready biodegradability	N	potentially P
	DT50, total system at 12°C	2561 d	vP
Toxicity	NOECaquatic	0.55 mg/L	not T
PBT/vPvB statement:	Atogepant is considered to be not PBT, nor vPvB		

Phase I			
Parameter	**Value**	**Unit**	**Conclusion**
PECsw, default	0.3	µg/L	≥ 0.01 threshold: Y
Other concerns			N

Table 2. Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Adsorption-Desorption Soil 1 = *silt clay loam*	OECD 106	Kfoc soil 1 = *769* L/kgoc	
Soil 2 = *clay loam*		Kfoc, soil 2 = *270* L/kgoc	
Soil 3 = *loamy sand*		Kfoc, soil 3 = *424* L/kgoc	
Sludge 1 = *Loughborough*		Kfoc, sludge 1 = *555* L/kgoc	
Sludge 2 = *Worlingworth*		Kfoc, sludge 2 = *434* L/kgoc	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = Calwich Abbey Lake	OECD 308	DT50, $_{water\ 1}$ = 20 d DT50, $_{whole\ system\ 1}$ = 1200 d % shifting to sediment = 49.4 (day 14)	20°C
Sediment 2 = Emperor Lake		DT50, $_{water\ 2}$ = 21 d DT50, $_{whole\ system\ 2}$=555 d % shifting to sediment = 38.6 (day 14)	20°C

Phase II Aquatic effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test, *Raphidocelis subcapitata*	OECD 201	NOEC	1700	µg/L	Inhibition of growth rate and yield
Daphnia sp. Reproduction Test, *Daphnia magna*	OECD 211	NOEC	550	µg/L	reproduction
Fish, Early Life Stage Toxicity Test, *Pimephales promelas*	OECD 210	NOEC	1600	µg/L	Survival, egg hatch, weight, length
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	5190	µg/L	respiration
Phase II Sediment effect studies					
Sediment dwelling organism *Chironomus riparius*	OECD 218	NOEC	4322	mg/kg	emergence and development rate, correction to 10% organic carbon

Phase II Secondary poisoning					
Bioaccumulation Test	OECD 305	BCF	0.806	L/kg	%lipid

Risk characterization				
Compartment	**PEC**	**PNEC**	**RQ**	**Conclusion**
STP	3 µg/L	519 µg/L	0.0058	No risk
Surface water	0.3 µg/L	55 µg/L	0.0054	No risk
Groundwater	0.0075 µg/L	55 µg/L	0.0014	No risk
Sediment	0.00845 mg/kgdw	43.22 mg/kgdw	0.00019	No risk

2.2.2. Discussion on non-clinical aspects

Considering the above data from Phase I and Phase II, atogepant is not expected to pose a risk to the environment. Considering the above data of the definitive hazard assessment, atogepant is not a PBT or vPvB substance.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of atogepant.

Considering the above data, atogepant is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies

Table 3. Description of Clinical Efficacy and Safety Study M24-305 – Pivotal

Study ID/ No. of Centers/ Locations/ Duration	FSFV, Cutoff Date, Enrollment Status, Total Randomized/ Randomization Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objectives	No. of Subjects by Arm Entered/ Completed[a]	Sex M/F[b] Median Age (Min, Max)	Diagnosis Inclusion Criteria	Primary Endpoint
M24-305/ 147/ Belgium, Czechia, Germany, Hungary, Italy, Poland, Portugal, Slovakia, Spain, Sweden, UK, Japan, China, South Korea, and Taiwan/ up to 16 weeks DB and at least 8 weeks OL for a total of 24 weeks	25 Mar 2024, 07 Jul 2025, Completed, 1,328/1,300	Phase 3, randomized, DB, placebo-controlled, multiple-attack (4 attacks), 4-treatment sequence	Atogepant 60 mg or matching placebo taken orally once to treat each qualifying migraine attack	Primary objective: To evaluate the efficacy of a single dose of atogepant 60 mg compared to placebo for the acute treatment of a single migraine attack Secondary objective: To evaluate the safety and tolerability of atogepant 60 mg for the acute treatment of migraine for a single attack and across multiple migraine attacks and to evaluate the consistency of effect across multiple attacks	**DB treatment period:** Sequence 1: 666/526 Sequence 2: 218/170 Sequence 3: 222/176 Sequence 4: 222/173 **OL treatment period:** 1,045/895	184/1,048 42.0 years (18, 74)	History of migraine (with or without aura) according to the ICHD-3 for ≥ 12 months prior to Visit 1/Screening, and history of 2 to 8 migraine attacks of moderate to severe headache pain in each of the 3 months prior to Visit 1/Screening per investigator judgment	Pain freedom (defined as a reduction in headache severity from moderate/severe at Baseline [predose] to no pain) at 2 hours after the DB dose for the first attack

DB = double-blind; ICHD-3 = third edition of the International Classification of Headache Disorders; FSFV = first subject first visit; M = male; F = female; OL = open-label; UK = United Kingdom

a. Number of subjects entered and completed each treatment period as of the interim cutoff date of 07 July 2025.
b. Based on the safety population 1.

2.4. Pharmacokinetics

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 Cmax 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 (Vz/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.

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 $\geq$ 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.

Bioanalytical Methods

During pivotal study M24-305 PK samples were taken that were needed for subsequent Population PK-PD Exposure-Response Analysis.

For Phase 3 Study M24-305, the matrix utilized was human dried blood. The bioanalytical methods were developed and validated at both Altasciences in Laval, Quebec Canada and Shanghai Xihua Scientific Co., Ltd. in China to analyze pharmacokinetic (PK) samples collected across different geographical regions.

The dried blood PK samples collected from Study M24-305 and included in this submission were analyzed with validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays for the quantification of atogepant using a stable isotopically labelled internal standard. A summary of the validated atogepant assay methods utilized for the clinical study are provided below.

Table 4. Tabular Listing Supporting Validated LC-MS/MS Bioanalytical Methods for Clinical Studies

Study Identifier	Sample Preparation; Detection	Bioanalytical Validation Report	Matrix	Linear Range (LLOQ to ULOQ); ng/mL	Analyte	BA Laboratory
M24-305	DSE; LC-MS/MS	ARG-W7-849(R1)	Mitra® (blood)	2.50 to 2500 ng/mL	Atogepant	Altasciences
	DSE; LC-MS/MS	XH23P610-R00	Mitra® (blood)	2.50 to 2500 ng/mL	Atogepant	Shanghai Xihua Scientific

BA = bioanalytical; DSE = Desorption Solvent Extraction; Mitra® = Volumetric Absorptive Micro-sampling (VAMS®); LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation

All methods provided in this submission successfully supported clinical PK sample analysis. Incurred sample reanalysis (ISR) was demonstrated in the clinical study supporting PK sample analysis for atogepant. All clinical PK samples for the study in this submission were collected, processed, and analyzed within the established stabilities (App. B and C, 2.7.1).

Population Pharmacokinetic Model

A previously developed population PK model for atogepant based on 12 Phase 1 studies, Phase 2/3 Study CGP-MD-01 as well as Phase 3 Study 3101-301-002 (overall n=1287 subjects, n= 11763 samples, thus about 9 samples per subject) was evaluated to describe observed atogepant concentrations from Phase 3 Study M24-305 (n=466 patients, n=823 samples, thus about 1.8 samples per subject) using a post hoc approach.

The model was a three-compartment model with sequential zero/first-order absorption and first order elimination. Healthy volunteers and migraine patients shared the same PopPK model parameters, except for apparent clearance, which was 22.9 L/h in healthy volunteers, while it was 23.7% lower in patients with episodic migraines (CL/F = 17.4 L/h). Since the dose setting in Study M24-305 more closely resembles the single dose setting in most healthy volunteers' studies, the parameter estimate of CL/F for healthy volunteers instead of migraine patients, who were administrated chronically for prevention, was used in the population PK model. Key parameter values of the final population PK model are shown in Table 5.

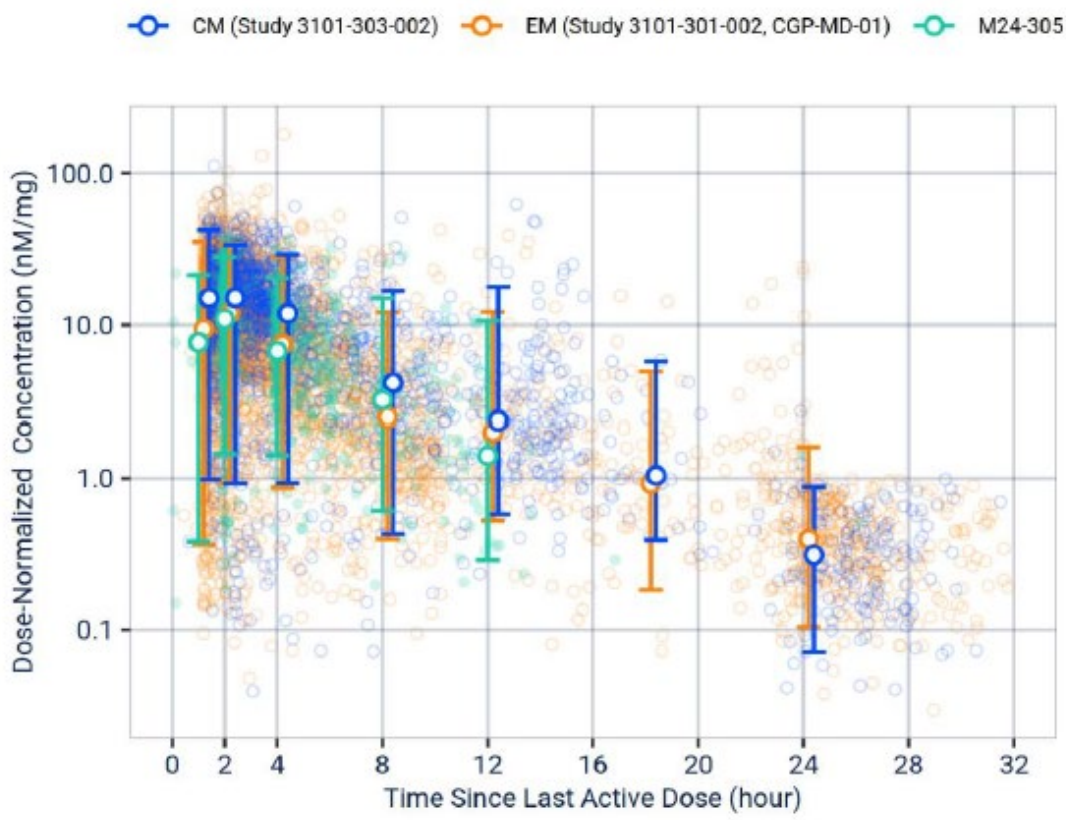
Table 5. Key Parameter Estimates and Variability of Atogepant Pharmacokinetics in Subjects Requiring Acute Treatment of Migraine

Parameter	Population Estimate	%RSE	95% Confidence Interval
Apparent central volume of distribution [V1/F(L)]	86.1	--	--
Apparent clearance healthy volunteers / subjects requiring acute treatment [CLhealthy/F (L/h)]	22.9	--	--
Apparent rapid peripheral volume of distribution [V2/F (L)]	40.5	--	--
Apparent slow peripheral volume of distribution [V3/F (L)]	13.0	--	--
Blood-plasma ratio	0.573	--	--
Duration zero-order absorption [Tk0 (h)]	0.908	--	--
Effect of severe hepatic impairment on apparent clearance	-0.366	--	--
Exponential dose effect on relative bioavailability	0.119	--	--
Exponential dose effect on zero-order absorption	0.199	--	--
Exponential weight effect on apparent central volume of distribution	0.411	--	--
Food effect on lag-time	0.672	--	--
Fraction zero-order absorption (Fk0)	0.693	--	--
Intercompartmental rapid clearance [Q/F (L/h)]	1.43	--	--
Intercompartmental slow clearance [Q2/F (L/h)]	1.68	--	--
Zero-order lag time [ALAG0 (h)]	0.276	--	--
Proportional Error Study 3101-301-002 and M24-305	0.491	--	--

Parameter	Population Estimate	%CV	%Shrinkage
IIV on CL/F	0.0243	15.7	75.9
IIV on Tk0	0.163	42.1	36.3
IIV on Frel	0.234	51.4	32.7
IIV on IOV Frel	0.0373	19.5	73.3
IIV on Q/F	0.471	77.5	94.9
IIV on V2/F	0.601	90.8	95.7

%RSE was calculated as the standard error of the estimator divided by the absolute value of the mean of the estimator multiplied by 100. %CV was calculated as SQRT(exp(ω^2)-1)*100).

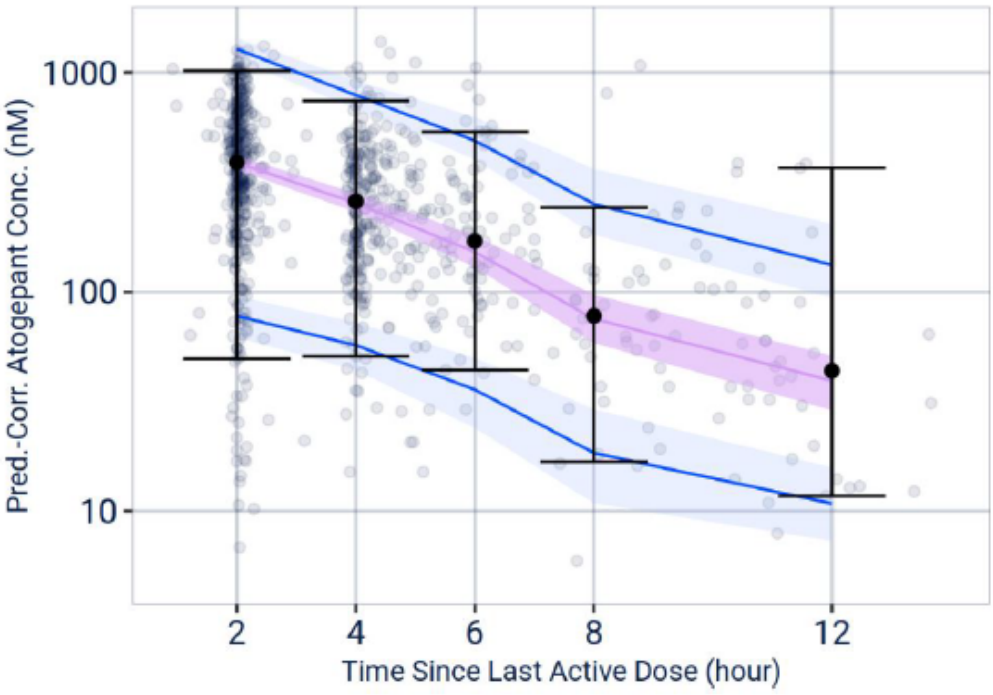
The dose-normalized observed atogepant concentration versus TSLD profiles in subjects requiring acute treatment of migraine was comparable to dose-normalized exposures in subjects with EM from Phase 2/3 Study CGP-MD-01 and Phase 3 Study 3101-301-002 and subjects with CM from Study 3101-303-002 (Figure 1).



Circles represent observed atogepant concentrations (normalized by the most recent prior dose). Framed circles with error bars represent the median and 5th to 95th percentiles for the binned observed data.

Figure 1. Dose-Normalized Observed Atogepant Concentrations in Subjects Requiring Acute Treatment of Migraine Compared to Subjects with EM from Phase 2/3 Study CGP-MD-01 and Phase 3 Study 3101-301-002 and Subjects with CM from Phase 3 Study 3101-303-002

Prediction-corrected VPCs for the atogepant concentrations in subjects requiring acute treatment of migraine are shown in Figure 2.



The blue lines represent the 90% PI of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. The black dots and error bars represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Circles denote observed concentrations.

Note: Time bins were chosen at 2, 4, 6, 8, and 12 hours since last active dose, and the data shown cut at time since last active dose of 14 hours.

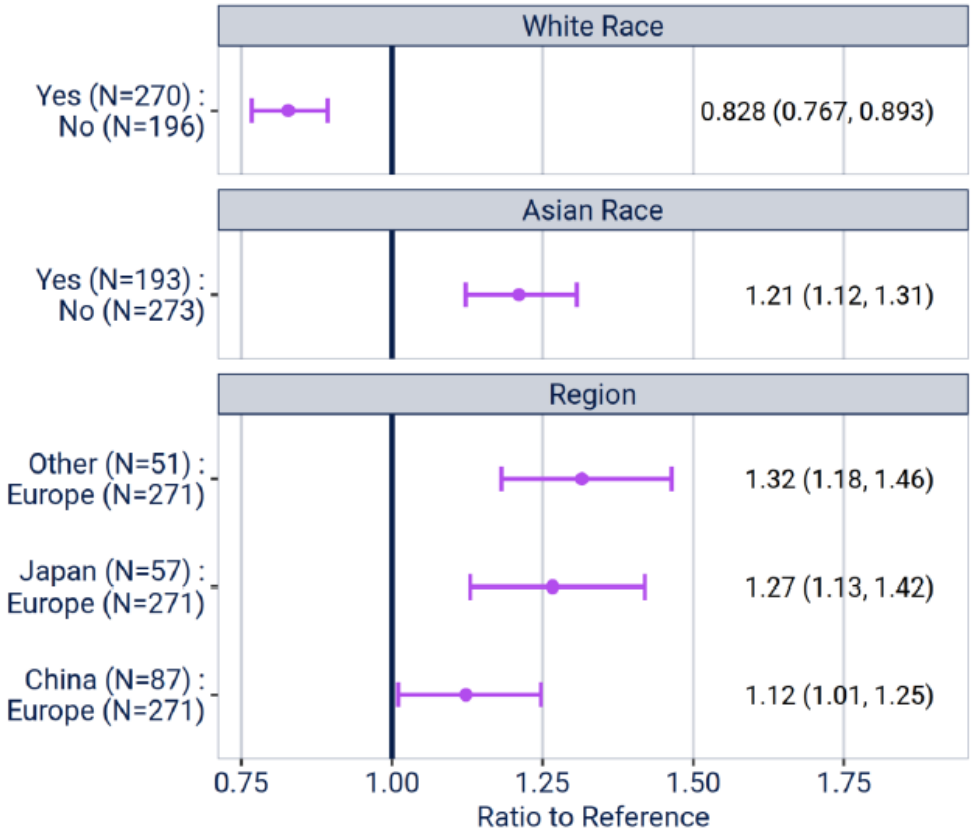
Figure 2. Prediction-Corrected Visual Predictive Checks of Atogepant Concentration in Subjects Requiring Acute Treatment of Migraine in Study M24-305

Model-predicted atogepant exposures, time above and time to reach specified threshold levels are summarized in Table 6.

Table 6. Summary Statistics of Individual Predictions of Atogepant Time Above and Time to Reach Specified Threshold Levels Using the Final Population Pharmacokinetic Model

Treatment Arm	Number of Subjects	Time above EC_{90} in 48 Hours (hour)	Time to achieve EC_{90} (hour)
60 mg Single Dose	466	19.7 (13.7, 28.2)	0.295 (0.287, 0.331)

Data presented as median (5th, 95th percentile). [a]EC_{90} based on CIDV model.



Dots and error bars represent geometric mean ratio and its 95% confidence interval of model-predicted exposures relative to reference groups. The vertical black line shows the exposure ratio of 1 relative to the reference group.

Note: Non-White race, non-Asian race and Europe region were chosen as reference covariate categories.

Figure 3. Model-Predicted Covariate Effects on Atogepant C2hr in Subjects Requiring Acute Treatment of Migraine

2.5. Pharmacodynamics

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 (Cmax > 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 (Ki-value 26 pM and 2.4 nM, respectively) could be of clinical relevance.

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

2.6. PK/PD modelling

Exposure-Response Analyses

Population Pharmacokinetics and Exposure-Response Analyses of Atogepant in Subjects Requiring Acute Treatment of Migraine: Analyses of Phase 3 Study M24-305

Population PK and exposure-response models were used to support the MAA filing, dose justification, and label optimization for the prophylaxis of migraine indication of atogepant. The Study M24-305 is a 24-week, Phase 3, multicentre, randomized, double-blind, placebo-controlled, multiple-attack study with an open-label extension to evaluate the efficacy, safety, tolerability, and the consistency of effect of atogepant for the acute treatment of migraine.

The clinical pharmacology objectives of the study were:

- to characterize the population PK of atogepant in subjects requiring acute treatment of migraine
- to characterize the relationships between atogepant plasma exposures and efficacy in subjects requiring acute treatment of migraine.

Population Pharmacokinetic Model

A previously developed population PK model for atogepant based on 12 Phase 1 studies, Phase 2/3 Study CGP-MD-01 as well as Phase 3 Study 3101-301-002 was evaluated to describe observed atogepant concentrations from Phase 3 Study M24-305 using a post hoc approach. The following factors proved to be significant in the current model:

- Dose on relative bioavailability and on absorption
- Food status on lag-time
- Liver function on clearance
- Concomitant medication
- Body weight on volume of distribution

See also section 9.2.

In addition, covariates investigated for PK effects included:

- Race (White, Black, Asian, other)
- Country/Region (Europe, Japan, China, Other [Taiwan, South Korea])

These covariates were not found to have a significant effect on the PK of atogepant.

Exposure Analyses for Efficacy

Atogepant exposure-response relationships for efficacy after the first attack were evaluated using quartile plots with concentration at 2 hours (C2hr), average concentration over 24 hours (Cavg24), average concentration over 48 hours (Cavg48) as exposure metrics.

Logistic regression analyses for efficacy endpoints were evaluated to characterize the relationship between atogepant C2hr, Cavg24, and Cavg48 as a predictor variable and endpoints of Study M24-305.

PK metrics of Atogepant

Model-predicted atogepant exposures, times above and time to reach specified threshold levels are summarized in the Tables below.

Table 7. Summary Statistics of Individual Predictions of Atogepant Exposures Using the Final Population Pharmacokinetic Model

Treatment Arm	Number of Subjects	Concentration at 2 Hours (nM)	Maximum Concentration (nM)	Average Concentration Over 24 Hours (nM)	Average Concentration Over 48 Hours (nM)
60 mg Single Dose	466	643 (312, 1234)	704 (400, 1277)	147 (74.6, 296)	75.8 (38.4, 153)

Data presented as median (5^{th}, 95^{th} percentile).

Table 8. Summary Statistics of Individual Predictions of Atogepant Time Above and Time to Reach Specified Threshold Levels Using the Final Population Pharmacokinetic Model

Treatment Arm	Number of Subjects	Time above EC_{90} in 48 Hours (hour)	Time to achieve EC_{90} (hour)
60 mg Single Dose	466	19.7 (13.7, 28.2)	0.295 (0.287, 0.331)

Data presented as median (5^{th}, 95^{th} percentile). EC_{90} based on capsaicin-induced dermal vasodilation (CIDV) model.

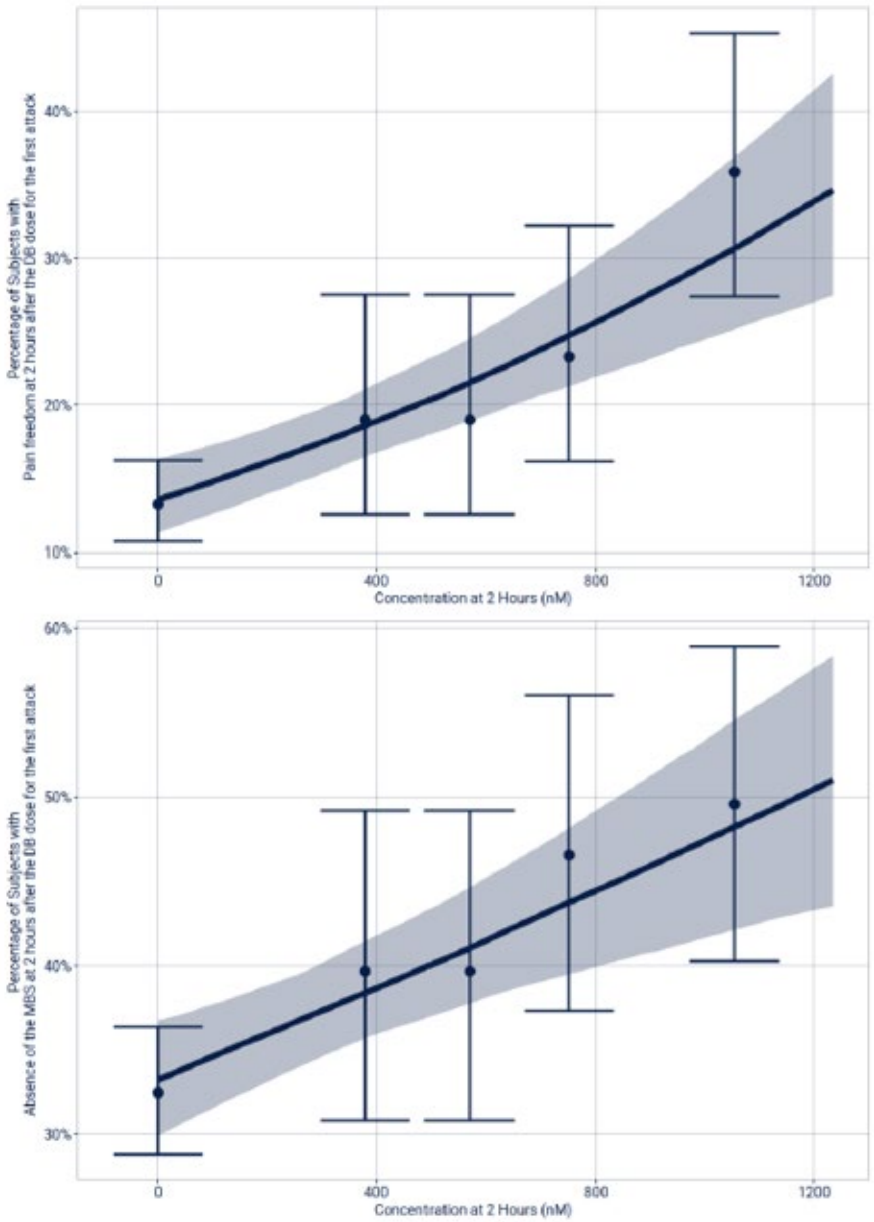
Exposure-Response Modelling

The primary efficacy endpoint, pain freedom at 2 hours after the double-blind (DB) dose for the first attack, along with other efficacy endpoints were evaluated for exposure response.

Non-linear and linear logistic regression models were developed to characterize the relationship between concentration at 2 hours as a predictor versus all efficacy endpoints. Linear shape logistic regression model was chosen for both primary (pain freedom at 2 hours after the DB dose for the first attack) and the key secondary (absence of the most bothersome symptom [MBS] at 2 hours after the DB dose for the first attack) endpoints.

A significant association between all investigated efficacy endpoints and concentration at 2 hours was observed ($p < 0.05$) across the evaluated range of exposures.

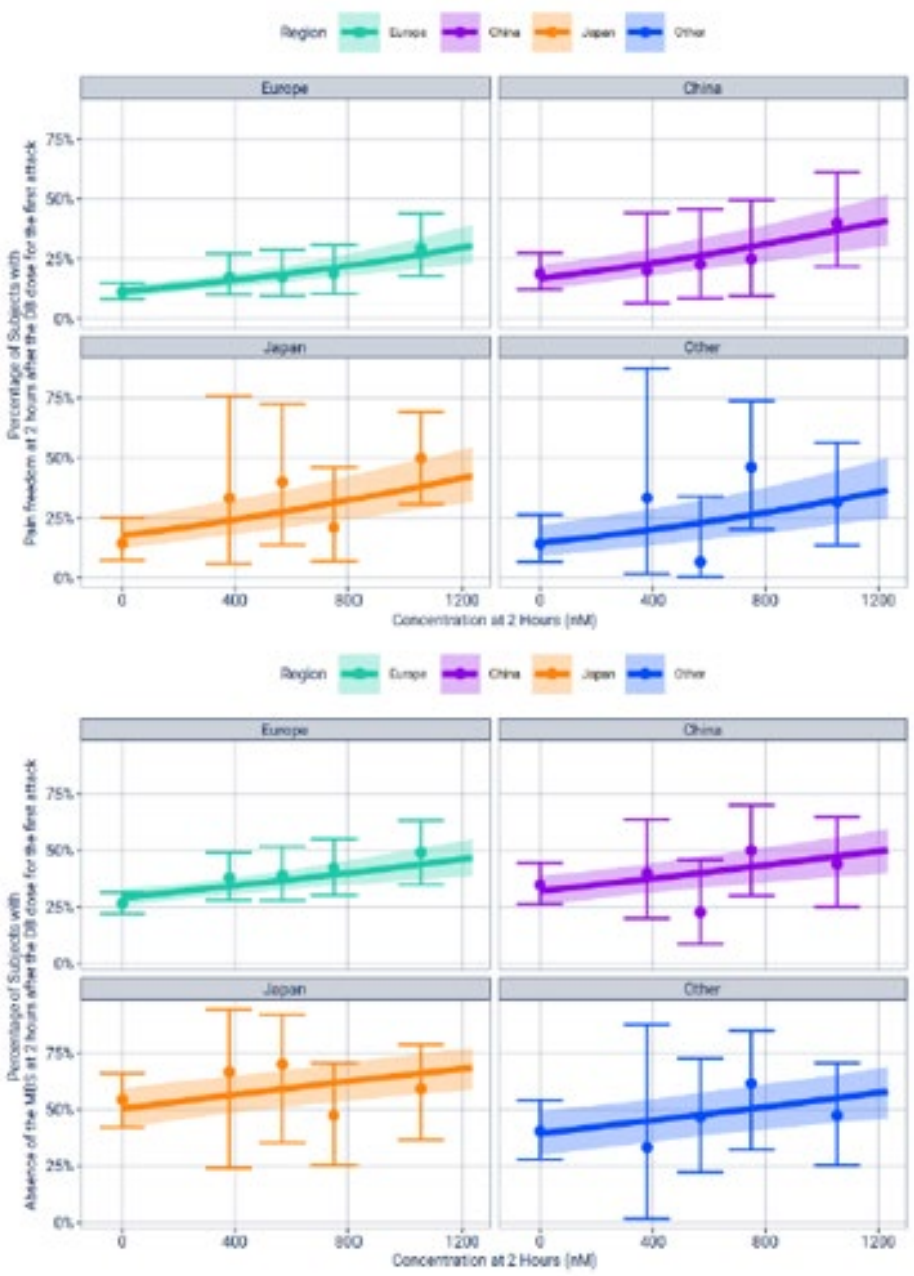
Figure 4. Observed versus Model-Predicted Exposure-Response Relationships Between Concentration at 2 Hours and Primary and Key Secondary Efficacy Endpoints



The solid lines represent median predicted responses and the shaded areas represent 95% CIs of the responses. The dots and error bars represent proportions and 95% binomial CIs of the binned observed responses.

Region, response to triptans, and prophylactic concomitant medication for migraine were included in the final model as pre-specified stratification factors, and region was identified as a significant factor. Predicted responses in comparison to observed primary and key secondary efficacy endpoints are shown below, stratified by region (Figure below). Aside from small shifts in overall likelihood of response being higher in Asian regions compared to other regions, the exposure-response trends across all regions are similar.

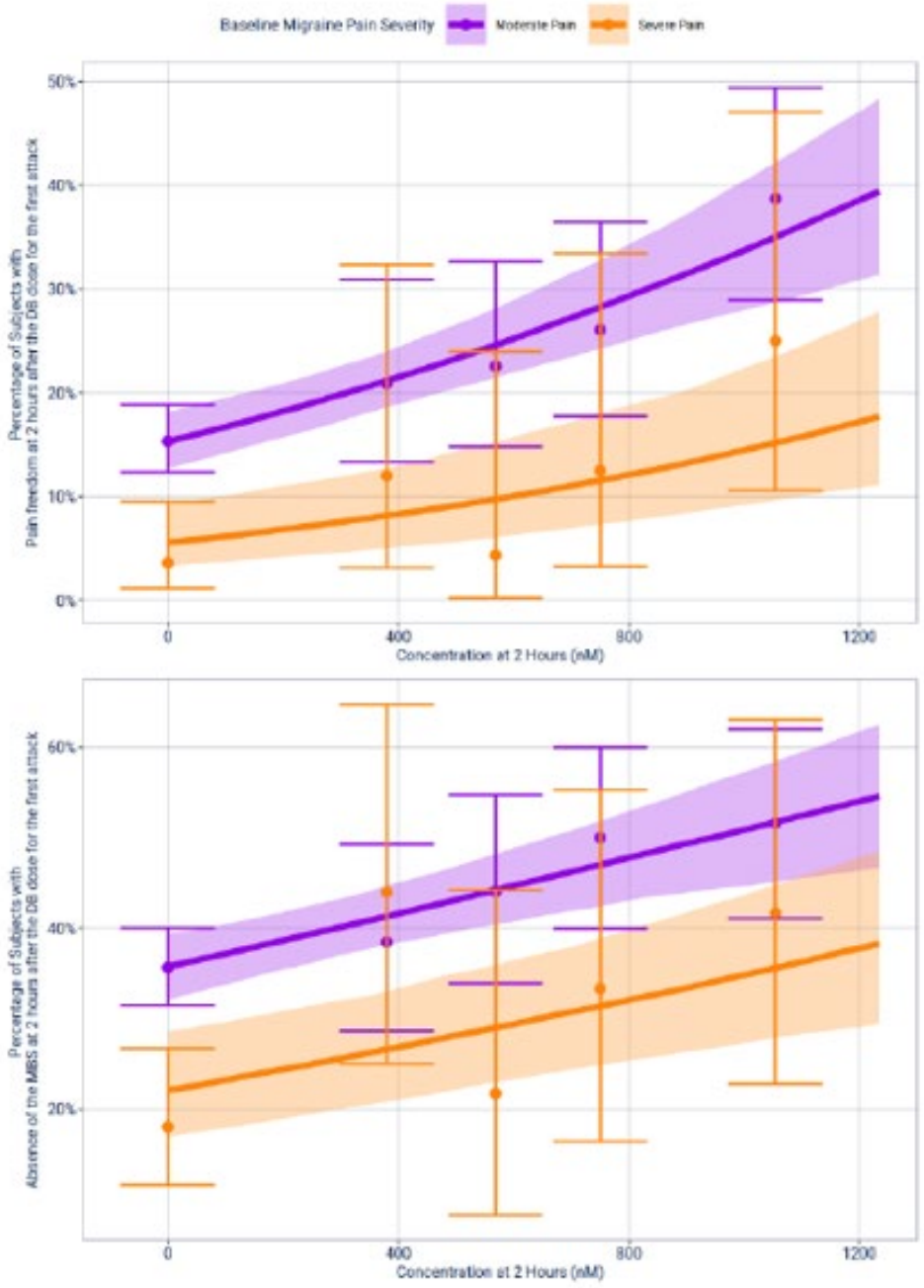
Figure 5. Observed versus Model-Predicted Exposure-Response Relationships Between Concentration at 2 Hours and Primary and Key Secondary Efficacy Endpoints Stratified by Region



The solid lines represent median predicted responses and the shaded areas represent 95% CIs of the responses. The dots and error bars represent proportions and 95% binomial CIs of the binned observed responses.

Covariates of interest were tested. Baseline migraine pain severity was identified as significant covariate on pain freedom and absence of the MBS at 2 hours after the DB dose for the first attack. Predicted responses in comparison to observed and parameter tables of the exploratory models including the significant covariates are provided in the Figure below.

Figure 6. Observed versus Model-Predicted Exposure-Response Relationships Between Concentration at 2 Hours and Primary and Key Secondary Efficacy Endpoints Stratified by Baseline Migraine Pain Severity



Note: The solid lines represent median predicted response and the shaded areas represent 95% CIs of the response. The dots and error bars represent median and 95% binomial CIs of binned observed responses.

Conclusions

The population PK model previously developed in subjects with EM adequately characterized atogepant PK in subjects requiring acute treatment of migraine. Atogepant PK showed model predicted C2hr of 643 nM, maximum concentration (Cmax) of 704 nM, Cavg24 of 147 nM, and Cavg48 of 75.8 nM for single 60 mg atogepant dose. Time above the CIDV based EC90 of 13.6 nM (Boinpally 2023) was 19.7 hours

over 48-hour interval after a single 60 mg dose. Time to achieve the CIDV based EC90 of 13.6 nM was 0.295 hours after a single 60 mg dose. Exposures were similar across regions.

The exposure-response model for primary and key secondary endpoints showed that atogepant efficacy is dependent on exposure (within the range observed at 60 mg dose tested in the study) in subjects requiring acute treatment of migraine. One of the pre-specified stratification factors, region, was statistically significant as a predictor. All categories of region show similar exposure-response trends, with small shifts in the overall likelihood of responses.

In covariate analysis, baseline migraine pain severity appeared to be a significant covariate, with lower response rate for severe attacks compared to moderate ones. Simulations of pain freedom at 2 hours after the DB dose for the first attack in different baseline migraine severity groups confirmed these results.

Since no TEAE was reported in ≥2% of participants within 48 hours after treating the first qualifying migraine attack in the DB treatment period, no exposure-safety analysis was conducted.

2.7. Discussion on clinical pharmacology

Previously, a popPK model has been developed based on 12 phase 1, 2/3 and 3 studies. Different covariates had shown a significant influence on the PK of atogepant, but their influence was not considered clinically relevant. This model was used to analyse the data for patients with acute migraine. Eta shrinkage on CL/F was high (75.9%), probably due to small sample size (1 sample in the elimination phase between 4-12 h). Exposures in Asian or other regions were higher than in Europeans (e.g., C2hr was 1.21-fold for Asian race versus other, 1.27-fold for Japan region versus Europe region, 1.12-fold for China region versus Europe region). These differences were not expected to be of clinical relevance.

With this model, different exposure metrics for patients with acute migraine were estimated, which were subsequently used in the exposure-response analyses. This is considered acceptable. Data from a total of 466 subjects requiring acute treatment of migraine from Study M24-305 who received atogepant and had at least one atogepant concentration greater than LLOQ were included in the population PK analysis. Exposure-response with quartiles of exposure (concentration at 2h) were analysed by nonlinear/linear regression. The E-R model for PEP and the first SEP showed relationship between exposure and response in Study M24-305 population. Pre-specified stratification factor - region, was statistically significant as a predictor. Baseline migraine pain severity was a significant covariate. No exposure safety analysis was conducted. There were small regional differences in exposure-response with trends towards higher efficacy in Asian patients compared to Europeans, which may, at least in part, be due to the higher exposure seen in Asian patients, since for all regions as well as for all severity states (moderate or severe), the response revealed to be concentration-dependent. This means that some patients, especially with severe migraine, would profit from higher exposure. Since no other dose is available, this is not further pursued.

2.8. Conclusions on clinical pharmacology

Within the context of the present procedure intended to extend the use of atogepant to treatment of acute migraine attacks, clinical pharmacology of atogepant is adequately characterized. There are no objections from a clinical pharmacology to approval of this application.

3. Clinical efficacy

3.1. Dose response study(ies)

No dedicated dose response study for the use of atogepant in acute migraine treatment was conducted.

3.2. Main study

Randomized, Double-Blind, Placebo-Controlled, Multiple-Attack Study with an Open-Label Extension to Evaluate the Efficacy, Safety, Tolerability, and the Consistency of Effect of Atogepant for the Acute Treatment of Migraine (ECLIPSE)

Interim Clinical Study Report, Atogepant/Protocol M24-305

Protocol Vers. 3.0	27 Jun 2024
First Subject First Visit	25 Mar 2024
Interim Cut-off Date	07 Jul 2025
Date of Interim CSR	03 Oct 2025

Study M24-305 is a multiple-attack study designed to assess the efficacy, safety, and tolerability of a single dose of atogepant 60 mg for the acute treatment of a single migraine attack as well as the consistency of effect across multiple migraine attacks.

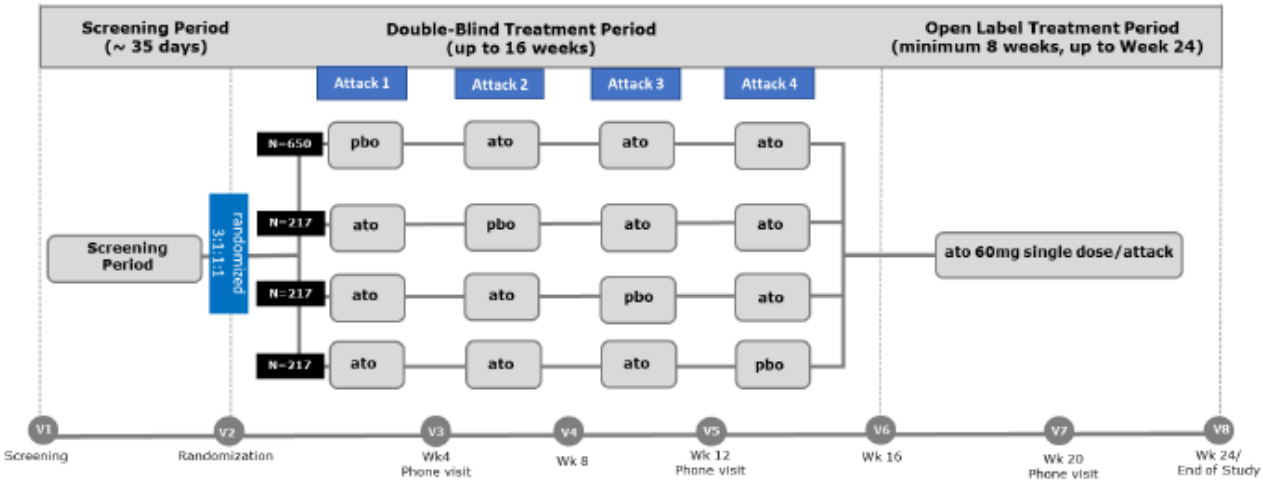
Study M24-305 comprises a main study and a triptan-unsuitable substudy. After the last participant was enrolled in the main study, the triptan-unsuitable substudy opened for enrolment. The substudy is being conducted to support Health Technology Assessment (HTA) requirements. The blinded triptan-unsuitable substudy is ongoing.

Methods

The Study M24-305 main study is a 24-week (up to 16-week double-blind [DB] period followed by a minimum 8-week OL period for a total of 24 weeks), multicentre, randomized, DB, placebo-controlled, multiple-attack study in adult subjects with a diagnosis of migraine (with or without aura) and who have 2 to 8 migraine attacks of moderate to severe headache pain in each of the 3 months prior to Screening (Visit 1).

Eligible subjects were randomized in a 3:1:1:1 ratio to 1 of 4 treatment sequences in which each subject received placebo for 1 qualifying migraine attack and atogepant 60 mg for 3 qualifying migraine attacks during the DB period, resulting in a 1:1 allocation of study drug (placebo:atogepant) for the first qualifying migraine attack.

Figure 7. Study M24-305 – Study Design Schematic



Notes: The 4 qualifying migraine attacks depicted on the study schematic were to illustrate treatments for each sequence group and did not necessarily correspond to the schedule of study visits on the horizontal axis, as the timing of each qualifying migraine attack differed for individual subjects. An End of DB Period visit (not depicted on study schematic) occurred for each subject after treating 4 qualifying migraine attacks during the DB period. A follow-up phone call was conducted 30 days after the last study visit to determine the status of any ongoing AEs or the occurrence of any new AEs.

Randomization in the main study was stratified by: 1) region (Europe, China, Japan, Other); 2) subject's previous use of and response to triptans (Triptan Unsuitable, Triptan Experienced, Triptan Naïve); and 3) current use of prophylactic concomitant medication for migraine (yes/no).

Treatment with DB Study Drug

Subjects were provided with DB study drug to treat 4 qualifying migraine attacks of moderate or severe headache pain intensity within 16 weeks after randomization. Each qualifying migraine attack was to be treated with a single dose of study drug. A qualifying migraine attack was defined as meeting all the following criteria:

- The onset of the migraine headache is within the previous 4 hours;
- The severity of the migraine headache pain is moderate or severe;
- Presence of at least 1 of the following migraine-associated symptoms:
    - photophobia, phonophobia, or nausea;
- Rescue medication has not been taken within 48 hours prior to taking study drug;
- The migraine headache is a new headache, meaning that no other headache has occurred in the previous 48 hours;
- The migraine headache is not already resolving on its own.

After treating 4 qualifying migraine attacks during the DB period of the main study, subjects entered an OL period until the end of the study at Week 24. The DB period has completed, and the OL period is ongoing.

Treatment with OL Study Drug

Subjects were instructed to treat each qualifying migraine attack with a single dose of OL atogepant 60 mg during the OL treatment period. Qualifying migraine attacks during the OL treatment period were defined as meeting all the following criteria:

- The onset of the migraine headache is within the previous 4 hours;
- The severity of the migraine headache pain can be mild, moderate, or severe;
- Rescue medication has not been taken within 48 hours prior to taking study drug;
- The migraine headache is a new headache, meaning that no other headache has occurred in the previous 48 hours;
- The migraine headache is not already resolving on its own.

Note that the definition of a qualifying migraine for the DB period differed from that of the OL period, which allowed treatment of *mild*, moderate, or severe migraine headache pain and omitted the requirement for presence of ≥ 1 migraine-associated symptom.

In Study M24-305, subjects used an electronic diary (eDiary) to record details associated with their migraine attacks, including, but not limited to, date and time of study drug dosing, efficacy assessments (e.g., headache pain severity, absence or presence of migraine-associated symptoms, recurrence of headache pain) including health outcomes assessments, and use of rescue medication.

Study participants

Subjects 18 to 75 years (inclusive) with a history of migraine (with or without aura) according to the ICHD-3 for ≥ 12 months prior to Visit 1/Screening, and with a history of 2 to 8 migraine attacks of moderate to severe headache pain in each of the 3 months prior to Visit 1/Screening per investigator judgment.

Oral migraine medications used for prophylaxis on-label or off-label (e.g., topiramate, amitriptyline, beta blockers, flunarizine, venlafaxine, etc.), and injectable onabotulinum toxin A and other therapies used for migraine prevention are permitted provided that the treatment is stable for at least 3 months prior to Visit 2/Randomization and continues without change in dose throughout the study.

Subjects were excluded if presenting with

- a history of an average of 15 or more headache days (HD) per month in the 6 months prior to Visit 1/Screening per the investigator's judgment, or a current diagnosis of chronic migraine (CM) as defined by ICHD-3.
- Clinically significant laboratory abnormalities as determined by the investigator, or laboratory values meeting any of the following criteria at Visit 1/Screening:
  - ALT or AST > 1 × ULN;
  - Total bilirubin > 1 × ULN (except for subjects with a diagnosis of Gilbert's disease);
  - Serum albumin < 2.8 g/dL [4.06 µmol/L]
- Subject has taken medication for acute treatment of headache (including acetaminophen, NSAIDs, triptans, ditans, ergotamine, opioids, gepants, or combination analgesics) 10 or more days per month in any of the 3 months prior to Visit 2/Randomization.
- Subject has been exposed to any gepant within 30 days prior to Visit 2/Randomization. Subject has been exposed to injectable monoclonal antibodies blocking the CGRP pathway within 6 months prior to Visit 2/Randomization.

Outcomes/endpoints

Primary Efficacy Endpoint

- Pain freedom (defined as a reduction in headache severity from moderate/severe at baseline [pre-dose] to no pain) at 2 hours after the DB dose for the first attack

Key Secondary Endpoints

- Absence of the MBS at 2 hours after the DB dose for the first attack (coprimary endpoint for China)
- Pain relief (defined as the reduction of a moderate/severe migraine headache at baseline [pre-dose] to a mild headache or to no headache) at 2 hours after the DB dose for the first attack
- Sustained pain relief from 2 to 24 hours (defined as pain relief at 2 hours after the DB dose with no administration of rescue medication and no occurrence of a moderate/severe headache from 2 to 24 hours) after the DB dose for the first attack
- Sustained pain relief from 2 to 48 hours after the DB dose for the first attack
- Use of rescue medication within 24 hours after the DB dose for the first attack
- Ability to function normally at 2 hours after the DB dose for the first attack
- Sustained pain freedom from 2 to 24 hours (defined as pain freedom at 2 hours after the DB dose with no administration of rescue medication and no occurrence of a mild/moderate/severe headache from 2 to 24 hours) after the DB dose for the first attack
- Sustained pain freedom from 2 to 48 hours after the DB dose for the first attack
- Absence of photophobia at 2 hours after the DB dose for the first attack
- Absence of phonophobia at 2 hours after the DB dose for the first attack
- Pain freedom at 8 hours after the DB dose for the first attack
- Ability to function normally 8 hours after the DB dose for the first attack
- Pain relief at 1 hour after the DB dose for the first attack
- Absence of nausea at 2 hours after the DB dose for the first attack
- Pain relief at 30 minutes after the DB dose for the first attack
- Ability to function normally at 1 hour after the DB dose for the first attack

Statistical methods

Analyses of the primary efficacy endpoint (and coprimary efficacy endpoints, if applicable) were conducted on the modified intent-to-treat (mITT) 1 population (based on treatment as randomized), using a generalized linear mixed-effect model (GLMM). Missing data were imputed as nonresponder. The GLMM with nonresponder imputation is referred as the primary approach. The key secondary efficacy endpoints were analyzed using the same methods. The mITT 1 population consists of all randomized subjects who received at least 1 dose of study drug during the DB period, recorded a baseline migraine headache severity measurement, and had at least 1 post-dose migraine headache severity or migraine-associated symptom measurement at or before the 48-hour time point based on the headache eDiary for any attack during the DB period.

Results

Disposition

Study M24-305 was conducted internationally at sites in Belgium, Czechia, Germany, Hungary, Italy, Poland, Portugal, Slovakia, Spain, Sweden, United Kingdom, Japan, China, South Korea, and Taiwan. A total of 1,328 subjects were randomized to DB treatment, and 1,232 subjects took ≥ 1 dose of DB study drug to treat a qualifying migraine attack during the DB period. The majority of subjects completed the DB period. A total of 982 subjects treated ≥ 1 migraine qualifying attack during the OL period.

Table 9. Subject Disposition During the DB Period (ITT Population)

The randomization strata are summarized in the Table below. The analyses that use data on the previous use of and response to triptans and current use of prophylactic concomitant medication for migraine were performed based on the actual strata derived from the eCRF.

Table 10. Randomization Strata (ITT Population)

	Treatment Sequence 1 (N=666) n (%)	Treatment Sequence 2 (N=218) n (%)	Treatment Sequence 3 (N=222) n (%)	Treatment Sequence 4 (N=222) n (%)	Total (N=1328) n (%)
Strata from IRT					
Response to triptans					
Triptan Unsuitable	95 (14.3)	30 (13.8)	31 (14.0)	31 (14.0)	187 (14.1)
Triptan Experienced	449 (67.4)	149 (68.3)	150 (67.6)	150 (67.6)	898 (67.6)
Triptan Naïve	122 (18.3)	39 (17.9)	41 (18.5)	41 (18.5)	243 (18.3)
Current use of prophylactic concomitant medication					
Yes	178 (26.7)	59 (27.1)	59 (26.6)	59 (26.6)	355 (26.7)
No	488 (73.3)	159 (72.9)	163 (73.4)	163 (73.4)	973 (73.3)
Actual Strata Derived from eCRF					
Response to triptans					
Triptan Unsuitable	95 (14.3)	32 (14.7)	36 (16.2)	37 (16.7)	200 (15.1)
Triptan Experienced	448 (67.4)	145 (66.8)	144 (64.9)	144 (64.9)	881 (66.4)
Triptan Naïve	122 (18.3)	40 (18.4)	42 (18.9)	41 (18.5)	245 (18.5)
Missing	1	1	0	0	2
Current use of prophylactic concomitant medication					
Yes	149 (22.4)	44 (20.2)	51 (23.0)	51 (23.0)	295 (22.2)
No	517 (77.6)	174 (79.8)	171 (77.0)	171 (77.0)	1033 (77.8)
Region					
Europe	405 (60.8)	136 (62.4)	135 (60.8)	136 (61.3)	812 (61.1)
China	121 (18.2)	39 (17.9)	41 (18.5)	38 (17.1)	239 (18.0)
Japan	81 (12.2)	26 (11.9)	27 (12.2)	27 (12.2)	161 (12.1)
Other	59 (8.9)	17 (7.8)	19 (8.6)	21 (9.5)	116 (8.7)

IRT = interactive response technology, eCRF = electronic case report form. The other region includes Taiwan and South Korea.

Withdrawal by Subject	32 (4.8)	9 (4.1)	11 (5.0)	10 (4.5)	62 (4.7)
Withdrawal by Subject - Adverse Event	0	0	0	0	0
Study Terminated by Sponsor	0	0	0	0	0
Logistical problem [geo-political restrictions]	0	0	0	0	0
Subject Did Not Treat 4 Qualifying Attacks during Double-Blind Period	95 (14.3)	31 (14.2)	32 (14.4)	36 (16.2)	194 (14.6)
Other	10 (1.5)	6 (2.8)	2 (0.9)	3 (1.4)	21 (1.6)

N = Number of subjects in the Population. n = Number of subjects within a specific category.

[1] Subjects who completed DB period without 4 qualifying attacks but entered the OL period refer to those subjects who received DB doses but did not experience 4 qualifying attacks, and either received OL doses or were ongoing in the OL period without discontinuing from the study.

over the 3 months prior to enrolment, and most subjects had a diagnosis of migraine without aura. Overall, 66.6% of subjects reported use of a triptan or triptan combination and 57.9% reported use of an NSAID or NSAID combination for acute treatment of migraine. Migraine history was similar across the 4 treatment sequences.

Table 11. Migraine History (Safety Population 1)

	Treatment Sequence 1 (N=623)	Treatment Sequence 2 (N=199)	Treatment Sequence 3 (N=202)	Treatment Sequence 4 (N=208)	Total (N=1232)
Migraine Diagnosis - n (%)					
With Aura	119 (19.1)	43 (21.6)	37 (18.3)	47 (22.7)	246 (20.0)
Without Aura	442 (70.9)	138 (69.3)	138 (68.3)	137 (66.2)	855 (69.5)
Both	62 (10.0)	18 (9.0)	27 (13.4)	23 (11.1)	130 (10.6)
Missing	0	0	0	1	1
Migraine Disorder Duration in Years					
n	622	199	202	205	1228
Mean (SD)	19.04 (12.309)	19.79 (12.335)	18.94 (12.581)	20.00 (12.067)	19.30 (12.310)
Median	17.70	18.30	16.50	18.50	17.70
Min, Max	0.4, 63.3	1.1, 53.8	1.4, 58.2	0.2, 50.8	0.2, 63.3
Does the subject have menstrual migraine? - n/N1 (%) [1]					
Yes	159/484 (32.9)	55/156 (35.3)	41/150 (27.3)	53/158 (33.5)	308/948 (32.5)
No	325/484 (67.1)	101/156 (64.7)	109/150 (72.7)	105/158 (66.5)	640/948 (67.5)
Not Applicable	45	12	16	15	88
Missing	4	2	1	5	12
Average Number of Mild, Moderate or Severe Migraine Attacks Per Month Over the Past 3 Months					
n	615	195	201	205	1216
Mean (SD)	5.6 (2.15)	5.5 (2.23)	5.6 (2.00)	5.6 (2.00)	5.6 (2.11)
Median	5.0	5.0	5.0	5.0	5.0
Min, Max	2, 15	2, 14	2, 12	2, 14	2, 15
Average Number of Moderate to Severe Migraine Attacks Per Month Over the Past 3 Months					
n	623	198	202	207	1230
Mean (SD)	4.5 (1.64)	4.2 (1.54)	4.4 (1.60)	4.5 (1.67)	4.4 (1.62)
Median	4.0	4.0	4.0	4.0	4.0
Min, Max	2, 8	2, 8	2, 8	2, 8	2, 8
Does the subject have a contraindication to triptan medications, regardless of prior triptan use?					
Yes	12 (1.9)	1 (0.5)	7 (3.5)	4 (1.9)	24 (1.9)
No	611 (98.1)	198 (99.5)	195 (96.5)	204 (98.1)	1208 (98.1)
Acute Migraine Treatment, n (%)					
Yes	621 (99.7)	199 (100)	202 (100)	206 (99.0)	1228 (99.7)
Triptan or Triptan Combination	418 (67.1)	135 (67.8)	132 (65.3)	135 (64.9)	820 (66.6)
Ditan	6 (1.0)	2 (1.0)	2 (1.0)	1 (0.5)	11 (0.9)
Ergot or Ergot Combination	10 (1.6)	2 (1.0)	3 (1.5)	1 (0.5)	16 (1.3)
NSAID or NSAID Combination	353 (56.7)	116 (58.3)	116 (57.4)	128 (61.5)	713 (57.9)
Opioid or Opioid Combination	25 (4.0)	11 (5.5)	9 (4.5)	3 (1.4)	48 (3.9)
Antiemetic Agent	46 (7.4)	14 (7.0)	17 (8.4)	24 (11.5)	101 (8.2)
Other	137 (22.0)	40 (20.1)	39 (19.3)	34 (16.3)	250 (20.3)
No	2 (0.3)	0	0	2 (1.0)	4 (0.3)

N = Number of subjects in the Population. N1 = Number of subjects who answered the question. n = Number of subjects with non-missing values in the specific category.
[1] The summary of menstrual migraine includes only female subjects.
Menstrual migraine is defined by ICHD-3 as migraine attacks with or without aura occurring within 2 days (+/- 2 days) of menstruation in at least 2 out of 3 menstrual cycles.
The planned treatment sequences were used in the table.

Baseline Efficacy Parameters

The baseline efficacy parameters reflect the migraine characteristics recorded by subjects on the eDiary immediately prior to treating a qualifying migraine attack. For the first attack, baseline migraine headache severity was reported as moderate pain by 80.4% of subjects and as severe pain by 19.6% of subjects overall.

For the first attack, the presence of pre-dose photophobia, phonophobia, and nausea were reported by approximately 78.7%, 71.3%, and 60.6% of subjects, respectively. Few subjects reported the presence of pre-dose vomiting (6.8%) for the first attack.

Photophobia, phonophobia, and nausea were identified as the MBS for the first attack in 44.1%, 24.5%, and 31.4% of subjects, respectively. The baseline efficacy parameters were similar across the 4 treatment sequences and across the 4 qualifying migraine attacks treated during the DB period.

Table 12. Baseline Efficacy Parameters Modified Intent-to-Treat 1 Population, Study M24-305

Outcomes and estimation

First attack

Treatment with atogepant 60 mg resulted in significantly higher response rates compared with placebo for the primary efficacy endpoint (pain freedom at 2 hours after taking the DB dose for the first attack) and significantly better response rates for 12 of the 16 ranked key secondary efficacy endpoints (adjusted $p \leq 0.0001$), including:

- Higher response rates for absence of the MBS, pain relief, absence of photophobia, absence of phonophobia, and the ability to function normally at 2 hours after taking the DB dose for the first attack
- Higher response rates for pain freedom at 8 hours, sustained pain freedom at both 2 to 24 hours and 2 to 48 hours, sustained pain relief at both 2 to 24 hours and 2 to 48 hours, and the ability to function normally at 8 hours after taking the DB dose for the first attack
- Lower rates of rescue medication use within 24 hours after taking the DB dose for the first attack

Parameters Attack	Treatment Sequence 1 (N=618) n/N1 (%)	Treatment Sequence 2 (N=199) n/N1 (%)	Treatment Sequence 3 (N=199) n/N1 (%)	Treatment Sequence 4 (N=207) n/N1 (%)	Total (N=1223) n/N1 (%)
Migraine Headache Severity					
Attack 1					
Moderate Pain	501/612 (81.9)	164/198 (82.8)	149/198 (75.3)	162/206 (78.6)	976/1214 (80.4)
Severe Pain	111/612 (18.1)	34/198 (17.2)	49/198 (24.7)	44/206 (21.4)	238/1214 (19.6)
Missing	1	0	0	0	1
Attack 2					
Moderate Pain	474/580 (81.7)	145/194 (74.7)	155/196 (79.1)	153/195 (78.5)	927/1165 (79.6)
Severe Pain	106/580 (18.3)	49/194 (25.3)	41/196 (20.9)	42/195 (21.5)	238/1165 (20.4)
Attack 3					
Moderate Pain	431/549 (78.5)	135/177 (76.3)	143/188 (76.1)	144/185 (77.8)	853/1099 (77.6)
Severe Pain	118/549 (21.5)	42/177 (23.7)	45/188 (23.9)	41/185 (22.2)	246/1099 (22.4)
Missing	1	0	0	0	1
Attack 4					
Moderate Pain	393/521 (75.4)	132/168 (78.6)	136/171 (79.5)	131/171 (76.6)	792/1031 (76.8)
Severe Pain	128/521 (24.6)	36/168 (21.4)	35/171 (20.5)	40/171 (23.4)	239/1031 (23.2)

Baseline = predose.
N = Number of subjects in the Population.
N1 = Number of subjects treated with study drug for the specific migraine attack and had available assessments during the DB treatment period.
n = Number of subjects within a specific category.

Table 13. Analysis Results for the Primary and Key Secondary Efficacy Endpoints (Regions Other Than China) with Multiplicity Adjustment (Study M24-305 – mITT 1 Population)

Endpoint Treatment	N	Point Estimate n (%)[a]	Between Group Treatment Effect Versus Placebo Odds Ratio (95% CI)[b]	p value	Adjusted p value
P1: Pain freedom at 2 hours after the DB dose for the first attack					
Placebo	612	80 (13.1)			
Atogepant	602	146 (24.3)	2.36 (1.76, 3.15)	< 0.0001	< 0.0001
S1: Absence of the MBS at 2 hours after the DB dose for the first attack					
Placebo	612	200 (32.7)			
Atogepant	602	263 (43.7)	1.77 (1.41, 2.24)	< 0.0001	< 0.0001
S2: Pain relief at 2 hours after the DB dose for the first attack					
Placebo	612	333 (54.4)			
Atogepant	602	434 (72.1)	2.35 (1.85, 2.98)	< 0.0001	< 0.0001
S3: Sustained pain relief from 2 to 24 hours after the DB dose for the first attack					
Placebo	612	164 (26.8)			
Atogepant	602	348 (57.8)	4.04 (3.18, 5.15)	< 0.0001	< 0.0001
S4: Sustained pain relief from 2 to 48 hours after the DB dose for the first attack					
Placebo	612	142 (23.2)			
Atogepant	602	311 (51.7)	3.77 (2.95, 4.82)	< 0.0001	< 0.0001
S5: Use of rescue medication within 24 hours after the DB dose for the first attack					
Placebo	613	327 (53.3)			
Atogepant	602	91 (15.1)	0.14 (0.11, 0.19)	< 0.0001	< 0.0001
S6: Ability to function normally at 2 hours after the DB dose for the first attack					
Placebo	613	245 (40.0)			
Atogepant	602	288 (47.8)	1.68 (1.29, 2.18)	0.0001	0.0001
S7: Sustained pain freedom from 2 to 24 hours after the DB dose for the first attack					
Placebo	612	39 (6.4)			
Atogepant	602	107 (17.8)	3.58 (2.44, 5.25)	< 0.0001	0.0001
S8: Sustained pain freedom from 2 to 48 hours after the DB dose for the first attack					
Placebo	612	35 (5.7)			
Atogepant	602	100 (16.6)	3.62 (2.43, 5.39)	< 0.0001	0.0001

Endpoint Treatment	N	Point Estimate n (%)[a]	Between Group Treatment Effect Versus Placebo Odds Ratio (95% CI)[b]	p value	Adjusted p value
S9: Absence of photophobia at 2 hours after the DB dose for the first attack					
Placebo	612	256 (41.8)			
Atogepant	602	309 (51.3)	1.74 (1.37, 2.19)	< 0.0001	0.0001
S10: Absence of phonophobia at 2 hours after the DB dose for the first attack					
Placebo	612	300 (49.0)			
Atogepant	602	364 (60.5)	1.96 (1.55, 2.48)	< 0.0001	0.0001
S11: Pain freedom at 8 hours after the DB dose for the first attack					
Placebo	612	163 (26.6)			
Atogepant	602	359 (59.6)	4.28 (3.36, 5.45)	< 0.0001	0.0001
S12: Ability to function normally 8 hours after the DB dose for the first attack					
Placebo	613	214 (34.9)			
Atogepant	602	393 (65.3)	3.93 (3.08, 5.01)	< 0.0001	0.0001
S13: Pain relief at 1 hour after the DB dose for the first attack					
Placebo	612	255 (41.7)			
Atogepant	602	242 (40.2)	1.04 (0.83, 1.30)	0.7269	0.7269
S14: Absence of nausea at 2 hours after the DB dose for the first attack					
Placebo	612	410 (67.0)			
Atogepant	602	435 (72.3)	1.24 (0.97, 1.60)	0.0893	0.7269
S15: Pain relief at 30 minutes after the DB dose for the first attack					
Placebo	612	152 (24.8)			
Atogepant	602	116 (19.3)	0.82 (0.63, 1.06)	0.1292	0.7269
S16: Ability to function normally at 1 hour after the DB dose for the first attack					
Placebo	613	194 (31.6)			
Atogepant	602	194 (32.2)	1.06 (0.75, 1.48)	0.7569	0.7569

CI = confidence interval; DB = double-blind; GLMM = generalized linear mixed model; MBS = most bothersome migraine-associated symptom; P = primary efficacy endpoint; S = secondary efficacy endpoint

Adjusted p values: using fixed-sequence procedure to control the overall type I error rate for multiple comparisons.

a. The point estimate for the primary and all key secondary endpoints is responder rate.

b. The odds ratios between group treatment differences for the primary and all key secondary endpoints are derived from the GLMM methods.

Sensitivity Analyses for the Primary Efficacy Endpoint

Three sensitivity analyses were performed to evaluate the robustness of the primary approach of the primary efficacy endpoint, as summarized below (details are provided in SAP).

- GLMM (conducted on mITT 1 population) with baseline headache severity of the first attack used as the covariate and attacks in the model changed to time points

- GLMM (conducted on mITT 1 population) with outcomes as pain freedom at 2 hours across 4 attacks based on observed data without nonresponse imputation assuming missing at random
- Logistic regression model (conducted on safety population 1), assuming a binary distribution for the response and a logit link. Subjects with missing data for the primary endpoint were treated as treatment failures.

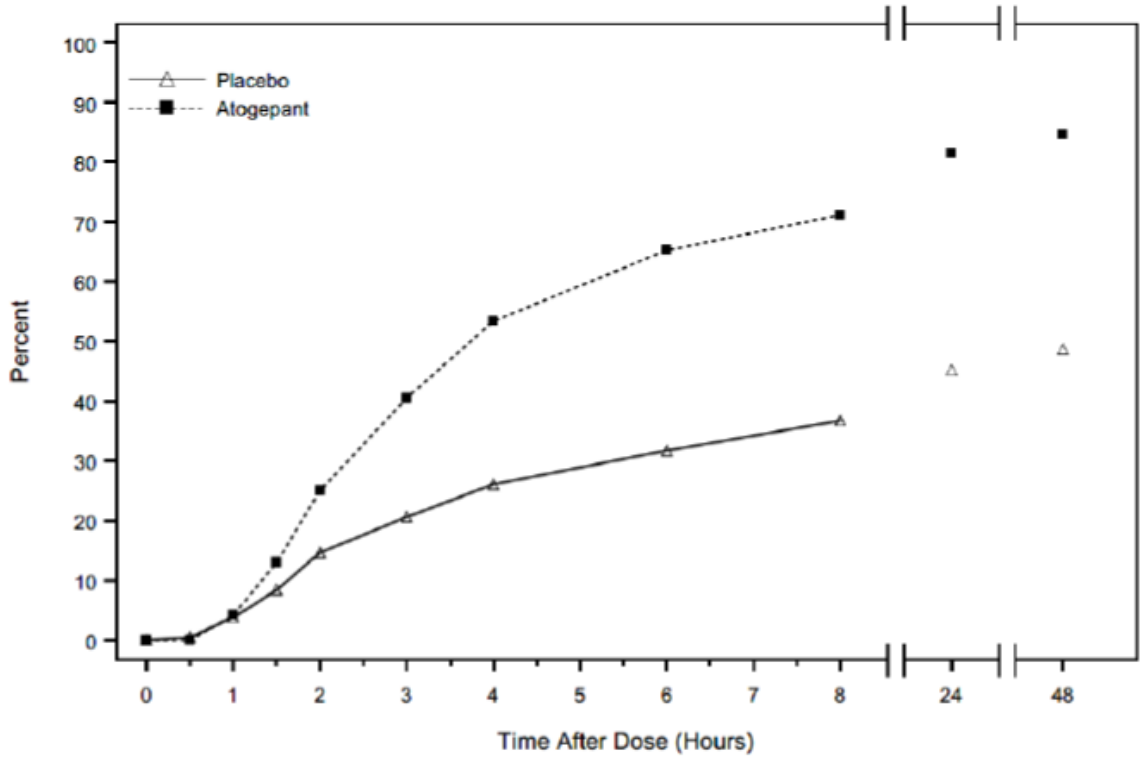
The results of the sensitivity analyses support the robustness of the primary analysis results.

Time Course of Efficacy (DB Treatment Period)

Pain Freedom

The efficacy of atogepant for providing pain freedom after treating the first migraine attack was evident at 1.5 hours post-dose (responder rate: atogepant 12.5%, placebo 7.7%; nominal p = 0.0007), with the difference in response rates for atogepant compared with placebo increasing substantially over time and persisting through 48 hours.

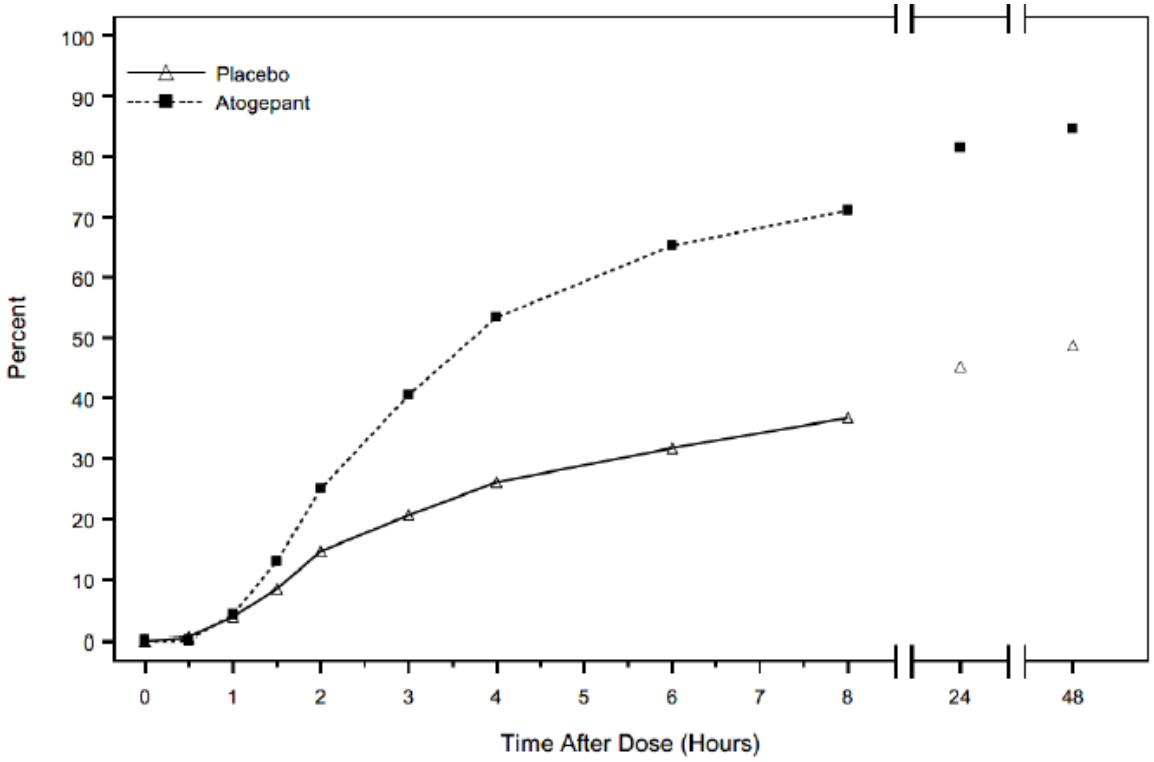
Figure 8. Kaplan-Meier Plot of Time to Pain Freedom Within 48 Hours After the DB Dose for the First Attack (mITT 1 Population)



Absence of the Most Bothersome Migraine-Associated Symptom

The efficacy of atogepant resulting in the absence of the MBS after treating the first migraine attack was evident at 1.5 hours post-dose (responder rate: atogepant 30.4%, placebo 25.3%; nominal p = 0.0087), with the difference in response rates for atogepant compared with placebo increasing substantially over time and persisting through 48 hours.

Figure 9. Kaplan-Meier Plot of Time to Absence of the MBS Within 48 Hours After the DB Dose for the First Attack (mITT 1 Population)



Subgroup Analyses

Baseline Headache Severity

Analysis of pain freedom at 2 hours after the DB dose for the first attack showed higher response rates with atogepant compared with placebo for both subgroups, those with moderate and those with severe baseline headache pain. Analyses of Attacks 2, 3, and 4 corroborate these findings, with consistently higher response rates with atogepant compared with placebo.

Of note, subjects with moderate baseline headache pain had higher responder rates for pain freedom and absence of MBS at 2 hours post-dose than those with severe baseline headache pain, regardless of study drug taken. Despite this observation, atogepant consistently showed higher response rates than placebo in both baseline severity groups.

Table 14. Subgroup Analysis of Pain Freedom at 2 Hours after the DB Dose for the First Attack by Baseline Headache Severity, Modified Intent-to-Treat 1 Population

			Model-Based Results		
			Response Rate	Odds Ratio Compared to Placebo	
Baseline Headache Severity Attack Treatment	N_OBS@	Responder n (%)	Point Estimate $(%)	[95% CI]	Odds Ratio [95% CI]	P-value
Moderate (N1=976)						
Attack 1						
Placebo	501	76 (15.2)	15.2	[12.33, 18.65]		
Atogepant	475	130 (27.4)	27.4	[23.51, 31.56]	2.10 [1.53, 2.88]	<0.0001***
Severe (N1=238)						
Attack 1						
Placebo	111	4 (3.6)	4.3	[1.75, 10.28]		
Atogepant	127	16 (12.6)	10.6	[6.12, 17.66]	2.61 [0.90, 7.61]	0.0781

@Number of subjects in the subgroup who received the treatment for the specified attack and have baseline headache severity for that attack. Missing data were imputed as non-responder.
$ The point estimate is responder rate.
N1 = Number of subjects in the sub-group population.
A logistic model was applied to analyze the data on the first migraine attacks for each subgroup. The logistic model includes treatment group, historical triptan-response stratum (Triptan Unsuitable, Triptan Experienced, or Triptan Naïve), use of medication for migraine prevention (yes/no), and region (Europe, China, Japan, and other).
* P-value <=0.05; **P-value <=0.01; ***P-value <=0.001.

Current Preventive Migraine Medication Use

Analysis of pain freedom at 2 hours after the DB dose for the first attack showed higher response rates with atogepant compared with placebo for both subgroups, subjects with current use of prophylactic concomitant medication for migraine and those without. Analyses of Attacks 2, 3, and 4 corroborate these findings, with consistently higher response rates with atogepant compared with placebo.

Table 15. Subgroup Analysis of Pain Freedom at 2 Hours after the DB Dose for the First Attack by Preventive Migraine Medication Use, Modified Intent-to-Treat 1 Population

			Model-Based Results		
			Response Rate	Odds Ratio Compared to Placebo	
Preventive Migraine Medication Use Attack Treatment	N_OBS@	Responder n (%)	Point Estimate $(%)	[95% CI]	Odds Ratio [95% CI]	P-value
Yes (N1=274)						
Attack 1						
Placebo	138	15 (10.9)	10.5	[6.55, 16.31]		
Atogepant	132	38 (28.8)	27.2	[20.61, 35.06]	3.21 [1.73, 5.93]	0.0002***
No (N1=949)						
Attack 1						
Placebo	474	65 (13.7)	12.6	[10.00, 15.82]		
Atogepant	470	108 (23.0)	23.6	[20.07, 27.59]	2.14 [1.54, 2.98]	<0.0001***

@ Number of subjects in the subgroup who received the treatment for the first attack and have baseline headache severity for the attack. Missing data were imputed as non-responder.
$ The point estimate is responder rate.
N1 = Number of subjects in the sub-group population.
A generalized linear mixed model (GLMM) was applied to analyze the data on four migraine attacks for each subgroup. The GLMM includes treatment group, attack, treatment group-by-attack interaction, historical triptan-response stratum (Triptan Unsuitable, Triptan Experienced, or Triptan Naïve), region (Europe, China, Japan, and other), and baseline headache severity (moderate or severe).
* P-value <=0.05; **P-value <=0.01; ***P-value <=0.001.

Historical Triptan-Response Strata

Analysis of pain freedom at 2 hours after the DB dose for the first attack showed higher response rates with atogepant compared with placebo for all 3 triptan-response strata. Analyses of Attacks 2, 3, and 4 corroborate these findings, with consistently higher response rates with atogepant compared with placebo for all 3 triptan-response strata.

Table 16. Subgroup Analysis of Pain Freedom at 2 Hours after the DB Dose for the First Attack by Historical Triptan-Response Stratum, Modified Intent-to-Treat 1 Population

			Model-Based Results		
			Response Rate		Odds Ratio Compared to Placebo
Triptan-Response Stratum Attack Treatment	N_OBS@	Responder n (%)	Point Estimate $(%)	[95% CI]	Odds Ratio [95% CI]	P-value
Triptan Unsuitable (N1=188)						
Attack 1						
Placebo	88	5 (5.7)	4.9	[1.99, 11.44]		
Atogepant	96	21 (21.9)	21.4	[14.29, 30.79]	5.32 [1.90, 14.85]	0.0016**
Triptan Experienced (N1=815)						
Attack 1						
Placebo	415	53 (12.8)	12.3	[9.48, 15.70]		
Atogepant	396	98 (24.7)	24.8	[20.85, 29.27]	2.36 [1.65, 3.40]	<0.0001***
Triptan Naïve (N1=220)						
Attack 1						
Placebo	109	22 (20.2)	17.3	[11.55, 25.09]		
Atogepant	110	27 (24.5)	26.2	[19.16, 34.83]	1.70 [0.95, 3.06]	0.0754

@ Number of subjects in the subgroup who received the treatment for the first attack and have baseline headache severity for the attack. Missing data were imputed as non-responder.
$ The point estimate is responder rate.
N1 = Number of subjects in the sub-group population.
A generalized linear mixed model (GLMM) was applied to analyze the data on four migraine attacks for each subgroup. The GLMM includes treatment group, attack, treatment group-by-attack interaction, region (Europe, China, Japan, and other), use of medication for migraine prevention (yes/no), and baseline headache severity (moderate or severe).
* P-value <=0.05; **P-value <=0.01; ***P-value <=0.001.

Consistency of Effect Across Multiple Attacks During the DB Period

Atogepant demonstrated within-subject consistent response across multiple migraine attacks, which was defined as achievement of the specified efficacy endpoint (pain freedom at 2 hours post-dose, pain relief at 2 hours post-dose, sustained pain freedom from 2 to 24 hours and 2 to 48 hours post-dose, and sustained pain relief from 2 to 24 hours and 2 to 48 hours post-dose) for at least 2 of the 3 migraine attacks treated with atogepant 60 mg during the DB period.

Table 17. Achievement of Consistent Pain Freedom and Pain Relief After Dosing with Atogepant During the DB Treatment Period (mITT 1 Population)

	Total (N = 1223) n/N1 (%) [95% CI]
Achievement of consistent pain freedom at 2 hours after DB atogepant for ≥ 2 of 3 attacks	290/1101 (26.3) [23.7, 28.9]
Achievement of consistent pain relief at 2 hours after DB atogepant for ≥ 2 of 3 attacks	870/1097 (79.3) [76.9, 81.7]
Achievement of consistent sustained pain freedom from 2 to 24 hours after DB atogepant for ≥ 2 of 3 attacks	215/1107 (19.4) [17.1, 21.8]
Achievement of consistent sustained pain freedom from 2 to 48 hours after DB atogepant for ≥ 2 of 3 attacks	187/1108 (16.9) [14.7, 19.1]
Achievement of consistent sustained pain relief from 2 to 24 hours after DB atogepant for ≥ 2 of 3 attacks	702/1095 (64.1) [61.3, 67.0]
Achievement of consistent sustained pain relief from 2 to 48 hours after DB atogepant for ≥ 2 of 3 attacks	604/1096 (55.1) [52.2, 58.1]

CI = confidence interval; DB = double-blind; N = number of subjects in the population; N1 = number of subjects who experienced at least 2 successes or 2 failures in the endpoints across at least 2 attacks treated with atogepant during the DB treatment period; n = number of subjects who achieved consistent pain freedom or pain relief for the specified endpoint

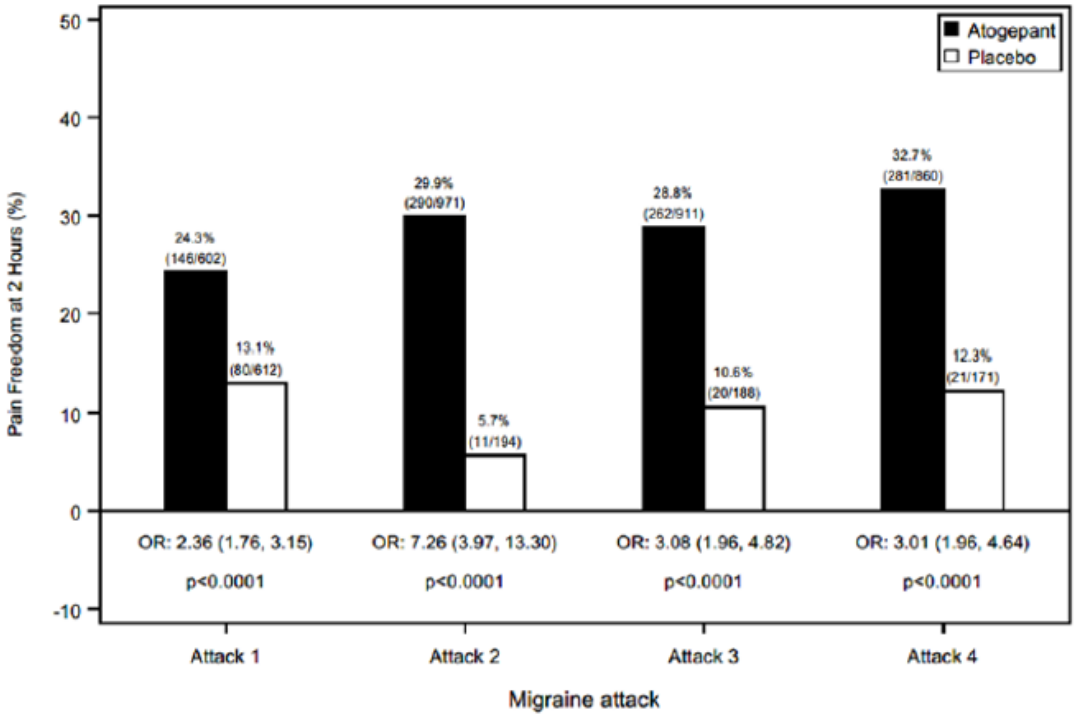
Percentages are calculated as 100 × (n/N1); 95% CI is for the consistency of response endpoint.

Pain Freedom at 2 Hours After the DB Dose

The percentage of subjects achieving consistent pain freedom at 2 hours post atogepant treatment for at least 2 out of 3 attacks was 26.3%. This magnitude of within-subject consistency endpoint for pain freedom at 2 hours was similar to the absolute responder rates observed at 2 hours after atogepant treatment across each of the 4 single attacks (24.3% to 32.7%) during the DB treatment period.

Atogepant 60 mg showed markedly higher response rates than placebo for achieving pain freedom at 2 hours after taking study drug for each of the 4 treated qualifying migraine attacks (nominal $p < 0.0001$).

Figure 10. Percentage of Subjects Achieving Pain Freedom at 2 Hours After Treating Each Migraine Attack During the DB Treatment Period (mITT 1 Population)



Ancillary analyses

Exploratory analyses were conducted for the endpoints listed below to further evaluate the within-subject treatment response for the subset of subjects who were treated with atogepant for 3 migraine attacks (N1 = 1033) during the DB treatment period. Atogepant demonstrated consistent within-subject treatment response as follows:

- 8.1% of subjects achieved pain freedom at 2 hours post-dose for each of 3 attacks; 26.9% of subjects achieved pain freedom at 2 hours post-dose in at least 2 of 3 attacks.

Table 18. Consistency of Pain Freedom Response at 2 Hours after 3 DB Atogepant Treatment, Modified Intent-to-Treat 1 Population

	Atogepant (N=1223) n (%)
N1	1033
1/3 attacks	272 (26.3)
2/3 attacks	194 (18.8)
3/3 attacks	84 (8.1)
>= 2/3 attacks	278 (26.9)

Pain freedom at 2 hours is defined as a reduction in headache severity from moderate/severe at baseline [predose] to no pain at 2 hours after the DB dose. Missing data were imputed as non-responder.
N = Number of subjects in the Population.
N1 = Number of subjects with 3 qualifying attacks treated with atogepant during the DB treatment period.
n = Number of subjects in the specific category.
Percentages are calculated as 100 x (n/N1).

- 43.9% of subjects achieved pain relief at 2 hours post-dose for each of 3 attacks; 79.6% of subjects achieved pain relief at 2 hours post-dose in at least 2 of 3 attacks.
- 5.3% of subjects achieved sustained pain freedom from 2 to 24 hours post-dose for each of 3 attacks; 19.7% of subjects achieved sustained pain freedom from 2 to 24 hours post-dose in at least 2 of 3 attacks.

Table 19. Consistency of Sustained Pain Freedom Response from 2 to 24 Hours after 3 DB Atogepant Treatment, Modified Intent-to-Treat 1 Population

	Atogepant (N=1223) n (%)
N1	1033
1/3 attacks	261 (25.3)
2/3 attacks	149 (14.4)
3/3 attacks	55 (5.3)
>= 2/3 attacks	204 (19.7)

Pain freedom at 2 hours is defined as a reduction in headache severity from moderate/severe at baseline [predose] to no pain at 2 hours after the DB dose. Sustained pain freedom from 2 to 24 hours is defined as pain freedom at 2 hours after the DB dose with no administration of rescue medication and no occurrence of a mild/moderate/severe headache from 2 to 24 hours after the DB dose. Indeterminable cases were imputed as non-responder.
N = Number of subjects in the Population.
N1 = Number of subjects with 3 qualifying attacks treated with atogepant during the DB treatment period.
n = Number of subjects in the specific category.
Percentages are calculated as 100 x (n/N1).

- 4.5% of subjects achieved sustained pain freedom from 2 to 48 hours post-dose for each of 3 attacks; 17.2% of subjects achieved sustained pain freedom from 2 to 48 hours post-dose in at least 2 of 3 attacks

Table 20. Consistency of Sustained Pain Freedom Response from 2 to 48 Hours after 3 DB Atogepant Treatment, Modified Intent-to-Treat 1 Population

	Atogepant (N=1223) n (%)
N1	1033
1/3 attacks	249 (24.1)
2/3 attacks	131 (12.7)
3/3 attacks	47 (4.5)
>= 2/3 attacks	178 (17.2)

Pain freedom at 2 hours is defined as a reduction in headache severity from moderate/severe at baseline [predose] to no pain at 2 hours after the DB dose. Sustained pain freedom from 2 to 48 hours is defined as pain freedom at 2 hours after the DB dose with no administration of rescue medication and no occurrence of a mild/moderate/severe headache from 2 to 48 hours after the DB dose. Indeterminable cases were imputed as non-responder.
N = Number of subjects in the Population.
N1 = Number of subjects with 3 qualifying attacks treated with atogepant during the DB treatment period.
n = Number of subjects in the specific category.
Percentages are calculated as 100 x (n/N1).

- 28.5% of subjects achieved sustained pain relief from 2 to 24 hours post-dose for each of 3 attacks; 64.3% of subjects achieved sustained pain relief from 2 to 24 hours post-dose in at least 2 of 3 attacks

- 21.8% of subjects achieved sustained pain relief from 2 to 48 hours post-dose for each of 3 attacks; 55.5% of subjects achieved sustained pain relief from 2 to 48 hours post-dose in at least 2 of 3 attacks

3.3. Discussion on clinical efficacy

The use of atogepant 60 mg QD is currently approved for the prophylaxis of migraine in adults who have at least 4 migraine days per month. In order to support the use of atogepant in acute migraine, Study M24-305 was conducted as a multiple-attack study designed to assess the efficacy, safety, and tolerability of a single dose of atogepant 60 mg for the acute treatment of a single migraine attack as well as the consistency of effect across multiple migraine attacks. Eligible subjects could continue to use their routine migraine preventive medication (apart from other CGRP antagonists) throughout the study 24 weeks overall study duration (up to 16 weeks to treat 4 qualifying migraine attacks, followed by a minimum of 8 weeks OL). Patients with CM or medication overuse were excluded. Subjects had to present with a diagnosis of migraine (with or without aura) and have 2 to 8 migraine attacks of moderate to severe headache pain in each of the 3 months prior to Screening. The patient population (ICHD-3 criteria) was adequately chosen and is considered representative for clinical practice (26.7% current use of prophylactic medication, 20% of migraine type with aura, mean of 5.6 average migraine attacks per month [4.4 of these rated as moderate to severe], 85.1% female, mean age 41.5 years).

A total of 1.328 subjects were randomized in a 3:1:1:1 ratio to 1 of 4 treatment sequences in which each subject received placebo for 1 qualifying migraine attack and atogepant 60 mg for 3 qualifying migraine attacks during the DB period, resulting in a 1:1 allocation of study drug (placebo:atogepant) for the first qualifying migraine attack. Of these, 187 subjects (15.2%) discontinued study treatment during the DB period. The most common reason for study treatment discontinuation was not treating of 4 qualifying migraine attacks during the DB period (14.6%, with similar percentages across treatment sequences – between 14.2% and 16.2%). During the DB period, 84.2% of subjects treated 4 qualifying migraine attacks. In total 1,045 subjects entered the OL period and 85.6% completed the OL period.

Subjects were provided with DB study drug to treat 4 qualifying migraine attacks of moderate or severe headache pain intensity within 16 weeks after randomization. Each qualifying migraine attack was to be treated with a single dose of study drug. A qualifying migraine attack was defined as meeting all the

following criteria: the onset of the migraine headache is within the previous 4 hours; the severity of the migraine headache pain is moderate or severe; presence of at least 1 of the following migraine-associated symptoms: photophobia, phonophobia, or nausea; rescue medication has not been taken within 48 hours prior to taking study drug; the migraine headache is a new headache, meaning that no other headache has occurred in the previous 48 hours; the migraine headache is not already resolving on its own.

During an OL period, study participants were allowed to treat each qualifying migraine attack with a single dose of OL atogepant 60 mg. However, a definition of qualifying migraine attacks was different, compared to DB period – treatment of mild migraine headaches was allowed and there was no requirement for presence of ≥ 1 migraine-associated symptom.

Efficacy of atogepant 60 mg as-needed in acute migraine attacks was consistently shown across primary and for 12 of the 16 ranked key secondary efficacy endpoints (adjusted $p \leq 0.0001$). The primary efficacy endpoint was pain freedom (defined as a reduction in headache severity from moderate/severe at baseline to no pain) at 2 hours after the DB dose for the first attack. Atogepant treatment resulted in 24.3% of subjects achieving pain freedom at 2 hours post-dose as compared to placebo (13.1%; OR 2.36 [1.76, 3.15], $p < 0.0001$). Analyses of the primary efficacy endpoint and coprimary efficacy endpoints if applicable were conducted on the mITT1 population, using a GLMM. Missing data were imputed as nonresponder. The statistical methods used as well as a sample size calculation are endorsed.

Within-subject consistency of effect was examined following the recommendations of the IHS[1], i.e. response in at least four attacks with at least one of the four attacks being treated with placebo. Within-subject consistent response across multiple migraine attacks was defined as achievement of the specified efficacy endpoint (pain freedom at 2 hours post-dose, pain relief at 2 hours post-dose, sustained pain freedom from 2 to 24 hours and 2 to 48 hours post-dose, and sustained pain relief from 2 to 24 hours and 2 to 48 hours post-dose) for at least 2 of the 3 migraine attacks treated with atogepant 60 mg during the DB period. The design is overall acceptable, despite the fact that it does not allow for placebo comparison in terms of consistency. Placebo comparison would have required inclusion of an additional treatment sequence over the DB period with 3 attacks being treated with placebo and 1 attack treated with atogepant. Pain freedom at 2 hours post-dose in $\geq$ 2 out 3 atogepant treated attacks was achieved by 26.3% of subjects.

The rate of patients achieving pain freedom at 2 hours post-dose was about similar across the four attacks treated during DB period. There was no sign for attrition of effect. Robustness of effect was shown across pre-specified subgroups, resp. strata (patients with concomitant preventive medication, according to baseline headache severity, and according to historical triptan response). Baseline severity of headache pain considerably impacts on response to atogepant treatment. While 27.4% of patients with moderate baseline headache pain achieved pain freedom at 2 hours post-dose with atogepant (placebo: 15.2%), pain freedom was achieved by only 10.6% atogepant patients if pain was severe at baseline (placebo 4.3%). Superiority over placebo was not achieved for atogepant in the subgroup of attacks with severe baseline pain ($p=0.0781$). The 60 mg atogepant dose was the only dose tested in acute migraine and, at the same time, constitutes the MDD. There is no option to offer higher atogepant doses for patients with severe headache pain at baseline. Dose finding data over a wider range of atogepant doses were not conducted.

The relevance of within-patient consistency data (and associated, the difficulty of achieving consistent effect over multiple attacks) is illustrated by exploratory data examining 2-hours pain freedom within-

[1] Diener HC et al. Guidelines of the International Headache Society for controlled trials of acute migraine attacks in adults: Fourth edition. Cephalalgia 2019; 39(6):687-710.

subject response rates in 1/3 (26.3%), 2/3 (18.8%), and 3/3 (8.1%) attacks that were treated with atogepant (summing up to 26.9% response in ≥ 2 out of 3 attacks).

Overall, it is concluded that the efficacy of atogepant 60 mg as-needed in acute migraine was adequately demonstrated across relevant endpoints in study M24-305.

3.4. Conclusions on the clinical efficacy

Study M24-305 demonstrates the favourable effect of atogepant 60 mg, to be taken as needed, in the treatment of acute migraine attacks.

4. Clinical safety

Introduction

The safety data from Study M24-305 for the as-needed use of atogepant 60 mg for the acute treatment of migraine are supported by the safety data from the clinical development program for the prophylaxis of migraine in adults, which includes long-term, open-label safety data for subjects with exposure to atogepant for ≥ 52 weeks. These data demonstrate that atogepant 60 mg once daily is safe and well tolerated for the prophylaxis of migraine in adults, thereby providing support for the indication for the long-term use of atogepant for the acute treatment of migraine.

Study M24-305 demonstrated that atogepant 60 mg was safe and well tolerated in adults for the acute treatment of migraine with or without aura. No new safety signals were observed compared with the established safety profile of atogepant for the prophylaxis of migraine in adults.

Patient exposure

All safety analyses for the Study M24-305 DB treatment period were performed using safety population 1. Safety population 1 consists of all subjects who received at least 1 dose of study drug during the DB treatment period. Safety analyses for the OL period were performed using safety population 2. Safety population 2 consists of all subjects who received at least 1 dose of study drug during the OL treatment period.

Of the 1328 subjects who were randomized into the DB treatment period, 1232 subjects received at least 1 dose of DB study drug (Safety Population 1). A total of 1045 subjects (78.7%) completed the DB treatment period. *'Subject did not treat 4 qualifying attacks during DB period'* and '*withdrawal by subject*' were the most frequently reported (> 4%) primary reasons for study discontinuation during the DB treatment period.

Of the 1045 subjects who entered the OL period, 895 subjects (85.6%) completed the OL period. As of the 07 July 2025 data cutoff date, 84 subjects (8.0%) were ongoing in the study. '*Withdrawal by subject*' was the most frequently reported primary reason for study discontinuation during the OL period.

As of the end of the DB treatment period, 1232 subjects treated at least 1 migraine attack with DB study drug (Safety Population 1). As of the data cutoff date of 07 July 2025, 982 subjects treated at least 1 migraine attack with atogepant during the OL period (Safety Population 2), with a maximum 43 attacks treated by 1 subject.

The mean duration of study participation in the DB period was 73.3 days, and the mean duration of study participation in the OL period was 119.8 days.

Table 21. Number of Migraine Attacks Treated by Period (Safety Population 1)

Period Number of Migraine Attacks Treated	Treatment Sequence 1	Treatment Sequence 2	Treatment Sequence 3	Treatment Sequence 4	Total
Double-blind Treatment Period					
n	623	199	202	208	1232
Mean (SD)	3.7 (0.82)	3.7 (0.70)	3.8 (0.61)	3.7 (0.81)	3.7 (0.77)
Median	4.0	4.0	4.0	4.0	4.0
Q1, Q3	4.0, 4.0	4.0, 4.0	4.0, 4.0	4.0, 4.0	4.0, 4.0
Min, Max	1, 4	1, 4	1, 4	1, 4	1, 4
Number of Attacks Treated - n1 (%)					
1	36 (5.8)	5 (2.5)	4 (2.0)	12 (5.8)	57 (4.6)
2	32 (5.1)	14 (7.0)	8 (4.0)	9 (4.3)	63 (5.1)
3	33 (5.3)	13 (6.5)	15 (7.4)	14 (6.7)	75 (6.1)
4	522 (83.8)	167 (83.9)	175 (86.6)	173 (83.2)	1037 (84.2)
>=1	623 (100)	199 (100)	202 (100)	208 (100)	1232 (100)
Open-label Treatment Period					
n					982
Mean (SD)					9.8 (6.65)
Median					8.0
Q1, Q3					5.0, 14.0
Min, Max					1, 43

n = Number of subjects entering a specific period with treated attacks; n1 = Number of subjects in the specific category.
The percentage is calculated as 100 * (n1/n).
The planned treatment sequences were used in the table.

The mean age of subjects in Safety Population 1 (85.1% female) was 41.5 years (< 40 years [n=519 (42.1%)], 40 – 64 years [n=686 (55.7%)], ≥ 65 years [n=27 (2.2%)]).

Adverse events

An AE is considered a TEAE if it starts on or after the date/time of the first dose of the study drug. However, AEs that occur more than 30 days after one study drug administration and before the next study drug administration, or more than 30 days after the last study drug administration, will not be considered a TEAE. All AEs presented in the CSS are considered treatment-emergent unless otherwise indicated.

In this 4-sequence study, subjects received 3 doses of atogepant and 1 dose of placebo across 4 qualifying migraine attacks during the DB period. Treatment-emergent adverse events (TEAEs) were linked to a specific study drug based on their timing. The linked study drug for a TEAE is the latest study drug taken prior to the occurrence of the TEAE.

TEAEs were further defined as follows:

- TEAE 1: a TEAE that is assigned to a DB dose of a study drug
- 48-hour TEAE 1: a TEAE 1 that is reported within 48 hours following an administration of DB study drug
- TEAE 2: a TEAE that is assigned to an OL dose of atogepant
- 48-hour TEAE 2: a TEAE 2 that is reported within 48 hours following an administration of OL study drug

AEs for the First Migraine Attack During the DB Period

Thirty-four subjects (5.6%) who took atogepant and 34 subjects (5.4%) who took placebo to treat the first migraine attack reported at least 1 48-hour TEAE. Following the first migraine attack, there were no 48-hour TESAEs, severe TEAEs, or TEAEs leading to study treatment discontinuation in subjects who received atogepant. One subject each in the atogepant and placebo treatment groups experienced a TEAE that led to discontinuation of study treatment.

Table 22. Overview of Adverse Events for the First Migraine Attack During the DB Period (Safety Population 1)

	Placebo (N=624) n (%)	Atogepant (N=607) n (%)
48-hour Treatment-emergent adverse events 1 (TEAE 1)	34 (5.4)	34 (5.6)
48-hour TEAE 1 related to study treatment	16 (2.6)	24 (4.0)
Severe 48-hour TEAE 1	1 (0.2)	0
Serious 48-hour TEAE 1	0	0
48-hour TEAE 1 leading to discontinuation of study treatment	1 (0.2)	0
48-hour TEAE 1 leading to death	0	0
TEAE 1	84 (13.5)	76 (12.5)
TEAE 1 related to study treatment	20 (3.2)	25 (4.1)
Severe TEAE 1	1 (0.2)	0
Serious TEAE 1	1 (0.2)	0
TEAE 1 leading to discontinuation of study treatment	1 (0.2)	1 (0.2)
TEAE 1 leading to death	0	0
All deaths	0	0

An AE will be considered as a treatment emergent adverse event (TEAE) if it starts on or after the date/time of the first dose of the study drug. However, AEs that occur more than 30 days after one study drug administration and before the next study drug administration, or more than 30 days after the last study drug, will not be considered as TEAEs.

TEAE 1 is defined as a TEAE that is assigned to a DB dose of a study drug. 48-hour TEAE 1 is a TEAE 1 that is reported within 48 hours following an administration of the DB study drug.

Subjects are counted only once within each category and treatment group.

N = number of subjects in the Population. n = number of subjects within a specific category.

Percentages are calculated as 100 × (n/N)

AEs for All Migraine Attacks During the DB Period

Over the entire DB period, more TEAEs were reported with atogepant (27.3% of subjects) than with placebo (11.4% of subjects). One hundred eleven subjects (9.3%) who received atogepant and 49 subjects (4.2%) who received placebo during the DB period reported at least 1 48-hour TEAE. However, it should be noted that during the DB period, subjects treated 3 migraine attacks with atogepant and 1 migraine attack with placebo.

Adverse Events by Frequency

TEAEs for All Migraine Attacks During the DB Period

During the DB period, subjects treated 3 migraine attacks with atogepant and 1 migraine attack with placebo. The TEAEs experienced by ≥ 2% of subjects during the entire DB period were nasopharyngitis and upper respiratory tract infection.

Within 48 hours after treating any migraine attack during the DB period, the only TEAE reported in ≥ 1% of subjects was nausea (atogepant, 1.3%; placebo, 0.3%).

Table 23. Number (%) of Subjects with Common (⩾ 2%) Treatment-Emergent Adverse Events 1 (TEAE 1) During the DB Period by Preferred Term (Safety Population 1)

MedDRA 28.0 Preferred Term	Placebo (N=1177) n (%)	Atogepant (N=1195) n (%)	Total (N=1232) n (%)
Nasopharyngitis	15 (1.3)	45 (3.8)	57 (4.6)
Upper respiratory tract infection	5 (0.4)	25 (2.1)	28 (2.3)

An AE will be considered as a treatment emergent adverse event (TEAE) if it starts on or after the date/time of the first dose of the study drug. However, AEs that occur more than 30 days after one study drug administration and before the next study drug administration, or more than 30 days after the last study drug, will not be considered as TEAEs.
TEAE 1 is defined as a TEAE that is assigned to a DB dose of a study drug.
N = number of subjects in the Population.
n = number of subjects within a specific category.
Percentages are calculated as 100 x (n/N).

Adverse Drug Reactions

Within the atogepant program, adverse drug reactions (ADRs) are determined by evaluating TEAEs in placebo-controlled migraine studies that occur with a ≥ 2% overall incidence rate in any of the atogepant groups and at a rate at least 2% greater than placebo.

Any additional ADRs are determined by evaluating all other AEs (in all analysis sets) that did not meet the above criterion but may represent an ADR; this includes review of events with incidence rates < 2%.

All AEs that met either criterion above were evaluated using medical judgment to determine if there was a plausible causal relationship between the AE and atogepant, including evaluation of the extent to which the AE was consistent with the pharmacology of study drug and the consistency of the pattern of symptoms across multiple studies.

Based on the above, nausea was identified as an ADR in Study M24-305. Although the incidence of nausea within Study M24-305 was < 2%, nausea occurred in subjects who treated migraines with atogepant at > 2 times the rates reported for subjects who treated migraines with placebo during the DB treatment period. A plausible causal relationship is also consistent with the pharmacology of study drug, as calcitonin gene-related peptide (CGRP) antagonism can decrease gastrointestinal motility.

Serious adverse event/deaths/other significant events

No subjects treated with atogepant 60 mg or placebo reported TESAEs within 48 hours after dosing for the first migraine attack during the DB period of the study.

The following TESAEs were reported for 1 subject (< 0.1%) each after taking atogepant during the DB period: abscess jaw, rectal cancer stage I, uterine leiomyoma, migraine with aura, suicidal ideation, and cervical dysplasia. These TESAEs were considered by the investigator as having no reasonable possibility of being related to study drug.

There was 1 case of a subject reporting serious AE of suicidal ideation / increased suicidal thoughts three days after having received the 3rd atogepant dose during the DB treatment period. Atogepant was withdrawn, the patient was hospitalized. The Investigator's judgement of no reasonable possibility of relation to study treatment is endorsed. The patient's medical history included autism spectrum disorder, burn out, and complex post-traumatic stress disorder. In this context, 112.5 mg venlafaxine QD was

prescribed prior to enrolment. The patient experienced suicidal ideation in the past, but without intent and without plan. This case was categorized as serious as it required or prolonged hospitalization.

Adverse Events of Special Interest

Protocol-specified adverse events of special interest (AESIs) monitored throughout the study were:

- Suicidal ideations with intent, with or without a plan (i.e., Type 4 or 5 on the C-SSRS), or any suicidal behaviours. No subject met this criterion during the study.
- Elevated ALT and/or AST ≥ 3 × ULN. 5 subjects had treatment-emergent elevations that met this criterion during the study.
- Potential Hy's law cases: elevated ALT or AST ≥ 3 × ULN and an elevated total bilirubin ≥ 2 × ULN and, at the same time, an alkaline phosphatase value < 2 × ULN. No potential Hy's law cases occurred during the study.

Laboratory findings

No treatment-emergent elevations of ALT and/or AST ≥ 3 × ULN were observed during the DB period. During the DB period, 1 subject had a postbaseline ALT elevation ≥ 3 × ULN and total bilirubin ≥ 2 × ULN after taking placebo to treat the first migraine attack. This ALT elevation occurred > 30 days after the DB dose and therefore was not treatment emergent. The elevations were assessed by the Hepatic Event Adjudication Committee (HEAC) as unlikely related to treatment, with the confounding factor of "choledocholithiasis weeks after a single dose of IMP".

During the OL period, 5 subjects (0.5%) had postbaseline ALT and/or AST values ≥ 3 × ULN. No concurrent elevations of ALT and/or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN were observed.

- The HEAC assessed 2 of 5 cases of aminotransferase values ≥ 3 × ULN as possibly related to study drug, with the confounding factor of positive anti-smooth muscle antibody identified for 1 case and diclofenac as well as no workup for other causes identified for 1 case.
- The HEAC assessed 3 of 5 cases as unlikely related to study drug, with confounding factors related to exercise for each case (muscle injury from weight training, rhabdomyolysis following intensive exercise, muscle injury from vigorous exercise).

4.1. Discussion on clinical safety

Acute migraine study M24-305 comprised up to 16 weeks DB treatment to treat 4 qualifying acute migraine attacks (3 x atogepant, 1 x placebo) followed by minimum 8 weeks OL treatment (overall 24 week duration). Long-term safety data for the use of atogepant (60 mg QD) in migraine prophylaxis were obtained during the initial MAA procedure. As agreed upon during scientific advice, it is acceptable to integrate the newly generated safety data for acute as-needed use of atogepant into the established long-term safety profile obtained in migraine prophylaxis.

The safety of atogepant for acute migraine treatment was adequately characterized including particular monitoring of AEs of special interest, i.e. liver enzyme elevations (elevated ALT and/or AST ≥ 3 x ULN, cases of Hy's law) and suicidal ideation / behaviours.

No new safety signals were identified compared with the safety profile established during the clinical development program for the prophylaxis of migraine in adults. Currently labelled common adverse reactions are decreased appetite, nausea, constipation, fatigue / somnolence, and weight decrease. In acute study M24-305, the TEAEs experienced by ≥ 2% of subjects during the entire DB period were nasopharyngitis (atogepant 3.8%, placebo 1.3%) and upper respiratory tract infection (atogepant 2.1%,

placebo 0.4%). It is noted that during the DB period, subjects treated 3 migraine attacks with atogepant and 1 migraine attack with placebo.

Within 48 hours after treating any migraine attack during the DB period, the only TEAE reported in ≥ 1% of subjects was nausea (atogepant, 1.3%; placebo, 0.3%). Nausea is the only common adverse reaction proposed for inclusion in a newly introduced subsection *Acute Treatment of migraine* of SmPC section 4.8. This is acceptable.

Narratives were provided on subjects presenting with AESI. One serious case of increased suicidal thoughts was observed in a patient three days after receipt of the third atogepant dose during DB treatment. Medical history includes autism spectrum disorder, burn out, and complex post-traumatic stress disorder. The patient experienced suicidal ideation in the past. Study medication was discontinued. The Investigator's judgement of no reasonable possibility of relation to atogepant is endorsed.

Elevations of ALT/AST (defined as ≥ 3 x ULN) have been observed in atogepant patients during migraine prophylaxis trials and were labelled in SmPC section 4.8 accordingly. During the OL period of study M24-305, 5 subjects (0.5%) had postbaseline ALT and/or AST values ≥ 3 × ULN. The elevations were assessed by the Hepatic Event Adjudication Committee (HEAC). Three out of these 5 cases were adjudicated as unlikely to be related to atogepant, with confounding factors related to exercise for each case (muscle injury from weight training, rhabdomyolysis following intensive exercise, muscle injury from vigorous exercise). The two remaining cases are possibly related to study medication, since no confounding factors could be identified. In one case, enzyme elevations were observed 11 days after last treatment (after a total of 8 atogepant doses), in the other case atogepant treatment was continued. Liver enzymes returned to normal within two weeks.

4.2. Conclusions on clinical safety

The safety of as-needed atogepant 60 mg use for the treatment of acute migraine attacks was adequately characterized and no new or concerning safety issues have been identified. Nausea was added in a newly introduced subsection of SmPC section 4.8. Liver enzyme elevations are labelled as uncommon adverse reaction for both prophylactic and acute migraine treatment.

4.2.1. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

4.3. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.2 is acceptable:

The CHMP endorsed this advice without changes.

Safety concerns

Table 24 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in patients with significant cardiovascular or cerebrovascular diseases Use in pregnant women Long-term safety beyond 1 year

Considering the data in the safety specification, the safety concerns listed above are appropriate.

Pharmacovigilance plan

10.2.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities include adverse reactions reporting and signal detection.

None other forms of routine pharmacovigilance activities are foreseen.

10.2.2 Additional pharmacovigilance activities

The safety concerns of missing information are supported by four Category 3 studies (all ongoing):

- An open-label, 3 years study 3101-312-002;
- Observational cohort study P22-419;
- Prospective observational study P22-392
- PASS P24-433, an observational non-interventional study.

The final protocol submission dates were removed for the following Category 3 additional pharmacovigilance studies: 3101-312-002, P22-419 and P22-392. Registration in the HMA EMA RWD Catalogue and the dates were added for two observational studies and PASS. The study information (Rational and study objectives) was updated and milestones were added for PASS P24-433. The due dates were updated to adjust to the new timelines (the proposed changes are underlined). The proposed update of milestones and dates of Category 3 studies are acceptable.

Table 25. On-going and planned additional pharmacovigilance activities

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
A Phase 3, multicenter, open-label 156-week extension study to evaluate the long-term safety and tolerability of oral atogepant for the prevention of migraine in participants with chronic or episodic migraine: Study 3101312002 is ongoing for a total of 3 years	To evaluate the long-term safety and tolerability of atogepant 60 mg once daily in participants when taken for 156 weeks for the prevention of chronic migraine (CM) or episodic migraine (EM).	Long-term safety beyond 1 year	Draft Protocol Submission Study Completion Final Report Submission	10/2020 11/2025 02/2026
Observational Study to Assess Pregnancy Outcomes Following Exposure to Atogepant: PMR 4152-7; Study P22-419 Ongoing	To describe and compare the incidence of pregnancy outcomes in women with migraine who are exposed to atogepant during pregnancy	Use in pregnant women	Draft Protocol Submission Registration in the HMA EMA RWD Catalogue Annual Interim Report Submissions Study Completion Final Report Submission	02/2024 08/2025 From 02/2024 to 02/2029 02/2030 04/2031

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Atogepant pregnancy Exposure Registry: PMR 4152-6; Study P22-392 Ongoing	To prospectively evaluate maternal, fetal, and infant outcomes through 12 months of age among women exposed to atogepant during pregnancy compared to comparator groups	Use in pregnant women	Draft Protocol Submission Registration in the HMA EMA RWD Catalogue Annual Interim Report Submissions Study Completion Final Report Submission	02/2024 08/2025 From 02/2024 to 02/2035 02/2036 02/2037
PASS of atogepant in patients with significant cardiovascular or cerebrovascular diseases: Study P24-433 Ongoing	To characterize the safety of atogepant in patients with significant cardiovascular or cerebrovascular diseases	Use in patients with significant cardiovascular or cerebrovascular diseases	Draft Protocol Submission Registration in the HMA EMA RWD Catalogue First Annual Interim Report Submission Interim Report Submission Study Completion Final Report Submission	11/2023 08/2025 12/31/2026 12/31/2028 09/2030 12/2031

*Category 1 studies are imposed activities considered key to the benefit risk of the product.

Category 2 studies are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.

Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Routine risk minimisation measures for atogepant and description of routine risk minimisation measures by safety concern are the same as for previously approved therapeutic indication. This is acceptable as atogepant is already authorised for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

4.4. Update of the Product information

As a consequence of this new indication, sections X, Y, Z of the SmPC have been updated. The Package Leaflet has been updated accordingly.

<Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed <by QRD> and accepted by the CHMP.>

4.4.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Aquipta current product information. The bridging report submitted by the MAH has been found acceptable.

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

Migraine is a highly prevalent disease, occurring in approximately 14% of people worldwide. In the US and Europe, the prevalence is estimated to be 11% to 12%, with higher rates among women (16% to 18%) than men (6% to 7%). Migraine is particularly common among individuals between the ages of 25 and 55 years.

Migraine is a chronic neurological disease typically characterized by attacks of throbbing, unilateral headache of moderate to severe pain intensity, sensitivity to light (photophobia), sensitivity to sound (phonophobia), nausea and/or vomiting. In about 25% of individuals, migraine headache may be preceded by aura.

It is currently thought that migraine has a neurologic aetiology. The brains of patients with migraine are characterized by a generalized neuronal hyperexcitability, evidenced by increased response to visual, sensory, auditory, and nociceptive stimuli. Additionally, migraine attacks involve release of neurotransmitters and activation of pain pathways, including the trigeminal nerve. Migraine pain appears to involve nociceptive neurons in the dura mater being stimulated and releasing vasoactive neuropeptides such as CGRP. The trigeminal nerve pathway transmits nociception from the meninges via intermediate pathways to the cortex. CGRP is a neuropeptide that modulates nociceptive signalling and causes vasodilation that has been associated with migraine pathophysiology.

5.1.2. Available therapies and unmet medical need

According to current treatment guidelines, paracetamol or unspecific NSAIDs like acetyl salicylic acid, ibuprofen, etc. rank among first-line therapies for the acute treatment of migraine; however, these are typically used for less severe migraine attacks.

Major progress in targeted acute treatment of migraine symptoms was achieved with the advent of the triptans in the nineties. Triptans target 5-HT1B and 5-HT1D receptors, and their mechanism is thought to involve cranial vessel constriction and inhibition of proinflammatory neuropeptide release. As the gold standard for acute treatment of migraine, triptans represent 28% to 36% of prescribed acute migraine medications.

However, triptans are not efficacious for all patients; rates of pain freedom at 2 hours post-dose with triptans in a meta-analysis are in the range of placebo-subtracted 20% to 40%.[2] Triptans are contraindicated in patients with coronary artery disease, peripheral vascular disease, cerebrovascular disease, or uncontrolled hypertension, and are not well tolerated by all patients due to their AE profile.

In view of incomplete response to currently available migraine medications and limitations of use due to CV contraindications and risk of developing MOH, a need exists for new therapeutic alternatives for the acute treatment of migraine. Based on its pharmacological profile and lack of CV contraindications, atogepant potentially offers a contribution to the currently available treatment options.

5.1.3. Main clinical studies

In order to support the use of atogepant in acute migraine, Study M24-305 was conducted as a multiple-attack study designed to assess the efficacy, safety, and tolerability of a single dose of atogepant 60 mg for the acute treatment of a single migraine attack as well as the consistency of effect across multiple migraine attacks. Eligible subjects could continue to use their routine migraine preventive medication (apart from other CGRP antagonists) throughout the study 24 weeks overall study duration (up to 16 weeks to treat 4 qualifying migraine attacks, followed by a minimum of 8 weeks OL). Patients with CM or medication overuse were excluded. The patient population (ICHD-3 criteria) was adequately chosen and is considered representative for clinical practice (26.7% current use of prophylactic medication, 20% of migraine type with aura, mean of 5.6 average migraine attacks per month, 85.1% female, mean age 41.5 years).

A total of 1.328 subjects were randomized in a 3:1:1:1 ratio to 1 of 4 treatment sequences in which each subject received placebo for 1 qualifying migraine attack and atogepant 60 mg for 3 qualifying migraine attacks during the DB period, resulting in a 1:1 allocation of study drug (placebo:atogepant) for the first qualifying migraine attack.

5.2. Favourable effects

Efficacy of atogepant 60 mg as-needed in acute migraine attacks was consistently shown across primary and for 12 of the 16 ranked key secondary efficacy endpoints (adjusted $p \leq 0.0001$). Atogepant treatment resulted in 24.3% of subjects achieving pain freedom at 2 hours post-dose as compared to placebo (13.1%; OR 2.36 [1.76, 3.15], $p < 0.0001$).

Rates of patients achieving sustained pain freedom with atogepant from 2 to 24 hours, resp. from 2 to 48 hours post-dose were lower, as could be expected. As commonly observed, placebo response rates for sustained pain freedom are also substantially lower, so that atogepant separates significantly from placebo for these two endpoints (sustained pain freedom: 2-24 h: atogepant 17.8%, placebo 6.4% [OR 3.58 (2.44, 5.25) $p < 0.0001$; 2-48 h: atogepant 16.6%, placebo 5.7% [OR 3.62 (2.43, 5.39) $p < 0.0001$).

Photophobia, phonophobia, and nausea were identified as the MBS for the first attack in 44.1%, 24.5%, and 31.4% of subjects, respectively. Absence of the MBS at 2 hours was achieved by 43.7% atogepant patients as compared to 32.7% for placebo (OR 1.77 [1.41, 2.24], $p < 0.0001$).

The efficacy of atogepant for providing pain freedom after treating the first migraine attack was evident at 1.5 hours post-dose (responder rate: atogepant 12.5%, placebo 7.7%; nominal p =

[2] Ferrari MD et al. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia. 2002;22(8):633-58

0.0007), with the difference in response rates for atogepant compared with placebo increasing substantially over time and persisting through 48 hours.

Acute rescue medication within 24 hours after the first attack was used significantly less frequently in atogepant patients (15.1%) as compared to placebo (53.3%, $p < 0.0001$).

Within-subject consistency of effect was examined following the recommendations of the IHS[1], i.e. response in at least four attacks with at least one of the four attacks being treated with placebo. Within-subject consistent response across multiple migraine attacks was defined as achievement of the specified efficacy endpoint (pain freedom at 2 hours post-dose, pain relief at 2 hours post-dose, sustained pain freedom from 2 to 24 hours and 2 to 48 hours post-dose, and sustained pain relief from 2 to 24 hours and 2 to 48 hours post-dose) for at least 2 of the 3 migraine attacks treated with atogepant 60 mg during the DB period. The design is overall acceptable, despite the fact that it does not allow for placebo comparison in terms of consistency. Placebo comparison would have required inclusion of an additional treatment sequence over the DB period with 3 attacks being treated with placebo and 1 attack treated with atogepant. Pain freedom at 2 hours post-dose in $\geq$ 2 out 3 atogepant treated attacks was achieved by 26.3% of subjects.

The rate of patients achieving pain freedom at 2 hours post-dose was about similar across the four attacks treated during DB period. There was no sign for attrition of effect. Robustness of effect was shown across pre-specified subgroups, resp. strata (patients with concomitant preventive medication, according to baseline headache severity, and according to historical triptan response).

5.3. Uncertainties and limitations about favourable effects

Effect size

In terms of the primary efficacy endpoint, pain freedom at 2 hours post-dose, which is generally used to compare efficacy between different substances, the effect size of atogepant appears to be below of what can typically be expected by triptans in acute migraine therapy. In study M24-305, 24.3% of atogepant patients achieved pain freedom at 2 hours post-dose as compared to placebo (13.1%).

Response in attacks with severe baseline pain

Robustness of effect was examined across pre-specified subgroups, resp. strata (patients with concomitant preventive medication, according to baseline headache severity, and according to historical triptan response). Baseline severity of headache pain considerably impacts on response to atogepant treatment. While 27.4% of patients with moderate baseline headache pain achieved pain freedom at 2 hours post-dose with atogepant (placebo: 15.2%), pain freedom was achieved by only 10.6% atogepant patients if pain was severe at baseline (placebo 4.3%). Hence, in the subgroup of attacks with severe baseline pain, atogepant only numerically separated from placebo ($p=0.0781$). The 60 mg atogepant dose was the only dose tested in acute migraine and, at the same time, constitutes the MDD. There is no option to offer higher atogepant doses for patients with severe headache pain at baseline. Dose finding data over a wider range of atogepant doses were not generated. Despite these limitations the overall subgroup analyses support a clinically relevant treatment effect of atogepant.

No placebo comparison for consistency

Within-subject consistency of effect was examined following the recommendations of the IHS[1], i.e. response in at least four attacks with at least one of the four attacks being treated with placebo. The design is overall acceptable, despite the fact that it does not allow for placebo comparison in terms of consistency. Placebo comparison would have required inclusion of an additional treatment sequence

over the DB period with 3 attacks being treated with placebo and 1 attack treated with atogepant. The relevance of demonstration of within-subject consistent efficacy is underlined in particular for those therapies with effect sizes below treatment alternatives in the single attack treatment setting. Despite this limitation, the findings provide supportive evidence of within-subject consistency of effect with atogepant across multiple migraine attacks.

5.4. Unfavourable effects

Acute migraine study M24-305 comprised up to 16 weeks DB treatment to treat 4 qualifying acute migraine attacks (3 x atogepant, 1 x placebo) followed by minimum 8 weeks OL treatment (overall 24 week duration). Long-term safety data for the use of atogepant (60 mg QD) in migraine prophylaxis were obtained during the initial MAA procedure. As agreed upon during scientific advice, it is acceptable to integrate the newly generated safety data for acute as-needed use of atogepant into the established long-term safety profile obtained in migraine prophylaxis.

The safety of atogepant for acute migraine treatment was adequately characterized including particular monitoring of AEs of special interest, i.e. liver enzyme elevations (elevated ALT and/or AST > 3 x ULN, cases of Hy's law) and suicidal ideation / behaviours.

No new safety signals were identified compared with the safety profile established during the clinical development program for the prophylaxis of migraine in adults. Currently labelled common adverse reactions are decreased appetite, nausea, constipation, fatigue / somnolence, and weight decrease. In acute study M24-305, the TEAEs experienced by ≥ 2% of subjects during the entire DB period were nasopharyngitis (atogepant 3.8%, placebo 1.3%) and upper respiratory tract infection (atogepant 2.1%, placebo 0.4%). It is noted that during the DB period, subjects treated 3 migraine attacks with atogepant and 1 migraine attack with placebo.

Within 48 hours after treating any migraine attack during the DB period, the only TEAE reported in ≥ 1% of subjects was nausea (atogepant, 1.3%; placebo, 0.3%). Nausea is the only common adverse reaction proposed for inclusion in a newly introduced subsection Acute Treatment of migraine of SmPC section 4.8.

Narratives were provided on subjects presenting with AESI. Elevations of ALT/AST (defined as ≥ 3 x ULN) have been observed in atogepant patients during migraine prophylaxis trials and were labelled in SmPC section 4.8 accordingly. During the OL period of study M24-305, 5 subjects (0.5%) had postbaseline ALT and/or AST values ≥ 3 × ULN. The elevations were assessed by the Hepatic Event Adjudication Committee (HEAC). Three out of these 5 cases were adjudicated as unlikely to be related to atogepant, with confounding factors related to exercise for each case (muscle injury from weight training, rhabdomyolysis following intensive exercise, muscle injury from vigorous exercise). The two remaining cases are possibly related to study medication, since no confounding factors could be identified. In one case, enzyme elevations were observed 11 days after last treatment (after a total of 8 atogepant doses), in the other case atogepant treatment was continued. Liver enzymes returned to normal within two weeks. Like in migraine prophylaxis, liver enzyme elevations (ALT/AST increased) were also uncommonly observed in acute migraine, which was labelled accordingly.

5.5. Uncertainties and limitations about unfavourable effects

There is little uncertainty about the unfavourable effects. As already known from atogepant's clinical programme in migraine prophylaxis, and in line with other migraine treatment options of CGRP-antagonistic pathway, atogepant was overall well tolerated. No new or concerning safety issues have been identified in the pivotal study. Based on experiences from migraine prophylaxis trials 301 (EM) and 303 (CM) incl. long-term extension, AESIs like e.g. liver enzyme elevations were adequately

monitored in the acute migraine study M24-305. Elevations of AST/ALT ≥ 3 x ULN were observed in 5 atogepant subjects. Like confirmed by HEAC, there is reasonable possibility for relation to atogepant in 2 of these cases.

5.6. Effects Table

Table 26. Effects Table for atogepant 60 mg QD (Aquipta®) for acute treatment of migraine with or without aura in adults (Study M24-305, data cut-off: 07 July 2025)

Effect	Short description	N	Point Estimate n (%)	Odd ratio (95% CI)	Adjusted p value	Uncertainties / Strength of evidenc
Favourable Effects						
P1	**Pain freedom at 2 hours, DB, 1st attack** Placebo Atogepant	612 602	80 (13.1) 146 (24.3)	2.36 (1.76, 3.15)	< 0.0001	High strength of evidence
S1	**Absence of MBS at 2 hours, DB, 1st attack** Placebo Atogepant	612 602	200 (32.7) 263 (43.7)	1.77 (1.41, 2.24)	< 0.0001	High strength of evidence
S5	**Use of rescue medication within 24 h, DB, 1st attack** Placebo Atogepant	613 602	327 (53.3) 91 (15.1)	0.14 (0.11, 0.19)	< 0.0001	
S7	**Sustained pain freedom, 2 to 24 hours, DB, 1st attack** Placebo Atogepant	612 602	39 (6.4) 107 (17.8)	3.58 (2.44, 5.25)	< 0.0001	
Unfavourable Effects						

Effect	Short description	N	Point Estimate n (%)	Odd ratio (95% CI)	Adjusted p value	Uncertainties / Strength of evidenc
Liver enzyme elevations (AST / ALT ≥ 3 x ULN)						
• Liver enzyme elevations known as uncommon adverse reaction for atogepant from migraine prevention trials • Also found in 5 atogepant patients in acute migraine treatment. Two out of these cases without confounding factors and adjudicated as *reasonable possibility for relation to atogepant*.						

Abbreviations: DB Double-blind, MBS Most bothersome symptom, ULN Upper limit normal

Benefit-risk assessment and discussion

5.6.1. Importance of favourable and unfavourable effects

Pivotal Study M24-305 consistently demonstrated the efficacy of atogepant 60 mg QD in acute migraine treatment across the primary (pain freedom at 2 hours post-dose) and secondary endpoints, like absence of MBS at 2 hours post-dose, sustained pain freedom from 2 to 24, resp. 2 to 48 hours post-dose, and the reduction in acute rescue medication use. The overall favourable study results with regard to efficacy go along with good tolerability in the acute migraine treatment setting. The favourable safety profile observed for atogepant in migraine prevention was confirmed for the as-needed use of atogepant 60 mg QD to treat acute migraine attacks. There was no new safety signals detected in the acute migraine setting.

Unfavourable effects like liver enzyme elevations (AST / ALT ≥ 3 x ULN) that are already labelled as adverse reactions of atogepant for migraine prevention were also observed in patients using atogepant for acute migraine.

5.6.2. Balance of benefits and risks

The risks associated the use of atogepant in acute migraine attacks are considered low based on the existing long-term safety profile established for atogepant 60 mg QD in migraine prevention and randomized placebo-controlled data obtained from study M24-305 in acute migraine. In terms of efficacy, placebo superiority could be shown in acute migraine for as-needed atogepant 60 mg across relevant primary and secondary endpoints along current guideline provisions.

The overall B/R of atogepant in the proposed indication for acute treatment of migraine with or without aura in adults is considered positive.

5.6.3. Additional considerations on the benefit-risk balance

None

5.7. Conclusions

The overall B/R of Aquipta for the extension of indication to include *Acute treatment of migraine with or without aura in adults* is considered positive.

6. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variation(s) accepted		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II
B.II.e.5.a.2	B.II.e.5.a.2 Change outside the range of the currently approved pack sizes	Variation type IB
B.II.e.5.a.2	B.II.e.5.a.2 Change outside the range of the currently approved pack sizes	Variation type IB
B.II.e.5.a.1	B.II.e.5.a.1 Change within the range of the currently approved pack sizes	Variation type IA_IN

A grouped application comprised of 1 Type II Variation and 3 Type I Variations, as follows: Type II (C.I.6): Extension of indication to include acute treatment of migraine with or without aura in adults, based on interim results from study M24-305; this is a 24-week, global, Phase 3, multicenter, randomized, double blind, placebo-controlled, multiple-migraine attack study with an open label period to evaluate the safety and efficacy of atogepant in adult participants for the acute treatment of migraine (ECLIPSE). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.2 of the RMP is approved. Type IB (B.II.e.5.a.2): Addition of pack size of 7 tablets for 10mg strength tablets. Type IB (B.II.e.5.a.2): Addition of pack size of 2 tablets for 60mg strength tablets. Type IAIN (B.II.e.5.a.1): Addition of pack size of 7 tablets for 60mg strength tablets.

The group of variations leads to amendments to the annex(es) I, IIIA, and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, IIIA, IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.