22 June 2023
EMA/CHMP/326142/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aquipta

International non-proprietary name: atogepant

Procedure No. EMEA/H/C/005871/0000

Note

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

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List of abbreviations

5-HT	5-Hydroxytryptamin, serotonin
ABs	Antibodies
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AGP	Atogepant
AI	Accumulation index
AL	Abuse liability
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time 0 to infinity
$AUC_{0\text{-}t}$	Area under the concentration-time curve from time 0 to time of last quantifiable concentration
AUCtau	Area under the concentration-time curve during one dosing interval at steady state
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BID	Bis in die (twice daily)
BP	Blood pressure
bpm	Beats per minute
CAD	Coronary artery disease
CGIc	Clinical Global Impression of Change
CGIs	Clinical Global Impression of Severity
CGRP	Calcitonin gene-related peptide
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIDV	Capsaicin-induced dermal vasodilation
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent oral clearance
CLR	Renal clearance
CM	Chronic migraine
Cmax	Maximum plasma concentration
CNS	Central nervous system
CrCl	Creatinine clearance
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
CVWR	Within-subject Coefficient of variation
CVA	Cerebrovascular accident
CVD	Cardiovascular Disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DBS	Dried blood spot
DDI	Drug-Drug interaction
DILI	Drug-induced liver injury
EC50	Maximal drug effect
ECG	Electrocardiogram
EE	Ethinylestradiol
EM	Episodic migraine
Emax	Maximum effectiveness
Emin	Minimum effectiveness
EOT	End of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLMEM	Generalised linear mixed effect model
GMR	Geometric mean ratio
HA	Headache
HD	Headache day

HLT	High Level Term
HME-OCT	Hot melt extrudate oral compressed tablet
HR	Heart rate
HRQoL	Health-related quality of life
HV	Healthy volunteer
ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd ed.
IHS	International Headache Society
IND	Investigational New Drug
ITT	Intent-to-treat
Iv	Intravenous
Ki	Inhibitory constant
LFT	Liver function test
LNG	Levonorgestrel
LS mean	Least squares mean
LTS	Long-term safety Set
MAA	Marketing Authorisation Application
MAO	Monoamine oxidase
MD	Migraine day
MedDRA	Medicinal Dictionary for Regulatory Activities
MI	Multiple imputation
MIDAS	Migraine Disability Assessment Test
mITT	Modified intent-to-treat
MQoLQ	Migraine Quality of life Questionnaire
MP	Medicinal product
MS	Member state
NDA	New drug application
NEAE	Newly emergent adverse event
NSAID	Nonsteroidal anti-inflammatory drug
OAT	Organic anion transporter
OC	Oral contraceptive
OCT	Organic cation transporter
OLE	Open-label extension (phase)
PBO	Placebo
PBPK	Physiologically based pharmacokinetics
PCS	Placebo-controlled Safety Set
PD	Pharmacodynamic
PGIc	Patient Global Impression of Change
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PMF	Pre-market formulation
popPK	Population pharmacokinetics
PPI	Proton pump inhibitor
PRN	Pro re nata (when needed)
PT	Preferred term
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
Rdnm	Dose normalised ratio
RMP	Risk management plan
SAD	Single ascending dose
SAE	Serious adverse event
SBP	Systolic blood pressure
SCS	Summary of Clinical Safety
SD-OCT	Spray dried oral compressed tablet
SGF	Simulated gastric fluid
SIF	Simulated intestinal fluid
SL	Sublingual
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Query
SoC	Standard of care
SOC	System organ class
S-STS	Sheehan Suicidality Tracking Scale
TBL	Total bilirubin
TBM	To be marketed

TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TIA	Transient ischaemic attack
t½	Elimination Half-life
tmax	Time to maximum concentration
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AbbVie Deutschland GmbH & Co. KG submitted on 24 June 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Aquipta, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 February 2021.

The applicant applied for the following indication:

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0046/2020)

- on the agreement of a paediatric investigation plan (PIP) for the use of atogepant in the prevention of migraine headaches in the subset of the paediatric population from 6 to less than 18 years of age, and
- on the granting of a waiver in the paediatric population from birth to less than 6 years of age.

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

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance atogepant contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received HTA/EMA Scientific Advice (EMA/H/SA/3835/1/2018/HTA/II) in June 2018.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	24 June 2022
The procedure started on	14 July 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	30 September 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	17 October 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 October 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	10 November 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 January 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	6 March 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 March 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	30 March 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	7 June 2023

to all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Aquipta on	22 June 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	22 June 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Migraine is a serious, chronic, disabling neurological disease characterised by attacks of moderate to severe headache (HA) pain associated with other symptoms such as nausea, vomiting, photophobia, and phonophobia. Migraine attacks typically last from 4 to 72 hours if untreated or unsuccessfully treated. People with migraine may experience an aura prior to the onset of their headache.

2.1.2. Epidemiology

Migraine is a highly prevalent disease, occurring in 11% to 12% of people in Europe, with higher rates among women (16% to 18%) than men (6% to 7%) (Goadsby et al. 2002). The disease is particularly common among individuals between the ages of 25 and 55 years. Migraine has been reported to be the second highest cause of years lived with disability, interfering significantly with occupational, educational, household, family, and social responsibilities (GBD 2017). Because of intense pain and other burdensome symptoms including photophobia, phonophobia, nausea, and vomiting (Linde and Dahlöf 2004; Ford et al. 2017), patients with migraine report extensive limitations in life activities (Leonardi et al. 2010).

People with migraine have higher lifetime rates of comorbid depression, anxiety, panic disorder, sleep disturbances, chronic pain syndromes, and suicide attempts (Buse et al. 2009; MRF 2017). They are also at higher risk for ischaemic stroke and other cardiovascular diseases (Blumenfeld et al. 2011; Sacco and Kurth 2014).

2.1.3. Aetiology and pathogenesis

It is currently thought that migraine has a neurologic aetiology (Goadsby et al. 2002; Goadsby 2009; Amin et al. 2013). The brains of patients with migraine are characterised by a generalised neuronal hyperexcitability, evidenced by increased response to visual, sensory, auditory, and nociceptive stimuli, and migraine attacks involve release of neurotransmitters and activation of pain pathways, including the trigeminal nerve (Xavier et al. 2017; Dodick 2018). 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.

The calcitonin gene-related peptide (CGRP) is a neuropeptide that modulates nociceptive signalling and causes vasodilation that has been associated with migraine pathophysiology.

2.1.4. Clinical presentation, diagnosis

Standard diagnostic criteria are based the International Classification of Headache Disorders (ICHD-3 beta version). They have been developed by the Headache Classification Committee of the International Headache Society (IHS).

Migraine without aura (1.1) is described as recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the HA are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia. For a firm diagnosis to be established, the patient has to present with at least five attacks, that fulfil a list of respective criteria. As opposed to episodic forms of migraine, chronic migraine (Code 1.3) requires headache to occur on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month.

2.1.5. Management

A Guideline on Clinical Investigation of Medicinal Products for the Treatment of Migraine was released by the EMA in 2007. Further guidance is obtained from the International Headache Society that issued two guidance documents for preventive treatment of migraine attacks: The first one for preventive treatment in CM patients (Tassorelli et al, 2018) and the second one for preventive treatment in EM patients (Diener HC et al. 2020).

Currently approved preventive treatment options include anticonvulsant topiramate (e.g., Topamax), ß-blockers like metoprolol or propranolol, Botox, CGRP antagonist biologics (Aimovig, Ajovy, and Emgality), and most recently, another orally administered CGRP antagonist (rimegepant, Vydura), which has been approved for preventive treatment of EM in adults. Botox (botulinum toxin type A from Clostridium botulinum) is indicated in the EU for prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine). Preventive treatment of CM with Botox requires multiple bilateral intramuscular injections divided across 7 specific head and neck muscle areas, with a recommended retreatment schedule of every 12 weeks. All three antibodies (ABs) are indicated in the EU for prophylaxis of migraine in adults who have at least 4 migraine days per month.

Although forming the mainstay of current preventive migraine therapy, these options are not optimal for many patients due to limited effectiveness, poor tolerability, contraindications, and the need for dose titration over multiple visits for some medications.

Several epidemiological surveys indicate that available migraine preventive treatments are significantly underutilised in clinical practice (D'Amico et al. 2006), which supports the need for greater dialogue concerning migraine prevention between patients and physicians. Given the pharmacological profile of available per oral preventive medications (topiramate, ß-blockers), the choice of treatment should be based on the presence of comorbid and coexisting illness in order to improve compliance and minimise side effects (Silberstein 2015). However, compliance with preventive treatment remains a challenge. Low adherence to migraine prophylaxis treatment with antidepressants, antiepileptics, or beta blockers at 6 month follow-up was reported (Berger et al. 2012).

2.2. About the product

Atogepant (AGN-241689, MK-8031, L-004880174, AGP) is presented as a selective, high-affinity, orally administered, small molecule calcitonin gene-related peptide (CGRP) receptor antagonist.

Calcitonin gene-related peptide is an endogenous 37 amino acid peptide contained within pain-signalling nociceptive afferents, and is thought to play a causal role in migraine (Edvinsson 2018, Moreno-Ajona 2020). Multiple lines of clinical evidence point to a role for CGRP in migraine pathophysiology: 1) serum levels of CGRP are elevated during migraine; 2) treatment with anti-migraine drugs returns CGRP levels to normal coincident with pain relief; and 3) intravenous (IV) CGRP infusion produces lasting pain in non-migraineurs and migraineurs.

Treatment with a CGRP receptor antagonist is thought to relieve migraine by: 1) blocking CGRP-induced neurogenic vasodilation (returning dilated intracranial arteries to normal); 2) halting the cascade of CGRP-induced neurogenic inflammation (which leads to peripheral and central sensitisation); and/or 3) inhibiting the central relay of pain signals from the trigeminal nerve to the caudal trigeminal nucleus (Durham 2004).

2.3. Type of application and aspects on development

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.4. Quality aspects

Introduction

The finished product is presented as tablets containing 10 mg and 60 mg of atogepant as active substance.

Other ingredients are: polyvinylpyrrolidone/ vinyl acetate copolymer, vitamin E polyethylene glycol succinate, mannitol, microcrystalline cellulose, sodium chloride, croscarmellose sodium, colloidal silicon dioxide, sodium stearyl fumarate.

The product is available in aluminium foil and PVC/PE/PCTFE blisters.

Active substance

General information

The chemical name of atogepant is (3'*S*)-*N*-[(3*S*,5*S*,6*R*)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl]-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta [*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide hydrate corresponding to the molecular formula $C_{29}H_{23}F_6N_5O_3 \bullet H_2O$. It has a molecular weight of 621.544 g/mol as monohydrate form and the following structure:

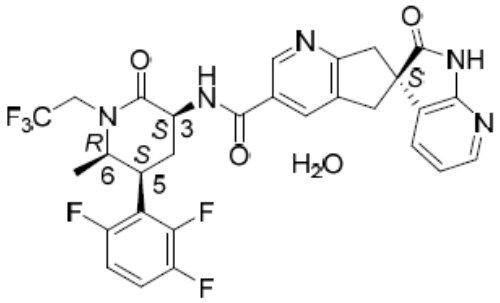


Figure 1: Active substance structure

The chemical structure of atogepant was elucidated by a combination of spectroscopic methods, including UV-VIS, Infrared spectroscopy (FT-IR), Nuclear Magnetic Resonance Spectroscopy (1H-NMR, 13C-NMR, 19F-NMR) and Mass Spectrometry (LC-MS).

The active substance appears as a white to off-white non-hygroscopic powder. Atogepant is freely soluble in Ethanol, soluble in methanol, sparingly soluble in acetone, slightly soluble in acetonitrile and insoluble in water. Its partition coefficient (LogP) was determined to be 2.4 and two pKa values were determined to be pKa1= 2.2 (pyridinium group) and pKa2= 10.2 (lactam group).

Atogepant has four chiral centres and is manufactured as a single stereoisomer. Enantiomeric purity is controlled routinely by chiral HPLC and achiral HPCL methods at intermediate stage and at release.

The solid-state properties of the active substance were determined by X-Ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC), and Thermogravimetric Analysis (TGA). XRPD results confirmed that atogepant is present in crystalline monohydrate form.

Comprehensive screening studies for polymorphs, salts, co-crystals were conducted for Atogepant. In free-base form, a monohydrate, a trihydrate, and a few solvates (ethyl acetate, chloroform, and methanol solvates) were obtained. No salt form was isolated for atogepant. The free-base monohydrate form was the more thermodynamically stable form of the two hydrates.

Manufacture, characterisation and process controls

A single manufacturer for atogepant active substance is proposed. Atogepant is synthesised in multiple steps process using two well-defined starting materials and with acceptable specifications.

The starting materials initially proposed by the applicant were re-defined as intermediates following a MO raised to achieve appropriate control of the synthesis steps. As crucial part of the synthesis, these steps were placed under GMP control. Sufficient information regarding their synthesis and relevant impurities has been provided for all of them and they are considered acceptable and are controlled by suitable specifications as requested by the CHMP.

Critical steps of the synthesis have been described and sufficient in process controls are applied. Control of critical steps comprises an updated critical process parameter study, based on which specific operational parameters are defined. The manufacturing process and the control strategy is described in sufficient detail. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Impurity limits are justified based on spike/purge studies. Absence of controls on individual impurities has been justified by results of spike/purge studies. The control strategy for residual solvents is justified; validated analytical methods are described.

Potential impurities were discussed and characterised, including organic impurities from both starting materials as well as formed during synthesis, degradation products, inorganic impurities (elemental impurities), residual solvents, and nitrosamine impurities. Information on origin/formation of impurities, their fate and control strategies was included, supported by historical ranges, and control strategies. Most of potential process-related impurities are purged during synthesis as supported by results of spike/purge studies; only the Epimer impurity is included for routine control at NMT 0.20 %, which is accepted.

The manufacturing process has evolved during the process development. The proposed manufacturing process is based on modifications of the original process. These modifications regard mainly the synthetic route for the spiroacid intermediate. As for the lactam salt intermediate and the final step, the overall synthetic steps have remained consistent. During development, minor changes have been made to reagents, solvents, and manufacturing conditions.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme.
Changes introduced have been presented in sufficient detail and have been justified.

The active substance is packaged in in double lined low-density polyethylene (LDPE) which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes appropriate tests and limits for appearance (visual), identification (IR spectroscopy), water content (Ph. Eur.), assay (HPLC-UV), related substances (HPLC-UV), residual solvents (GC-FID), specific rotation (Ph. Eur), sulfated ash (Ph. Eur).

The active substance specification is considered acceptable and has been set based on relevant guidelines and batch data. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

A second method for identification of the active substance was requested to be included to the applicant along with single-crystal XRD for confirmation of absolute stereochemistry for identification of the chiral form, in line with ICH Q6A requirements. The applicant did not include a second method for identification and the justification provided was that identity is tested by infrared (IR) spectroscopy, and since the IR test is specific, a second identification test is not needed per ICH Q6A. With respect to addition of single-crystal XRD for confirmation of absolute stereochemistry for identification of the chiral form, the control of all the chiral centres by HPLC methods either at the intermediate stage or at the final active substance stage ensures the stereochemistry of atogepant molecule. In addition, the chiral identity of the active substance is confirmed by the routine specific rotation test during release testing. Therefore, it was considered not necessary to implement a single-crystal XRD test as a routine test to confirm the stereochemistry.

A detailed risk assessment on the potential presence and formation of nitrosamines during synthesis is provided following the recommendations of EMA/CHMP/428592/2019 Rev.1. The risk assessment includes the syntheses of re-defined starting material, all raw materials, equipment, process water and packaging materials, as well as potential cross-contamination. Though secondary and/or tertiary amines are present several synthesis stages, the risk of formation of nitrosamines is concluded low as no

nitrosating/oxidating reagents are present at any stage. An updated genotoxic risk assessment is provided for impurities introduced by the re-defined starting materials, other raw materials, synthesis intermediates, and synthesis by-products. The evaluation was performed according to ICH M7 using two complementary statistical models. As for ICH M7 Class 1-3 impurities, the proposed Option 4 quality control strategy has been completed by new data on the required purge considering the TTC for lifetime use, and the calculated purge ratio. This approach is acceptable for impurities for which purge ratios with sufficient reliability were obtained. For several compounds with borderline purge ratio values, analytical results generated with commercial batches are provided, which confirmed the theoretical calculations. All values were found below 30 % of the PDE resp. acceptable limit based on the TTC. The Option 4 approach for these borderline compounds has been justified.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 17 batches of varying batch size, including toxicological, clinical and stability batches, was provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three primary commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package in a container closure system representative of that intended for the market for up to 48 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

A supportive batch was monitored on stability for 36 months at long term conditions (25ºC / 60% RH) and 6 months at accelerated conditions (40ºC / 75% RH). Three additional supportive batches using the proposed commercial manufacturing process were monitored on stability for up to 60 months at 25ºC / 60% RH and 6 months at 40ºC / 75% RH.

The following parameters were tested*:* appearance, assay, related substances, water content, specific rotation, x-ray powder diffraction, water activity, microbial enumeration test. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. A post-approval stability protocol was provided to continue on-going stability studies for the primary batches through the re-test period. Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Photostability testing following the ICH guideline Q1B was performed on a primary stability batch. No significant degradation was observed; the results support the conclusion that the active substance does not need protection from light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months in the proposed container without specific storage conditions.

Finished medicinal product

Description of the product and pharmaceutical development

The finished medicinal product is an immediate release oral tablet, presented in two strengths, containing 10 mg atogepant and 60 mg atogepant, respectively. The 10 mg strength is presented as a white to off-white, round biconvex tablet with "A" and "10" debossed on one side. The 60 mg strength is presented as white to off-white, oval biconvex tablet with "A60" debossed on one side.

Formulation development

The formulation development for Atogepant IR oral tablets has been systematically and extensively addressed.

The choice and function of each excipient has been presented. Compatibility with the AS has been investigated and drove the selection of excipients. The formulation was amenable to manufacture via hot melt extrusion and direct compression. The finished product quality attributes were consistently met.

Atogepant is categorised as a Biopharmaceutics Classification System (BCS) II molecule. The poor aqueous solubility of atogepant presented a great challenge for the development of conventional solid oral tablet formulations with desired immediate release attributes. Several oral formulations (both solution and tablet formulations) were explored. Formulation development studies were conducted to select the appropriate excipients. The focus was to achieve immediate release tablets with excellent physical-chemical stability. Several experiments were conducted to understand the effect of polymers, surfactant levels, extrudate particle size distribution and disintegrants on finished product dissolution.

The objective of the pharmaceutical development of the finished product was to produce a stable dosage form of atogepant of consistent quality containing 10mg or 60mg of atogepant.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, with exception of vitamin E polyethylene glycol succinate which meets USP/NF quality standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The formulation used during clinical studies is the same as that intended for marketing.

The history of formulations used for clinical studies and the compositions of the various formulations used during development were presented and found acceptable. PK studies and in vitro studies informed formulation optimisation. Based on these studies the commercial formulation was determined

Dissolution method development

The development of the QC dissolution method has been sufficiently described. The proposed method is a compendial method (Ph. Eur. 2.9.3) using Apparatus 2 (Paddle) at 75 rpm rotation speed in 0.1 HCl. Specificity, accuracy, linearity, range, precision, robustness and sample solution stability were demonstrated.

The discriminatory power of the dissolution method has been demonstrated.

Information was requested through a raised MO for the dissolution limit set in the specifications. The specification limits for the dissolution testing was revised following the MO. The acceptance criterion for in-vitro dissolution at release was set to NLT Q 85 % after 15 minutes to suitably reflect the

discriminatory power of the in-vitro dissolution method, in compliance with the dissolution method development report supplied.

Manufacturing process development

The finished product manufacturing process was designed to consistently produce finished product meeting the criteria of the target product profile and finished product quality attributes of appearance, content uniformity, assay, impurities/degradation products, active substance polymorphic form, intermediate and finished product physical and chemical stability, identity and dissolution.
The manufacture of the proposed finished product consists of four main steps: pre-blending, hot melt extrusion (HME) and milling, final blending and tablet compression.

The manufacturing process development studies were conducted to identify the key process parameter set points for unit operations including pre-blending, hot melt extrusion, milling, blending with extra-granular excipients and tablet compression. The focus was to achieve intermediates with acceptable blend uniformity, content uniformity, extrudate particle size distribution and finished tablets with immediate release properties, acceptable physical appearance and mechanical strength.

A control strategy with the aim to mitigate risks during finished product manufacture was established, investigating e.g. the impact of raw materials and different machine settings in every single process step on the finished product CQAs, resulting in stipulating process parameter ranges for the commercial drug manufacture. Risk categorisation along with respective justification are provided for the drug manufacturing steps extrusion, extrudate milling and tablet compression.

In summary, the pharmaceutical development is sufficiently discussed. The primary packaging is aluminium foil and PVC/PE/PCTFE blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Critical steps of the manufacturing process have been defined and are appropriately controlled. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Due to the hot-melt extrusion step, the manufacturing process was considered non-standard during assessment. Thus, process validation data of production scale batches were requested and a validation report has been submitted.

Based on validation data provided, the overall conclusion was that the manufacturing process implemented at the intended finished product manufacturing site is regarded as capable of consistently producing the proposed finished product meeting the predefined specifications.

Product specification

The finished product release and shelf-life specifications include appropriate tests and limits for physical appearance (visual), identification (HPLC-UV), assay (HPLC-UV), content uniformity (HPLC-UV), degradation products (HPLC-UV), dissolution (Ph. Eur.), water content (Ph. Eur.), microbial enumeration test (Ph. Eur.), test for specified microorganisms (Ph. Eur.).

The specifications are in accordance with ICH Q6A. Sufficient information on control of the finished product has been provided. The parameter specification for the dissolution testing has been revised appropriately during the procedure.

Possible degradation products have been discussed with regard to the impurity profile of the active substance. The possible degradation pathway of the finished product as well as on the test performed on elemental impurities have been sufficiently described. The mutagenicity of impurities with reference to the finished product has been sufficiently addressed.

The applicant has provided a risk assessment for elemental impurities. Batch analysis data on four representative batches of atogepant bulk tablets and six primary stability samples using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of the finished product has been presented.

The finished product is released on the market a) based on the above release specifications, through traditional final product release testing.

Batch analysis results are provided for three primary stability batches, three phase 3 clinical batches and two supportive batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three pilot scale batches for the 10 mg strength and from three commercial scale batches for the 60 mg strength of finished product stored for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Also supportive stability data of Phase 3 clinical batches packaged in bottles have been presented. The batches of the medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for physical appearance, assay, degradation products, dissolution, microbial enumeration tests, water content, water activity, photostability study. The analytical procedures used are stability indicating. No significant changes have been observed. The observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

In addition, 1 batch per strength (10 mg and 60mg) was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Productsto determine the effect of light exposure on the product and to demonstrate that adequate packaging has been implemented to protect the

product from photo damage. Results for appearance, assay, degradation products and dissolution remained practically unchanged. Based on the results, atogepant tablets are considered inherently photo stable in the proposed packaging under normal use conditions.

Thermal cycling study was performed for the finished product. The packaged tablets were exposed to three complete cycles of low and high temperature conditions. All test results are comparable to those of the controls and were within specifications. No adverse effects on the product quality were observed as a result of the exposure to the low and high temperature cycling conditions. Based on available stability data, the proposed shelf-life of 36 months without any special storage conditions as stated in the SmPC (section 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The major objection (MO) raised during the procedure regarding the selection of the starting materials for the active substance synthesis and the nitrosamine impurities risk assessment have been resolved by provision of the requested data and information.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

Recommendations for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical testing strategy was developed to support the proposed indication. In support of the atogepant investigation in human subjects, a series of non-clinical pharmacology, pharmacokinetic, and toxicology studies have been conducted.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro

In *in vitro* binding experiments, atogepant shows high affinity to the native and recombinant human CGRP receptor (K_i 16 - 26 pM). However, there are marked interspecies differences. Whereas atogepant shows also high affinity to the rhesus monkey CGRP receptor (K_i 9 pM), affinity to the mice, rat and rabbit CGRP receptor is considerably lower (Ki values of 130, 700 and 2100 pM, respectively).

In *in vitro* functional studies, it could be shown that atogepant is an inhibitor of αCGRP-induced cAMP response in HEK293 cells, expressing the human or rhesus monkey CGRP receptor, with an IC_{50} of 30 and 50 pM, respectively.

In isolated coronary, meningeal and cerebral artery segments, atogepant inhibited the vasodilatory effect of αCGRP. In contrary to the triptan zolmitriptan, atogepant had no own vasoconstrictive effects. However, whereas in distal coronary artery segments the inhibitory effect of atogepant was apparently competitive in nature (right shift of the αCGRP dose response curve, no decrease in maximal effect) with a pK_b of 9.4 to 8.4, in middle meningeal and cerebral artery segments, atogepant antagonised the αCGRP effect apparently in a non-competitive manner (reduction of αCGRP´s E_{max}, without affecting its potency).
These results suggest that the vasodilatory effects of CGRP in distal coronary artery segments on one and on middle meningeal and cerebral artery segments on the other hand are mediated by different receptors and that more than one receptor type is involved in the antagonistic effects of atogepant (see "Discussion on non-clinical aspects").

In vivo

A specific animal model for the evaluation of prophylactic effects of atogepant on migraine was not provided by the applicant. As a surrogate pharmacological parameter for clinical efficacy of atogepant in the prophylaxis of migraine, inhibition of capsaicin-induced dermal vasodilatation (CIDV), an effect considered to be mediated largely by release of CGRP, was used by the applicant.

Species-differences are obvious for functional activity of atogepant *in vivo*. CIDV in the forearm of rhesus monkeys was inhibited by atogepant in a concentration-dependent manner with an IC_{50} of about 1 nM. In a CIDV assay in rats, a plasma concentration of 3.7 µM resulted in 47% inhibition of dermal blood flow (Report PD003). In a rabbit CIDV assay, a plasma concentration of 41 µM was associated with a 43% inhibition of dermal blood flow (Report PD003). For humans, an IC_{50} for inhibition of CIDV of 1.5 nM was reported (Study CGP-PK-04).

Overall, these *in vivo* studies confirm the existence of large (for the CIDV response more than 1000 fold) interspecies differences.

2.5.2.2. Secondary pharmacodynamic studies

In an *in vitro* screening assay, atogepant showed no appreciable affinity (IC_{50} > 10 µM) to a broad panel of human drug receptors and drug transporters.

However, atogepant showed antagonistic activity at the human amylin 1 and adrenomedullin 2 receptor, members of the calcitonin/CGRP receptor family, in the low (IC_{50} 2.4 nM) respectively high (IC_{50} 400 nM) nanomolar range. Since total atogepant plasma concentrations for the 60 mg clinical dose amount to

about 1.2 µM, with free (unbound) atogepant plasma concentrations of about 60 nM, affinity to these additional receptors could be of clinical relevance (see "Discussion on non-clinical aspects").

Atogepant attenuated CGRP-induced decreases in blood pressure and increases in heart rate in rhesus monkeys (IC_{50} about 1.1 nM).

In an *in vivo* PET assay with [^{11}C]atogepant in rhesus monkeys, atogepant (in plasma levels up to 229 nM) showed low (about 25%) brain CGRP receptor occupancy, suggesting that atogepant does not penetrate the blood brain barrier well (see also "Distribution").

2.5.2.3. Safety pharmacology programme

Cardiovascular / respiratory function

In vitro

In an electrophysiological evaluation on hERG channels, stably expressed in CHO-K1 cells, using standard whole-cell voltage-clamp techniques, atogepant exhibited weak hERG current inhibition (23.9% inhibition at 28 µM), which suggests that atogepant is unlikely to alter ventricular repolarisation in humans at clinically effective doses.

In vivo

Atogepant had no prominent *in vivo* effects on cardiovascular parameters in guinea pigs, rats and rhesus monkeys:
- In a rat telemetry study, there were no effects on any haemodynamic parameter after single-dose treatment with doses of 2 and 10 mg/kg.
- In an exploratory cardiovascular study in anaesthetised guinea pigs, there were no test-article related effects on HR, PR interval, QRS interval, or QT/QTcB intervals up to a cumulative dose of 6 mg/kg atogepant (plasma level 7.7 ± 1.1 µM).
- Effects of atogepant on cardiovascular and respiratory function and on body temperature were also evaluated in conscious telemetered rhesus monkeys. There were no relevant atogepant-related effects on blood pressure parameters (SBP, DBP, and MBP), HR, ECG parameters (PR, QRS, RR, and QT intervals), heart rate-corrected QT interval (QT_{ci} interval) or QT:RR interval relationship, respiratory parameters (rate and depth of respiration) and body temperature after single oral doses of 5 and 30 mg/kg or after daily oral doses of 75 mg/kg atogepant for 3 consecutive days.

Neurological function

Atogepant did not show relevant neurobehavioral effects in mice and rats:
- There were no significant effects on neurological function in conscious mice after a single oral dose of 100 mg/kg.
- There were no effects on nervous system function in rats at single doses of up to 20 mg/kg. Test article-related effects in rats treated with the high dose of 250 mg/kg were limited to decreases in mean body temperature (-1.1 °C) and a decrease in the number of line crosses and rearing activity in the open field test (1 out of 6 rats).

Abuse liability

In studies evaluating the risk for physical dependence and the reinforcing potential in rats, atogepant did not show a relevant signal for abuse liability.

Summary

Plasma levels of the high dose atogepant groups in the safety pharmacology studies usually exceeded the atogepant plasma levels observed for the 60 mg QD clinical atogepant dose. Overall, the findings of

the safety pharmacology studies with atogepant do not provide a critical safety signal for the use of atogepant for the prophylaxis of migraine in humans.

2.5.2.4. Pharmacodynamic drug interactions

Non-clinical pharmacodynamic drug interaction studies have not been included in this application.

2.5.3. Pharmacokinetics

Methods of analysis
Liquid chromatography tandem mass spectrometry (LC-MS/MS) methods were established for measurement of atogepant plasma levels in different species. [^{14}C]atogepant derived radioactivity was determined by liquid scintillation counting. Metabolite structures were determined by MS.

All analytical methods were appropriately described in full detail, no discrepancies have been spotted between the studies. The validation of the bioanalytical methods included the linearity, sensitivity, accuracy, precision, dilution, selectivity, recovery, matrix effect, carryover and reanalysis of incurred samples (ISR). The bioanalytical methods for mouse, rat, rabbit, and monkey plasma samples were successfully validated for atogepant according to testing site standard operating procedures (SOPs) and Food and Drug Administration (FDA)/ICH guidance on method validation in support of Good Laboratory Practice (GLP) studies.

Absorption
Atogepant demonstrated low clearance in rats, moderate clearance in rhesus monkeys and a short plasma half-life (about 1 to 4 hours) in both species. The oral bioavailability was about 27% in both species. The volume of distribution V_{dss} amounted to 0.9 L/kg in rats and 3.2 L/kg in rhesus monkeys.

Distribution
Tissue distribution
Following oral dosing in rats, [^{14}C]atogepant was widely distributed to tissues. Most tissues had concentrations similar to those in blood, except for central nervous system tissues, eye and bone, which had negligible concentrations. Radioactivity levels in pigmented tissues (e.g., eye uvea and skin) were similar between pigmented and albino rats, suggesting no specific association of [^{14}C]atogepant-derived radioactivity with melanin.

Plasma protein binding / Distribution in blood cells
The unbound fraction of atogepant was 4.3, 11.3, and 4.7% in rat, monkey, and human plasma, respectively. Atogepant does not show a preferential partition into red blood cells; the blood to plasma concentration ratios were 0.6, 0.9, and 0.8 in rat, monkey, and humans, respectively.

Metabolism
Following incubation with human liver microsomes and hepatocytes, two oxidative metabolites, M1 and M2 (N-oxide formation respectively 5-hydroxylation on the azaoxindole moiety) were observed. These metabolites were also observed following incubation with mouse, rat, and monkey hepatocytes.

In rat, atogepant is mainly metabolised to M1 and M2. Secondary metabolites including double and triple oxidations and several glucuronide conjugates were also detected.

In monkey, atogepant is also mainly metabolised to M1 and M2. The major circulating component was atogepant with low, but detectable levels of M1 and metabolite M23 (dioxygenated methylated glucuronide of atogepant).

In vitro reaction phenotyping experiments indicated that oxidative metabolism of atogepant in human liver preparations is predominantly CYP3A4-mediated, with a minor involvement of CYP2D6.

In humans, atogepant is susceptible to drug-drug interactions with compounds such as ketoconazole that are known to inhibit CYP3A4. Results from clinical (drug-drug interaction) DDI studies with itraconazole (CGP-PK-02) and rifampin (CGP-PK-12) confirm that atogepant is a target of DDIs with strong CYP3A4 inhibitors and inducers.

Excretion

Following IV or oral administration to bile-duct cannulated rats and monkeys, atogepant was eliminated predominately in the form of metabolites into bile. Most of the dose was recovered in excreta within 72 hours.

Table 1: Excretion of atogepant into urine, bile and feces

Species and Route, (n)	Dose (mg/kg)	Percent of Total Dose Recovered (0-72 hr)			
		Urine	Bile	Feces	Total %
Rat P.O., (n = 4)	5 mg/kg	12.6 ± 5.1	49.4 ± 4.3	27.0 ± 1.3	92.6 ± 2.5
Monkey P.O., (n = 3)	10 mg/kg	4.4 ± 1.2	45.1 ± 10	24.2 ± 1.8	73.7 ± 8.3
Rat IV, (n = 3)	2 mg/kg	9.2 ± 3.3	54.8 ± 4.1	18.4 ± 4.5	83.0 ± 1.3
Monkey IV, (n = 3)	2 mg/kg	8.4 ± 1.5	66.5	7.3	80.8 ± 3.8

P.O. = Oral; IV = Intravenous
Data presented as mean ± standard deviation

Atogepant was transferred into the milk of lactating rats at concentrations that were approximately 2-to 2.5-fold of those achieved in the maternal plasma.

Pharmacokinetic drug interactions

Inhibition of liver enzymes: Atogepant is not an inhibitor of CYP 1A2 or 3A4. Atogepant displayed weak inhibition of CYP 2B6, CYP 2C8, CYP 2C9, CYP 2D6 and CYP 2C19. Atogepant is not a potent inhibitor of MAO-A or UGT1A1.

Induction of liver enzymes: Atogepant is an inducer of CYP3A4 *in vitro*; however, "relative induction score" modeling indicated no clinically-relevant induction potential. Atogepant is not an inducer of CYP1A2 or CYP2B6.

Interaction with drug transporters

Atogepant is a substrate but not an inhibitor of P-gp and BCRP at clinically-relevant concentrations. Atogepant is not a substrate of OAT3, OCT2 or MATE1. Atogepant is a mild inhibitor of OCT1 and MATE1 but not MATE-2K at clinically-relevant concentrations. Atogepant is a substrate of hepatic uptake transporters OATP1B1, OATP1B3 and renal uptake transporter OAT1. At clinically-relevant concentrations, atogepant is not an inhibitor of OATP1B1, OATP1B3, OCT2, OAT1 and OAT3. Atogepant is unlikely to disrupt bile acid homeostasis since it showed mild inhibition of BSEP and no inhibition of MRP3, MRP4 and NTCP.

Based on *in vitro* studies and reported clinically efficacious plasma concentrations, atogepant is not anticipated to cause drug-drug interactions through CYP inhibition or induction or through drug transporter inhibition at therapeutic doses.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Dedicated single dose toxicity studies have not been included in this application.

2.5.4.2. Repeat dose toxicity

The applicant conducted a robust repeat-dose toxicity programme in 3 species (mice, rats and monkeys). All pivotal studies were GLP compliant. Duration of repeat dose toxicity studies is in line with ICH M3(R2) recommendations. There was no atogepant related mortality in repeat dose toxicity studies in mice (up to 100 mg/kg/day for 3 months), rats (up to 100 mg/kg/day for 6 months, 200 mg/kg/day for 3 months), and rhesus monkeys (up to 300 mg/kg/day for 9 months).

Main observations in the rodent (mouse, rat) studies were post-dose salivation, decreased body weight gain, reversible epithelial vacuolation in the small intestine or parathyroid gland and a slight elevation of liver ALT transaminase.

In a 3-month rat study, decreases in body weight gain (16 %, in males only) and increased vacuolation in the parathyroid gland were observed at 200 mg/kg/day. The vacuolation of epithelium of the small intestine, primarily in the jejunum at 20 and 200 mg/kg/day, was limited to the villous tip and not associated with degeneration or necrosis of the epithelial cells. There was no increase in the severity of this change in the 6-month study (with a 1-month recovery period) as compared to the findings from the 2-week study. This is consistent with the observation that the vacuolation was seen only in highly differentiated surface epithelium, which is replaced within 3 to 5 days as a result of cellular turnover in the small intestine of rats. Absence of crypt hyperplasia after 6 months of dosing further supports the assumption that the turnover is unaffected in rats with vacuolation. In addition, no neoplastic changes were observed in the intestines in the carcinogenicity studies in rats or mice. In the 6-month study. the described change was shown to be reversible after a 1-month recovery period and therefore considered by the applicant to be of minimal toxicologic significance and not adverse. Additionally, these findings were not observed in rhesus monkeys. The applicant considers that the NOAEL for atogepant in rats was 100 mg/kg/day in the 6-month study with an $AUC_{0\text{-}24hr}$ of 192.5 µM•hr, which represents an approximately 33-fold margin over the clinical exposure of about 5.75 µM•hr following 60 mg QD dosing.

There were no atogepant-related antemortem changes, gross or histomorphologic findings in the first 3-month monkey study at doses of 4, 15, and 150 mg/kg/day. In the second 3-month monkey study, at a dose of 300 mg/kg/day, designed to achieve a 50-fold margin to the clinical target dose for the migraine prophylaxis indication, very slight, focal arterial inflammation and arterial medial hypertrophy was observed in the artery of the tunica albuginea of the testes and epididymis in 1 out of 3 male monkeys. The nature of the finding in this single male monkey is considered to be incidental by the applicant. This male monkey with the findings of vascular injury had the highest exposure at the end of Week 13. The mean exposure (AUC) in this study (300 mg/kg/day) on Day 1 was higher (336 µM•hr) than the exposure at 150 mg/kg/day (206 µM•hr); however, the average exposures at the end of the study were similar between 300 mg/kg/day (110 µM•hr with vascular injury) and 150 mg/kg/day (109 µM•hr, without vascular injury). The vascular finding was not reproduced in a later 9-month monkey study with doses up to 300 mg/kg/day with 4/sex/group. In this study, there were no test article-related

antemortem changes, gross or histomorphologic findings and the mean exposure (AUC) at the 300 mg/kg/day NOAEL was 70.7 µM•hr (Week 39) which represents an approximate 12-fold margin of safety over the reported clinical exposure of about 5.75 µM•hr following 60 mg QD dosing.

In the 9-month study, systemic exposure to atogepant was independent of sex and increased with increasing dose. Mean $AUC_{0\text{-}24\ hr}$ and C_{max} values of atogepant were approximately dose proportional from 15 to 40 mg/kg/day and less than dose proportional from 40 to 300 mg/kg/day on Study Day 1 and in Study Weeks 5 and 39. In Study Week 13, mean $AUC_{0\text{-}24\ hr}$ and C_{max} values of atogepant were less than dose proportional across all dose groups.

2.5.4.3. Genotoxicity

Atogepant was negative in *in vitro* Ames tests and *in vitro* chromosome aberration assays in CHO cells. An oral *in vivo* micronucleus test was performed as part of a 2-week repeat-dose toxicity study in rats. No signs of micronucleated PCEs were observed. AUC-based safety margins for the 60 mg QD human dose were 22-fold as derived from the 250 mg/kg/day dose in the micronucleus test ($AUC_{0\text{-}24h}$ 5.75 µM•hr vs. 124 µM•hr, respectively). Taken together, atogepant is not considered to be genotoxic *in vitro* and *in vivo*.

2.5.4.4. Carcinogenicity

Atogepant was assessed for its carcinogenic potential in mice and rat 104-week carcinogenicity studies. There were no indications of carcinogenic effects nor were any preneoplastic lesions observed in either species. AUC-based safety margins in the mouse study for the 60 mg QD human dose at the high dose (M + F combined) were approximately 9-fold ($AUC_{0\text{-}t}$ 5.75 µM•hr vs. 52 µM•hr, respectively). AUC-based safety margins in the rat study for the 60 mg QD human dose as derived from the high dose at day 28 were approximately 24-fold in males ($AUC_{0\text{-}t}$ 5.75 µM•hr vs. 135 µM•hr, respectively) and 37-fold in females ($AUC_{0\text{-}t}$ 5.75 µM•hr vs. 214 µM•hr, respectively).

In the 2-year oral carcinogenicity study in mice, non-neoplastic findings attributed to atogepant were limited to minimal epithelial vacuolation in the duodenum observed in preterminally euthanised males at 75 mg/kg/day and females at 160 mg/kg/day.

Overall, based on these data, no carcinogenic risk is expected for patients.

2.5.4.5. Reproductive and developmental toxicity

A complete programme of reproductive and developmental toxicity studies has been performed with atogepant, including studies on fertility and early embryonic development in rats, on embryo-fetal development in rats and rabbits and on pre- and postnatal development in rats. The studies have been performed in accordance with the ICH S5 (R3) guideline, except for a lack of statistical analysis of the fertility and early embryonic development study and the definitive embryo-fetal developmental studies. All pivotal studies were conducted under GLP regulation. In all studies atogepant was administered orally as the free base hydrate form in 100% PEG 400. Control animals received vehicle only. Toxicokinetics of atogepant were investigated in rats and rabbits in the embryo-fetal developmental toxicity studies.

Species-specific differences in *in vitro* affinity for the CGRP-receptor have been observed, with lower affinity for the rat (K_i 0.7 nM) and rabbit (K_i 2.1 nM) compared to human (K_i 0.026 nM) and monkey (K_i 0.009 nM), which could potentially compromise the relevance of these species to human. However,

considering the lowest mean free C_{max} levels from the definitive EFD studies in rats and rabbits, the exposure is approximately 66-fold and 119-fold, respectively, above the K_i-value for CGRP-receptor affinity. Regarding the CIDV-data, the plasma concentration for 47 % inhibition of dermal blood flow in rats is similar to the mean C_{max} value obtained at the NOAEL of 15 mg/kg/day (lower mid-dose) in the EFD-study. For the rabbit, the plasma concentration to achieve 43 % inhibition in the CIDV assay (41 µM) is approximately 5-fold above the highest mean C_{max}-value from the definitive EFD study in rabbits. These data suggest that the reproduction and developmental toxicity studies in rats and rabbits are adequate to evaluate both on-target and off-target effects of atogepant, possibly with some limitations in case of the rabbit for the on-target effects based on the data of the CIDV assay.

Data from the literature suggest that CGRP and related neuropeptides may have essential roles in fetal development and control of fetoplacental/uteroplacental vascular tone as potent vasodilators and inhibition of CGRP receptor activity may be associated with impairment of uteroplacental blood flow, resulting in fetal growth retardation. The relevance of these data for the findings observed in the reproduction and developmental toxicity studies with atogepant is not known.

In the **male and female fertility and early embryonic developmental toxicity study,** rats were treated with atogepant at doses of 0 (vehicle), 5, 10, or 125 mg/kg/day. There was no test article-related reproductive toxicity at any dose level as assessed by mating performance, fertility, embryonic-fetal survival, testicular weights, and sperm number and motility. The only test article-related effect was a decrease in mean body weight gain and mean food consumption in males in the 20 and 125 mg/kg/day dose groups and in females in the 125 mg/kg/day dose group. The NOAEL for female and male fertility parameters in rats was 125 mg/kg/day. The NOAELs for general toxicity parameters were 20 mg/kg/day (females) and 5 mg/kg/day (males). Based on limited toxicokinetic data from the embryo-fetal developmental toxicity study in rats, the estimated AUC-based safety margin at the NOAEL of the male and female fertility to the maximum human exposure at the therapeutic dose of 60 mg QD (AUC: 5.75 µM*hr) is approximately 17-fold.

There were no effects of atogepant on reproductive organs in male and female animals in repeated dose toxicity studies in rats and monkeys.

In the **preliminary embryo-fetal developmental toxicity study in rats and rabbits,** atogepant-related maternal effects were limited to a decrease in maternal body weight gain and maternal food consumption in the two highest dose groups (250 and 750 mg/kg/day) in rats and in rabbits in the highest dose group (325 mg/kg/day). Also at these dose levels, developmental toxicity as evidenced by decreases in mean live fetal weight were observed in rats and rabbits.

In the **definitive GLP embryo-fetal developmental toxicity study in rats**, atogepant was administered at dose levels of 0 (vehicle), 5, 15, 125, or 750 mg/kg/day. There were atogepant-related transient decreases in maternal food consumption at ≥ 125 mg/kg/day. At these dose levels, developmental toxicity was also evident in the fetuses, including a slight decrease in mean fetal weights, a slight decrease in the mean number of ossified sacrocaudal vertebrae, and a slight increase in the incidence of fetuses with incompletely ossified skull bones, respectively. Furthermore, a dose-dependent increase in fetuses and litters with azygos vein variation at ≥ 15 mg/kg/day were observed. The NOAEL for both maternal and developmental toxicity were 15 mg/kg/day. Based on toxicokinetic data in rats, the estimated AUC-based safety margin at the NOAEL to the maximum human exposure at the therapeutic dose of 60 mg QD (AUC: 5.75 µM*hr) is approximately 4-fold.

In the **definitive GLP embryo fetal developmental toxicity study in rabbits,** atogepant was administered at dose levels of 0 (vehicle), 30, 90 or 130 mg/kg/day. There were atogepant-related decreases in maternal body weight gain and food consumption at 130 mg/kg/day. At this dose, increased incidences of litters and fetuses with visceral variations of absent caudate lobe of the lung and of skeletal sternebral variations (misaligned, misshapen or extra ossification sites above first sternebra) were

observed. The NOAEL for maternal toxicity (F0 females) and developmental toxicity (F1 litters) were 90 mg/kg/day Based on toxicokinetic data in rabbits, the estimated AUC-based safety margin at a NOAEL of 90 mg/kg/day to the maximum human exposure at the therapeutic dose of 60 mg QD (AUC: 5.75 µM*hr) is approximately 3-fold.

In the **GLP pre- and postnatal developmental toxicity study in rats,** atogepant was administered at dose levels of 0 (vehicle), 15, 45 or 125 mg/kg/day. In addition, the maternal milk and plasma (dams) concentrations of atogepant were determined. However, no toxicokinetic analysis was performed. There was no atogepant-related mortality and no evidence of maternal toxicity or effects on maternal performance in the F0 generation dams at ≤ 125 mg/kg/day, except for a slight non-significant decrease in gestation body weight gain and gestation and lactation food consumption. In the F1 generation, pre-weaning pup- and post-weaning male body weights were statistically significant lower at 125 mg/kg/day. Partly significant lower body weight gain and food consumption were also observed in post-weaning males. Analysis of atogepant milk concentrations showed that atogepant is excreted in a substantial amount into rat milk with a milk:plasma concentration ratio of 2- to 2.5-fold. The NOEL for maternal toxicity and maternal performance and the NOAEL for development of the F1 generation was 45 mg/kg/day Based on toxicokinetic data from the embryo-fetal developmental toxicity study in rats, the estimated AUC-based safety margin at the NOAEL for maternal toxicity is approximately 17-fold and at the NOEL for development of the F1 generation is approximately 5-fold to the maximum human exposure at the therapeutic dose of 60 mg QD (AUC: 5.75 µM*hr) is.

Toxicity to juvenile animals

No paediatric indication is currently proposed for atogepant. Nevertheless, potential adverse effects of atogepant on juvenile animals were investigated in rats in two oral studies, a non-GLP DRF study and a pivotal GLP study. In the DRF study, juvenile rats were treated for 2-weeks from PND 28 through PND 42 (corresponding to a child age of approximately 2-12 years) with dose levels of 0 (vehicle), 10, 30 or 150 mg/kg/day and in the pivotal 6-week study, juvenile animals received atogepant doses of 0 (vehicle), 10, 30, or 300 mg/kg/day from PND 28 through PND 71 (corresponding to a child age of approximately 2-18 years) followed by a treatment-free recovery period through PND 99 (4-weeks). Both studies included toxicokinetic investigations. Also bone assessment and neurohistopathology investigations were performed in the main study. The toxicity profile in juvenile rats was generally comparable to that in adult rats (increase in ALT, vacuolation of epithelium in small intestine, decrease in thymus weight) with the exception of bone findings in males. The findings in bone (decrease in distal femur total area, total BMX and cortical/subcortical BMC) were not considered adverse by the applicant and were associated with minimal effects on male terminal body weights.

2.5.4.6. Toxicokinetic data

Toxicokinetic data are listed alongside with the respective associated toxicity studies.

2.5.4.7. Tolerance

Not applicable.

2.5.4.8. Other toxicity studies

Immunotoxicity
The applicant has provided a weight of evidence review in accordance with ICH S8 which did not reveal any concerns.

Dependence
In studies evaluating the risk for physical dependence and the reinforcing potential in rats, atogepant did not show a relevant signal for abuse liability.

Impurities
In total about 130 starting materials, raw materials, intermediates and potential manufacturing impurities were subjected to *in silico* analysis for potential mutagenicity concerns. Overall, the toxicological assessment of potential mutagenic impurities is comprehensive and the applied methodology is in line with ICH M7(R1).

Epimer (AGN-242245) is a process-related impurity, which was present above the toxicological qualification limit of NMT 0.15%. *In silico* analyses revealed no mutagenic potential of this impurity. It was present in batches used in toxicology studies (e.g. 9-month monkey study, NOAEL 300 mg/kg/day) at levels up to 0.64%. The proposed specification limit of NMT 0.2% is thus justified from a toxicological point of view.

Several impurities with structural alerts were considered as non-mutagenic (Class 5) based on provided negative and GLP-conform Ames tests or by referencing to publicly available mutagenicity data (e.g. ECHA registration dossiers, OECD, or publications). Impurities with specific structural alerts (e.g. also present in the drug substance or known Ames negative impurities), were overruled by expert statements and classified as non-mutagenic (Class 4). These approaches are agreed. On request the *in silico* reports (DEREK, Sarah, Case Ultra) were provided.

Other studies - Phototoxicity
A 3-day phototoxicity study of atogepant in female pigmented rats with doses up to 40 mg/kg/day followed by a single ultraviolet ray exposure did not result in any skin reactions or ocular observations indicative of phototoxicity.

Other studies – Mechanistic studies: Prediction of hepatotoxic potential of atogepant
In vitro assays related to known hepatotoxicity mechanisms (bile acid transporter inhibition, oxidative stress, and mitochondrial dysfunction) were conducted with atogepant and 2 predecessor CGRP receptor antagonists that were discontinued because of clinical hepatotoxicity, telcagepant and MK-3207. Subsequently, those results were parameterised into the "DILIsym" model along with proposed clinical dose and PBPK models for each compound. Results of the "DILIsym" modeling suggest that atogepant has a reduced risk of causing clinically relevant elevations of ALT in excess of 3-fold the upper limit of normal (≥ 3X ULN) compared to telcagepant and MK-3207.

2.5.5. Ecotoxicity/environmental risk assessment

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

The calculation of the predicted environmental concentration (PEC) in Phase I for atogepant has been based on default values. The PECsurface water value exceeds the action limit of 10 ng/l. Consequently, a respective Phase II environmental risk assessment was partially performed by the applicant.

As the Koc values are less than 10000 kg/L and the Kd values are less than 3700 kg/L, Tier B terrestrial studies were not required for atogepant. The log Kow for atogepant was determined to be 3.33. Valid data on a resulting OECD 305 fish bioconcentration study were delivered. On the study on Aerobic Transformation in Aquatic Systems (OECD 308) atogepant is classified as vP as DT50 total system was 2561 d (at 12°C).

Aquatic tests on algae (OECD 201), daphnia (OECD 211), and fish (OECD 210) were acceptable. The OECD 209 Activated Sludge Respiration Inhibition Test can be accepted as now the solubility limit at pH

7 is used as NOEC. The PEC/PNEC ratios for surface water and groundwater were substantially less than one and the PEC/PNEC ratio for microorganisms was substantially less than 0.1. Thus, atogepant is unlikely to represent a risk to the aquatic compartment.

According to the study on Aerobic Transformation in Aquatic Systems (OECD 308) a strong shift of test substance to the sediment was determined. Therefore, a Phase II Tier B Sediment-Water Chironomid Toxicity Test (OECD 218) study was conducted to assess the potential impact of atogepant on sediment dwelling midges. The PEC/PNEC ratio for sediment was substantially less than one. Thus, atogepant is unlikely to represent a risk to sediment dwelling organisms and no further testing is required.

As a result of the above considerations, the API Atogepant monohydrate does not pose a risk to the environment when used according to the SmPC.

Table 2: Summary of main study results

Substance (INN/Invented Name): Atogepant					
CAS-number (if available): 1374248-81-3					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	3.33 (pH 7)			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	3.33			Pot B
	BCF (kinetic, lipid and growth corrected)	0.806 L/kg^{-1}			not B
Persistence	$DT_{50total\ system}$	2561 d (12°C)			vP
Toxicity	NOEC	550 µg/L			not T
PBT-statement:	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default	0.3	µg/L			> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{foc}soil = 270, 424, 769 K_{foc}sludge = 555, 434			List all values
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Calwich Abbey Lake: $DT_{50,\ water}$ = 20 d $DT_{50,\ whole\ system}$ = 1200 d % shifting to sediment = 49.4 (day 14) Emperor Lake $DT_{50,\ water}$ = 21 d $DT_{50,\ whole\ system}$ = 555 d % shifting to sediment = 38.6 (day 14)			at 20°C
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test,*Raphidocelissubcapitata*	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,*Pimephalespromelas*	OECD 210	NOEC	1600	µg/L	Survival, egg hatch, weight, length
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	5190	µg/L	Respiration
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	0.806 L/kg^{-1}	L/kg	%lipids:
Sediment dwelling organism *Chironomus riparius*	OECD 218	NOEC	4322	mg/kg	emergence and development rate, correction to 10% organic carbon

2.5.6. Discussion on non-clinical aspects

Pharmacology

Primary and secondary pharmacodynamics

A specific animal model for the evaluation of prophylactic effects of atogepant on migraine was not provided by the applicant. As a surrogate pharmacological parameter for clinical efficacy of atogepant, inhibition of capsaicin-induced dermal vasodilatation (CIDV), an effect considered to be mediated largely by release of CGRP, was used by the applicant.

In isolated coronary, meningeal and cerebral artery segments, atogepant inhibited the vasodilatory effect of αCGRP. However, while in distal coronary artery segments the inhibitory effect of atogepant was apparently competitive in nature, in middle meningeal and cerebral artery segments, atogepant antagonised the αCGRP effect apparently in a non-competitive manner.

These results suggest that more than one receptor type is involved in the observed antagonistic effects of atogepant and that the vasodilatory effects of CGRP on distal coronary artery segments and on middle meningeal and cerebral artery segments are mediated via different receptors.

In conclusion, 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 (≥ 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 respectively 2.4 nM) could be of clinical relevance. However, the precise mechanism of atogepant in the prophylaxis of migraine remains to be established.

Safety pharmacology

Plasma levels of the high dose atogepant groups in the safety pharmacology studies usually exceeded atogepant plasma levels observed for the 60 mg QD clinical atogepant dose. Overall, the findings of the safety pharmacology studies with atogepant do not provide a critical safety signal for the use of atogepant for the prophylaxis of migraine in humans.

Pharmacodynamic drug interactions

Non-clinical pharmacodynamic drug interaction studies have not been included in this application. This is considered acceptable, since a non-clinical pharmacodynamic model for evaluation of prevention of migraine is not available. Potential pharmacodynamic interactions from concomitant use of atogepant with other gepants or with CGRP antibodies, used for acute treatment of migraine, were discussed on the clinical level (see Clinical Aspects).

Pharmacokinetics

The ADME data submitted for rat and rhesus monkey provide supporting evidence for the use of these species in the atogepant toxicity studies.

Based on *in vitro* studies and clinically efficacious plasma concentrations, atogepant is not anticipated to cause drug-drug interactions through CYP inhibition or induction or through drug transporter inhibition at therapeutic doses.

Toxicity

Overall, the non-clinical toxicology programme is largely in line with the recommendations of the ICH M3(R2) guideline. However, the following points are specifically addressed:

Single dose toxicity

Dedicated single dose toxicity studies have not been performed with atogepant. However, in accordance with the "Questions and answers on the withdrawal of the Note for guidance on single dose toxicity" (EMA/CHMP/SWP/81714/2010) this is considered acceptable, since relevant information on acute toxicity of atogepant can be obtained from the available repeat dose toxicity studies.

Repeat dose toxicity

In accordance with ICH M3(R2) recommendations, the applicant conducted oral repeat-toxicity studies for up to 3 months in mice, up to 6 months (with a 1-month recovery period) in rats and up to 9 months in rhesus monkeys. In addition, information on chronic toxicity of atogepant is available from the 2-year carcinogenicity studies in mice and rats (see below).

In the pivotal repeat dose toxicity studies, at the NOAEL, AUC-based exposure multiples of >1 compared with the clinical exposure at the 60 mg QD dose were observed (see "Estimation of safety margins for atogepant", below).

Main observations in the rodent (mouse, rat) studies were post-dose salivation, decreased body weight gain, reversible epithelial vacuolation in the small intestine or parathyroid gland and a slight elevation of liver ALT transaminase.

In the 9-month rhesus monkey study, no relevant atogepant-related toxicity was observed up to the highest tested dose of 300 mg/kg/day.

Overall, the repeat dose toxicity studies do not indicate a critical safety signal for the use of atogepant for the prophylaxis of migraine in humans.

Genotoxicity

Based on the submitted data, atogepant is not considered to be genotoxic *in vitro* and *in vivo*.

Carcinogenicity

Based on the data from the 2-year oral carcinogenicity studies with atogepant in mice and rats, no carcinogenic risk is expected for patients.

In the mouse study, non-neoplastic findings attributed to atogepant were limited to minimal epithelial vacuolation in the duodenum observed in preterminally euthanised males at 75 mg/kg/day and females at 160 mg/kg/day.

Reproductive and developmental toxicity

A complete programme of reproductive and developmental toxicity studies has been performed with atogepant, including studies on fertility and early embryonic development in rats, on embryo-fetal development in rats and rabbits and on pre- and postnatal development in rats. The studies have been performed in accordance with the ICH S5 (R3) guideline, except for a lack of statistical analysis of the fertility and early embryonic development study and the definitive embryo-fetal developmental studies.

Species-specific differences in *in vitro* affinity for the CGRP-receptor have been observed, with lower affinity for the rat (Ki, 0.7 nM) and rabbit (Ki, 2.1 nM) compared to human (Ki, 0.026 nM) and monkey (Ki, 0.009 nM), which could potentially compromise the relevance of these species to human. However, plasma C_{max}-levels in the rat and rabbit reproduction and developmental toxicity studies are well above the respective K_i-value for CGRP-receptor affinity, suggesting adequacy for evaluation of on- and off-target effects in these species.

Data from the literature, discussed by the applicant, suggest that CGRP and related neuropeptides may have essential roles in fetal development and control of fetoplacental/uteroplacental vascular tone as potent vasodilators and antagonism of CGRP receptor activity may be associated with impairment of uteroplacental blood low, resulting in fetal growth retardation. The relevance of these data for the findings observed in the reproduction and developmental toxicity studies with atogepant is unknown.

In the definitive embryo-fetal developmental toxicity studies in rats and rabbits some findings were observed with an unclear relation to treatment. In rats, a dose-dependent increase in resorptions and post-implantation loss at ≥ 125 mg/kg/day and of fetuses and litters with azygos vein variation at ≥ 15 mg/kg/day were observed. In rabbits, increased incidences of litters and fetuses with visceral variations of absent caudate lobe of the lung and of skeletal sternebral variations (misaligned, misshapen or extra ossification sites above first sternebra) were observed at 130 mg/kg/day. Whereas in rats the increase in resorptions and postimplantation losses are likely incidental, for the azygos vein variation a relation to treatment cannot be excluded for the highest dose group, since the incidence was above the historical control. Nevertheless, this has no great impact on the overall risk assessment and on the NOAEL, which is already set at a dose level of 15 mg/kg/day for developmental toxicity of the F1 litters. However, it was included in section 5.3 of the SmPC.

Also, for the increased incidences of litters and fetuses with visceral variations of absent caudate lobe of the lung and of skeletal sternebral variations (misaligned, misshapen or extra ossification sites above first sternebra) observed in rabbits an association with atogepant treatment cannot be excluded since the incidences were above the historical control. The NOAEL for developmental toxicity of the F1 litters should be lowered to 90 mg/kg/day.

For the pre-postnatal study in rats, in the F1 generation pre-weaning pup- and post-weaning male- body weights were statistically significantly lower at 125 mg/kg/day as well as a partly significant lower body weight gain and food consumption were also observed in post-weaning males. Analysis of atogepant milk concentrations showed that atogepant is excreted in a substantial amount into rat milk with a milk:plasma concentration ratio of 2- to 2.5-fold. Also, in the juvenile toxicity studies with atogepant in rats, an atogepant-related body weight loss, associated with further findings was observed in males. Therefore, the relevance to humans is currently not known Although the body weight loss was not considered as adverse it is mentioned in section 5.3 of the SmPC, together with the approximately 5-fold safety margin to human exposure at the MRHD based on the TK data extrapolated from the rat EFD study at the NOEL of 45 mg/kg/day,

Although no paediatric indication is currently proposed for atogepant, two juvenile animal toxicity studies in rats have been performed. The toxicity profile in juvenile rats was generally comparable to that in adult rats (increase in ALT, vacuolation of epithelium in small intestine, decrease in thymus weight) with the exception of bone findings in males.

Phototoxicity

A 3-day phototoxicity study of atogepant in female pigmented rats with doses up to 40 mg/kg/day followed by a single ultraviolet ray exposure did not result in any skin reactions or ocular observations indicative of phototoxicity.

According to the ICH S10 "Guideline on phototoxicity testing", for new active substances, in the EU a validated *in vitro* alternative method should generally be used before considering animal testing. A tiered approach could include (i) an evaluation whether a compound absorbs wavelengths between 290 and 700 nm. Absorption with a molar extinction coefficient (MEC) less than 1000 L mol^{-1} cm^{-1} is not considered to result in a photosafety concern (ii) For compounds with a MEC greater than 1000 L mol^{-1} cm^{-1}, an *in vitro* phototoxicity assay should be considered. The currently most widely used *in vitro* assay for phototoxicity is the "*In vitro* 3T3 Neutral Red Uptake Phototoxicity Test" (3T3 NRU-PT) for which a guideline is available (OECD Test No. 432).

However, the ICH S10 guideline also clearly spells out, that in cases, where an *in vivo* animal phototoxicity study has already been conducted, there is no reason to subsequently conduct an *in vitro* phototoxicity assay. In conclusion, for atogepant no additional non-clinical *in vitro* phototoxicty testing is requested.

Estimation of safety margins for atogepant

Marked interspecies difference in the *in vitro* affinity for the CGRP receptor exist with the rat (Ki, 0.7 nM), mouse (Ki, 0.13 nM), and rabbit (Ki, 2.1 nM) having lower affinity for the CGRP receptor than monkey (Ki, 0.009 nM) and human (Ki, 0.026 nM). Despite this, pharmacologically relevant plasma levels were likely achieved in the rat and rabbit studies as supported by the CIDV assay (a biomarker for peripheral target activity of CGRP) and the fact that plasma levels measured in safety pharmacology and toxicology studies were significantly greater than respective K_i values in these species. Although CIDV data in the mouse are not available, a pharmacologically relevant exposure was likely achieved in mouse safety assessment studies, as the affinity of atogepant for the mouse CGRP receptor is higher than for the rat one. The high-dose (i.e., 300 mg/kg/day) exposure achieved in the monkey 9-month study resulted in a C_{max} (on Day 1) that exceeded the EC_{50} in the monkey CIDV assay (1 nM) by more than 10,000-fold. Thus, the rat, mouse, rabbit, and monkey studies are considered to provide an appropriate toxicity evaluation for both on- and off-target related toxicity.

The exposure multiples achieved in the pivotal toxicology studies are shown below.

Table 3: Margins of safety for atogepant

Study	**Doses (mg/kg)**	**NOAEL**	**Margin (AUC)[a]**
6 Month Rat	10, 30, 100	100	33x
9 Month Monkey	15, 40, 300	300	12x
Embryofetal Development Rat	5, 15, 125, 750	15 (developmental)	4x
Embryofetal Development Rabbit	30, 90, 130	130 (developmental)	8x
Fertility Rat	5, 20, 125	125	17x[b]
Pre/postnatal Development Rat	15, 45, 125	125	17x[b]
Carcinogenicity Mouse	M: 5, 20, 75 F: 5, 30, 160	75 160	9x

Carcinogenicity Rat	M: 10, 20, 100 F: 25, 65, 200	100 200	24x/37x

[a] Exposure multiples based on AUC at a 60 mg QD dose (AGN Clinical Study CGP-PK-02)

[b] Exposure data from GLP Embryo-fetal Development study at 125 mg/kg/day

2.5.7. Conclusion on the non-clinical aspects

The submitted non-clinical data are considered sufficient to support the marketing approval of atogepant for the prophylaxis of migraine.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 4: Phase 1 PK studies in healthy subjects

Study ID	
MK-8031 P001	Single ascending dose study in healthy young male subjects investigating (Part I) safety and PK of atogepant 1, 2.5, 5, 10, 20, 40, and 50 mg; and (Part II) PD of atogepant 0.4, 2.5 or 30 mg (provided as AIB, for on-site oral solution formulation)
MK-8031 P002	Single and multiple ascending dose study in healthy young males investigating safety, PK and PD of atogepant Part I: Single doses of 40 mg, 100 mg, 170 mg, or 200 mg spray dried OCT, or placebo. Part II: Multiple doses of atogepant 50, 100, or 170 mg once daily or 30 mg twice daily (SD-OCT) or placebo
MK-8031 P004	A 28-day multiple dose PK study with repeated once daily doses of 170 mg atogepant to evaluate safety, tolerability, and PK
CGP-PK-03	Mass balance study with single oral dose of 50 mg [14C]-atogepant (~200 µCi) to determine the absorption, distribution, metabolism and excretion profile of atogepant in healthy male subjects

Table 5: Phase 1 PK studies investigating intrinsic factors

Study ID	
MK-8031 P003	A single dose study to evaluate the safety, tolerability, and PK of 40 mg atogepant in elderly subjects

3101-101-002	A randomized, double-blind, placebo-controlled study to evaluate the PK, safety, and tolerability of 10 mg, 30 mg, and 60 mg once daily, and 60 mg twice daily atogepant in healthy Japanese and Caucasian subjects
3101-104-002	A single-centre, open-label, pharmacokinetic study of atogepant in adult healthy Chinese participants
CGP-PK-01	An open-label, single dose study to evaluate safety and PK of 60 mg atogepant in patients with impaired hepatic function and subjects with normal hepatic function

Table 6: Phase 1 studies investigating extrinsic factors and PD

Study ID	
CGP-PK-02	Phase 1, drug-drug interaction study to assess the effect of co-administration of strong CYP3A4 inhibitor itraconazole on the PK of 60 mg atogepant
CGP-PK-12	Phase 1, drug-drug interaction study to assess the effect of strong OATP inhibitor (single dose rifampin) and CYP3A4 inducer (600 mg rifampin once daily for 5 days) on the PK of 60 mg atogepant
CGP-PK-14	An open-label, multiple-dose, 2-cohort, drug-drug interaction study between atogepantand topiramate in healthy participants
3101-103-002	A study to evaluate the effects of quinidine gluconate, a P-gp inhibitor, on single dose pharmacokinetics of 60 mg atogepant in healthy adult subjects
MK-8031 P005	A Phase 1 drug-drug interaction study to assess the potential interaction between 60 mg atogepant and oral contraceptives. A majority of migraine patients are young women, who are likely to be taking oral contraceptives. Therefore, this study was conducted to determine whether concomitant administration of atogepant and oral contraceptives could lead to a PK interaction
MK-8031 P008	An explorative biocomparison study to evaluate the bioavailability of different PMF formulations of 60 mg atogepant in healthy volunteers (Included famotidine DDI)
3101-102-002	A Phase 1, drug-drug interaction study to evaluate the effect of the co-administration of the proton pump inhibitor esomeprazole on the oral bioavailability and PK parameters of 60 mg atogepant
CGP-PK-13	A Phase 1, drug-drug interaction study to evaluate the effect of concomitant use of sumatriptan, the most commonly used triptan for the treatment of headaches and migraines, and 60 mg atogepant
CGP-PK-06	A Phase 1, drug-drug interaction study to evaluate the effect of concomitant use of the NSAID naproxen, and acetaminophen, both commonly used for the treatment of headaches and migraines, and 60 mg atogepant
3101-106-002	A Phase 1b, open-label, fixed-sequence, safety, tolerability and drug-drug interaction study between atogepant and ubrogepant in participants with a history of migraine
3101-105-002	A single dose study investigating the effects of a high fat meal on the oral bioavailability of atogepant 60 mg IR tablet formulation

CGP-PK-04	A single dose study to evaluate the effects of a supratherapeutic dose of 300 mg atogepant on cardiac repolarisation (QTcF)

Table 7: Description of phase II/III clinical efficacy and safety study – dose-finding, supportive

Study ID/ No. of Centers[a]/ Locations/ Duration	Study Status FPFV LPLV Randomized Actual/ Planned	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objectives	No. of Subjects by Arm Randomized/ Completed[b]	Sex M/F Median Age (Min, Max)[c]	Diagnosis Inclusion Criteria	Primary Endpoints
CGP-MD-01/ 80/ US/ 12 weeks of double-blind treatment	Completed 06 Sep 2016[d] 23 April 2018[e] 834/810	Phase 2/3, randomized, double-blind, placebo controlled, parallel-group	Atogepant 10 mg QD, Atogepant 30 mg QD, Atogepant 60 mg QD, Atogepant 30 mg BID, Atogepant 60 mg BID, Placebo Orally	To evaluate the safety and tolerability of the following doses and dose regimens of atogepant (10 mg QD, 30 mg QD, 30 mg BID, 60 mg QD, and 60 mg BID) for the preventive treatment of migraine in participants with EM. To characterize the dose/response relationship across the following doses and dose regimens (10 mg QD, 30 mg QD, 30 mg BID, 60 mg QD, and 60 mg BID) for the preventive treatment of migraine in participants with EM. To prospectively test for superiority of the following doses and dose regimens of atogepant (10 mg QD, 30 mg QD, 30 mg BID, 60 mg QD, and 60 mg BID) versus placebo for the preventive treatment of migraine in participants with EM.	Atogepant 10 mg QD: 94/80 Atogepant 30 mg QD: 185/149 Atogepant 60 mg QD: 187/164 Atogepant 30 mg BID: 89/70 Atogepant 60 mg BID: 93/73 Placebo: 186/148	111/714 39 years (18, 74)	EM Adults with a history of migraine with or without aura for ≥ 1 year and who had 4-14 migraine days during the 28-day baseline period	Change from baseline in mean monthly migraine days across the 12-week treatment period

BID = twice daily; CM = chronic migraine; EM = episodic migraine; FPFV = first participant first visit; LPLV = last participant last visit; max = maximum; min = minimum; QD = once daily; US = United States

a. Number of sites that screened participants.

b. Reflects the number of participants who completed the 12-week double-blind treatment period of the study.

c. Demography is based on data from the safety population (all participants who took at least 1 dose of study drug).

d. Reflects the date the first participant enrolled.

e. Reflects the date the last participant completed.

Table 8: Description of phase III clinical efficacy and safety studies – primary

Study ID/ No. of Centers[a]/ Locations/ Duration	Study Status FPFV LPLV Randomized Actual/ Planned	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objectives	No. of Subjects by Arm Randomized/ Completed[b]	Sex M/F Median Age (Min, Max)[c]	Diagnosis Inclusion Criteria	Primary Endpoints
3101-301-002/ 136/ US/ 12 weeks of double-blind treatment	Completed 14 Dec 2018 19 June 2020 910/872	Phase 3, randomized, double-blind, placebo controlled, parallel-group	Atogepant 10 mg, Atogepant 30 mg, Atogepant 60 mg, Placebo orally QD	To evaluate the safety and tolerability of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg QD for the preventive treatment of migraine in participants with EM. To prospectively test for superiority of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg QD versus placebo for the preventive treatment of migraine in participants with EM.	Atogepant 10 mg QD: 222/193 Atogepant 30 mg QD: 230/207 Atogepant 60 mg QD: 235/204 Placebo: 223/201	101/801 41 years (18, 73)	EM Adults with a history of migraine with or without aura for ≥ 1 year and who had 4-14 migraine days during the 28-day baseline period	Change from baseline in mean monthly migraine days across the 12-week treatment period
3101-303-002/ 142/ US, Canada, China, Czech Republic, Denmark, France, Germany, Italy, Japan, Republic of Korea, Poland, Russian Federation, Spain, Sweden, Taiwan, UK/ 12 weeks of double-blind treatment	Completed 11 March 2019 20 Jan 2022 778/750	Phase 3, randomized, double-blind, placebo-controlled, parallel-group	Atogepant 30 mg BID, Atogepant 60 mg QD, Placebo orally	To evaluate the safety and tolerability of atogepant 30 mg BID and 60 mg QD for the preventive treatment of migraine in participants with CM. To prospectively test for superiority of atogepant 30 mg BID and 60 mg QD versus placebo for the preventive treatment of migraine in participants with CM.	Atogepant 30 mg BID: 257/231 Atogepant 60 mg QD: 262/233 Placebo: 259/230	96/677 43 years (18, 74)	CM Adults with a history of CM for ≥ 1 year and who had ≥ 15 headache days during the 4-week baseline period **AND** ≥ 8 days during the baseline period that qualify as being a migraine day	Change from baseline in mean monthly migraine days across the 12-week treatment period

BID = twice daily; CM = chronic migraine; EM = episodic migraine; FPFV = first participant first visit; LPLV = last participant last visit; max = maximum; min = minimum; QD = once daily; US = United States

a. Number of sites that screened participants.

b. Reflects the number of participants who completed the 12-week double-blind treatment period of the study.

c. Demography is based on data from the safety population (all participants who took at least 1 dose of study drug).

Table 9: Completed phase III long-term studies

3101-302-002	Long-term safety and tolerability	Open-label, long-term safety Adults with a history of migraine with or without aura for ≥ 1 year and who had 4-14 migraine days during the 28-day baseline period De novo participants who did not participate in any previous atogepant study and participants who completed Study CGP-MD-01	52 weeks of open-label treatment	SoC preventive migraine medication (196) Atogepant 60 mg QD (543) **Total: 739**
3101-309-002	Long-term safety and tolerability	Open-label, long-term safety Adults with a history of migraine with or without aura for ≥ 1 year and who had 4-14 migraine days during the 28-day baseline period Rollover participants who completed Study 3101-301-002	40 weeks of open-label treatment	Atogepant 60 mg QD (685) **Total: 685**

Table 10: Ongoing phase III studies

3101-304-002[b]	Efficacy and safety	Multicenter, randomized, double-blind, placebo-controlled, parallel-group Adults with a history of migraine with or without aura for ≥ 1 year and who had 4-14 migraine days during the 28-day baseline period who have failed 2 to 4 classes of oral prophylactic treatment	12 weeks of double-blind treatment	Placebo (150) Atogepant 60 mg QD (150) Total: 300 **ISS cutoff: 207**
3101-306-002	Long-term safety and tolerability	Multicenter, open-label, long-term safety extension, conducted in Japan Japanese adults who either complete Study 3101-303-002 or who are de novo	52 weeks of open-label treatment	Atogepant 60 mg QD (140) Total: at least 140 **ISS cutoff: 155**
3101-311-002	Safety and tolerability	Multicenter, open-label, safety extension conducted in China Chinese adults who complete Study 3101-303-002	12 weeks of open-label treatment	Atogepant 60 mg QD (120) Total: 120 **ISS cutoff: 3**
3101-312-002	Long-term safety and tolerability	Multicenter, open-label, long-term safety extension Adults who complete either Study 3101-303-002 or Study 3101-304-002	104 weeks of open-label treatment	Atogepant 60 mg QD (670) Total: 670 **ISS cutoff: 286**

BID = twice daily; CM = chronic migraine; QD = once daily; SoC = standard-of-care

a. Atogepant 60 mg BID was studied in only 91 participants in Study CGP-MD-01.

b. Study 3101-304-002 is ongoing and blinded; therefore, data from this study are not included in the analysis sets (see Section 2.7.4.1.1.2).

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

Atogepant drug substance is categorised as a BCS II molecule. The poor aqueous solubility of atogepant drug substance presented a great challenge for the development of conventional solid oral tablet formulations with desired immediate release attributes. The formulation evolution through different clinical stages was as follows.

Initially, to support the first-in-human SAD Phase 1 study (Study MK-8031 P001), an oral solution formulation with atogepant was developed.

Later, solid oral dosage formulations were explored in Phase 1 clinical studies.

The HME-OCT formulation was used for all Phase 2 and Phase 3 clinical studies and is the to-be-marketed tablet formulation.

Early SAD using an oral solution

A Single-Dose Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of MK-8031 (Study MK-8031 P001)

In Part I of early SAD study P001 single doses of 1, 2.5, 5, 10, 20, 40, and 50 mg (on-site solution formulation) and placebo were administered in healthy, young male subjects. Subjects were assigned to 1 of 2 alternating panels (A or B) consisting of 8 subjects each (n = 6 active, n = 2 placebo per dose level). Subjects received alternating single rising oral doses of AGP or placebo in up to 5 treatment periods (Periods 1 through 5). There was a minimum 7-day washout between treatment periods for any given subject. All doses were administered after an overnight fast.

Following oral administration of single doses of atogepant (solution; 1 to 50 mg dose), atogepant was absorbed rapidly with median Tmax values ranging from 1 to 2 hours post-dose. The plasma profile declined generally bi-exponentially post-Cmax. Approximately 90% of the total AUC was contained in the first 24 hours.

An exploratory analysis of dose proportionality over the dose range 1-mg to 50-mg was conducted. Estimates and 95% CIs [1 represents exact dose proportionality] for the slope from the power model were 1.01 (0.96, 1.05) for AUC0-∞, 0.96 (0.91, 1.01) for Cmax, 1.02 (0.97, 1.07) for C2hr, and 0.97

(0.90, 1.04) for C24hr, suggesting approximately dose proportional increases for these PK parameters over the 1-mg to 50-mg dose range.

Early tablet SD-OCT formulation

A Single and Multiple Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Atogepant (Study MK-8031 P002)

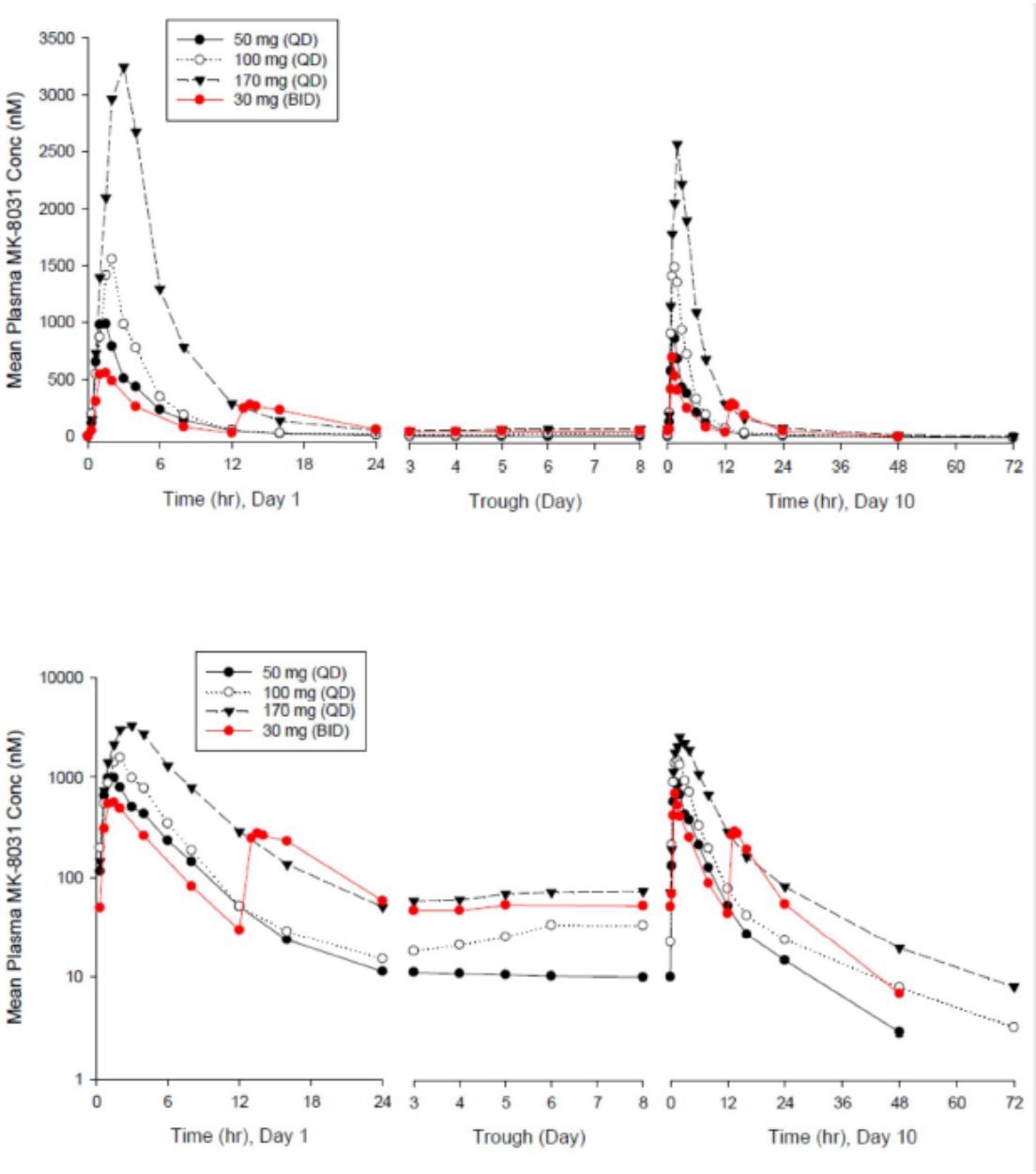
Study P002 was a 2-part study in which a SD-OCT formulation of atogepant was administered to healthy young subjects in a single-dose extension study (Part I) and a multiple rising–dose study (Part II). In Part I, single doses of 40 mg (with and without food), 100 mg (fasted), 170 mg (fasted), and 200 mg (fasted) atogepant or placebo were administered in 5 periods to a single panel of 8 subjects (n = 6 active, n = 2 placebo at each dose level).

In Part II, multiple doses of 50 mg, 100 mg, and 170 mg atogepant or placebo were administered fasted daily for 10 days in sequential panels of 8 subjects (n = 6 active, n = 2 placebo at each dose level). One additional panel received 30 mg atogepant or placebo twice daily for 10 days. Blood samples for assessment of plasma concentrations of atogepant were taken on Days 1 and 10 at pre-dose and 20 minutes, 40 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours post-dose. On Days 3, 4, 5, and 8, blood was collected pre-dose. Additionally, on Day 10, samples were taken at 48 and 72 hours post-dose.

Similar to the on-site solution formulation in Study P001, atogepant was absorbed rapidly after oral administration of single doses of the SD-OCT formulation from 40 to 200 mg to healthy subjects in Part I of study P002. The median Tmax values ranged from 1.0 to 1.5 hours post-dose. The plasma profile declined generally bi-exponentially post-Cmax, and the apparent terminal t1/2 appeared to be about 11 hours. The AUC0-∞ and Cmax of single doses of 40 mg atogepant OCT appeared to be about 2-fold and 3-fold higher, respectively, given as the tablet formulation compared to those observed for oral solution at 40 mg in Study MK-8031 P001. The difference appeared to be due to a higher bioavailability and a potentially faster rate of absorption for the tablet formulation compared to solution formulation.

In Part II, multiple doses of atogepant (SD-OCT) were administered once daily for 10 days in a total of 4 panels of 8 subjects each (6 active, 2 placebo). Upon review of individual concentration-time profiles at different dose levels, it appeared that most subjects reached steady state by Day 3. The AUC0-24h and Cmax geometric mean accumulation ratios (Day 10/Day 1) ranged from 1.16 to 0.77, demonstrating minimal accumulation, which is generally consistent with expectation based on the single-dose PK profile (bi-exponential decay with 11-hour terminal t1/2).

Figure 2: Arithmetic Mean Plasma Concentration of Atogepant vs. Time Following Administration of Multiple Oral Doses to Healthy Fasted Young Male Subjects (PK Population; MK-8031 P002 [Part II])



Top panel = linear; bottom panel = log-linear
Source: Derived from Module 5.3.3.1, MK-8031 P002 CSR, Figures 11-3 and 11-4

Comparative BA between the TBM and the early tablet formulation

An Explorative Biocomparison Study to Evaluate the Bioavailability of Different PMF Formulations (SD-OCT and HME-OCT) of Atogepant in Healthy Volunteers (Study MK-8031 P008)

Study P008 was a single-site, open-label, single-dose, randomised, 5-way crossover trial of atogepant in healthy adult subjects (N = 15, males and females). The purpose of this study was to evaluate the relative bioavailability of different premarket formulations (PMF) of atogepant, namely SD-OCT and HME-OCT, and to evaluate the effect of famotidine on the PK of atogepant. Each subject received Treatments

A to E in a randomised crossover fashion in Periods 1 to 5, with famotidine administered as described below:

- Treatment A: Single oral dose of 60 mg atogepant as one 10 mg and one 50 mg SD-OCT
- Treatment B: Single oral dose of 60 mg atogepant as 1 HME-OCT (low-compression force)
- Treatment C: Single oral dose of 60 mg atogepant as 1 HME-OCT (high-compression force)
- Treatment D: Single oral dose of 60 mg atogepant as 1 HME-OCT (low-compression force) in the presence of famotidine pre-treatment, and in the fasting state. (Famotidine treatment consisted of one dose of famotidine 20 mg in the evening on Day -1 and one dose of famotidine 20 mg in the morning of Day 1. Two hours after the morning dose on Day 1, the atogepant dose was given)
- Treatment E: Single oral dose of 10 mg atogepant as 1 HME-OCT (one compression force)

All treatments were administered in the fasting state.

Table 11: Arithmetic mean (SD) PK parameter values of atogepant following single oral dose administration of 60 mg atogepant (Phase I SD-OCT tablets) and in two test formulations (PMF low compression HME-OCT and PMF high compression HME-OCT) to healthy subjects under fasting conditions (PK population; MK-8031 P008)

Dose (mg)	AUC_{0-24h} (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)	C_{max} (ng/mL)	C_{24h} (ng/mL)	T_{max} (h) [a]	Apparent Terminal $t_{1/2}$ (h)
60 (SD-OCT) (A)	4616.8 (4713.3)	4906.5 (5153.9)	1038.0 (917.3)	20.9 (39.0)	1.50 (1.00-2.00)	10.2 (9.22)
60 (Low compression, HME-OCT) (B)	4327.1 (3796.0)	4568.5 (4140.0)	1019.9 (736.3)	16.4 (24.9)	1.50 (0.67-2.00)	8.02 (3.72)
60 (High compression, HME-OCT) (C)	4266.7 (3258.9)	4502.1 (3542.5)	959.6 (580.0)	16.1 (20.5)	1.50 (0.67-2.00)	8.98 (8.02)
GMR (90% CI) Low compression HME-OCT/SD-OCT	1.00 (0.86, 1.17)	0.99 (0.85, 1.16)	1.07 (0.85, 1.34)	0.92 (0.78, 1.09)	NA	NA
GMR (90% CI) High compression HME-OCT/SD-OCT	1.03 (0.88, 1.21)	1.03 (0.88, 1.20)	1.05 (0.83, 1.33)	1.01 (0.85, 1.21)	NA	NA

[a] Median (minimum – maximum)

NA = Not applicable

Source: Module 5.3.1.2, MK-8031 P008 CSR, Table 11-1

Study P008 is important to the overall PK development, since it is intended to deliver comparative BA data between the SD-OCT and the HME-OCT tablet formulation, and thereby to build the bridge to previous PK study P002. At the same time, a low-compression force version of the tablet is tested vs a high-compression force version.

The extent and rate of absorption were similar between the SD-OCT tablet and the HME-OCT tablet formulation. Indeed, GMRs were close to 1. Formally, however, study P008 did not demonstrate bioequivalence between the formulations, since the upper limit of general 80-125% criteria for the 90%CIs was exceeded for Cmax (GMR Cmax high compression: 1.05 [0.83, 1.33], GMR Cmax low compression:1.07 [0.85, 1.34]).

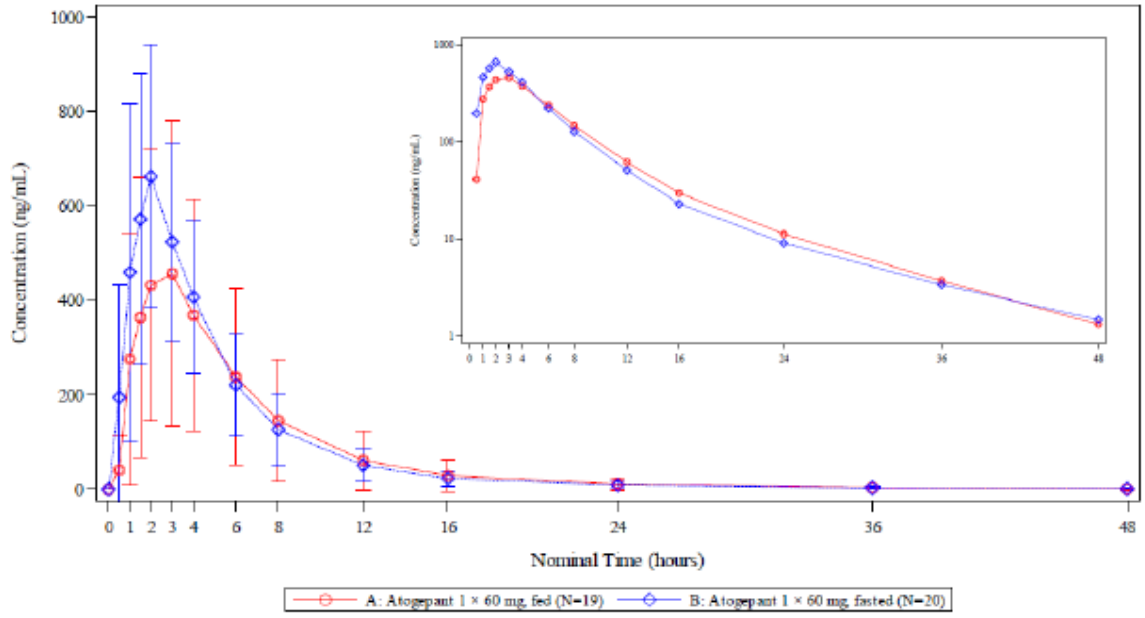
Median Tmax was 1.5 hours after Phase 1 SD-OCT tablets and HME-OCT low- and high-compression tablet formulations.

Effect of food –HME-OCT formulation

Single-Centre, Randomised, Open-Label, Single-Dose, Two-Period Crossover Study to Evaluate the Effect of a High-Fat Meal on the Pharmacokinetics of an Immediate-Release Tablet Formulation of Atogepant (Study 3101-105-002)

In food study 105, subjects were randomly assigned to receive interventions A and B in 1 of 2 sequences, with a washout of at least 7 days between each study intervention. The 2 study interventions were: (A) single dose of 60 mg atogepant under fed conditions; (B) single dose of 60 mg atogepant under fasted conditions. Blood samples for assessment of plasma concentrations of atogepant were taken at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours post-dose.

Table 12: Arithmetic mean (SD) plasma atogepant concentration-time profiles following single dose oral administration of 60 mg atogepant under fed or fasted conditions to healthy subjects (PK population; 3101-105-002)



Inset: Mean profile, semilogarithmic scale

Table 13: Statistical comparisons of plasma atogepant PK parameters following single dose oral administration of 60 mg atogepant under fed or fasted conditions in healthy adult subjects (PK population; 3101-105-002)

	Fed (Test)		Fasted (Ref)		Ratios of GLSMs (%)		Intra-CV%		
							A	B	Inter-
Parameter (units)	N	GLSM	N	GLSM	Test/Ref	90% CIs	(Test)	(Ref)	CV%
AUC_{0-t} (h*ng/mL)[a]	19	2558.05	20	3130.99	81.70	71.57 – 93.26	23.80[a]		50.29
$AUC_{0-\infty}$ (h*ng/mL)	18	2606.55	20	3158.38	82.53	71.77 – 94.89	34.50	3.62	49.89
C_{max} (ng/mL)	19	527.40	20	677.01	77.90	64.14 – 94.62	40.75	29.73	30.32

[a] Results for AUC_{0-t} were provided from a model without the repeated statement (which allowed the variance of the response to vary across different treatments), because the model did not converge.

Mixed-effects model with natural logarithm-transformed values of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}, as the dependent variable, terms for study intervention, sequence, and period as fixed independent variables and subject nested in sequence as a random effect.

Study intervention was a single dose of 60 mg atogepant immediate-release formulation (1 × 60 mg tablet), under fed and fasted conditions.

Source: Module 5.3.1.1, 3101-105-002 CSR, Table 14.2.3 and Table 14.2.2

Since the 90% CI of the GLSM ratio was not contained within the default equivalence limits of 80.00% to 125.00% for AUC0-t, AUC0-∞, or Cmax, the high-fat meal was demonstrated to have a statistically significant effect on atogepant exposure for the IR tablet (HME-OCT) formulation. Administration under fed conditions reduced AUCs by approximately 18%, reduced Cmax by approximately 22%, and no change in median Tmax.

Distribution

Mass balance

A Study of the Mass Balance and Metabolism of [14C]-Atogepant in Healthy Male Subjects (Study CGP-PK-03)

Mass balance study PK-03 was a single-centre, open-label, single-dose study in which 6 healthy male subjects aged 19 through 55 years were enrolled.

Following a single oral dose of 50 mg (~ 200 µCi) [14C]-atogepant in healthy male subjects, the median Tmax values were 1 hour and 1.5 hours post-dose with mean terminal elimination t1/2 values of 18.46 hours and 11.64 hours for atogepant and total radioactivity, respectively. Atogepant contributed to approximately 75% of the total radioactivity systemic exposure (AUC).

Table 14: Arithmetic mean (SD) of atogepant and total radioactivity following a single oral 50 mg (~200 µCi) Dose of [14C]-atogepant in healthy male subjects (PK population; CGP-PK-03)

PK Parameter	Atogepant	Total Radioactivity	Ratio of Atogepant/Total Radioactivity
C_{max} (ng/mL or ng-Eq/mL)	367.33 (189.44)	349.31 (82.6)	1.00 (0.29)
T_{max} (h)[a]	1 (0.98 – 2.98)	1.5 (1 – 2.98)	NC
AUC_{0-t} (ng.h/mL or h*ng-Eq/mL)	2176.33 (959.97)	2711.72 (758.86)	0.78 (0.17)
$AUC_{0-\infty}$ (ng.h/mL or h*ng-Eq/mL)	2222.97 (965.55)	2967.43 (779.02)	0.73 (0.17)
$t_{1/2}$ (h)	18.46 (11.88)	11.64 (6.84)	NC
% dose excreted in urine	4.84 (1.63)	7.86 (1.83)	0.61 (0.11)

a. Median (range)
Source: Module 5.3.3.1, CGP-PK-03 CSR, Table 11-1

Approximately 8% and 81% of the radioactive dose of 14C-atogepant was recovered in urine and faeces, respectively through the last collection interval. Thereof, approximately 5% of the administered dose was recovered as parent drug (atogepant) in urine. Atogepant was the only peak detected over 1% of the radioactive dose in urine. In faeces, 42% of the dose was recovered as parent drug due to unabsorbed drug, biliary excretion, intestinal secretion, or a combination. Most of the administered radioactivity was recovered in the first 24 hours (~ 90%).

Table 15: Arithmetic Mean (SD) urinary and faecal recovery of radioactivity following a single oral 50 mg (~200 µCi) dose of [14C]-atogepant in healthy male subjects (PK population; CGP-PK-03)

Percent of Dose		
Urine	Feces	Total
7.86 ± 1.83	80.64 ± 3.35	88.50 ± 2.40

Source: Module 5.3.3.1, CGP-PK-03 CSR, Table 11-2

Special populations

Impaired renal function

In the human ADME study with ^{14}C-atogepant (Study CGP-PK-03), approximately 8% of the total administered radioactivity was recovered in urine, most radioactivity (approximately 81%) was found in the faecal samples. Thus, biliary/hepatic route of elimination is the major route of elimination of atogepant, while the renal route plays a minor role. A clinical pharmacology study to evaluate the impact of renal impairment on the PK of atogepant was not conducted, and instead, physiologically based pharmacokinetic (PBPK) modelling based on the atogepant 60 mg QD dose along the population PK approach was used to assess the impact of renal impairment.

In the covariate screening (Report CGP-MS-03), renal function (as measured by creatinine clearance in mild and moderately impaired patients) did not have a statistically significant effect on any structural PK parameter. The atogepant 10 mg QD dose is recommended in patients with severe renal impairment or end-stage renal disease (ESRD).

Impaired hepatic function

An Open-Label, Single Dose, Pharmacokinetic Study of Atogepant in Patients with Impaired Hepatic Function and Subjects with Normal Hepatic Function (Study CGP-PK-01)

Study PK-01 was a multi-centre, open-label, PK study of atogepant in 32 subjects with impaired hepatic function (8 mild, 8 moderate, 8 severe) and 8 subjects with normal hepatic function. The objective of the study was to assess the PK, safety, and tolerability profiles of atogepant in subjects with impaired hepatic function and matched healthy subjects with normal hepatic function after a single dose administration. Subjects received a single 60 mg dose of atogepant on Day 1.

Table 16: Summary of statistical analysis of plasma atogepant PK parameters following single dose oral administration of 60 mg atogepant in participants with mild, moderate, or severe hepatic impairment (test) as compared with participants with normal hepatic function (reference), PK population

Hepatic Group	PK Parameter	Geometric Least Squares Mean		Ratio of Geometric Means	90% Lower CI	90% Upper CI
		Test	Reference	Test/Reference		
Mild impairment	C_{max} (ng/mL)	586.89	538.55	108.97	72.72	163.31
	AUC_{0-t} (ng•h/mL)	3249.63	2612.14	124.40	89.78	172.38
	AUC_{0-inf} (ng•h/mL)	3273.58	2633.43	124.31	89.93	171.83
Moderate impairment	C_{max} (ng/mL)	474.85	538.55	88.17	58.83	132.14
	AUC_{0-t} (ng•h/mL)	2976.87	2612.14	113.96	82.25	157.91
	AUC_{0-inf} (ng•h/mL)	3028.57	2633.43	115.00	83.20	158.97
Severe impairment	C_{max} (ng/mL)	515.45	538.55	95.71	63.86	143.44
	AUC_{0-t} (ng•h/mL)	3601.63	2612.14	137.88	99.51	191.05
	AUC_{0-inf} (ng•h/mL)	3633.22	2633.43	137.97	99.81	190.71

Compared with subjects with normal hepatic function, the maximum plasma concentrations of atogepant were generally unchanged in subjects with mild, moderate, or severe hepatic impairment (+9%, -12%, -4% respectively). The overall extent of atogepant systemic exposures (AUC) were slightly higher (14% to 38% higher) in subjects with hepatic impairment as compared with subjects with normal hepatic function; but these changes are unlikely to be clinically relevant.

In participants with mild, moderate, or severe hepatic impairment administered a single oral dose of 60 mg atogepant, percentage of plasma protein-bound atogepant was 97.4%, 97.1%, and 95.3%, respectively, as compared with 98.2% in participants with normal hepatic function. The unbound fraction of plasma atogepant was 2.6-fold higher in severe hepatic impairment group compared to participants with normal hepatic function.

Table 17: Summary of atogepant plasma protein-binding (expressed as percent bound) in participants with mild, moderate, or severe hepatic impairment and in participants with normal hepatic function following single dose oral administration of 60 mg atogepant (PK population, CGP-PK-01)

Hepatic Group	0 hr (Predose)	2 hr
Mild-impaired (N=8)	97.03 ± 0.75	97.36 ± 0.70
Moderate-impaired (N=8)	96.60 ± 0.94	97.05 ± 0.62
Severe-impaired (N=8)	94.48 ± 1.21	95.34 ± 0.85
Normal Hepatic Function (N=8)	97.89 ± 0.54	98.21 ± 0.46

PK in elderly female vs elderly male

A Single Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-8031 in Elderly Subjects (Study MK-8031 P003)

Study P003 was a double-blind, randomised, placebo-controlled, parallel, single-dose study in healthy elderly male and elderly female subjects. Subjects were divided in 2 panels of 8 subjects each: Panel A: 8 healthy elderly female subjects (n = 6 active and 2 placebo); and Panel B: 8 healthy elderly male subjects (n = 6 active and 2 placebo). Subjects received a single oral dose of 40 mg atogepant or matching placebo in a randomised fashion.

Table 18: Arithmetic mean (SD) and statistical comparisons of plasma PK for atogepant following the administration of a single oral dose of 40 mg atogepant in healthy elderly females and males (PK population; MK-8031 P003)

	Elderly Females		Elderly Males		(Elderly Females / Elderly Males)			
Pharmacokinetic Parameter	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	GMR	90% CI	rMSE[a]	P-value
$AUC_{0-\infty}$ (ng•h/mL)	6	3246.8 (1967.4)	6	2456.2 (694.0)	1.10	(0.59, 2.05)	0.60	0.796
C_{max} (ng/mL)	6	736.3 (396.5)	6	457.5 (131.6)	1.38	(0.73, 2.60)	0.60	0.375
T_{max} (h)[b]	6	1.26 (0.67 - 2.00)	6	2.00 (1.00 - 4.00)	NC	NC	NC	NC
Apparent terminal $t_{1/2}$ (h)	6	9.97 (5.07)	6	8.31 (3.74)	NC	NC	NC	NC

P-value: P-value for the comparison elderly females vs. elderly males.

a. rMSE: Square root of the residual variance component from the ANOVA model. rMSE *100% approximates the between-subject percent coefficient of variation (%CV) on the raw scale.

b. Median (range)

Source: Module 5.3.3.3, MK-8031 P003 CSR, Table 11-1, Table 11-3

Following a single dose of 40 mg of atogepant, AUC0-∞ was 10% greater (GMR [90% CI] of 1.10 [0.59, 2.05]) and Cmax was 38% greater in elderly females than in elderly males. The median Tmax occurred earlier in elderly females (1.26 hours) than in elderly males (2.00 hours).

Pharmacokinetic interaction studies

In vivo interaction with CYP and transporter inhibitors and inducers

The following drug-drug interactions have been investigated in clinical studies:

- itraconazole (CYP3A4 and P-gp inhibitor; Study CGP-PK-02
- rifampin (potent CYP3A4 and P-gp inducer and OATP inhibitor; Study CGP-PK-12
- topiramate (mild inducer of CYP3A4)
- quinidine gluconate (P-gp inhibitor; Study 3101-103-002)

Table 19: PK parameters of atogepant following single doses of atogepant alone, and following concomitant administration of CYP3A4, P-gp or OATP inhibitors/inducers

Study	Atogepant	CYP/ P-gp/ OATP Inhibitor or Inducer	Daily Dose (timing)	N	C_{max}[a] (ng/mL)	$AUC_{0-\infty}$[a] (ng•h/mL)	GM Ratio (90% CIs)	
							C_{max}	AUC
CGP-PK-02	60 mg single dose	-	-	40	740	3470	NC	NC
		Itraconazole	200 mg, QD (7 days)	40	1580	18900	2.15 (1.95, 2.37)	5.51 (5.09, 5.96)
CGP-PK-12	60 mg single dose	-	-	31	711	3000	NC	NC
		Rifampin	600 mg single dose	31	1550	8130[b]	2.23 (1.99, 2.50)	2.85 (2.60, 3.12)
		Rifampin	600 mg QD (5 days)	31	487	1130[c]	0.70 (0.60, 0.81)	0.39 (0.35, 0.44)
CGP-PK-14	Atogepant	60 mg	Atogepant	25	626.06	3015.38[d]	NC	NC
	Atogepant + Topiramate	60 mg + 25 through 100 mg	Atogepant	21	491.38	2298.75[d]	75.8 (67.5, 85.1)	74.6 (68.7, 80.9)
	Topiramate	25 through 100 mg	Topiramate	24	7.71	76.51[d]	NC	NC
	Atogepant + Topiramate	60 mg + 200 mg	Topiramate	22	7.28	72.57[d]	93.8 (87.0, 101)	94.5 (88.1, 101)
3101-103-002	60 mg single dose	-		24	660	2902	NC	NC
		Quinidine gluconate	648 mg BID (3 days)	24	644	3527	1.04 (0.89, 1.22)	1.26 (1.11, 1.43)

a. Arithmetic Mean
b. AUC_{0-24h}
c. N = 28
NC = Not calculated
Source: Module 5.3.3.4, CGP-PK-02 CSR, Table 11-1; Module 5.3.3.4, CGP-PK-12 CSR Table 11-1, Table 11-2, Table 11-3; Module 5.3.3.4, CGP-PK-14 CSR Table 11-9, Table 11-10; Module 5.3.3.4, 3101-103-002 CSR, Table 11-1

Co-administration of atogepant with itraconazole increased atogepant Cmax by 2.15-fold and AUC by 5.5-fold. Thus, CYP3A4 inhibition by itraconazole or other strong CYP3A4 inhibitors will result in a clinically significant increase in the exposure of atogepant. The lowest dose of atogepant (10 mg) should be used with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin).

A statistically significant increase in atogepant systemic exposure (2.85-fold for AUC0-24h and 2.23-fold for Cmax) was observed following co-administration of single-dose atogepant 60 mg and single-dose rifampin 600 mg compared with administration of single-dose atogepant 60 mg alone. The increases in atogepant Cmax and AUC when co-administered with OATP inhibitors could be clinically significant and

atogepant dose adjustment is recommended. A lower dose of atogepant (10 or 30 mg) should be considered with concomitant OATP inhibitors (e.g., cyclosporine).

In vivo interaction with commonly used concomitant medications

Table 20: PK parameters following single doses of atogepant alone, and following concomitant administration of other medications commonly used in the migraine patient population

Study	Treatment	Daily Dose (timing)	Analyte	n	C_{max}[a] (ng/mL)	$AUC_{0-\infty}$[a] (ng•h/mL)	GM Ratio	
							C_{max}	AUC
MK-8031 P005	Nordette-28	0.03 mg EE/0.15 mg LNG	Ethinyl estradiol	26	75.92[b]	846.45[b]	NC	NC
	Atogepant + Nordette-28	60 mg + 0.03 mg EE/0.15 mg LNG	Ethinyl estradiol	26	68.34[b]	848.36[b]	0.90 (0.84, 0.96)	1.00 (0.96, 1.05)
	Nordette-28	0.03 mg EE/0.15 mg LNG	Levonorgestrel	26	2.95[b]	40.09[b]	NC	NC
	Atogepant + Nordette-28	60 mg + 0.03 mg EE/0.15 mg LNG	Levonorgestrel	26	3.22[b]	47.89[b]	1.09 (1.03, 1.17)	1.19 (1.13, 1.26)
	Atogepant	60 mg	Atogepant	23	1164.8	NC	NC	NC
CGP-PK-06	Atogepant	60 mg	Atogepant	37	788.10	3673.44	NC	NC
	Atogepant + Acetaminophen	60 mg + 1000 mg	Atogepant	37	761.56	4161.84	1.00 (0.90, 1.11)	1.13 (1.04, 1.22)
	Atogepant + naproxen	60 mg + 500 mg	Atogepant	38	765.26	3577.09	1.00 (0.91, 1.11)	0.99 (0.92, 1.06)
	Acetaminophen	1000 mg	Acetaminophen	39	15.82[c]	62.30[c]	NC	NC
	Atogepant + acetaminophen	60 mg + 1000 mg	Acetaminophen	38	15.04[c]	60.97[c]	0.89 (0.81, 0.97)	0.94 (0.89, 0.99)
	Naproxen	500 mg	Naproxen	36	79.86[c]	1292.47[c]	NC	NC
	Atogepant + naproxen	60 mg + 500 mg	Naproxen	38	74.52[c]	1268.05[c]	0.94 (0.90, 0.97)	0.98 (0.96, 1.00)
CGP-PK-13	Atogepant	60 mg	Atogepant	27	840.78	3899.30	NC	NC
	Atogepant + Sumatriptan	60 mg + 100 mg	Atogepant	27	667.72	3729.28	0.79 (0.69, 0.89)	0.95 (0.86, 1.05)
	Sumatriptan	100 mg	Sumatriptan	27	74.14	306.86	NC	NC
	Atogepant + Sumatriptan	60 mg + 100 mg	Sumatriptan	27	71.27	316.64	0.95 (0.85, 1.07)	1.02 (0.97, 1.08)
CGP-PK-14	Atogepant	60 mg	Atogepant	25	626.06	3015.38[d]	NC	NC
	Atogepant + Topiramate	60 mg + 25 through 100 mg	Atogepant	21	491.38	2298.75[d]	75.8 (67.5, 85.1)	74.6 (68.7, 80.9)
	Topiramate	25 through 100 mg	Topiramate	24	7.71	76.51[d]	NC	NC
	Topiramate + Atogepant	60 mg + 200 mg	Topiramate	22	7.28	72.57[d]	93.8 (87.0, 101)	94.5 (88.1, 101)

In vivo interaction with gastric acid reducing agents (proton pump inhibitors, H2-receptor blockers)

DDI Famotidine (Study MK-8031 P008)

Table 21: Arithmetic mean (SD) and statistical comparison of plasma PK for atogepant following a single oral dose of 60 mg atogepant PMF low compression tablet with and without famotidine pretreatment to healthy subjects under fasting conditions (PK population; MK-8031 P008)

PK Parameter	Atogepant + Famotidine N	Atogepant + Famotidine Mean (SD)	Atogepant Alone N	Atogepant Alone Mean (SD)	Atogepant + Famotidine/ Atogepant GMR (90% CI)
AUC_{0-24} (ng·h/mL)	15	3796.0 (4218.5)	15	4327.1 (3796.0)	0.78 (0.66, 0.92)
$AUC_{0-\infty}$ (ng·h/mL)	15	4043.5 (4520.2)	15	4568.5 (4140.0)	0.79 (0.67, 0.93)
C_{max} (ng/mL)	15	568.5 (523.8)	15	1019.9 (736.3)	0.51 (0.41, 0.63)
C_{24h} (ng/mL)	15	18.4 (24.7)	15	16.4 (24.9)	1.18 (1.02, 1.36)
T_{max} (h)[a]	15	1.50 (0.67 - 4.00)	15	1.50 (1.00 - 2.00)	NC
$t_{1/2}$[a] (h)	15	9.15 (3.49)	15	8.02 (3.72)	NC

a. Median (range)
Source: Module 5.3.1.2, MK-8031 P008 CSR, Table 11-2

A possible interaction of atogepant with H2 receptor blocker famotidine was examined to explore the effect of gastric pH change on atogepant's PK. Concomitant use of 60 mg atogepant (single dose) with famotidine (20 mg in the evening of Day -1 and the morning of Day 1) appeared to reduce the bioavailability of atogepant, with Cmax reduced by approximately 50%, AUC reduced by approximately 20%, and Tmax unchanged in the presence of famotidine.

DDI Esomeprazole (proton pump inhibitor, Study 3101-102-002)

Table 22: Arithmetic mean (SD) of atogepant following a single oral dose of 60 mg atogepant when administered alone or in combination with esomeprazole 40 mg in healthy subjects (atogepant PK population; 3101-102-002)

PK Parameter, Unit	Atogepant Alone	Atogepant + Esomeprazole	GMR (%) of Atogepant + Esomeprazole/Atogepant Alone (90% CI)
C_{max}, ng/mL	792 (368)	594 (230)	76.63 (68.19 – 86.11)
AUC_{0-t}, ng•h/mL	3810 (1590)	3410 (1200)	91.61 (83.67 – 100.29)
$AUC_{0-\infty}$, ng•h/mL	3830 (1600)	3450 (1220)	92.04 (84.12 – 100.71)
T_{max}, h[a]	1.51 (1.00, 4.03)	3.00 (1.01, 6.03)	NC
$t_{1/2}$, h	8.48 (2.45)	9.80 (3.51)	NC
V_z/F, L	218 (101)	270 (132)	NC
CL/F, L/h	18.4 (7.8)	19.6 (7.1)	NC

N = 29
a. Median (range)
Source: Module 5.3.3.4, Study 3101-102-002 CSR, Table 11-1, Table 11-2

Concomitant use of 60 mg atogepant (single dose) with esomeprazole (multiple doses of 40 mg once daily for 5 days) appeared to reduce the rate of absorption (23% reduced Cmax, increased Tmax), but not the extent of absorption (AUC).

Modelling and Simulation

Three different PopPK models were developed using nonlinear mixed effects modelling during clinical development.

Firstly, a popPK (2016) was used to describe data from five phase 1 studies (n=99) through a two-compartment-model with first order absorption and linear elimination. As covariates, formulation on ka and Freal was used as well as dose on ka, famotidine treatment on Frel and gender on CL. This analysis has limited value due to the small sample size.

Secondly, (2019) more data was available for model development from nine phase 1 studies and one phase 2/3 study CGP-MD-01 (n=631). The final model describing these data best was a three-compartment model with linear elimination. Typical CL and V were estimated to be 18.2 L/h and 73 L, respectively. IIV was included on CL, ka, and intercompartmental CL. Dose had a significant influence on ka (lower with increasing dose level) and on Frel (higher with increasing dose level). Furthermore, the different drug formulations added complexity to model the absorption phase.

This model was evaluated using GOF checks and VPCs and this evaluation showed an appropriate fit of the model. This model was further used to test different efficacy models (see Dose-Response Modelling 2.2.3) and was used to simulate exposure in children aged six to less than 18 years of age.

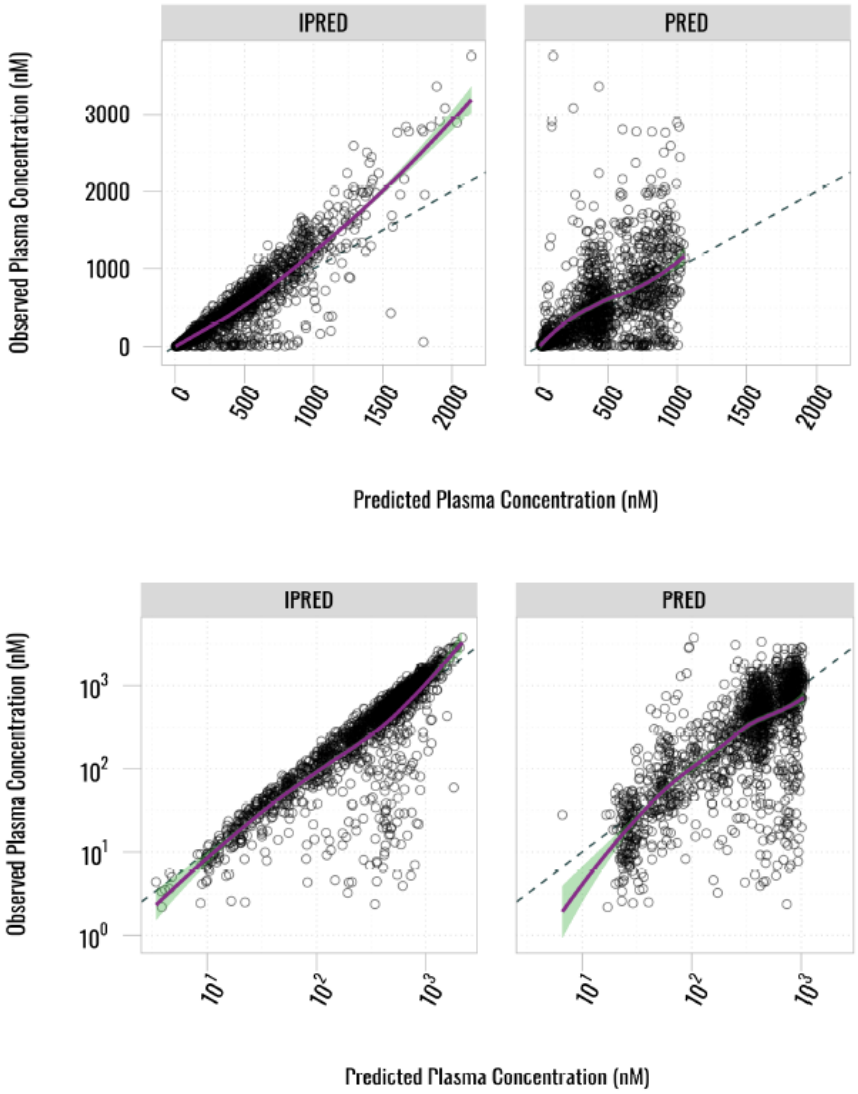
Thirdly, in 2020 phase 3 data from study 3101-301-002 was added to the dataset (n=1287 in total) resulting in 11766 observations combining HV data and patient data. Typical apparent clearance was 23.7% lower in patients (17.4 L/h) compared to healthy volunteers (22.9 L/h). Typical apparent volume of distribution was estimated as 86.1 L. IPREDs in GOF plots revealed a tendency to underprediction. Parameter estimates for the final PopPK model are listed below. GOF plots and VPCs are shown in Figure 3.

Table 23: Parameter estimates final PopPK model (Run 61) - all studies

Alias	Estimate	Relative SE (%)	95% CI
Apparent clearance healthy volunteers [CL/F (L·h^{-1})]	22.9	2.4	(21.8 - 23.9)
Duration zero-order absorption [Tk_0 (h)]	0.908	4.7	(0.824 - 0.992)
Apparent central volume of distribution [V_1/F (L)]	86.1	2.3	(82.2 - 89.9)
Intercompartmental rapid clearance [Q/F (L·h^{-1})]	1.43	10	(1.15 - 1.71)
Apparent rapid peripheral volume of distribution [V_2/F (L)]	40.5	7.3	(34.7 - 46.3)
Intercompartmental slow clearance [Q_2/F (L·h^{-1})]	1.68	7.4	(1.44 - 1.93)
Apparent slow peripheral volume of distribution [V_3/F (L)]	13.0	11.9	(9.96 - 16.0)
Zero-order lag time [ALAG$_0$ (h)]	0.276	0.5	(0.273 - 0.279)
Fraction zero-order absorption (F$_{k0}$)	0.693	2.9	(0.654 - 0.732)
Blood-plasma ratio	0.573	2	(0.550 - 0.596)
Itraconazole effect on apparent clearance	-0.662	0.6	(-0.669 - -0.654)
Rifampin effect on apparent clearance after first dose	-0.128	14.2	(-0.164 - -0.0924)
Rifampin effect on apparent clearance following multiple doses	0.818	3.9	(0.756 - 0.881)
Quinidine effect on apparent clearance	-0.285	3.4	(-0.305 - -0.266)
Itraconazole effect on relative bioavailability	0.949	11.4	(0.737 - 1.16)
Rifampin effect on relative bioavailability following multiple doses	-0.248	15.7	(-0.325 - -0.172)
Rifampin effect on relative bioavailability after first dose	1.42	11	(1.12 - 1.73)
Effect of severe hepatic impairment on apparent clearance	-0.366	19	(-0.503 - -0.230)
Food effect on lag-time	0.672	2.1	(0.644 - 0.699)
Exponential dose effect on relative bioavailability	0.119	11.2	(0.0928 - 0.145)
Formulation effect on zero-order absorption	-0.353	22.3	(-0.507 - -0.198)
Exponential weight effect on apparent central volume of distribution	0.411	11.7	(0.317 - 0.505)
Exponential dose effect on zero-order absorption	0.199	9	(0.164 - 0.234)
Apparent clearance patients [CL$_{pat}$/F (L·h^{-1})]	17.4	2	(16.8 - 18.1)
$\omega^2_{CL/F}$	0.0243	9.9	(0.0196 - 0.0290)
ω^2_{tk0}	0.163	5.8	(0.144 - 0.182)
ω^2_{Frel}	0.234	5	(0.211 - 0.257)
$\omega^2_{IOVFrel}$	0.0373	3.5	(0.0347 - 0.0399)
$\omega^2_{Q2/F}$	0.471	17.1	(0.313 - 0.629)
$Cov_{Q2,V3}$	0.422	14.6	(0.301 - 0.543)
$\omega^2_{V3/F}$	0.601	14.5	(0.430 - 0.772)
σ_{prop}	0.307	0.5	(0.304 - 0.310)
σ_{prop} (Study CGP-PK-02)	0.228	1.4	(0.222 - 0.235)
σ_{prop} (Study CGP-MD-01)	0.585	3.1	(0.550 - 0.620)
σ_{prop} (Study 3101-301-002)	0.491	2	(0.472 - 0.510)

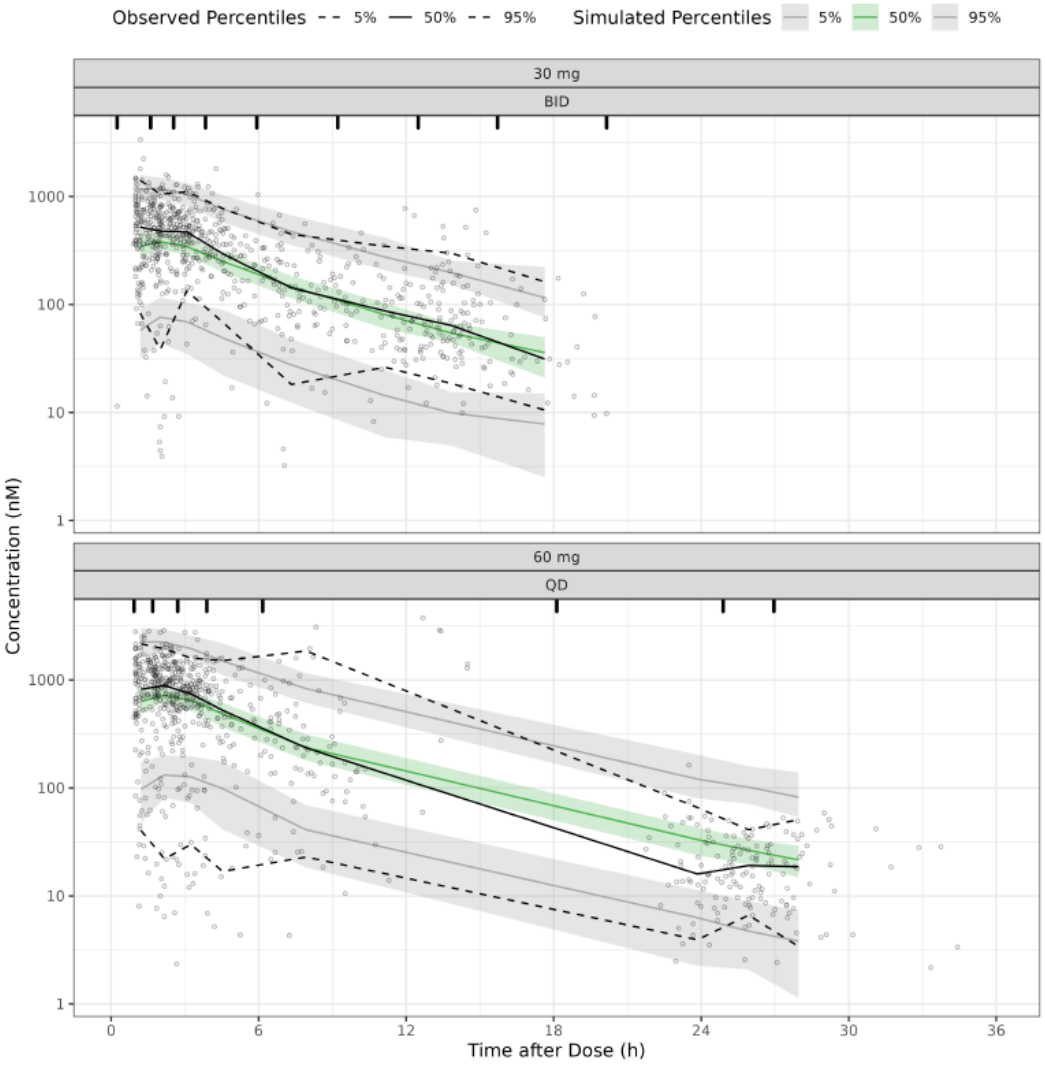
ω^2_X: variance of the IIV of parameter X, covariance $\omega^2_X\omega^2_Y$: covariance of the IIV of parameters X and Y, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$.

Figure 3: Observations (DV) versus Population and Individual Predictions



PRED: Population Predictions. **IPRED:** Individual Predictions. **Magenta line:** Loess smooth (95% CI) **Black line:** line of identity. Upper panel depicts observed and predicted concentrations on the normal scale whereas the lower plots show log-log concentrations

Figure 4: Visual Predictive Checks by Dosing Regimen



Circles: Observations, **Solid black line**: Median of the observed atogepant concentrations, **Solid green line**: Median of the simulated atogepant concentrations **Dashed Lines**: 2.5^{th} and 97.5^{th} percentiles of the observed atogepant concentrations, **Shaded Area**: The shaded areas indicate the 95% CI around the median (green area), and 2.5^{th} and 97.5^{th} percentiles of the simulated concentrations (gray areas).

This model was further used to develop a dose-response model as an exposure response model showed no clear relationship between exposure and response. The effect of two migraine days less per month compared to placebo was supported through efficacy simulation, but no clear atogepant dose- or exposure-response relationship was observed.

A combined PBPK model analysis for CYP3A4, P-gp, and BCRP was conducted using clinical data from study CGP-PK-12 (rifampicin DDI study) for development and studies 3101-101-002 (Japanese/Caucasian bridging study) and CGP-PK-02 (itraconazole DDI study) for verification. The aim was to predict plasma concentrations of atogepant after a single dose of 60 mg atogepant after dosing of a moderate CYP3A4 inhibitor, mild CYP3A4 inhibitor as well as the prediction of atogepant plasma concentrations following complete P-gp or BCRP inhibition. A first Addendum regarding PBPK modelling was submitted to predict the impact of OATP1B1/OATP1B3 and renal impairment. A second Addendum was submitted for atogepant impact as a perpetrator for OCT1, OCT2, and MATE1.

This modelling analysis was not accepted, as the platform is not qualified for the intended purpose.

In addition to that, a simplified PBPK model was presented suggesting that the AUC of atogepant is predicted to be 2.75-fold higher when co-administered with a moderate CYP3A4 inhibitor. This increase would be larger than predicted using the combined PBPK model. The applicant discussed whether dose adjustments are needed based on the generally expected increase in the AUC as atogepant appears to be a sensitive CYP3A4 substrate.

The platform for the combined PBPK model approach is not qualified, simulation results are not accepted. Therefore, results derived by PBPK modelling were removed from the SmPC. No additional analyses for BCRP were submitted. PBPK modelling is regarded as not sufficiently qualified to predict BCRP transporter interactions. As mentioned BRCP inhibitors were not prohibited in pivotal studies, the applicant provided the available clinical data and compare atogepant exposure in patients treated with and without BRCP inhibitor.

2.6.2.2. Pharmacodynamics

Mechanism of action

Atogepant is a potent antagonist of the human CGRP receptor. In the ligand-binding assays, atogepant exhibited very high affinity for human CGRP receptors (Ki = 15-26 pM) as well as monkey CGRP receptors (Ki = 9 pM).

Primary and Secondary pharmacology

Pharmacodynamics: Inhibition of CGRP-induced vasodilation

A Single-Dose Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Atogepant (Study MK-8031 P001)

This was a 2-Part study. Part II of Study P001 was a 4-period crossover study in 16 healthy male subjects who each received single oral doses of 0.4, 2.5, and 30 mg of atogepant (on-site formulation) and placebo, with PD assessments of the inhibition of Capsaicin-induced Dermal Vasodilation (CIDV).

Concomitant with dosing of atogepant or placebo, subjects received 2 single topical doses (300 µg/20 µL and 1000 µg/20 µL) of capsaicin solution (in ethanol/polysorbate 20/water [3:3:4]) at 2 time points via 10-mm rubber 'O' rings on the volar surface of each forearm (a total of 4 capsaicin applications). Capsaicin applications on each arm were timed so that the maximal blood flow response coincided with appropriate timepoints relative to the PK profile of atogepant (i.e., 0.5 and 4.5 hours). Laser Doppler scans of the subjects' forearms were conducted at baseline, 1 hour, and 5 hours as a measure of blood flow. Blood samples were also drawn at 1 hour and 5 hours to obtain plasma PK of atogepant.

Mean perfusion decreased in dose-dependent fashion compared with placebo following single dose administration of atogepant, both at 1 and 5 hours post-dose, regardless for the capsaicin concentration applied.

Evaluation of the Effects of a Single Supra-Therapeutic Dose of Atogepant on Cardiac Repolarisation in Healthy Participants (Study CGP-PK-04)

Part A of this study was designed to establish the safety, tolerability, and PK profile of a supra-therapeutic dose (300 mg) of atogepant, in order to determine whether this supra-therapeutic dose could be safely evaluated in Part B. The study design for Part B was designed to assess the effects of a supra-therapeutic dose of atogepant (300mg) on cardiac repolarisation.

Mean change-from-baseline QTcF (ΔQTcF) on atogepant followed closely the placebo pattern and did not suggest an effect on cardiac repolarisation. After a single, oral dose of 300 mg atogepant, the LS mean point estimate and upper 2-sided 90% CIs for the LS mean difference between atogepant and placebo QTcF intervals were lower than the 10-msec threshold at all timepoints. A maximum change in mean ΔΔQTcF of +0.6 msec was noted after 300 mg atogepant treatment at 24 hours postdose.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

A comprehensive PK study programme was provided to delineate the PK profile of atogepant (AGP) 10 and 60 mg tablets subject of the present MAA. During the clinical pharmacology programme, validated HPLC-MS/MS methods were used to determine the concentrations of atogepant and co-administered drugs in human plasma, whole blood (as measured using dry blood spot assay), and urine (as applicable in individual studies). In general, the bioanalytical methods are acceptable. The poor aqueous solubility of atogepant drug substance presented a great challenge for the development of conventional solid oral tablet formulations with desired immediate release (IR) attributes. Therefore, an oral solution formulation with atogepant dissolved in PEG 400, and/or water was developed for the initial first-in-human SAD study P001. Two bioavailability enhancing formulations were developed: an intermediate SD-OCT formulation and the HME-OCT proposed for commercialisation.

First-in-human study P001 demonstrated rapid absorption of AGP following single ascending doses of AGP, administered as on site solution, across the 1 mg to 50 mg dose range. Repetitive dosing of 5 mg in Periods 2 and 5 yielded reasonably similar blood levels pointing to a rather low intra-subject variability. Both the rate and extent of absorption increased in a dose dependent way. Exploratory data point to approximate dose proportionality, although the dataset is too limited for definite conclusion.

Early PK study P002 examined the bioavailability of single ascending doses of AGP using the intermediate spray-dried OCT tablet formulation (Part I). Higher doses between 40 mg and 200 mg were applied as compared to previous PK study P001. Inter-study comparison with study P001 (testing the oral solution) points to increased availability for the newly developed tablet. After SD administration of 40 mg AGP about 3-fold higher AUC values were observed with the spray-dried tablet formulation. Absorption was rapid with Tmax values of 1 -1.5 hrs and elimination was similar (elimination half-life of 9-11 hrs) across the 40-200 mg high dose range. About linear increases in the rate and extent of absorption were observed across the 40 mg to 170 mg range, while AUC and Cmax appeared to reach a plateau when the dose was further increased to 200 mg. Absolute bioavailability of atogepant was not determined.

Although (only) the intermediate SD-OCT tablet formulation was used in the multiple dose Part II of study P002, it is considered to contribute valuable information for the once-daily dose regimen pursued during the subsequent clinical development. Compatible with the elimination half-life of about 9-11 hrs found after single dose administration, no clinically relevant accumulation was observed after once daily doses of 50 mg, 100 mg, and 170 mg over 10 days. This is reflected by GMR comparison of AUC and Cmax between Day 1 and Day 10, and also by trough concentration levels observed pre-dose on intermediate Days 3, 4, 5, and 8. Pre-dose blood concentrations reach about plateau values after about third once-daily dosing. Apart from testing once daily dosing, study P002 also contained a dose arm with 30 mg twice daily dosing over 10 days. C24 hrs trough values after 30 mg BID dosing were remarkably high, higher than after 100 mg once daily dosing and almost reaching the level of the 170 mg once daily regime. The clinical significance of this overall less fluctuating plasma concentration profile following a twice daily dosing regimen was not clear at this stage. The 30 mg BID dose arm was taken over into phase II/III dose finding study CGP-MD-01.

Study P008 is important to the overall PK development, since it is intended to deliver comparative BA data between the SD-OCT and the HME-OCT tablet formulation, and thereby to build the bridge to previous PK study P002. The extent and rate of absorption were similar between the SD-OCT tablet and the HME-OCT tablet formulation. Indeed, GMRs were close to 1. Formally, however, study P008 did not demonstrate bioequivalence between the formulations, since the upper limit of general 80-125% criteria for the 90%CIs was exceeded for Cmax (GMR Cmax high compression: 1.05 [0.83, 1.33], GMR Cmax low compression 1.07 [0.85, 1.34]). It is reminded that comparative BA study P008 was exploratory and was not powered to demonstrate BE. Failure to formally conclude BE does not invalidate the transfer of data obtained for the intermediate SD-OCT formulation from study P002. Multiple dose study P002 yielded baseline information on AGP's PK profile after multiple once daily dosing over 10 days in terms of accumulation and elimination half-life. These data are considered meaningful to inform dosing regimens tested in subsequent dose finding study CGP-MD-01.

Food study 105 was conducted after finalisation of phase II/III dose finding study CGP-MD-01 and examined the 60 mg single dose of atogepant, ultimately proposed as regular daily dose in the SmPC. Ingestion of a standardised high-fat, high-calorie meal reduced AUC by about 18% and Cmax of atogepant by about 22%. Hence, a statistically significant food effect was observed. However, the time to Cmax (2 hrs) and elimination half-life (9-10 hrs) remained unaffected by the fed vs fasted condition. Section 4.2 of the SmPC specifies that /../ *is to be taken once daily orally with or without food*. This is acceptable given the fact that in pivotal trials 301 and 303, expanding over a 12-week outpatient DBT period, no restrictions were specified with regard to AGP administration in the fed resp. fasted state. Participants were merely instructed to take their study intervention at approximately the same time each day.

Mass balance study PK-03 showed that urinary excretion plays a minor role only as an elimination pathway. After oral administration of 50 mg radiolabelled atogepant, approximately 8% of the radioactive dose was recovered in urine. About 5% of atogepant was recovered in the urine as non-metabolised parent drug. The majority of the radioactivity (about 81%) was recovered in the faeces. A considerable portion of the 50 mg oral dose appears not to have been absorbed. About 42% of the administered dose was recovered in the faeces as parent compound. This finding may go along with the classification of atogepant as low soluble BCS class II drug. Data on expected absolute bioavailability in the relevant clinical dose range were not provided, however, respective data are requested. The metabolites of 14C-atogepant in plasma, urine, and faeces were profiled and characterised. At least 11 metabolites were detected in faeces and each represented < 10% of the radioactive dose. Metabolite M23 (dioxygenated methylated glucuronide of atogepant) represented approximately 15% of radioactivity exposure (AUC) in plasma and was not a long-lasting metabolite. No other metabolite represented more than 1% of the circulating radioactivity.

The focus of multiple dose study P004 was set on tolerability, in particular, any potential influence of 28-day once daily administration of 170 mg supra-therapeutic doses of AGP on hepatic enzymes, and vital signs were monitored. As regards PK, preliminary data obtained from MD of atogepant over 10 days in study P002 are largely confirmed. Comparison of AUC and Cmax GMRs between Day 28 and Day 1 does not reveal relevant accumulation.

Taken together, it is concluded that the PK profile of atogepant was adequately characterised. Rapid absorption was observed after administration of the HME-OCT tablet formulation with median Tmax values ranging from 1 to 2 hrs. Compatible with the elimination half-life of about 10-11 hrs, no accumulation occurred upon multiple once daily dosing. About dose-proportional increases in plasma levels were observed across the therapeutic dose range. With regular once daily administration, pre-dose trough levels reach about plateau values on the third day of dosing.

Pharmacokinetics in special populations

Dedicated studies were conducted in hepatically impaired subjects, in the elderly (incl. gender-related effects), and in Japanese resp. Chinese subjects as part of AGP's global development.

The hepatic impairment study PK-01 examined the impact of various degrees of hepatic impairment after administration of a therapeutic 60 mg single dose. Compared with participants with normal hepatic function, the maximum plasma concentrations of atogepant were generally unchanged in participants with mild, moderate, or severe hepatic impairment (+9%, -12%, -4% respectively). The overall extent of atogepant systemic exposures (AUC) were slightly higher (14% to 38% higher) in participants with hepatic impairment as compared with subjects with normal hepatic function. The results of study PK-01 are adequately reflected in the SmPC, which states in section 4.2 that no dose adjustment is required in patients with mild or moderate hepatic impairment. However, the use of atogepant should be avoided in patients with severe hepatic impairment. This is to be seen in the context that the fraction of unbound atogepant is about 3-fold higher in severely impaired subjects as compared to matched controls. SmPC section 5.2 adequately informs about the increase in unbound atogepant in line with the EMA Guideline on hepatic impairment.

No dedicated study in subjects with renal impairment was conducted. Mass balance study PK-03 demonstrated that the renal route of elimination plays a minor role in the clearance of atogepant. Only 8% of the total administered radioactivity was recovered in the urine. Posology recommendations in renally impaired subjects were derived from PBPK modelling. As patients with severe renal impairment or ESRD (CLcr< 30 mL/min) have not been studied, the use of the lowest effective dose of atogepant (10 mg) is recommended in those patients, which appears plausible. Dose modifications, recommended for special populations (strong CYP3A4 inhibitors, strong OATP inhibitors, severe renal impairment), were adequately justified.

Study P003 compared the PK profile of a 40 mg single dose (fasting condition) of atogepant in a group of elderly female vs elderly male subjects. The dataset of study P003 was limited consisting of 8 subjects per group only (2 of these received placebo). Therefore, data should be interpreted with caution. However, exposure of atogepant was considerably higher in elderly women as compared to elderly men (GMRs: AUC0-∞ 1.10 [0.59, 2.05], Cmax 1.38 [0.73, 2.60]).

As concerns between-age comparisons, study P003 does not allow for direct comparison of atogepant's PK profile between non-elderly and elderly subjects, because only elderly subjects were recruited. Instead, reference was made to historical data obtained from preceding study P002. Data are compared between young and elderly male subjects after administration of a single 40 mg dose of atogepant. The dataset is very limited, the young vs elderly population is represented by only N=6 subjects, respectively. The historical data comparison points to an increased AUC in the elderly by about 40% as compared to younger male subjects. Larger size population PK analyses, however, based on > 1900 subjects per comparison, show only marginal differences in the extent and rate of atogepant absorption in relation to gender or age. The PK of atogepant in children was not studied as the product is intended for adult subjects.

Pharmacokinetic Interactions

The pharmacokinetic interaction potential of atogepant was thoroughly characterised by a number of in vivo DDI studies.

In vitro testing revealed that atogepant is metabolised primarily via CYP3A4 with a minor contribution of CYP2D6. Co-administration of atogepant with prototype strong CYP3A4 inhibitor itraconazole (DDI Study PK-02) increased atogepantCmax by 2.15-fold and AUC by 5.5-fold. Thus, CYP3A4 inhibition by itraconazole or other strong CYP3A4 inhibitors will result in a clinically significant increase in the exposure of atogepant. The posology section of the SmPC specifies that the lowest dose of atogepant (10 mg QD)

should be used with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin). The proposed 10 mg dose corresponds to 1/6 of the regular 60 mg once daily dose. Given the 5.5-fold increase in atogepant's AUC, if co-administered itraconazole, the proposed dose adaptation for concomitant use with strong CYP3A4 inhibitors appears plausible.

Transporter assays have shown in vitro that atogepant is a substrate of P-gp, BCRP, OATP1B1, OATP1B3, and OAT1. Inhibition of the AOTP1B1 transporter, which is located basolateral on hepatocyte membranes, through rifampin (DDI Study PK-12) inhibits atogepant metabolism by inhibition of its influx into the hepatocyte. As a result, atogepant blood levels increase to a clinically relevant degree (2.85-fold for AUC0-24 and 2.23-fold for Cmax). Like in the case of co-administration with strong CYP3A4 inhibitors, the recommended daily dose of atogepant is limited to 10 mg if co-administered with strong OATP inhibitors. SmCP section 5.2 adequately reflects the data obtained from study PK-12.

In DDI Study 103, an increase in atogepantCmax and AUC by approximately 4% and 25%, respectively, was observed upon co-administration with the P-gp inhibitor quinidine gluconate. Based on these results, a clinically significant PK interaction between atogepant, a P-gp substrate, and P-pg inhibitors is not expected. It appears therefore justified not to specify any dose modification for atogepant when concomitantly administered with P-pg inhibitors.

Pre-clinical in vitro dissolution testing revealed that dissolution was most rapid and complete under acid conditions (0.1 N HCl). The impact of gastric pH and the potential interaction with a pH modifying agent (famotidine) was explored within comparative BA Study P008. Indeed, a notable decrease in Cmax (GMR 0.51) and in AUC (GMR 0.78) was observed after co-administration with the antacid agent famotidine as compared to atogepant given alone.

More specific insight into pH dependency of atogepant absorption was obtained from Study 102 examining the DDI between atogepant and PPI esomeprazole. A similar decreasing effect on atogepant's plasma level was observed for esomeprazole (Cmax [GMR 0.77], AUC [GMR 0.92]). Furthermore, the observed decrease in atogepant's rate and extent of absorption is compatible with in vitro data showing pH dependency for atogepant dissolution. Nonetheless, the applicant's conclusion that the observed effect is not considered clinically relevant and does not warrant particular posology recommendations is still endorsed. Throughout the phase II/III clinical study programme evaluating 12-week DBT with once daily atogepant dosing, concomitant antacid treatment was not prohibited. More than 10% of patients participating in pivotal trials actually reported concomitant PPI use (PPI use during DBT: pivotal EM study 301: 10.8%, pivotal CM study 303: 10.1%). A subgroup analysis for the primary efficacy endpoint was provided for those subjects receiving a PPI throughout studies 301 / 303. The numerical mean reduction of MDs per month in subjects taking antacid medication and the total study population was about similar.

Migraine prevalence peaks in women during childbearing ages. A DDI study examining the potential IA between atogepant (as a potential perpetrator of drug IA) and oral contraceptives is therefore of critical importance. In DDI Study P005, Nordette-28™ was adequately chosen as a two-component OC containing a standard oestrogen (EE) and gestagen (LNG) component. As compared to a SD of the OC given alone, multiple therapeutic doses of atogeoant did not relevantly interact with either the oestrogen or gestagen component. AUC levels for LNG were slightly increased (LNG: GMR AUC: 1.19), however, this is not considered clinically relevant from a safety perspective. Continuous atogepant administration did not compromise the contraceptive effect of a standard OC.

A total of four studies was conducted to examine potential DDI when atogepant is co-administered with other commonly used migraine medications. Atogepant is proposed for migraine prevention. It is common to use acute migraine medication like e.g. acetaminophen or NSAIDs, or triptans during migraine prophylactic treatment in case of an acute migraine attack. Accordingly, throughout pivotal trials 301 (EM) and 303 (CM), concomitant use of any triptan and / or any NSAID agent was permissible.

Three of these "migraine DDI" studies concerned the use of acute migraine medications on top of regular once daily atogepant use.

In DDI Study PK-06, no clinically relevant PK interaction between acute medication like acetaminophen (1000 mg) or naproxen (500 mg) and atogepant (60 mg) was observed in either direction. Equally, DDI Study PK-13 revealed no clinically relevant PK interaction with regular once daily atogepant 60 mg doses and intermittent sumatriptan 100 mg doses.

Ubrogepant is approved for the acute treatment of migraine (labelled as 50 mg or 100 mg dose, as needed). Both atogepant and ubrogepant share the same CGRP antagonist mode of action. In case of acute migraine attacks in patients already receiving CGRP-antagonist atogepant for prevention, it may be considered intuitive to choose an acute migraine medication with a different mechanism of action, e.g. a triptan or NSAIDs. However, there is a certain likelihood that physicians could prescribe ubrogepant for the acute treatment of breakthrough migraines in patients already taking migraine preventives. In DDI study 106, plasma levels under steady state conditions of atogepant alone were compared with steady state atogepant plus intermittent additional single doses of 100 mg ubrogepant doses. Intermittent single doses of ubrogepant did not have an impact on steady state atogepant plasma levels. However, the rate and extent of absorption after single dose administration of ubrogepant were significantly increased if administered on top of regular atogepant dosing as compared to ubrogepant given alone (Cmax GMR 125.6 [105.6, 149.5], AUC GMR 118.8 [108.7, 129.8]). Given the common molecular mode of action between both agents, increased exposure of ubrogepant single doses is to be seen in the context safety in healthy subjects resp. patients after administration of supra-therapeutic doses.

In clinical practice, it might occur in severe cases that patients receive two different migraine preventive agents at the same time. Throughout pivotal study 301 (EM) the concomitant use of any medication with demonstrated efficacy in migraine prevention (incl. e.g. amitriptyline, topiramate, propranolol) was prohibited. This is necessary in order not to confound the net effect of study medication (atogepant / placebo). DDI Study PK-14 examined the combined use of atogepant and topiramate. Topiramate is an approved treatment for adults for prophylaxis of migraine headache and is a mild inducer of CYP3A4 activity. The included Cohort 1 and Cohort 2 cover both scenarios that topiramate is added to ongoing atogepant therapy (Cohort 1), and Cohort 2 reflects the inverse scenario.

Additional 60 mg once daily atogepant administration in patients already receiving maintenance topiramate (100 mg BID) for migraine prevention has no clinically relevant impact on topiramate's rate and extent of absorption under steady state conditions (Cmax,ss, AUCss). However, atogepant exposure under steady state conditions (AUCss) was considerably decreased when regular topiramate (100 mg BID) was concomitantly administered (GMR AUCss: 74.55 [68.72, 80.87]). The information provided in SmPC section 5.2 that no significant interaction between atogepant and topiramate was observed, it was not felt to fully reflect the outcome of study PK-12. It is not considered that the concomitant use of both preventive agents should be avoided. However, the change in atogepant exposure (incl. the potential mechanism, i.e. CYP3A4 induction through topiramate) was more closely reflected in the SmPC.

Taken together, a number of clinically relevant IAs were explored. These mainly relate to changes in atogepant exposure if co-administered with strong CYP3A4 inhibitors or strong inhibitors of the OATP transporter (e.g. rifampin). Both IAs are adequately labelled. No clinically relevant IA was observed between atogepant and a standard two-component (EE, LNG) oral contraceptive.

Pharmacodynamics

The Thorough QTc study CGP-PK-04 appears well conducted. Moxifloxacin was included as positive control and yielded the expected results (QTc prolongation by 5 to 10 ms). This demonstrates an appropriate sensitivity of the study. Neither visual inspection of the results nor formal statistical analysis

gave any hint that atogepant could prolong the QT interval in a relevant way. As most of the migraine patients are females, subgroup analysis by gender (ΔQTcF and ΔΔQTcF estimates incl. 90% CI per time-point) was presented.

PK Modelling

Population PK (PopPK) modelling and simulation studies were conducted at four stages in the late-stage development of atogepant for the preventive treatment of migraine. CGP-MS-01 established a preliminary PopPK model based on a pooled dataset from 5 Phase 1 studies. CGP-MS-02, CGP-MS-03 and 3101-S02-000 each consisted of a reiteration of the PopPK modelling as well as exposure-response evaluation of efficacy endpoints in the pivotal clinical studies. In addition to the four PopPK modelling studies, a PBPK modelling study (3101-S04-000) was conducted to predict the exposure of atogepant following co-administration of weak and moderate CYP3A4 inhibitors and inhibitors of P-gp and BCRP.

Modelling revealed that formulation, dose, food status, liver function, concomitant medication and body weight were each found to have a statistically significant influence on the atogepant PK. Apparent central volume of distribution was found to increase exponentially with body weight. Duration of zero-order absorption increased at higher doses and the spray dried compression tablet formulation had a 35% shorter duration compared to the hot melt extrusion oral compressed tablet (HMEOCT) formulation; relative bioavailability was estimated to increase with increasing dose level and was approximately 1.24-fold higher at the 60 mg dose compared to the 10 mg dose. In addition, administration of atogepant following a high fat meal lengthened absorption lag time from 0.28 hours to 0.46 hours. Subjects with severe hepatic impairment had a 36.6% lower apparent systemic clearance. In the exposure-response modelling, there is no clear relationship between the assessed covariates of age, baseline monthly migraine days, gender, length of migraine history, previous use of migraine preventive medication, and use of acute medication and the treatment effect. Only baseline monthly migraine days affected the reduction in monthly migraine days, resulting in a lower overall treatment effect at higher baseline values.

2.6.4. Conclusions on clinical pharmacology

A comprehensive PK study programme was provided to delineate the PK profile of atogepant (AGP) 10 and 60 mg tablets subject of the present MAA. This includes PK characterisation in heathy subjects (including exploration of a suitable tablet formulation, and mass balance), special populations (hepatic impairment and others), and a number of relevant DDI studies.

Taken together, the pharmacokinetics of atogepant were adequately characterised to substantiate the proposed once daily dosing scheme. Rapid absorption was observed after administration of the HME-OCT tablet formulation with median Tmax values ranging from 1 to 2 hrs. Compatible with the elimination half-life of about 10-11 hrs, no accumulation occurred upon multiple once daily dosing. About dose-proportional increases in plasma levels were observed across the therapeutic dose range. With regular once daily administration, pre-dose trough levels reach about plateau values on the third day of dosing.

In terms of primary pharmacology, atogepant was characterised using the standard inhibition of CGRP-induced vasodilation model. Plausible results were obtained for inhibition of capsaicin-induced vasodilation through atogepant. The Thorough QTc study did not give any hint that a supra-therapeutic dose (300 mg) of atogepant could prolong the QT interval in a relevant way.

Overall, the characterisation of atogepant's clinical pharmacology profile is adequate.

2.6.5. Clinical efficacy

Primary evidence for efficacy is derived from 2 pivotal studies, Study 3101-301-002 ("Advance" study, conducted in the US) for the preventive treatment of migraine in participants with EM and Study 3101-303-002 ("Progress" study, conducted at 142 sites in the US, Europe, Russia, Japan, Korea and others) for the preventive treatment of migraine in participants with chronic migraine (CM).Additional supportive data is provided by dose-finding Study CGP-MD-01 for the preventive treatment of migraine in EM patients.

2.6.5.1. Dose response study(ies)

Dose finding study in EM patients

A Phase 2/3, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Multiple Dosing Regimens of Oral AGN-241689 in Episodic Migraine Prevention (Study CGP-MD-01)

Does finding study CGP-MD-01 was conducted at 78 clinical centres in the US from Sep 2016 to April 2018. It was a Phase 2/3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study comparing atogepant with placebo for the preventive treatment of migraine in participants with EM. A total of 834 eligible participants were randomised (1:2:1:2:1:2 ratio) to 12 weeks of double-blind treatment with either atogepant 10 mg QD, atogepant 30 mg QD, atogepant 30 mg BID, atogepant 60 mg QD, atogepant 60 mg BID, or placebo. To maintain the blind, investigational product will be administered orally twice daily for 12 weeks to all patients.

Efficacy endpoints

Primary

- Change from baseline in mean monthly migraine days (MD) across the 12-week DBT.

Secondary

- Change from baseline in mean monthly headache days (HD) across the 12-week DBT;
- Proportion of patients with at least a 50% reduction in mean monthly migraine days across the 12-week DBT;
- Change from baseline in mean monthly acute medication use days across the 12-week DBT.

Efficacy assessments were based on information recorded by the patient. An eDiary was used daily at home to collect data on headache duration, headache characteristics, symptoms, and acute medication use, which were collectively applied to define migraine, probable migraine, and headache days.

Efficacy evaluations will be based on the modified intention-to-treat (mITT) population which excludes patients never receiving treatment or not having baseline or any post-baseline diary data. Although bias may have been introduced, as the number of patients excluded from the mITT population due to potentially treatment-related reasons is quite high for MD-01, this issue is not further pursued given the supportive character of the study.

The primary endpoint will be analysed using a mixed model for repeated measurements (MMRM) similar to the primary analysis for main studies (see below). As no estimand is defined for Study MD-01 and data are not collected following treatment discontinuation, the MMRM targets a hypothetical estimand (effect if all had adhered). Although this is of less relevance for pivotal studies, it can be acceptable for this supportive dose finding study. Furthermore, a sensitivity analysis (pattern-mixture model approach

based on the copy-reference method (Carpenter et al, 2013)) is conducted and yields similar results as the primary analysis.

The overall type I error rate for multiple comparisons across active treatment doses and the primary and secondary efficacy parameters will be adequately controlled at the 0.05 level using a graphical approach by Bretz et al (2011).

Demographics

Mean age was 40.1 years. Most patients were female (86.5%). White and Black or African American patients accounted for 76.1% and 20.4% of the safety population, respectively. Mean BMI was 30.1 kg/m^2.

Overall, 99.6% of patients in the safety population took concomitant medications during the treatment period. The most frequently used concomitant medications (≥ 20% of patients) were ibuprofen (50.8%), Thomapyrin N (also known as Excedrin Migraine: aspirin, acetaminophen, caffeine) (40.7%), paracetamol (also known as acetaminophen; 26.7%), and sumatriptan (20.5%, [triptans as a class: 35.4%]).

As regards migraine history, 50.4% of patients reported history of migraine without aura, 22.3% of patients reported migraine with aura, and 27.3% reported migraine both with and without aura. The mean duration of migraine disorder was 19.37 years. Patients reported an average of 7.4 migraine days per month and 9.5 headache days per month in the 3 months prior to screening. At screening, nearly all patients (97.6%) reported current treatment for acute migraine, the most common of which were NSAIDs (67.5%) and triptans (36.2%). Only 28.1% of patients reported previous migraine prophylactic treatment.

Disposition of subjects

A total of 834 patients were randomised into the study and 825 (98.9%) received study treatment. Overall, 82% of patients completed the 12-week treatment period, and completion rates were similar across the 6 treatment groups (range 78.5% to 87.7%). The most common reason for premature discontinuation during the treatment phase was withdrawal of consent (6.7% overall).

Efficacy results

Statistically significant higher response rates were observed for all treatment arms of atogepant compared with placebo for the primary endpoint (P1) of mean monthly migraine days across the 12-week treatment period after multiplicity adjustment. No clear dose response was evident in the P1 results.

Table 24: Change from baseline in mean monthly migraine days across the 12-week treatment period (mITT Population), Study CGP-MD-01

			Atogepant				
	Statistics	Placebo (N=178)	10 mg QD (N=92)	30 mg QD (N=182)	60 mg QD (N=177)	30 mg BID (N=79)	60 mg BID (N=87)
Baseline	Mean	7.81	7.63	7.64	7.74	7.38	7.62
	SD	2.51	2.51	2.37	2.59	2.43	2.56
	SEM	0.19	0.26	0.18	0.19	0.27	0.27
	Median	8.00	7.00	7.54	7.26	7.00	7.00
	Min, Max	4.0, 14.0	4.0, 13.5	4.0, 13.4	4.0, 16.2	4.0, 12.8	3.2, 14.0
	n	178	92	182	177	79	87
Post-baseline (Month 1-3)	Mean	4.97	3.71	3.91	4.17	3.37	3.61
	SD	3.36	3.05	3.36	3.68	2.66	3.72
	SEM	0.25	0.32	0.25	0.28	0.30	0.40
	Median	4.54	3.04	3.10	3.35	3.12	2.67
	Min, Max	0.0, 18.2	0.0, 14.0	0.0, 14.3	0.0, 17.0	0.0, 11.6	0.0, 17.8
	n	178	92	182	177	79	87
Change from baseline	Mean	-2.85	-3.93	-3.73	-3.56	-4.00	-4.01
	SD	3.42	3.16	3.44	3.43	2.75	3.77
	SEM	0.26	0.33	0.26	0.26	0.31	0.40
	Median	-2.72	-3.85	-3.73	-3.55	-4.00	-4.28
	Min, Max	-13.4, 9.2	-10.7, 5.1	-12.0, 6.6	-12.0, 7.8	-10.0, 3.1	-13.0, 6.6
	n	178	92	182	177	79	87
MMRM [a]	LS Mean (SE)	-2.85 (0.23)	-4.00 (0.32)	-3.76 (0.23)	-3.55 (0.23)	-4.23 (0.35)	-4.14 (0.33)
	95% CI	-3.30, -2.39	-4.63, -3.36	-4.21, -3.31	-4.01, -3.10	-4.92, -3.55	-4.79, -3.48
CGP vs. Placebo	LSMD (SE)		-1.15 (0.40)	-0.91 (0.33)	-0.70 (0.33)	-1.39 (0.42)	-1.29 (0.41)
	95% CI		-1.93, -0.37	-1.55, -0.27	-1.35, -0.06	-2.21, -0.56	-2.09, -0.49
	p-value		0.0039	0.0056	0.0325	0.0010	0.0016

Post-baseline (Month 1 to 3) = average of monthly migraine days across the 12-week treatment period. n = Number of participants in the mITT Population.
[a] The model includes treatment group and visit as fixed effect, the baseline value as a covariate, and treatment group by visit and baseline by visit as interaction terms, with an unstructured covariance matrix. P-values are from the test between the atogepant dose group and placebo.

Statistically significant higher response rates were observed for all treatment arms of atogepant compared with placebo for the 1st secondary endpoint (S1) of change from baseline in mean monthly headache days across the 12-week treatment period, with a similar magnitude of change in headache days across the treatment arms.

Table 25: Change from baseline in mean monthly headache days across the 12-week treatment period (mITT Population), Study CGP-MD-01

		Atogepant				
	Placebo (N=178)	10 mg QD (N=92)	30 mg QD (N=182)	60 mg QD (N=177)	30 mg BID (N=79)	60 mg BID (N=87)
Baseline						
Mean	9.07	8.89	8.74	8.86	8.71	8.80
(SD)	2.70	2.70	2.51	2.76	2.73	3.12
Post baseline (Month 1 to 3)						
Mean	6.18	4.65	4.68	5.05	4.64	4.65
(SD)	3.82	3.20	3.56	4.04	3.15	4.36
Change from Baseline						
Mean	-2.89	-4.24	-4.06	-3.81	-4.08	-4.15
(SD)	3.78	3.37	3.66	3.65	3.01	4.02
MMRM						
LS Mean (SE)	-2.93 (0.25)	-4.31 (0.35)	-4.17 (0.25)	-3.86 (0.25)	-4.23 (0.38)	-4.32 (0.36)
95% CI	-3.42, -2.43	-4.99, -3.62	-4.66, -3.68	-4.36, -3.37	-4.97, -3.48	-5.03, -3.61
CGP vs. Placebo LSMD (SE)		-1.38 (0.43)	-1.24 (0.36)	-0.94 (0.36)	-1.30 (0.46)	-1.39 (0.44)
95% CI		-2.23, -0.54	-1.94, -0.55	-1.64, -0.24	-2.20, -0.41	-2.26, -0.53
p-value		0.0014	0.0005	0.0087	0.0044	0.0017

[a] The mixed-effect model for repeated measures (MMRM) included treatment group and visit as fixed effects, the baseline value as a covariate, and treatment group by visit and baseline by visit as interaction terms, with an unstructured covariance matrix. P-values were from the test between the atogepant dose group and placebo.
Post-baseline (Month 1-3) = average of monthly headache days across the 12-week treatment period.

The proportion of patients with at least a 50% reduction in mean monthly migraine days (S2) was higher in all atogepant treatment arms than in the placebo group (odds ratios ranging from 1.42 to 2.03), and the comparison with placebo was statistically significant after multiplicity adjustment for both BID treatment arms.

Table 26: Proportion of patients with at least 50% reduction in mean monthly migraine days across the 12-week treatment period (mITT population), Study CGP-MD-01

		Atogepant				
	Placebo (N=178)	10 mg QD (N=92)	30 mg QD (N=182)	60 mg QD (N=177)	30 mg BID (N=79)	60 mg BID (N=87)
Responders, n (%)	72 (40.4)	53 (57.6)	97 (53.3)	92 (52.0)	46 (58.2)	54 (62.1)
Non-responders, n (%)	106 (59.6)	39 (42.4)	85 (46.7)	85 (48.0)	33 (41.8)	33 (37.9)
Odds Ratio vs. Placebo [a]		1.50	1.46	1.42	1.83	2.03
(95% CI)		(0.98, 2.31)	(1.02, 2.08)	(1.00, 2.03)	(1.15, 2.91)	(1.30, 3.18)
p-value		0.0617	0.0369	0.0512	0.0113	0.0019

[a] Analyses were based on generalized linear mixed model for repeated measures. The model included treatment group and visit as fixed effect, the baseline value as a covariate, and treatment group by visit and baseline by visit as interaction terms, with an unstructured covariance matrix. P-values were from the test between the atogepant dose group and placebo.

A greater reduction from baseline in mean monthly acute medication use days (S3) was observed for all atogepant treatment arms compared with placebo (LSMD range -1.11 to -1.44 compared with placebo).

Table 27: Change from baseline in mean monthly acute medication use days across the 12-week treatment period (mITT population), Study CGP-MD-01

		Atogepant				
	Placebo (N=178)	10 mg QD (N=92)	30 mg QD (N=182)	60 mg QD (N=177)	30 mg BID (N=79)	60 mg BID (N=87)
Baseline						
Mean	6.57	6.16	6.62	6.79	6.20	6.37
(SD)	3.21	3.31	3.04	3.27	3.26	3.41
Post baseline (Month 1 to 3)						
Mean	4.18	2.65	2.73	3.16	2.61	2.88
(SD)	3.57	2.71	2.85	3.48	2.43	3.30
Change from Baseline						
Mean	-2.39	-3.51	-3.89	-3.63	-3.59	-3.49
(SD)	3.35	3.09	2.94	3.38	2.98	3.41
MMRM						
LS Mean (SE)	-2.42 (0.21)	-3.71 (0.29)	-3.86 (0.20)	-3.53 (0.21)	-3.77 (0.31)	-3.64 (0.29)
95% CI	-2.82, -2.01	-4.27, -3.15	-4.26, -3.46	-3.93, -3.13	-4.38, -3.16	-4.22, -3.06
CGP vs. Placebo LSMD (SE)		-1.30 (0.35)	-1.44 (0.29)	-1.11 (0.29)	-1.35 (0.37)	-1.22 (0.36)
95% CI		-1.99, -0.60	-2.01, -0.87	-1.68, -0.54	-2.08, -0.62	-1.93, -0.52
p-value		0.0002	<.0001	0.0001	0.0003	0.0007

[a] The mixed-effect model for repeated measures (MMRM) included treatment group and visit as fixed effects, the baseline value as a covariate, and treatment group by visit and baseline by visit as interaction terms, with an unstructured covariance matrix. P-values were from the test between the atogepant dose group and placebo.

Post-baseline (Month 1-3) = average of monthly acute medication use days across the 12-week treatment period.

In terms of acute medication reduction, treatment differences were statistically significant for the BID treatment arms of atogepant compared with placebo after multiplicity adjustment ($p \leq 0.0339$). However, the treatment differences in the QD arms did not achieve statistical significance after multiplicity adjustment because the results for the 50% responder endpoint (S2), which were placed higher in the testing hierarchy, did not achieve statistically significant separation from placebo for the corresponding doses.

Table 28: Summary of primary and secondary efficacy analyses with multiplicity adjustment (mITT population)

Decision Sequence	Atogepant				
	10 mg QD (N=92)	30 mg QD (N=182)	60 mg QD (N=177)	30 mg BID (N=79)	60 mg BID (N=87)
P1: Change from baseline in mean monthly migraine days across the 12-week treatment period LSMD (95% CI), atogepant vs. Placebo	-1.15	-0.91	-0.70	-1.39	-1.29
	(-1.93, -0.37)	(-1.55, -0.27)	(-1.35, -0.06)	(-2.21, -0.56)	(-2.09, -0.49)
Model p-value	0.0039	0.0056	0.0325	0.0010	0.0016
Adjusted p-value	0.0236	0.0390	0.0390	0.0034	0.0031
S1: Change from baseline in mean monthly headache days across the 12-week treatment period LSMD (95% CI), atogepant vs. Placebo	-1.38	-1.24	-0.94	-1.30	-1.39
	(-2.23, -0.54)	(-1.94, -0.55)	(-1.64, -0.24)	(-2.20, -0.41)	(-2.26, -0.53)
Model p-value	0.0014	0.0005	0.0087	0.0044	0.0017
Adjusted p-value	0.0236	0.0390	0.0390	0.0131	0.0083
S2: Proportion of patients with at least a 50% reduction in mean monthly migraine/probable migraine headache days across the 12-week treatment period Odds ratio (95% CI), atogepant vs. Placebo	1.50	1.46	1.42	1.83	2.03
	(0.98, 2.31)	(1.02, 2.08)	(1.00, 2.03)	(1.15, 2.91)	(1.30, 3.18)
Model p-value	0.0617	0.0369	0.0512	0.0113	0.0019
Adjusted p-value	0.1107	0.1107	0.1537	0.0339	0.0097
S3: Change from baseline in mean monthly acute medication use days across the 12-week treatment period LSMD (95% CI), atogepant vs. Placebo	-1.30	-1.44	-1.11	-1.35	-1.22
	(-1.99, -0.60)	(-2.01, -0.87)	(-1.68, -0.54)	(-2.08, -0.62)	(-1.93, -0.52)
Model p-value	0.0002	<.0001	0.0001	0.0003	0.0007
Adjusted p-value	0.1107	0.1107	0.1537	0.0339	0.0097

Adjusted p-values: using graphic approach to control the overall type I error rate for multiple comparisons. Refer to statistical analysis plan for details.
P1 model results are from Table 14.2.1.2; S1 model results are from Table 14.2.2.1; S2 model results are from Table 14.2.2.2; S3 model results are from Table 14.2.2.3.

2.6.5.2. Main study(ies)

Studies 301 and 303 were 12-week, Phase 3, multi-centre, randomised, double-blind, placebo-controlled, parallel-group studies comparing atogepant with placebo for the preventive treatment of migraine in participants with EM (Study 301; atogepant 10 mg, 30 mg, and 60 mg QD) and in participants with CM (Study 303; atogepant 30 mg BID and 60 mg QD). The primary efficacy endpoint in both studies was the change from baseline in mean monthly migraine days across the 12-week treatment period.

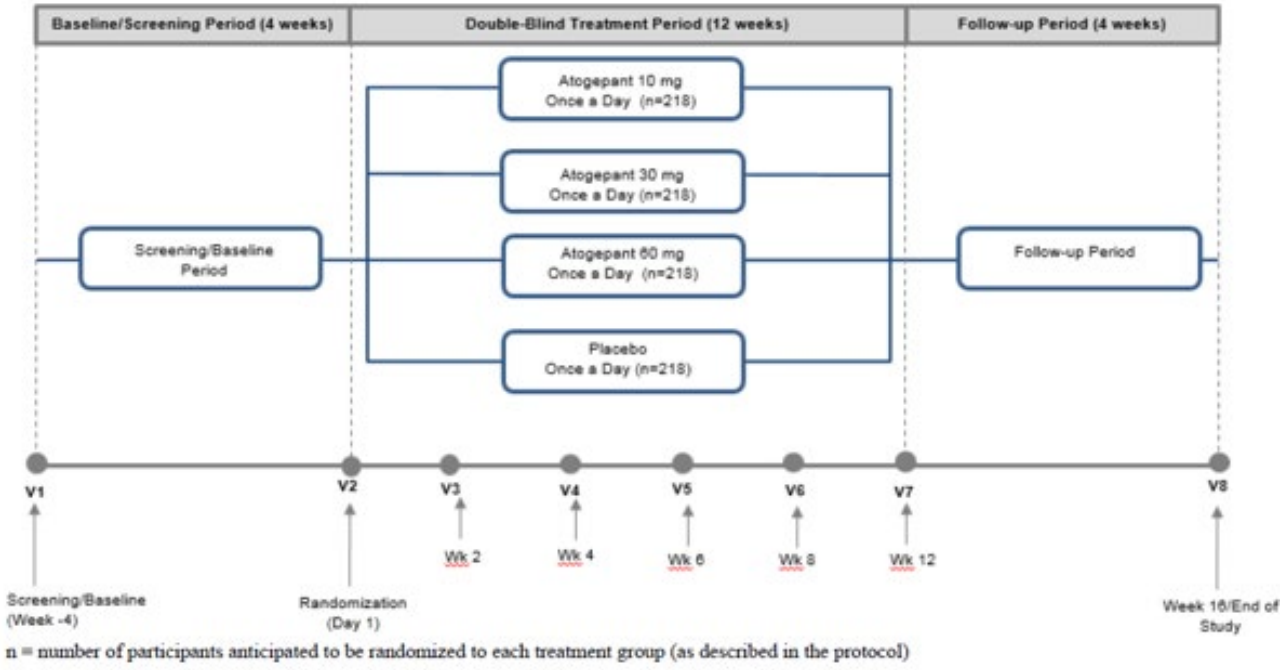
Pivotal Study 301 in EM

A Phase 3, Multicentre, Randomised, Double-Blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine (ADVANCE) (Study 3101-301-002)

This study was conducted in the US.

The study consisted of a 4-week screening and baseline period, a 12-week double-blind treatment period, and a 4-week safety follow-up period.

Figure 5: Study 3101-301-002 schema

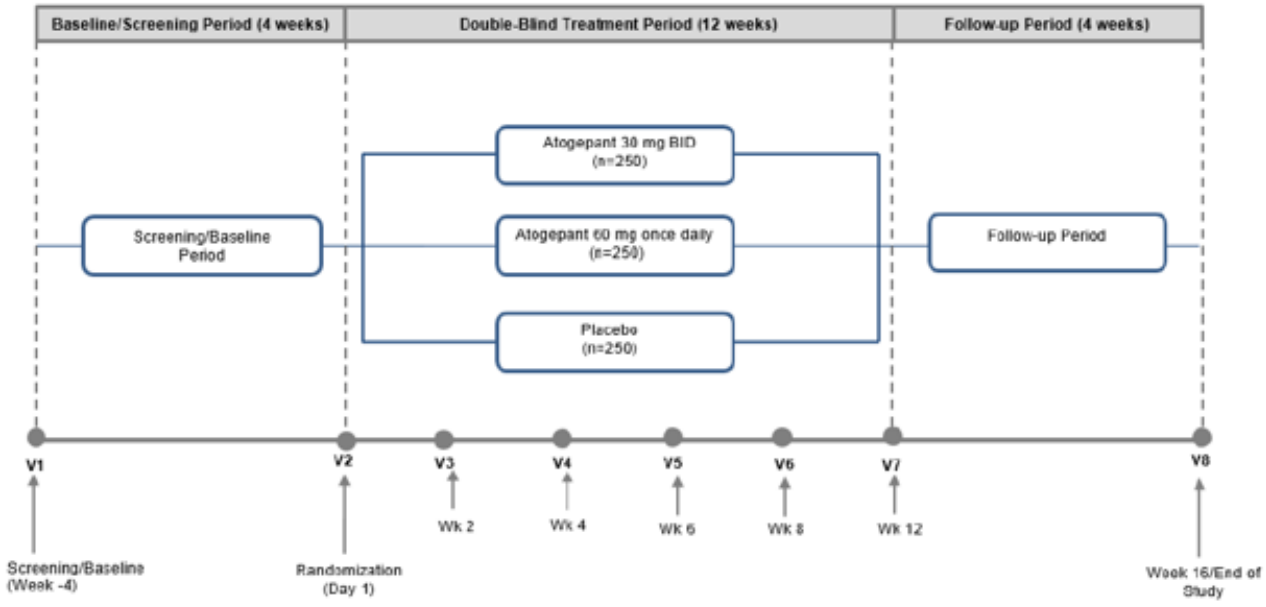


Pivotal Study 303 in CM

A Phase 3, Multicentre, Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Atogepant for the Prevention of Chronic Migraine (PROGRESS) (Study 3101-303-002)

142 sites in the United States, United Kingdom, Canada, China, Czech Republic, Denmark, France, Germany, Italy, Japan, Republic of Korea, Poland, Russian Federation, Spain, Sweden, and Taiwan screened subjects for study eligibility.

Figure 6: Study design schematic, study 3101-303-002



BID = twice daily

Methods

Study Participants

Study 3101-301-002 (Episodic Migraine)

The participants in Study 301 were generally representative of patients with EM in the general population with respect to demographics and baseline disease characteristics (Katsarava 2012).

The study enrolled participants 18 to 80 years of age who had a history of migraine with onset before age 50 years, with or without aura for at least 1 year consistent with a diagnosis according to the ICHD-3 criteria (ICHD-3 2018). Participants must have experienced 4 to 14 migraine days per month on average in the 3 months before screening (Visit 1) in the investigator's judgement. During the 28-day baseline period, participants had to experience 4 to 14 migraine days per electronic diary (eDiary).

Randomisation was stratified by prior exposure (yes, no) to a migraine prevention medication with proven efficacy.

Study 3101-303-002 (Chronic Migraine)

The study enrolled participants 18 to 80 years of age who had at least a 1-year history of CM consistent with a diagnosis according to the ICHD-3 criteria (ICHD-3 2018) with onset before age 50 years. Participants must have experienced, on average, ≥ 15 headache days per month in the 3 months prior to Visit 1 in the opinion of the investigator, ≥ 15 headache days during the 4-week screening/baseline period per the eDiary, and≥ 8 days during the 4-week screening/baseline period that qualify as being a migraine day per the eDiary.

Treatments

The HME-OCT tablet formulation (as described in section 3.3.1.1) at dose strengths of 10 mg, 30 mg, and 60 mg was used in phase II/III trials. Atogepant treatment arms examined once daily QD 10 mg, 30 mg, and 60 mg doses in EM study 301, and the highest 60 mg dose in CM study 303, administered either as QD 60 mg or 30 mg BID.

There were virtually no restrictions with regard to medication to be taken for acute migraine attacks throughout studies 301/303. Patients were allowed to take any triptan, ergot derivative, opioid, any other form of analgesic (incl. acetaminophen), any NSAID, or any antiemetic agent.

However, there were differences between EM study 301 and CM study 303 in terms of concomitant migraine preventive medication. In EM study 301, medications with demonstrated efficacy for the prevention of migraine (e.g., amitriptyline, topiramate, propranolol) were prohibited within 30 days prior to Visit 1 and throughout the study period. Injectable monoclonal antibodies blocking the CGRP pathway (e.g., Aimovig, Emgality, Ajovy) within 6 months prior to Visit 1 and through the study period, were prohibited.

In CM study 303, participants taking one medication with demonstrated efficacy for the prevention of migraine may be randomised provided that in the opinion of the investigator:

- Dose has been stable and the medication has been well-tolerated for at least 12 weeks prior to Visit 1 AND
- Participant is willing and able to maintain at a stable dose and dosage regimen during the study, which should be assessed to ensure compliance at each study visit

Enrolment of participants with current use of a migraine prevention medication will be capped at ~15%

Like in study 301, injectable monoclonal antibodies blocking the CGRP pathway (e.g., Aimovig, Emgality, Ajovy) within 6 months prior to Visit 1 and throughout the study period were prohibited.

Objectives

EM Study 301

- To evaluate the safety and tolerability of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg for the prevention of migraine in participants with EM.
- To prospectively test for superiority of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg versus placebo for the prevention of migraine in participants with EM.

Clinical Hypothesis
In individuals with EM, at least one of the atogepant doses, 10 mg, 30 mg, and 60 mg, is superior to placebo as measured by the change from baseline in mean monthly migraine days across the 12-week treatment period.

CM Study 303

- To evaluate the safety and tolerability of atogepant 30 mg BID and atogepant 60 mg once daily for the prevention of CM.
- To prospectively test for superiority of atogepant (30 mg BID and atogepant 60 mg once daily) versus placebo for the prevention of CM.

Clinical Hypothesis
In participants with CM, at least one dose of atogepant (30 mg BID and atogepant 60 mg once daily) is superior to placebo as measured by the change from baseline in mean monthly migraine days across the 12-week treatment period.

For EU filing, studies 301 and 303 target an estimand addressing the effect regardless of treatment discontinuation and acute migraine treatment (treatment policy strategy) and had other preventive migraine treatment not been available (hypothetical strategy). Although it can be argued whether it is reasonable to apply a hypothetical strategy for 'starting new preventive migraine treatment', the targeted estimand is agreed, as in both studies the number of patients that have started new preventive migraine treatment is very limited and use of alternative strategies to handle this intercurrent event is unlikely to relevantly change conclusions. Furthermore, the Copy-Reference analysis (pre-planned sensitivity analysis) as well as the requested and provided additional analysis (Jump-to-Reference analysis) can be interpreted to target estimands that use alternative strategies to handle the intercurrent event 'starting new preventive migraine treatment'. Labelling the targeted estimand as 'Off-treatment Hypothetical Estimand' is unusual and somewhat confusing, as the terms off-treatment and hypothetical relate to different concepts and it is unclear from the name to which intercurrent events these refer.

Outcomes/endpoints

Table 29: Summary of primary and secondary efficacy endpoints

Primary Analysis Population:	Study 3101-301-002 (ADVANCE) Europe: OTHE Other Regions: mITT	Study 3101-303-002 (PROGRESS) Europe: OTHE Other Regions: mITT	Study CGP-MD-01 mITT
Primary (P) and Secondary (S) Efficacy Endpoints			
Primary efficacy endpoint:	• Change from baseline in mean monthly migraine days across the 12-week treatment period [P1]		
Clinical secondary efficacy endpoints:	• Change from baseline in mean monthly headache days across the 12-week treatment period [S1] • Change from baseline in mean monthly acute medication use days across the 12-week treatment period [S2] • At least a 50% reduction in 3-month average of monthly migraine days [S3]		• Change from baseline in mean monthly headache days across the 12-week treatment period [S1] • Proportion of participants with at least a 50% reduction in mean monthly migraine days across the 12-week treatment period [S2] • Change from baseline in mean monthly acute medication use days across the 12-week treatment period [S3]
Health outcomes secondary efficacy endpoints:	• Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 [S4] • Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period [S5] • Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period [S6]	Europe: • Change from baseline in the HIT-6 total score at Week 12 [S4] • Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 [S5] All Regions Except Europe and Canada: • Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 [S4] • Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period [S5] • Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period [S6]	NA

AIM-D = Activity Impairment in Migraine - Diary; HIT-6 = Headache Impact Test; mITT = modified intent-to-treat; MSQ = Migraine Specific Quality of Life Questionnaire; NA = not applicable; OTHE = off-treatment hypothetical estimand

Note: Baseline for endpoints derived from eDiary data was from 28 days prior to the randomization date (Day 1). Baseline for MSQ and HIT-6 endpoints was from Day 1.

Migraine Day

A migraine day is defined as any calendar day on which a headache occurs which meets criteria A, B, and C **OR** meets criteria D and E, as listed below, as per participant eDiary. Calendar days begin at midnight and last until 11:59 PM (23:59).

A. Headache has at least two of the following four characteristics:
   i. Unilateral location
   ii. Pulsating quality
   iii. Moderate or severe pain intensity
   iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
B. At least one of the following:
   i. Nausea and/or vomiting
   ii. Photophobia and phonophobia
   iii. Typical aura (ie, visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins
C. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (ie, triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified

OR

D. Any headache which fulfills 1 criterion from (1) and at least 1 criterion from (2) **OR** fulfills at least 2 criteria from (1) and no criteria from (2).
   1) Headache characteristics:
      i. Unilateral location
      ii. Pulsating quality
      iii. Moderate or severe pain intensity
      iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
   2) Symptoms:
      i. Nausea and/or vomiting
      ii. Photophobia and phonophobia
      iii. Typical aura (ie, visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins
E. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (ie, triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified.

Headache Day

A headache day is defined as any calendar day on which headache pain lasting 2 hours or longer occurs unless an acute headache medication (e.g., ibuprofen, triptan) was used after the start of the headache, in which case no minimum duration will be specified.

Sample size

For Study 301/302, a total sample size of 218/250 per treatment group will provide at least 98%/96% power to detect the treatment difference between each of the 3/2 doses (assumed equally effective) and placebo for the primary efficacy endpoint (assumptions based on results from other prevention studies). This sample size was selected to provide sufficient power for the first 3 secondary endpoints as well and takes multiplicity control into account.

Randomisation and blinding (masking)

Participants will be randomised to the different treatment arms in an equal ratio using a centralised IWRS. Approximately 70% of randomised participants will have taken at least 1 prior migraine prevention medication with proven efficacy. Randomisation is stratified by prior exposure to a migraine prevention medication for study 301 (EM) and region, acute headache medication overuse, and migraine prevention medication exposure (further stratified based on the number of medications failed with unique mechanisms of action for study 303 (CM)).

A double-dummy design will be used to maintain study blind. Atogepant tablets and matching placebo will be provided in identical blister cards to maintain masking of the study.

Statistical methods

In line with the estimand, for EU filing, the Off-treatment Hypothetical Estimand (OTHE) population is used for analysis. It excludes randomised participants never receiving treatment or not having baseline or any post-baseline diary data (regardless of whether on or off study treatment). Data collected after treatment discontinuation is included in evaluations and data collected after new preventive migraine treatment was started is excluded. While inclusion of off-treatment data is supported, exclusion of randomised patients from the analysis population is generally not. However, although around 1 to 4 % of rand. patients were excluded from the OTHE population in both studies (majority due to missing post-baseline assessments), given the clear efficacy results of studies 301 and 303, it is highly unlikely that including all randomised patients will relevantly change conclusions. Hence, use of the OTHE population is supported. For US filling, the mITT population excluding all randomised patients never receiving study treatment or not having baseline or any post-baseline data (on study treatment) will be used.

The primary endpoint will be analysed using a mixed model for repeated measures (MMRM). The response variable is the change from baseline to each post-baseline month in monthly migraine days. The model will include treatment, visit, stratification factors, and treatment by visit interaction as categorical fixed effects as well as baseline and baseline-by visit interaction as covariates. Within-patient correlation will be modelled using an unstructured covariance matrix. Contrasts will be constructed to obtain the average treatment effects across the 12-week treatment period to compare each treatment group vs placebo. Although this analysis with its underlying missing-at-random (MAR) assumption is less aligned to the targeted estimand (unless no data are missing) as compared to imputation approaches based on placebo data (CR or J2R analysis), there are minimal to none differences in results for the CR and J2R analysis as compared to the primary analysis supporting overall robustness of results. Hence it is agreed to report results of the primary analysis in the SmPC.

Only few daily eDiary data are missing and impact of these on availability of primary/secondary endpoints as well as on results is negligible. Continuous secondary endpoints will be analysed similar to the primary endpoint. The 50% responder endpoint, defined as a participant with at least a 50% reduction from baseline in the 3-month average of monthly migraine days, will be assessed for each individual. A logistic regression model will be used to analyse the 50% responders across the 12-week treatment period.

The overall familywise error rate (FWER) will be controlled at $\alpha = 0.05$ for the primary and secondary endpoints between each dose level of atogepant vs placebo using a graphical approach with weighted-Bonferroni test procedure (Bretz 2009). For the primary and first three secondary endpoints this approach essentially corresponds to sequential testing vs placebo within each atogepant dose group with splitted alpha.

Results

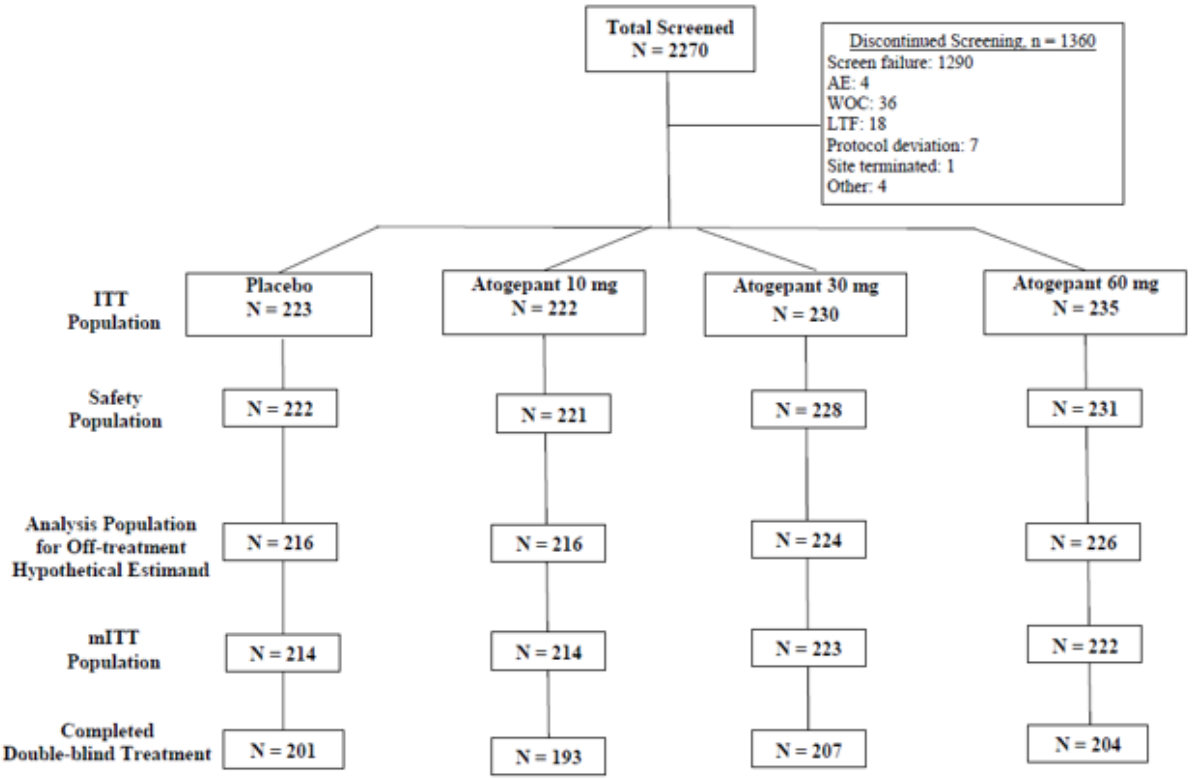
Participant flow

Study 301 in EM population

A total of 910 participants were randomised and included in the intent-to-treat population of Study 301. Overall, 805 participants completed the 12-week double-blind treatment period, and completion rates were similar across the 4 treatment groups (range 86.8% to 90.1% for all randomised patients).

A total of 88.5% of all randomised participants completed the study and 11.5% of participants discontinued the study in the double-blind treatment period. The most common reason for discontinuation, based on the total number of participants, was withdrawal by subject (3.8%), adverse events (2.7%), and protocol deviations (2.6%).

Figure 7: Participant disposition – study 301



Study 303 in CM population

Overall, 1489 subjects were screened for eligibility at 142 sites in the US, UK, Canada, China, CZ, DK, FR, DE, IT, Japan, Republic of Korea, PL, Russian Federation, ES, SE, and Taiwan. Of these, N=778 subjects were randomised.

The majority of randomised subjects (89.2%) completed the double-blind treatment period. The main reasons for discontinuation reported during DBT were AE and withdrawal by subject.

Table 30: Subject disposition – ITT population, study 303 (DBT extract)

Phase Disposition	Placebo (N=259) n (%)	Atogepant 30 mg BID (N=257) n (%)	Atogepant 60 mg QD (N=262) n (%)	Total (N=778) n (%)
Number of Participants Randomized	259 (100.0)	257 (100.0)	262 (100.0)	778 (100.0)
Number of Participants Treated	255 (98.5)	257 (100.0)	261 (99.6)	773 (99.4)
Double-Blind Treatment Period				
Number of Participants Entered	259 (100.0)	257 (100.0)	262 (100.0)	778 (100.0)
Number of Participants Completed	230 (88.8)	231 (89.9)	233 (88.9)	694 (89.2)
Number of Participants Discontinued	29 (11.2)	26 (10.1)	29 (11.1)	84 (10.8)
Reason for Discontinuation				
Adverse Event	10 (3.9)	13 (5.1)	9 (3.4)	32 (4.1)
Lack of efficacy	5 (1.9)	2 (0.8)	1 (0.4)	8 (1.0)
Withdrawal by subject	8 (3.1)	7 (2.7)	14 (5.3)	29 (3.7)
Lost to Follow-Up	0 (0.0)	1 (0.4)	3 (1.1)	4 (0.5)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Deviation	5 (1.9)	3 (1.2)	2 (0.8)	10 (1.3)
Non-compliance with study drug	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Study Terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Site Terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Baseline data

Study populations between Studies 301 and 303 were similar in terms of mean age (41-42 years) and gender partition (87-89% female) with differences as regards mean weight (US study 301: 83.9 kg, multiregional study 303: 69.5 kg), and BMI (301: 30.46 kg/m^2, 303: 25.52 kg/m^2) of participants.

Table 31: Migraine history – individual studies 3101-301-002 and 3101-303-002 (safety population)

	Study 3101-301-002 (EM)	Study 3101-303-002 (CM)
	Total	Total
N	902	773
Migraine Diagnosis, n (%)		
With Aura	146 (16.2)	103 (13.3)
Without Aura	406 (45.0)	462 (59.8)
Both	350 (38.8)	208 (26.9)
Migraine Disorder Duration in Years		
Mean (SD)	21.2 (12.63)	21.4 (12.18)
Migraine Prevention Medication in the Past, n (%)		
Yes	634 (70.3)	641 (82.9)
No	268 (29.7)	132 (17.1)
Average Number of Migraine Days per Month in Last 3 Months		
Mean (SD)	7.4 (2.47)	16.0 (5.91)
Average Number of Headache Days per Month in Last 3 Months		
Mean (SD)	9.3 (2.71)	21.1 (5.36)
Acute Medication Treatment,[a] n (%)		
Yes	896 (99.3)	760 (98.3)
Triptan	440 (48.8)	558 (72.2)
Ergot or Ergot Combinations	3 (0.3)	17 (2.2)
NSAID	569 (63.1)	540 (69.9)
Opiate or Opiate Combination	35 (3.9)	28 (3.6)
Antiemetic Agent	73 (8.1)	116 (15.0)
Barbiturates	6 (0.7)	2 (0.3)
Other	570 (63.2)	250 (32.3)

CM = chronic migraine; EM = episodic migraine; NSAID = nonsteroidal anti-inflammatory drugs; OTHE = off-treatment hypothetical estimand; SD = standard deviation

a. Medication(s) that the participant usually takes to treat migraine headaches.

Note: The safety population was defined as all participants who took at least 1 dose of study drug.

Source: Study 3101-301-002 CSR, Table 14.1-3.2.2 and Study 3101-303-002 CSR, Table 14.1-5.1.2

Numbers analysed

The number of participants included in each analysis population, overall and by treatment group, is summarised in on the following tables for studies 301 and 303.

Table 32: Analysis populations – all screened subjects (301)

Population	Placebo	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD	Total
Screened					2270
Intent-to-Treat	223	222	230	235	910
Safety	222	221	228	231	902
Modified Intent-to-Treat	214	214	223	222	873
Analysis Population for Off-Treatment Hypothetical Estimand	216	216	224	226	882

Table 33: Analysis populations – all screened subjects (303)

Country Population	Placebo	Atogepant 30 mg BID	Atogepant 60 mg QD	Total
Overall				
Screened				1489
Intent-to-Treat	259	257	262	778
Safety	255	257	261	773
Modified Intent-to-Treat	246	253	256	755
Off-treatment Hypothetical Estimand Population	249	254	257	760

BID = twice daily; ITT = intent-to-treat; eDiary = electronic diary; mITT = modified intent-to-treat; QD = once daily

The primary efficacy analysis population for EU filing is the Off-treatment Hypothetical Estimand (OTHE) population, while the mITT population used primarily for US filing.

Outcomes and estimation

Primary Efficacy Endpoint

Change from Baseline in Mean Monthly Migraine Days Across the 12-Week Treatment Period

In both studies 301 303, greater reductions from baseline in mean monthly migraine days across the 12-week treatment period were observed for each of the atogepant doses (10 mg, 30 mg, and 60 mg QD in Study 301 and 30 mg BID and 60 mg QD in Study 303) compared with placebo and were statistically significant after multiplicity adjustment.

Table 34: Change from baseline in mean monthly migraine days across the 12-week treatment period: individual studies 3101-301-002 and 3101-303-002 (OTHE population)

Study ID		Study 3101-301-002 (EM)				Study 3101-303-002 (CM)		
	Statistic	Placebo	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD	Placebo	Atogepant 30 mg BID	Atogepant 60 mg QD
	N	216	216	224	226	249	254	257
Baseline number of days	Mean (SD)	7.53 (2.394)	7.46 (2.466)	7.86 (2.311)	7.75 (2.334)	18.95 (4.795)	18.60 (5.090)	19.19 (5.291)
Change from baseline	LS mean (SE)	-2.47 (0.210)	-3.69 (0.209)	-3.85 (0.206)	-4.14 (0.205)	-5.09 (0.409)	-7.33 (0.406)	-6.75 (0.406)
Atogepant vs. placebo	LSMD		-1.22	-1.38	-1.66		-2.24	-1.66
	95% CI		-1.79, -0.65	-1.94, -0.81	-2.23, -1.10		-3.31, -1.16	-2.72, -0.59
	Nominal p-value		< 0.0001	< 0.0001	< 0.0001		< 0.0001	0.0024
	Adjusted p-value		< 0.0001	< 0.0001	< 0.0001		0.0001	0.0024

BID = twice daily; CI = confidence interval; CM = chronic migraine; EM = episodic migraine; LS = least squares; LSMD = least squares mean difference; OTHE = off-treatment hypothetical estimand; QD = once daily; SD = standard deviation; SE = standard error

Source: Study 3101-301-002 CSR, Table 14.2-1.6 and Table 14.2-1.1.B and Study 3101-303-002 CSR, Table 14.2-2.1.2 and Table 14.2-1.2

Secondary Efficacy Endpoint [S1]

Change from Baseline in Mean Monthly Headache Days Across the 12-Week Treatment Period

In both studies, greater reductions from baseline in mean monthly headache days across the 12-week treatment period were observed for each of the atogepant doses (10 mg, 30 mg, and 60 mg QD in Study 301 and 30 mg BID and 60 mg QD in Study 303) compared with placebo and were statistically significant after multiplicity adjustment.

Table 35: Change from baseline in mean monthly headache days across the 12-week treatment period: individual studies 3101-301-002 and 3101-303-002 (OTHE population)

Study ID		Study 3101-301-002 (EM)				Study 3101-303-002 (CM)		
	Statistic	Placebo	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD	Placebo	Atogepant 30 mg BID	Atogepant 60 mg QD
	N	216	216	224	226	249	254	257
Baseline number of days	Mean (SD)	8.45 (2.550)	8.43 (2.754)	8.78 (2.615)	8.99 (2.577)	21.42 (4.111)	21.17 (4.145)	21.54 (4.323)
Change from baseline	LS mean (SE)	-2.52 (0.225)	-3.94 (0.224)	-4.03 (0.220)	-4.17 (0.219)	-5.17 (0.403)	-7.32 (0.399)	-6.90 (0.399)
Atogepant vs. placebo	LSMD		-1.42	-1.51	-1.65		-2.14	-1.72
	95% CI		-2.03, -0.81	-2.11, -0.91	-2.25, -1.04		-3.20, -1.09	-2.78, -0.67
	Nominal p-value		< 0.0001	< 0.0001	< 0.0001		< 0.0001	0.0014
	Adjusted p-value		< 0.0001	< 0.0001	< 0.0001		0.0002	0.0024

BID = twice daily; CI = confidence interval; CM = chronic migraine; EM = episodic migraine; LS = least squares; LSMD = least squares mean difference; OTHE = off-treatment hypothetical estimand; QD = once daily; SD = standard deviation; SE = standard error

Source: Study 3101-301-002 CSR, Table 14.2-2.2 and Table 14.2-1.1.B and Study 3101-303-002 CSR, Table 14.2-3.1.2 and Table 14.2-1.2

Secondary Efficacy Endpoint [S2]

Change from Baseline in Mean Monthly Acute Medication Use Days Across the 12-Week DBT Period

In both studies, greater reductions from baseline in mean monthly acute medication use days across the 12-week treatment period were observed for each of the atogepant doses (10 mg, 30 mg, and 60 mg QD in Study 301 and 30 mg BID and 60 mg QD in Study 303) compared with placebo and were statistically significant after multiplicity adjustment.

Table 36: change from baseline in mean monthly acute medication use days across the 12-week treatment period: individual studies 3101-301-002 and 3101-303-002 (OTHE population)

Study ID		Study 3101-301-002 (EM)				Study 3101-303-002 (CM)		
	Statistic	Placebo	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD	Placebo	Atogepant 30 mg BID	Atogepant 60 mg QD
	N	216	216	224	226	249	254	257
Baseline number of days	Mean (SD)	6.50 (3.152)	6.58 (2.989)	6.66 (3.050)	6.88 (3.151)	15.31 (7.048)	14.53 (7.223)	15.45 (7.363)
Change from baseline	LS mean (SE)	-2.34 (0.184)	-3.68 (0.183)	-3.65 (0.181)	-3.78 (0.180)	-4.09 (0.389)	-6.61 (0.388)	-6.19 (0.383)
Atogepant vs. placebo	LSMD		-1.34	-1.31	-1.44		-2.52	-2.09
	95% CI		-1.84, -0.84	-1.81, -0.82	-1.93, -0.94		-3.52, -1.53	-3.09, -1.10
	Nominal p-value		< 0.0001	< 0.0001	< 0.0001		< 0.0001	< 0.0001
	Adjusted p-value		< 0.0001	< 0.0001	< 0.0001		0.0002	0.0024

BID = twice daily; CI = confidence interval; CM = chronic migraine; EM = episodic migraine; LS = least squares; LSMD = least squares mean difference; OTHE = off-treatment hypothetical estimand; QD = once daily; SD = standard deviation; SE = standard error

Source: Study 3101-301-002 CSR, Table 14.2-2.5 and Table 14.2-1.1.B and Study 3101-303-002 CSR, Table 14.2-3.2.2 and Table 14.2-1.2

Secondary Efficacy Endpoint [S3]

At Least a 50% Reduction in 3-Month Average of Monthly Migraine Days

In both studies, the proportion of participants with at least a 50% reduction from baseline in mean monthly migraine days across the 12-week treatment period was greater for each of the atogepant doses (10 mg, 30 mg, and 60 mg QD in Study 301 and 30 mg BID and 60 mg QD in Study 303) compared with placebo, and was statistically significant after multiplicity adjustment.

Table 37: Reduction of ≥ 50% in 3-month average of monthly migraine days: individual studies 3101-301-002 and 3101-303-002 (OTHE population)

Study ID		Study 3101-301-002 (EM)				Study 3101-303-002 (CM)		
	Statistic	Placebo	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD	Placebo	Atogepant 30 mg BID	Atogepant 60 mg QD
	N	216	216	224	226	249	254	257
Responders	n (%)	63 (29.2)	118 (54.6)	131 (58.5)	134 (59.3)	66 (26.5)	107 (42.1)	103 (40.1)
Atogepant vs. placebo	Odds ratio		2.91	3.46	3.55		2.03	1.90
	95% CI		1.95, 4.33	2.32, 5.14	2.39, 5.28		1.38, 2.98	1.29, 2.79
	Nominal p-value		< 0.0001	< 0.0001	< 0.0001		0.0003	0.0011
	Adjusted p-value		< 0.0001	< 0.0001	< 0.0001		0.0006	0.0024

BID = twice daily; CI = confidence interval; CM = chronic migraine; EM = episodic migraine; LS = least squares; LSMD = least squares mean difference; OTHE = off-treatment hypothetical estimand; QD = once daily; SD = standard deviation; SE = standard error

Source: Study 3101-301-002 Table 14.2-2.8 and Table 14.2-1.1.B and Study 3101-303-002 CSR, Table 14.2-3.3.2 and Table 14.2-1.2

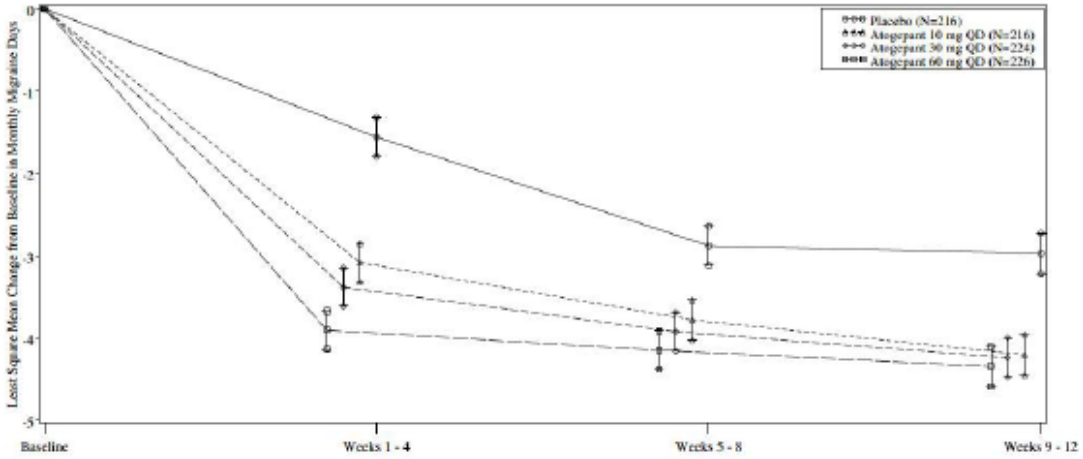
Time Course of Efficacy

Efficacy Across the 12-Week Treatment Period by 4-Week Interval

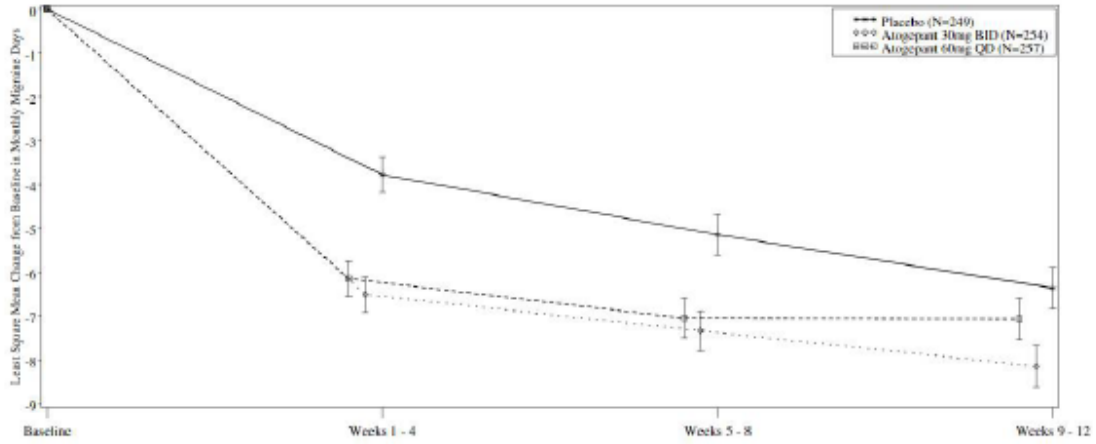
The time course of efficacy based on the least square mean change from baseline in the number of MDs during DBT in Studies 301 and 303 is presented in the figure below. In both studies, each of the atogepant doses (10 mg, 30 mg, and 60 mg QD in EM Study 301 and 30 mg BID and 60 mg QD in CM Study 303) separate from placebo, starting with the first month of treatment (Weeks 1 to 4), and provided similar reductions in the number of monthly migraine days during the 12-week BDT. In Study 301, a dose-response relationship was evident, particularly during the first month, with the atogepant 60 mg QD dose providing a numerically greater reduction in the number of monthly migraine days than the 10 mg and 30 mg QD doses.

Figure 8: Least square mean (± SE) of change from baseline in number of monthly migraine days (MMRM) during the double-blind treatment period – individual studies 3101-301-002 and 3101-303-002 (OTHE population)

Study 3101-301-002 (EM)



Study 3101-303-002 (CM)



BID = twice daily; CM = chronic migraine; EM = episodic migraine; MMRM = mixed-effects model for repeated measures; OTHE = off-treatment hypothetical estimand; QD = once daily; SE = Standard Error

Source: Study 3101-301-002 CSR, Figure 14.2-1.1B and Study 3101-303-002 CSR, Figure 14.2-2.1.2

Additional Health Outcomes Measures

A number of additional health outcomes measures were common to both Studies 301 and 303, including the Patient Global Impression of Change (PGIC), Patient Satisfaction with Study Medication (PSSM), Work Productivity and Activity Impairment Questionnaire: Migraine v2.0 (WPAI:MIGRAINE), Migraine Disability Assessment (MIDAS), Patient Global Impression of Severity (PGI-S), and Activity Level and Limitation. In addition, the MSQ v2.1, AIM-D, and HIT-6 were also administered at multiple time points in the study to construct additional endpoints.

Overall, results for these additional health outcomes measures were consistent with the results of the primary and secondary efficacy endpoints for both studies, with numerically greater improvements or greater reductions (i.e., improvement) from baseline observed for each of the atogepant treatment groups compared with placebo for the majority of measures.

Ancillary analyses

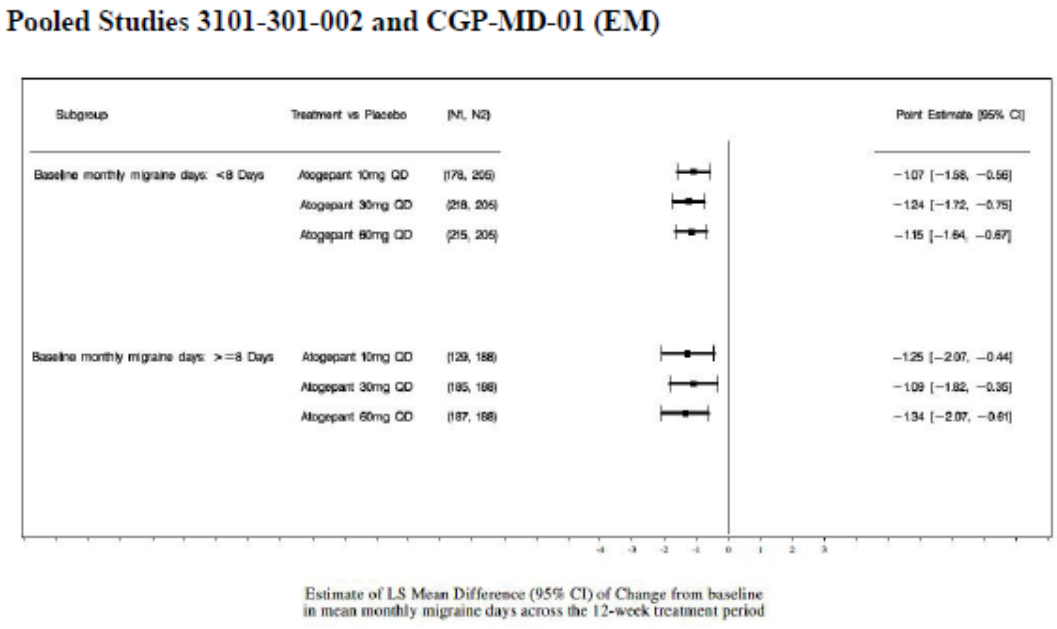
Subgroup Analyses

Subgroup analyses were conducted by age, sex, race, baseline BMI, baseline monthly MDs, exposure to migraine prevention medication with proven efficacy, and migraine prevention medication failures for the EM and CM studies. Specifically for Study 303, further subgroup analyses were conducted by region, acute medication overuse, current use of migraine prevention medication for the primary efficacy endpoint and each of the 3 clinical secondary efficacy endpoints.

Subgroup Analysis per Baseline Monthly MDs

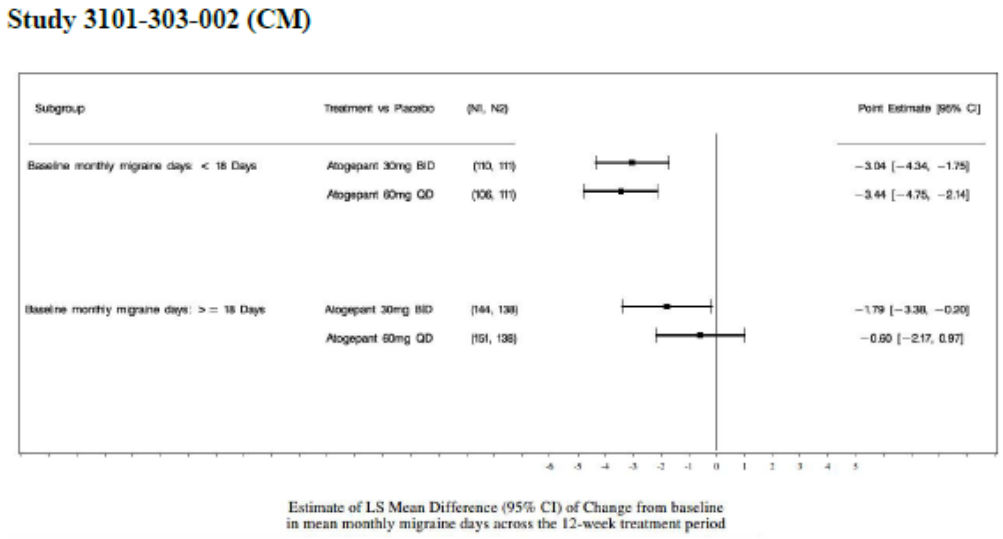
In the total pooled population across Studies 301 and MD-01 (atogepant QD and placebo treatment groups), baseline monthly migraine days was < 8 days for 54.2% of participants and ≥ 8 days for 45.8% of participants.

Figure 9: Forest plot of subgroup analysis for change from baseline in mean monthly migraine days across the 12-week treatment period by baseline monthly migraine days – pooled studies 301 and md-01 (efficacy analysis population)



In Study 303 (atogepant 30 mg BID, atogepant 60 mg QD, and placebo treatment groups), the mean baseline number of migraine days was 18.9 days. For CM Study 303, although a numerically greater treatment effect was observed for participants with baseline monthly migraine days < 18 days compared with participants with baseline monthly migraine days ≥ 18 days, the 95% CIs overlapped.

Figure 10: Forest plot of subgroup analysis for change from baseline in mean monthly migraine days across the 12-week treatment period by baseline monthly migraine days – study 303 (efficacy analysis population)

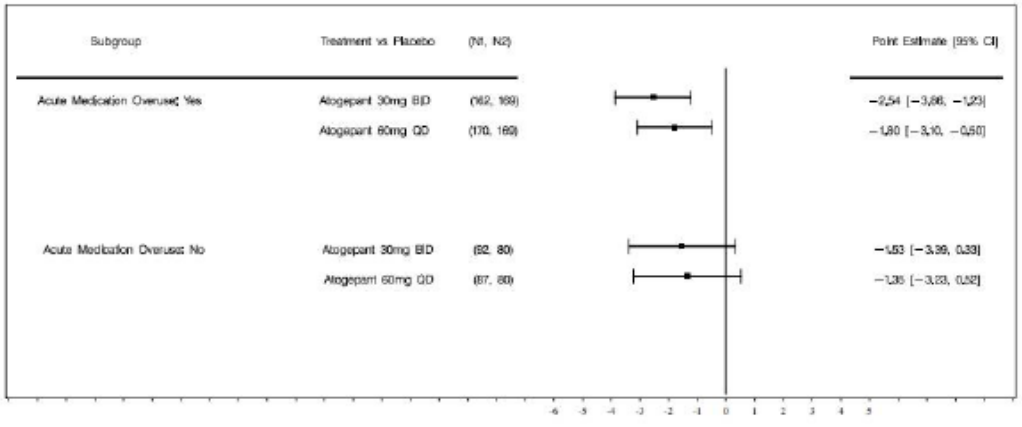


CI = confidence interval; CM = chronic migraine; EM = episodic migraine; LS = least squares; mITT = modified intent-ot-treat; N1 = treatment; N2 = placebo; OTHE = off-treatment hypothetical estimand
The efficacy analysis population is defined as the OTHE population for Studies 3101-301-002 and 3101-303-002 and the mITT population for Study CGP-MD-01.

Study 303 – Subgroup Analysis per Acute Medication Overuse

Both atogepant doses showed numerical improvement compared with placebo for the primary efficacy endpoint in participants with acute medication overuse and those without.

Figure 11: Forest plot of subgroup analysis for change from baseline in mean monthly migraine days across the 12-week treatment period by acute medication overuse status – study 303 (OTHE population)

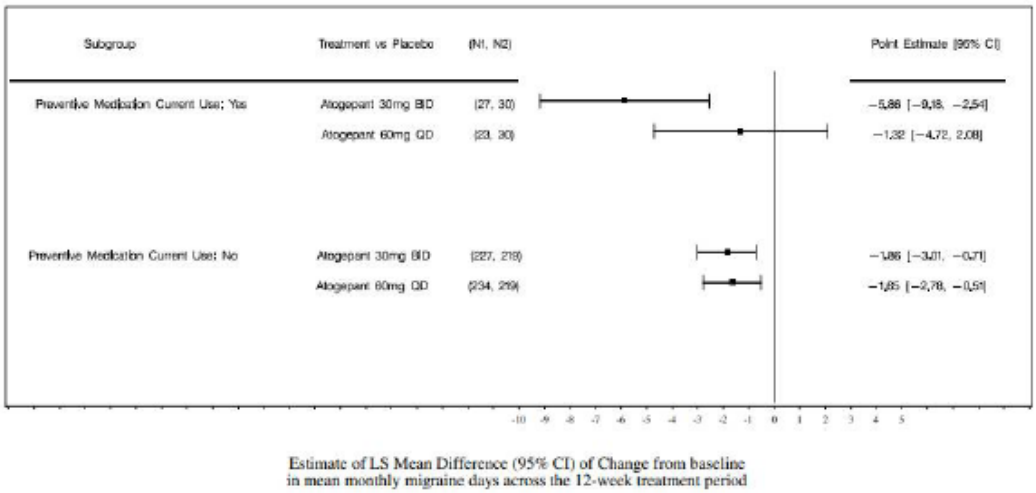


BID = twice daily; CI = confidence interval; LS = least squares; N1 = treatment; N2 = placebo; OTHE = off-treatment hypothetical estimand; QD = once daily

Study 303 – Subgroup Analysis per Current Preventive Medication Use

Both atogepant doses showed numerical improvement compared with placebo for the primary efficacy endpoint in participants with preventive medication current use and those without. A numerically greater treatment effect was observed for current users of preventive medications in the atogepant 30 mg BID treatment group compared with the atogepant 60 mg QD treatment group, however the 95% CIs overlapped for the 2 treatment groups.

Figure 12: Forest plot of subgroup analysis for change from baseline in mean monthly migraine days across the 12-week treatment period by preventive medication current use status – study 303 (OTHE population)



BID = twice daily; CI = confidence interval; LS = least squares; N1 = treatment; N2 = placebo; OTHE = off-treatment hypothetical estimand; QD = once daily

- ***Summary of main efficacy results***

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 38: Summary of efficacy for trial 3101-301-002

Title: A Phase 3, Multicentre, Randomised, Double-Blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine (ADVANCE)		
Study identifier	3101-301-002, NCT03777059	
Design	Phase 3, US multicentre, randomised, placebo-controlled, parallel group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine (EM). Participants were randomised to 1 of 4 treatment groups (placebo, atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg, administered once daily) in a 1:1:1:1 ratio.	
	Durationofmainphase:DurationofRun-inphase:DurationofExtension phase:	12-week double-blind treatment (DBT) 4-week screening and baseline period 4-week safety follow-up
Hypothesis	Superiority	

Title: A Phase 3, Multicentre, Randomised, Double-Blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine (ADVANCE)			
Study identifier	3101-301-002, NCT03777059		
Treatments groups (Total N=910 randomised (ITT); OTHE Population N=882)	Placebo (PBO)		216
	Atogepant (AGP) 10 mg QD		216
	Atogepant (AGP) 30 mg QD		224
	Atogepant (AGP) 60 mg QD		226
Endpoints and definitions, with Multiplicity Adjustment	Primary endpoint (P1)	MD reduction	Change from baseline in mean monthly migraine days (MD) across the 12-week treatment period
	Secondary endpoint (S1)	HD reduction	Change from baseline in mean monthly headache days (HD) across the 12-week treatment period
	Secondary endpoint (S2)	Acute medication use	Change from baseline in mean monthly acute medication use days across the 12-week treatment period
	Secondary endpoint (S3)	Responder, $\geq$ 50% MD reduction	$\geq$ 50% reduction in 3-month average of monthly migraine days
Database lock	06 July 2020		

Results and Analysis

Analysis description	**Primary endpoint: Change from baseline in mean monthly MDs across the 12-week DBT**				
Analysis population and timepoint description	OTHE population: all randomised participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data during the study, regardless of whether on study treatment or off study treatment. The primary and key secondary endpoints are the same for the US and the EU. The primary estimand in support of the EU filing is the off-treatment hypothetical estimand (OTHE).				
Descriptive statistics and estimate variability	Treatment group	PBO, N=216	Atogepant 10 mg QD, N=216	Atogepant 30 mg QD, N=224	Atogepant 60 mg QD, N=226
	Baseline number of monthly MDs, Mean (SD)	7.53 (2.394)	7.46 (2.466)	7.86 (2.311)	7.75 (2.334)
	LS Mean (SE) change from baseline	-2.47 (0.210)	-3.69 (0.209)	-3.85 (0.206)	-4.14 (0.205)
	LSMD (95% CI) Atogepant vs. Placebo		-1.22 (-1.79, -0.65)	-1.38 (-1.94, -0.81)	-1.66 (-2.23, -1.10)
	Adjusted p-value		<.0001	<.0001	<.0001
Analysis description	**Secondary endpoint (S1): Change from baseline in mean monthly headache days (HD) across the 12-week DBT**				
Descriptive statistics and estimate variability	Treatment group	PBO N=216	Atogepant 10 mg QD N=216	Atogepant 30 mg QD N=224	Atogepant 60 mg QD N=226
	Baseline number of monthly HDs, Mean (SD)	8.45 (2.550)	8.43 (2.754)	8.78 (2.615)	8.99 (2.577)
	LS Mean (SE) change from baseline	-2.52 (0.225)	-3.94 (0.224)	-4.03 (0.220)	-4.17 (0.219)

Title: A Phase 3, Multicentre, Randomised, Double-Blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine (ADVANCE)					
Study identifier	3101-301-002, NCT03777059				
	LSMD (95% CI) Atogepant vs. Placebo		-1.42 (-2.03, -0.81)	-1.51 (-2.11, -0.91)	-1.65 (-2.25, -1.04)
	Adjusted p-value		<.0001	<.0001	<.0001
Analysis description	**Secondary endpoint (S2): Change from baseline in mean monthly Acute Medication (Mx) Use Days across the 12-week DBT**				
Descriptive statistics and estimate variability	Treatment group	PBO N=216	Atogepant 10 mg QD N=216	Atogepant 30 mg QD N=224	Atogepant 60 mg QD N=226
	Baseline No. of monthly Acute Mx Use Days, Mean (SD)	6.50 (3.152)	6.58 (2.989)	6.66 (3.050)	6.88 (3.151)
	LS Mean (SE) change from baseline	-2.34 (0.184)	-3.68 (0.183)	-3.65 (0.181)	-3.78 (0.180)
	LSMD (95% CI) Atogepant vs. Placebo		-1.34 (-1.84, -0.84)	-1.31 (-1.81, -0.82)	-1.44 (-1.93, -0.94)
	Adjusted p-value		<.0001	<.0001	<.0001
Analysis description	**Secondary endpoint (S3): ≥ 50% reduction in 3-month average of monthly MDs**				
Descriptive statistics and estimate variability	Treatment group	PBO N=216	Atogepant 10 mg QD N=216	Atogepant 30 mg QD N=224	Atogepant 60 mg QD N=226
	Responders, n (%)	63 (29.2)	118 (54.6)	131 (58.5)	134 (59.3)
	Odds ratio (95% CI), Atogepant vs. Placebo		2.91 (1.95, 4.33)	3.46 (2.32, 5.14)	3.55 (2.39, 5.28)
	Adjusted p-value		<.0001	<.0001	<.0001
Notes	LS = least squares; LSMD = least squares mean difference; Adjusted p-values: using graphical approach to control the overall type I error rate for multiple comparisons				

Table 39: Summary of efficacy for trial 3101-303-002

Title: A Phase 3, Multicentre, Randomised, Double-Blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Chronic Migraine (PROGRESS)		
Study identifier	3101-303-002; EudraCT 2018-004337-32; NCT03855137	
Design	Phase 3, multicentre, randomised, placebo-controlled, parallel group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Chronic Migraine (CM). Participants were randomised to 1 of 3 treatment arms (placebo, atogepant 30 mg BID, atogepant 60 mg QD) in a 1:1:1 ratio. 142 sites in US, Canada, Europe, Russia, East Asia (Korea, Japan, China, Taiwan)	
	Durationofmainphase:DurationofRun-inphase:DurationofExtension	12-week double-blind treatment (DBT) 4-week screening and baseline period 4-week safety follow-up

Title: A Phase 3, Multicentre, Randomised, Double-Blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Chronic Migraine (PROGRESS)				
Study identifier	3101-303-002; EudraCT 2018-004337-32; NCT03855137			
	phase:			
Hypothesis	Superiority			
Treatments groups (Total N=778 randomised (ITT); OTHE Population N=760)	Placebo (PBO)		249	
	Atogepant (AGP) 30 mg BID		254	
	Atogepant (AGP) 60 mg QD		257	
Endpoints and definitions, with Multiplicity Adjustment	Primary endpoint (P1)	MD reduction	Change from baseline in mean monthly migraine days (MD) across the 12-week treatment period	
	Secondary endpoint (S1)	HD reduction	Change from baseline in mean monthly headache days (HD) across the 12-week treatment period	
	Secondary endpoint (S2)	Acute medication use	Change from baseline in mean monthly acute medication use days across the 12-week treatment period	
	Secondary endpoint (S3)	Responder, ≥ 50% MD reduction	≥ 50% reduction in 3-month average of monthly migraine days	
Database lock	21 April 2020			
Results and Analysis				
Analysis description	**Primary endpoint: Change from baseline in mean monthly MDs across the 12-week DBT**			
Analysis population and timepoint description	OTHE population: all randomised participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data during the study, regardless of whether on study treatment or off study treatment. The primary and key secondary endpoints are the same for the US and the EU. The primary estimand in support of the EU filing is the off-treatment hypothetical estimand (OTHE).			
Descriptive statistics and estimate variability	Treatment group	PBO N=249	Atogepant 30 mg BID N=254	Atogepant 60 mg QD N=257
	Baseline number of monthly MDs, Mean (SD)	19.0 (4.80)	18.6 (5.09)	19.2 (5.29)
	LS Mean (SE) change from baseline	-5.09 (0.409)	-7.33 (0.406)	-6.75 (0.406)
	LSMD (95% CI) Atogepant vs. Placebo		-2.24 (-3.31, -1.16)	-1.66 (-2.72, -0.59)
	Adjusted p-value		0.0001	0.0024
Analysis description	**Secondary endpoint (S1): Change from baseline in mean monthly headache days (HD) across the 12-week DBT**			
Descriptive statistics and estimate variability	Treatment group	PBO N=249	Atogepant 30 mg BID N=254	Atogepant 60 mg QD N=257
	Baseline number of monthly HDs, Mean (SD)	21.4 (4.11)	21.2 (4.15)	21.5 (4.32)
	LS Mean (SE)	-5.17	-7.32	-6.90

Title: A Phase 3, Multicentre, Randomised, Double-Blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Chronic Migraine (PROGRESS)				
Study identifier	3101-303-002; EudraCT 2018-004337-32; NCT03855137			
	change from baseline	(0.403)	(0.399)	(0.399)
	LSMD (95% CI) Atogepant vs. Placebo		-2.14 (-3.20, -1.09)	-1.72 (-2.78, -0.67)
	Adjusted p-value		0.0002	0.0024
Analysis description	**Secondary endpoint (S2): Change from baseline in mean monthly acute medication (Mx) use days across the 12-week DBT**			
Descriptive statistics and estimate variability	Treatment group	PBO N=249	Atogepant 30 mg BID N=254	Atogepant 60 mg QD N=257
	Baseline No. of monthly acute Mx use days, Mean (SD)	15.3 (7.05)	14.5 (7.22)	15.5 (7.36)
	LS Mean (SE) change from baseline	-4.09 (0.389)	-6.61 (0.388)	-6.19 (0.383)
	LSMD (95% CI) Atogepant vs. Placebo		-2.52 (-3.52, -1.53)	-2.09 (-3.09, -1.10)
	Adjusted p-value		0.0002	0.0024
Analysis description	**Secondary endpoint (S3): ≥ 50% Reduction in 3-month average of monthly migraine days**			
Descriptive statistics and estimate variability	Treatment group	PBO N=249	Atogepant 30 mg BID N=254	Atogepant 60 mg QD N=257
	Responders, n (%)	66 (26.5)	107 (42.1)	103 (40.1)
	Odds ratio (95% CI), Atogepant vs. Placebo		2.03 (1.38, 2.98)	1.90 (1.29, 2.79)
	Adjusted p-value		0.0006	0.0024
Notes	LS = least squares; LSMD = least squares mean difference; Adjusted p-values: using graphical approach to control the overall type I error rate for multiple comparisons			

- ***Supportive study***

Persistence of Efficacy

The long-term studies of atogepant for the preventive treatment of migraine in participants with CM are ongoing. No study results are available.

The long-term efficacy of atogepant for the preventive treatment of migraine in participants with EM was evaluated in Study 3101-302-002.

Long-term Study 302 in EM

A Phase 3, Multi-centre, Randomised, Open-Label Study to Evaluate the Long-Term Safety and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants with Episodic Migraine (Study 3101-302-002)

Study 302 was a multi-centre, randomised, open-label, 52-week, long-term safety study conducted at 111 centres in the United States (111 centres screened participants and 106 centres randomised at least 1 participant). Participants were randomised in a 5:2 ratio to one of the following treatment groups:

- atogepant 60 mg once daily (n = 546) or
- oral SOC migraine preventive medication (n = 198).

All participants randomised to oral SOC migraine preventive medication were treated with an oral medication recognised as safe and effective for the preventive treatment of migraine.

The following 2 groups of participants were eligible to participate in this study:

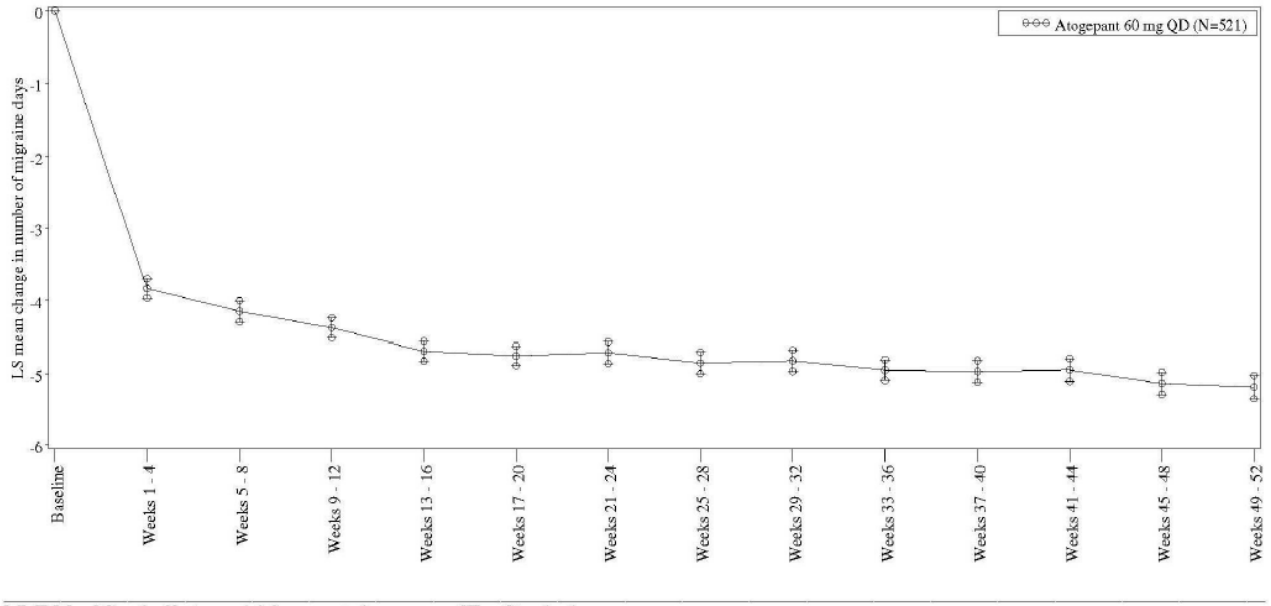
- **De Novo Participants**: participants with no previous exposure to atogepant and who met the inclusion criteria and did not meet the exclusion criteria
- **Study MD-01 Completers**: participants who completed Study CGP-MD-01 (Visit 8) without significant protocol deviations (e.g., noncompliance to protocol required procedures) and who met the inclusion criteria and did not meet the exclusion criteria

Study MD-01 Completers experienced a gap of at least 6 months from the time of completion of Study MD-01 to the start of this long-term safety study. Thus, they had to re-establish study eligibility and had their baseline migraine days re-established (completed at least 20 out of 28 days in the eDiary) during the screening period (but the migraine days were not used as inclusion/exclusion criteria for randomisation).

Of the 543 participants in the atogepant group for the safety population, 428 participants and 362 participants received atogepant for at least 180 days and at least 360 days, respectively.

Efficacy endpoints for long-term efficacy evaluation were not classified as primary, secondary, or additional. Efficacy variables include frequency of migraine days, headache days, acute medication use days, and health outcomes assessments. All efficacy analyses were performed using the modified intent to treat (mITT) population, consisting of all randomised participants who received at least 1 dose of atogepant, had an evaluable baseline period of eDiary data and had at least 1 evaluable postbaseline 4-week period of eDiary data. The mITT population was defined only for the atogepant arm, as no clinical efficacy measurements were collected from participants in the oral standard of care (SOC) migraine preventive medication arm. The purpose of the SOC arm is to collect comparative safety data for 52 weeks.

Figure 13: Least square mean (±SE) of change from baseline in the number of monthly migraine days (MMRM) during the treatment period (mITT Population), study 302



MMRM = Mixed-effects model for repeated measures, SE = Standard error.
The model includes visit (derived as month) as a categorical fixed effect, and the baseline score, baseline-by-visit interaction as covariates, with an unstructured covariance matrix.

2.6.6. Discussion on clinical efficacy

AbbVie Inc. has developed atogepant as an IR tablet in 2 dose strengths containing 10 mg, resp. 60 mg atogepant which is proposed to be indicated for prophylaxis of migraine in adults who have at least 4 migraine days (MD) per month. By using the broad term "migraine" in the proposed indication wording, this is understood to comprise both episodic (EM, Episodic Migraine) and chronic (CM, Chronic migraine) forms of the disease. Another member of the gepant family (rimegepant) was recently approved for prophylactic treatment of episodic migraine. Hence, atogepant is introduced as the first orally administered CGRP antagonist for use across the full spectrum of migraine preventive treatment.

The clinical data package is comprehensive and adequate. It comprises phase II/III dose finding, pivotal efficacy/ safety studies in both the EM and CM population, and additional long-term tolerability studies, which also provide data to support maintenance of effect.

Primary evidence for efficacy is derived from 2 pivotal studies, Study 3101-301-002 ("Advance" study, conducted in the US) for EM prevention and Study 3101-303-002 ("Progress" study, conducted at 142 sites in the US, Europe, Russia, Japan, Korea and others) for the preventive treatment of CM. Additional supportive data are provided by dose-finding Study CGP-MD-01 for EM prophylaxis.

Furthermore, two long-term open-label studies in EM (Study 3101-302-002) [52-week duration] and Study 3101-309-002 [40-week duration]) were conducted. Persistence of efficacy data in EM were obtained from long term study 302 including de novo participants and patients who completed dose finding Study CGP-MD-01. In long-term study 309, including rollover patients, who completed EM study 301, maintenance of effect was not recorded.

Design and conduct of clinical studies

Studies 301 and 303 were 12-week, Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies comparing atogepant with placebo for the preventive treatment of migraine in

participants with EM (Study 301; atogepant 10 mg, 30 mg, and 60 mg QD) and in participants with CM (Study 303; atogepant 30 mg BID and 60 mg QD). The primary efficacy endpoint in both studies was the change from baseline in mean monthly migraine days across the 12-week treatment period (DBT).

Essential features of prevention studies 301 and 303 are accordant with EU Guideline provisions (CPMP/EWP/788/01 Rev.1). The frequency of migraine attacks is documented during an initial prospective 1-month baseline period. Additionally, eligible subjects had to present with pre-defined frequency of migraine attacks per month within the last 3 months prior to Screening visit. The double-blind treatment period covers a 12 week duration. During double-blind treatment, subjects were randomised to receive either atogepant or placebo, an active control arm was not included. Large and highly variable placebo effects have been observed in past migraine prevention trials. Therefore, placebo control is indispensable. An active control arm would have provided added information to contextualise the clinical effect of the test medication, however, is not considered essential from the regulatory perspective.

The designs of studies 301 and 303 are similar. The major difference between the two studies lies in the target population (EM vs CM) and the atogepant dose range that was tested. While all once daily dose arms examined in dose finding study CGP-MD-01 (10 mg QD, 30 mg QD, 60 mg QD) were taken over into pivotal EM study 301, only the highest total daily dose of 60 mg atogepant (tested for the QD and BID dosing interval) was carried forward to the pivotal CM study 303. This may be explained by the expectation that higher dose requirements are given in the more severely affected CM population. In essence, however, the lower 10 and 30 mg daily doses were not tested in CM patients. The posology section of the proposed SmPC does not differentiate between EM and CM. The general dose recommendation is 60 mg atogepant per day. Only in case of concomitant use of either strong CYP3A4 inhibitors or strong OATP inhibitors and in patients with severe renal impairment the dose should be reduced to 10 mg QD.

Inclusion criteria applied throughout pivotal studies align with the standard ICHD-3 diagnostic criteria (ICHD-3, 2018). In EM study 301, a minimum number of 4 MDs per month at baseline is required for study eligibility. Subjects with medication overuse (triptans $\geq$ 10 days/month, or simple analgesics $\geq$ 15 days/month etc.) were excluded. Eligible EM patients must not have $\geq$ 15 headache days (HD) per month on average across the 3 month prior to Visit 1. Conversely, in CM study 303, a minimum number of $\geq$ 15 HDs per month during the 3-month prior to screening and during the 1-month baseline is required for study eligibility. During the baseline period, $\geq$ 8 of these have to qualify as a MD. Other than in EM study 301, subjects with medication overuse were not excluded in the CM population of study 303. Medication overuse is prevalent across CM patients. Inclusion of medication overuse is therefore considered to adequately reflect the target population.

Throughout pivotal studies 301 / 303 for prevention of EM resp. CM any medication to be taken for acute migraine attacks (incl. triptans, NSAIDs, acetaminophen etc.) was permissible. As concerns concomitant preventive migraine medication, there were differences between the EM and the CM study. While any medication with demonstrated efficacy for the prevention of migraine (e.g. amitriptyline, topiramate, propranolol etc.) was prohibited in EM study 301, participants of CM study 303 could take one preventive medication with demonstrated efficacy, provided that the dose has been stable for at least 12 weeks prior to Visit 1. Enrolment of participants with current use of a migraine prevention medication was capped at ~15%. There is no objection against allowing concomitant use of another stably dosed preventive medication on top of atogepant in study 303. This is considered to reflect clinical practice in the more severely affected CM population. At study entry, about 83% of CM subjects reported the use of preventive medication in the past.

In both studies, injectable monoclonal antibodies blocking the CGRP pathway (e.g., Aimovig, Emgality, Ajovy) within 6 months prior to Visit 1 and throughout the study period, were prohibited. It is unclear

whether there is any space for further improvement in patients already receiving biological CGRP ABs. Exclusion of subjects with concomitant injectable CGRP antibodies is therefore acceptable.

Standard and clinically meaningful efficacy endpoints were tested. The change from baseline in mean monthly migraine days across the 12-week DBT was defined as primary endpoint. Further secondary endpoints were tested for superiority of atogepant over placebo while controlling for multiplicity in studies 301/303. The three most relevant was the change from baseline in mean monthly headache days across the 12-week DBT [S1], change from baseline in mean monthly acute medication use days across the 12-week [S2], and ≥ 50% reduction in 3-month average of monthly MDs as responder analysis [S3].

Factually, throughout dose finding study MD-01 and pivotal studies 301/303 identical efficacy endpoints were applied in terms of migraine resp. headache days. Like in dose finding study MD-01 (after implementation of SAP Addendum, 2019-04-11), migraine days (MD) in the narrow sense (per IHS Treatment Guideline) and probable migraine days (PMD) are grouped together and summarised into "Migraine days" in the definition of the primary endpoint of studies 301/303.

Definition of a MD in the narrow sense combines criteria as laid down in the IHS Guidelines and diagnostic criteria ICHD-3. A minimum 2-hour headache duration was defined by the applicant for all phase II/III studies (unless acute medication was taken earlier). Therefore, it differs from IHS Guidelines of the International Headache Society that issued two guidance documents for preventive treatment of migraine attacks: The first one for preventive treatment in CM patients (Tassorelli C et al. 2018), and the second one for preventive treatment in EM patients (Diener HC et al. 2020). These guidance documents specify different definitions of what constitutes a "Migraine Day". While in the EM population a MD is defined as a day with headache lasting at least 30 minutes without intake of analgesics, the guidance for chronic migraine requires the headache to last for at least 4 hours (all other criteria identical). The applicant's defined minimum 2-hour duration of headache is therefore somewhat in-between the two guidance documents. The advantage of defining a uniform endpoint across trials is acknowledged. Furthermore, current guidelines recommend early intervention in acute attacks, i.e. to take acute migraine medication early after the onset migraine headache. By early intervention, the practical sequelae of differences in minimum headache duration are unclear anyway.

Combined measurement of MDs and PMDs (grouped together as primary endpoint "MDs") is acceptable given the variable character of migraine. Symptomatology may vary from one attack to the following within one subject and from one subject to another. It can therefore be expected that on some days not all diagnostic criteria may formally be fulfilled to qualify for a MD in the narrow sense. A reduction of these *probable* MDs as compared to baseline is, however, still regarded as a relevant clinical benefit.

Apart from clinical primary and secondary endpoints as outlined above, additional health-related secondary efficacy endpoints were measured, like the Migraine Specific Quality of Life Questionnaire (MSQ) v2.1, the Activity Impairment in Migraine-Diary (AIM-D) Performance of Daily Activities and Physical Impairment Domain Scores, and the Headache Impact Test (HIT-6).

Overall, it is concluded that standard endpoints were defined in pivotal studies 301/303 that are considered to adequately measure the efficacy of atogepant across the full spectrum of episodic and chronic migraine as compared to placebo. Specified inclusion and exclusion criteria adequately define the proposed target population in line with current ICHD-3 diagnostic criteria. Essential design features of pivotal studies 301/303 are concordant with EU Guideline provisions. There are no major objections related to the design or conduct of pivotal studies in support of the atogepant MAA.

Efficacy data and additional analyses

Phase II/III Dose-finding Study MD-01

The total daily dose range tested in dose-finding study MD-01 ranged from 10 mg to a maximum atogepant dose of 120 mg per day. Apart from dose variation, study MD-01 also examined two different dosing intervals, i.e. once daily vs twice daily regimens. The results of study MD-01 demonstrated atogepant 10 mg QD, 30 mg QD, 60 mg QD, 30 mg BID, and 60 mg BID were superior to placebo (statistically significant after multiplicity adjustment), as measured by the reduction in mean monthly MDs across the 12-week DBT. Secondary endpoints like reduction of HDs, responder analyses of $\geq$ 50% reduction of MDs, and reduction of acute migraine medication use go along the results obtained for the primary endpoint. The positive effect of atogepant in prevention of EM did not reveal a clear dose response relationship. Therefore, the sponsor's decision to take over all three QD dose arms (10 mg, 30 mg, 60 mg) into pivotal EM study 301 appears plausible. The effect achieved with twice daily dosing of atogepant was noticeable. Across all efficacy endpoints, the results obtained with 30 mg BID atogepant were numerically more favourable as compared to the 60 mg QD dose arm. This was not further explored in EM study 301, which followed dose finding study MD-01, however, a BID dose arm was re-explored in the pivotal CM study 303, which was initiated later on.

Pivotal Studies 301/303: Baseline

Pivotal studies 301 (US) and 303 (multiregional incl. US, UK, Canada, China, CZ, DK, FR, DE, IT, Japan, Republic of Korea, PL, Russian Federation, ES, SE, and Taiwan) were conducted in different regions. The population of study 303 was composed of 35% European, 30% North American, and 35% East Asian participants. Demographic features like age (42 years) and gender proportions (87-88% female) were essentially similar between the two studies. There are no issues raised with regard to transferability of study results across regions.

Baseline characteristics of migraine reflect the differences between the EM (study 301) and CM (study 303) population. The more severe disease burden in CM participants (Safety Population) is reflected by the higher portion of subjects with previous migraine prevention attempts (82.9% vs 70.3% in EM), the higher number of MDs per month (16.0 vs 7.4 in EM), and the higher number of monthly HDs (21.1 vs 9.3 in EM). The higher number of monthly MDs and HDs in CM subjects goes along with the higher portion of CM subjects usually taking triptans for acute attacks (72.2% in CM, 48.8% in EM).

A considerable portion of included subjects was overweight. In the total safety population, mean baseline weight was 84.20 kg and mean baseline BMI was 30.56 kg/m^2. Overall, 25% of participants weighed ≥ 96.4 kg and 25% of participants had a BMI ≥ 34.96 kg/m^2. Further reflection is requested to justify that the included study population reflects the target population in terms of BMI.

Pivotal Studies 301/303: Disposition

Completion rates were high in study 301 (total completion 88.5%) and similar across treatment arms (ranging from 86.8% for atogepant 10 mg to 90.1% for the placebo arm, related to all randomised participants). The rates of subjects discontinuing for adverse events were about equal between the highest 60 mg atogepant dose arm (2.6%) and placebo subjects (2.7%). Lack of efficacy was reported very rarely as reason for discontinuation with only one placebo subject and one participant receiving atogepant 60 mg (0.4% each). Like in study 301, the overall completion rate was high in CM study 303 (89.2%). Completion rates for DBT were almost identical across the atogepant 30 mg BID, atogepant 60 mg QD, and placebo arm (89-90%).

In studies 301 and 303, significant Protocol deviations mainly refer to "Exclusion criteria met" (4.5 to 7.3%), "Prohibited concomitant medication taken" (301: 9% for placebo / atogepant 30 mg QD), and

"Study procedure not performed per protocol" (13.2% in study 303). Protocol deviations did not impact data integrity.

Pivotal Studies 301/303: Primary endpoint

The difference in disease severity between the EM and CM population is documented by the number of baseline mean monthly MDs. While EM patients present with 7-8 MDs per month, about 18-19 MDs are reported for CM patients during the 28-day baseline period. Like it could be observed in previous migraine prevention trials, a considerable placebo response was observed in both populations. Both EM and CM placebo patients reduced the number of mean monthly MDs by up to one third (EM: -2.5 MD [-32.8%], CM: -5.1 MD [-26.9%]). Superiority over placebo was shown for all atogepant treatment arms across the two trials. A numerical dose-response relationship was evident for the change from baseline in mean monthly MDs across the 12-week treatment period in Study 301, with greater reductions seen with increasing atogepant dose from 10 to 60 mg QD (LSMD over placebo: 10 mg QD: -1.22, 30 mg QD: -1.38, 60 mg QD: -1.66). The placebo-corrected mean reduction from baseline in mean monthly migraine days observed with the atogepant 60 mg QD dose was the same in the EM and CM studies (LSMD of –1.66 in both Study 301 and Study 303).

Apart from testing dose response in EM study 301 across the once daily 10, 30, 60 mg dose range, the effect of changing the dosing interval from once daily to twice daily was examined for the highest 60 mg daily dose in the CM population. A noticeable difference was observed in favour of the twice daily dosing schedule in terms of the net difference over placebo for the reduction of mean monthly MDs (Study 303: LSMD over placebo: 30 mg BID: -2.24, 60 mg QD: -1.66). The favourable treatment effect of the 30 mg BID regime (as compared to 60 mg QD) was analogously observed in phase II/III dose finding study MD-01 (reduction in mean monthly MDs from baseline: 30 mg BID: -4.0, 60 mg QD: -3.56). It also translates into most relevant secondary endpoints, like reduction of HDs, reduction of acute medication use, and 50% response rates. Further plausibility for the favourable outcome in the 30 mg BID treatment arm is provided by PK study P002. In study P002, plasma levels were compared for different atogepant doses after repetitive dosing over 10 days. C24 hrs trough values after 30 mg BID dosing were remarkably high, higher than after 100 mg once daily dosing and almost reaching the level of the 170 mg once daily regime.

Both in EM study 301 and CM study 303, subjects were followed up for another 4-week period after termination of the 12-week DBT or early discontinuation. According to the Schedule of Procedures of Study 301, participants' eDiary entries regarding headache were evaluated only in those patients who terminated early, but not in patients who completed the entire 12-week DBT. Hence, no data were provided on potential rebound of migraine after cessation of study medication in (all) participants of studies 301/303.

Pivotal Studies: Secondary endpoints

A Headache Day (HD) is defined as any calendar day on which headache pain lasting 2 hours or longer occurs unless an acute headache medication (e.g. ibuprofen, triptan) was used after the start of the headache. As such, a HD captures days with headache irrespective of any other migraine-specific symptoms. In particular in CM patients, where tension type headache and migraine headache often overlap, and who complain about highly frequent or almost continuous headache, measurement of HD is an important parameter for disease burden. Accordingly, reduction of HD from baseline during the 12-week DBT was placed highest in hierarchical multiplicity testing [S1] of secondary endpoints. The results obtained for the S1 secondary endpoint are similar to those obtained for the primary MD reduction endpoint. Statistically significant superiority over placebo after multiplicity adjustment was achieved for each of the atogepant dosages tested in studies 301 and 303. Numerically more favourable results were obtained with increasing doses across the QD (10 mg, 30 mg, 60 mg) dose arms in EM study 301. The net treatment effect over placebo was more favourable for the 30 mg BID dose arm as compared to the

60 mg QD dose arm in study 303 (LSMD for HD reduction from baseline: 30 mg BID: -2.14, 60 mg QD: -1.72).

At baseline, acute medication (incl. both unspecific analgesics and triptans) was used on a mean of 6-7 days among EM patients and on about 15 days in the CM population. The change from baseline in mean monthly acute medication use days [S2] was second in hierarchical testing of secondary endpoints. For both the Acute Medication Use Day and the Triptan Use Day (which was singled out) secondary endpoint significant superiority over placebo could be demonstrated for each atogepant dose arm.

In terms of the $\geq$ 50% reduction in 3-month average of monthly MDs [S3], statistically significant superiority over placebo was achieved for each atogepant dose arm tested across studies 301 / 303. In study 301, more than 50% of subjects allocated to one of the atogepant dose arms achieved a reduction by $\geq$ 50% in the 3-month average of monthly MDs (atogepant: 10 mg QD: 54.6%, 30 mg QD: 58.5%, 60 mg QD: 59.3%; placebo 29.2%). This underlines the clinical relevance of the improvement achieved in terms of the primary MD reduction from baseline across all atogepant dose arms. Among the more severely affected CM population of study 303, response rates were slightly lower (30 mg BID: 42.1%, 60 mg QD: 40.1%). Nonetheless, the probability of achieving a $\geq$ 50% reduction in the 3-month average of monthly MDs was still about twice as high for atogepant as compared to placebo (OR: 30 mg BID: 2.03, 60 mg QD: 1.90).

Time course

The major part of the overall treatment effect is achieved within the first 4-week dosing interval of the 12-week DBT in both the EM and CM population. Thereafter, the reduction of mean monthly MDs is maintained or even slightly increases. The dose response relation across the three QD dose arms of study 301 is consistently observed across the three 28-day intervals of the 12-week DBT. In CM study 303, the more favourable effect of the 30 mg BID dosing regimen as compared to the 60 mg QD dosing scheme gets more pronounced with ongoing treatment duration.

The course of treatment effect was further analysed per week for the first 28-day period of the DBT of studies 301 and 303. In both EM and CM patients, the treatment effect starts within the first week of treatment. There was no clear tendency of increasing or decreasing effect of atogepant over the four 1-week intervals of the first 28-day treatment interval. This is considered to provide valuable information to the prescriber when the treatment effect of atogepant is evaluated within the context of clinical monitoring.

Health Outcome Measures

A number of Health Outcomes Measures were recorded throughout or at the end of 12-week DBT of studies 301 and 303, e.g. Patient Global Impression of Change [PGI-C], Patient Global Impression of Severity [PGI-S], Headache Impact Test Questionnaire [HIT-6], Migraine-Specific Quality of Life Questionnaire [MSQ v2.1], Migraine Disability Assessment Questionnaire [MIDAS], or the Activity Impairment in Migraine-Diary [AIM-D]. Overall, results for these patient-reported outcomes measures were consistent with the results of the primary and secondary efficacy endpoints for both studies, with numerically greater improvements or greater reductions (i.e., improvement) from baseline observed for each of the atogepant treatment groups compared with placebo for the majority of measures.

Subgroups

Several subgroup analyses were performed to explore the effect of baseline factors in the EM (pooled studies 301 and MD-01) and CM population. Atogepant showed consistently greater reductions from baseline in mean monthly migraine days compared with placebo across the demographic subgroups of sex, age (< 40 years; ≥ 40 to < 65 years), race, and BMI. In the Forest Plot presentation for MD reduction, atogepant does separate from placebo in the small subgroup of both EM and CM subjects aged

≥ 65 years. However, the sample sizes were too small per dose group to infer a clinically meaningful difference.

As concerns subgroup per baseline MD, among EM subjects, the portions of patients with < or ≥ 8 migraine days at baseline were about comparable (54.2% resp. 45.8%). In both subgroups, the reduction of mean monthly MDs was significant over placebo across the three atogepant QD dose arms. In the most severely affected subgroup of CM patients with ≥ 18 MDs per month at baseline, atogepant only numerically separates from placebo for the atogepant 60 Mg QD dose arm (LSMD: -0.60 [-2.17, 0.97]), while the atogepant 30 mg BID dose arm reaches statistical significance over placebo (LSMD: -1.79 [-3.38, -0.20]). The more favourable result, obtained in study 303 for the subgroup with the highest disease burden (≥ 18 MDs at baseline) for the atogepant 30 mg BID dose arm as compared to 60 mg QD, aligns with the generally more favourable results observed for the twice daily dosing regimen across primary and secondary efficacy endpoints.

Subgroup analyses were also conducted in EM and CM patients per prior use of migraine preventive medication use. Among EM patients, the portions of subjects with (52.4%) or without (47.6%) prior use of prophylactic treatment were about equal. The net difference over placebo in terms of monthly MD reduction was more favourable in those EM participants that reported prior use of migraine preventive Mx. The more favourable result in subjects with prior prophylaxis experience may be explained by differences in the placebo response between both subgroups. The placebo response was more pronounced in prevention in naïve patients (MD change from baseline: -3.17) as compared to EM subjects reporting prior preventive treatment (MD change from baseline -2.04). Results obtained in the CM population were comparable to the EM population (Study 303: MD change from baseline, placebo response: prior use yes: -4.78, prior use no: -6.98). Again, the outcome in the 30 mg BID dose arm was more favourable as compared to the atogepant 60 mg QD dose arm.

Subgroup analyses per number of failures to previous migraine preventive treatment attempts revealed that the effect of atogepant in terms of reduction of monthly MDs was maintained regardless of the number of previous preventive treatment failures. As evidenced by the net treatment effect over placebo per atogepant dose arm, there was no tendency for a decline in atogepant's efficacy with increasing number of previous treatment failures across the EM and CM population.

The stratification factors unique to Study 303 allowed subgroup analyses by region, acute medication overuse, and preventive medication current use.

While EM Study 301 was conducted at US sites only, CM study 303 comprises different global regions (North America 29.5%, Europe 35.2%, East Asia 35.3%). The effect of atogepant was consistent across regions.

In CM Study 303, participants were stratified for acute headache medication overuse (MoH), which was prevalent in 63.8% of recruited subjects. On average, acute headache medication was taken on 15-16 days during the 28-day baseline period. Across the two atogepant dose arms, point estimates reflecting the net effect over placebo for monthly reduction of MDs were more favourable in those subjects with MoH as compared to those without. The effect of atogepant was consistent regardless of whether subjects presented with acute medication overuse or not.

Concomitant preventive migraine medication was permissible throughout study 303 and was actually taken by 10.5% of recruited CM patients. The subgroup analysis per current preventive medication use showed efficacy of atogepant to be maintained regardless of whether additional concomitant migraine preventive medication was taken or not. Due to the small sample size of participants with concomitant prophylactic treatment the CIs for the point estimates for the net effect over placebo in terms of monthly MD reduction were considerably wider in this subgroup.

Persistence of effect

In open-label, long-term study 302, the daily use of 60 mg atogepant QD (N=546) was compared to SOC (N=198) over a 52-week treatment period in EM patients, either recruited de novo (85.6%) or taken over from dose finding study MD-01 (14.4%). Participants randomised to oral SOC migraine preventive medication (topiramate: 35.7%, beta-blockers 26.0%, tricyclic antidepressants 25.5%) were included to contextualise safety results.

It was primarily designed to examine safety of long term atogepant use in EM patients. However, efficacy was also monitored in those subjects randomised to atogepant. In atogepant patients, a clinically relevant reduction in mean monthly MDs was achieved within the 1st month and was sustained over the 1-year treatment period. Atogepant treatment led to a reduction in the LS mean number of monthly MDs in the first month (Weeks 1-4) of 3.84 days with continued improvement during the remainder of the 52-week treatment period to a LS mean reduction of -5.19 days in the last month (Weeks 49 to 52).

It has to be considered that with ongoing treatment duration the portion of likely atogepant responders is expected to accumulate. However, study completion is high. About two thirds of subjects allocated to atogepant 60 mg QD remains in treatment until week 52 (335/521 [64.3%]). Long term study 302 is concluded to provide supportive evidence of long-term efficacy (52 weeks duration) of atogepant 60 mg once daily in EM patients.

2.6.7. Conclusions on the clinical efficacy

Dose-finding study MD-01 and pivotal studies 301 (EM population) and 303 (CM population) were designed concordant with IHS and EMA guidance and provide a sound database demonstrating evidence for the benefit of atogepant in preventive migraine treatment across the full spectrum of episodic and chronic forms of the disease.

Atogepant in dosages of 10, 30, and 60 mg QD in EM and 60 mg QD and 30 mg BID in CM demonstrated superiority over placebo in reducing the frequency of both migraine days [primary P1], as well as the frequency of headache days [secondary S1] and the associated use of medication for the acute treatment of migraine [S2]. Higher response rates were seen with each atogepant dosage compared with placebo for participants with ≥ 50% reduction in the 3-month average of monthly migraine days [S3].

A numerical dose-response relationship was evident for the change from baseline in mean monthly MDs across the 12-week DBT in EM Study 301, with greater reductions seen with increasing atogepant dose from 10 to 60 mg QD. Only the highest maximum daily dose of 60 mg tested in EM study 301 was taken over in CM Study 303. To explore the potential impact of the once daily vs twice daily dosing regimen, the 60 mg daily dose was examined across a 60 mg QD and a 30 mg BID treatment arm in CM Study 303. The placebo-corrected mean reduction from baseline in mean monthly migraine days observed with the atogepant 60 mg QD dose was the same in the EM and CM studies (LSMD of –1.66 in both Study 301 and 303).

The robustness of the primary and secondary endpoint results [S1-3] after multiplicity adjustment for each of the atogepant dosages tested in studies 301/303 was confirmed across several subgroup analyses, like e.g. prior use of prevention medication, concomitant use of another prophylactic medication (study 303), or prevalent medication overuse (study 303).

The onset of clinical effect of atogepant is early. In both the EM and CM population, the major part of the overall treatment effect in terms of MD reduction is achieved within the first 28-day period of the 12-week DBT of studies 301 and 303.

In terms of persistence of effect, supportive efficacy data are obtained from open-label, long-term study 302 in EM patients for treatment with atogepant 60 mg QD over 52 weeks. A clinically relevant reduction

in mean monthly MDs was achieved within the 1st month and was sustained over the 1-year treatment period.

Overall, there are no objections with regard to efficacy for the proposed use of atogepant in migraine prevention. The choice of the dosing interval of the 60 mg daily dose of atogepant was further elucidated. The numerically most favourable outcome across primary and secondary endpoints in studies MD-01 (EM) and pivotal study 303 (CM) was observed for the 30 mg BID dosing regimen. However, the applicant applied for the 60 mg QD once daily as regular dosing scheme only. It is established that compliance with migraine preventive treatment remains a challenge. Therefore, the potential advantage of a once daily dosing regimen is evident in terms of compliance. On the other hand, administration of the most effective treatment is equally expected to positively impact on patient compliance. A 30 mg tablet formulation was tested in Study 301, i.e. is available. Nonetheless, the proposed posology strategy is to confine to the uniform 60 mg once daily dosing schedule in order to provide a simple and convenient posology scheme, which the applicant assumes will best promote patient compliance.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Safety data from the clinical studies included in the application have been organised into 4 distinct analysis sets for the ISS based on study design and populations.

Placebo-controlled (PCS) analysis set (Group 1a): pooled data from the 3 completed double-blind placebo-controlled studies of atogepant administered orally for 12 weeks for the prevention of migraine in participants with EM (Studies 301 and MD-01) and participants with CM (Study 303).

Long-term safety (LTS) analysis set (Group 2a): pooled data from 4 atogepant open-label LTS studies up to 104 weeks duration (completed Studies 302 and 309 in participants with EM, and ongoing Studies 306 and 312 in participants with CM).

Although extension Study 312 enrolled completers from Studies 303 and 304, the latter study is ongoing and still blinded. Therefore, data from participants who rolled over from Study 304 are not included in the LTS analysis set for this application. At the time of the 10 January 2022 ISS data cut-off date, Study 312 included a 52-week open-label treatment period (the protocol was subsequently amended to include a 104-week open-label treatment period).

An interim update of LTS data cut-off (11 October 2022) was provided within the course of the procedure with focus on hepatic safety. LTS studies 306 and 312 are still ongoing. The comprehensive analysis of the LTS safety dataset, as presented within this document (and Module 2.7.4) refers to the initial data cut-off (10 January 2022).

All atogepant analysis set (Group 3a): pooled data from all atogepant-treated participants in Phase 2/3 and Phase 3 Studies MD-01, 301, 302, 303, 306, 309, 311, and 312.

Phase 1 analysis set (Group 4a): pooled data from 20 Phase 1 clinical pharmacology studies (19 conducted in healthy participants [including participants with hepatic impairment in Study CGP-PK-01] and 1 conducted in participants with migraine [Study 3101-106-002, a drug-drug interaction study with ubrogepant]).

Across all studies in the atogepant clinical development programme, 3230 unique participants were exposed to ≥ 1 dose of atogepant, including 2626 participants in Phase 2/3 and Phase 3 studies and 604 participants in Phase 1 clinical pharmacology studies. The Placebo-controlled Analysis Set (PCS) included

N=2500 subjects in total, N=1837 of these received atogepant and N=663 received placebo. The Long-term safety Set (LTS) included N=1858 subjects in total, 1662 received atogepant 60 mg QD and N=196 received SOC.

Table 40: Number of treated participants by clinical trial group (as of 10 january 2022)

Clinical Trial Group	Atogepant n	Placebo n	Standard of Care[a] n
Phase 1 studies[b]	604	132	-
Placebo-controlled studies (Studies CGP-MD-01, 3101-301-002, 3101-303-002)	1837	663	-
Open-label safety studies (Studies 3101-302-002, 3101-306-002, 3101-309-002, 3101-311-002, 3101-312-002)	1665[c]	-	196

a. Standard-of-care group was included only in Study 3101-302-002.
b. Some participants were exposed to both atogepant and placebo due to crossover study design.
c. Total includes 1662 participants in the long-term safety analysis set (Group 2a) and 3 participants from 12-week open-label Study 3101-311-002.

Source: ISS (R&D/22/0367) Table 1-3.1.2 and Table 2-1.2.2

- ***Adverse events***

The percentages of participants who had AEs were generally similar across treatment groups in the analysis sets. Most individual AE preferred terms were reported at low rates in all treatment groups. The majority of AEs were mild or moderate in severity, with few severe AEs in any treatment group.

Table 41: Overview of adverse events in the placebo-controlled analysis set (safety population)

		Atogepant				
	Placebo (N = 663) n (%)	10 mg QD (N = 314) n (%)	30 mg QD (N = 411) n (%)	60 mg QD (N = 678) n (%)	30 mg BID (N = 343) n (%)	60 mg BID (N = 91) n (%)
TEAEs	344 (51.9)	178 (56.7)	234 (56.9)	396 (58.4)	197 (57.4)	53 (58.2)
Deaths	0	0	0	0	0	0
TESAEs	7 (1.1)	3 (1.0)	2 (0.5)	9 (1.3)	4 (1.2)	0
TEAEs leading to discontinuation	21 (3.2)	13 (4.1)	14 (3.4)	21 (3.1)	18 (5.2)	6 (6.6)

BID = twice daily; QD = once daily; TEAE = treatment-emergent adverse events; TESAE = treatment-emergent serious adverse events

Source: ISS (R&D/22/0367) Table 5-1.1.1, Table 6-1.3.1, Table 5-1.5.1, Table 6-1.1.1

Placebo-controlled Analysis Set

The most common AEs in any atogepant group (≥ 5% of participants) were nausea, constipation, fatigue, and upper respiratory tract infection.

For the following AEs the majority of cases were considered by the Investigator to be related to study drug:

- **Constipation** was reported for 2.0% of participants in the placebo group, compared with 6.1%, 6.3%, and 7.5% in the atogepant 10, 30, and 60 mg QD groups, respectively, and 9.0% and 6.6% in the atogepant 30 and 60 mg BID groups, respectively.
- **Nausea** was reported for 3.3% of participants in the placebo group compared with 5.1%, 5.6%, and 9.0% in the atogepant 10, 30, and 60 mg QD groups, respectively, and 8.2% and 9.9% in the atogepant 30 and 60 mg BID groups, respectively; the incidence of nausea increased with higher doses of atogepant.
- **Fatigue** was reported for 2.6% of participants in the placebo group compared with 1.3%, 2.4%, and 3.2% in the atogepant 10, 30, and 60 mg QD groups, respectively, and 3.8% and 9.9% in the atogepant 30 and 60 mg BID groups.

Table 42: Number and percentage of participants with common AEs (≥ 2% of participants in any treatment group) by preferred term in the placebo-controlled analysis set

Preferred Term	Placebo (N=663) n (%)	Atogepant 10 mg QD (N=314) n (%)	Atogepant 30 mg QD (N=411) n (%)	Atogepant 60 mg QD (N=678) n (%)	Atogepant 30 mg BID (N=343) n (%)	Atogepant 60 mg BID (N=91) n (%)	Atogepant Overall (N=1837) n (%)
Nausea	22 (3.3)	16 (5.1)	23 (5.6)	61 (9.0)	28 (8.2)	9 (9.9)	137 (7.5)
Constipation	13 (2.0)	19 (6.1)	26 (6.3)	51 (7.5)	31 (9.0)	6 (6.6)	133 (7.2)
Upper respiratory tract infection	31 (4.7)	15 (4.8)	27 (6.6)	21 (3.1)	12 (3.5)	6 (6.6)	81 (4.4)
Nasopharyngitis	23 (3.5)	7 (2.2)	19 (4.6)	33 (4.9)	11 (3.2)	3 (3.3)	73 (4.0)
Urinary tract infection	15 (2.3)	5 (1.6)	20 (4.9)	20 (2.9)	12 (3.5)	3 (3.3)	60 (3.3)
Fatigue	17 (2.6)	4 (1.3)	10 (2.4)	22 (3.2)	13 (3.8)	9 (9.9)	58 (3.2)
Dizziness	10 (1.5)	5 (1.6)	8 (1.9)	18 (2.7)	12 (3.5)	3 (3.3)	46 (2.5)
Decreased appetite	1 (0.2)	5 (1.6)	4 (1.0)	19 (2.8)	7 (2.0)	4 (4.4)	39 (2.1)
Blood creatine phosphokinase increased	5 (0.8)	9 (2.9)	5 (1.2)	11 (1.6)	7 (2.0)	2 (2.2)	34 (1.9)
Somnolence	7 (1.1)	9 (2.9)	8 (1.9)	13 (1.9)	3 (0.9)	0 (0.0)	33 (1.8)
Sinusitis	9 (1.4)	8 (2.5)	5 (1.2)	11 (1.6)	6 (1.7)	2 (2.2)	32 (1.7)
Diarrhoea	12 (1.8)	3 (1.0)	6 (1.5)	14 (2.1)	4 (1.2)	3 (3.3)	30 (1.6)
Gastroenteritis	8 (1.2)	3 (1.0)	10 (2.4)	10 (1.5)	5 (1.5)	0 (0.0)	28 (1.5)
Insomnia	8 (1.2)	5 (1.6)	2 (0.5)	11 (1.6)	5 (1.5)	2 (2.2)	25 (1.4)
Arthralgia	11 (1.7)	3 (1.0)	7 (1.7)	7 (1.0)	7 (2.0)	0 (0.0)	24 (1.3)
Vomiting	10 (1.5)	4 (1.3)	1 (0.2)	11 (1.6)	4 (1.2)	3 (3.3)	23 (1.3)
Abdominal pain	5 (0.8)	2 (0.6)	3 (0.7)	7 (1.0)	6 (1.7)	2 (2.2)	20 (1.1)
Abdominal pain upper	6 (0.9)	2 (0.6)	4 (1.0)	5 (0.7)	8 (2.3)	0 (0.0)	19 (1.0)
Muscle strain	2 (0.3)	5 (1.6)	5 (1.2)	4 (0.6)	0 (0.0)	2 (2.2)	16 (0.9)
Vertigo	4 (0.6)	3 (1.0)	3 (0.7)	4 (0.6)	4 (1.2)	2 (2.2)	16 (0.9)
Weight decreased	3 (0.5)	1 (0.3)	0 (0.0)	9 (1.3)	0 (0.0)	2 (2.2)	12 (0.7)
Choking	1 (0.2)	0 (0.0)	2 (0.5)	1 (0.1)	0 (0.0)	2 (2.2)	5 (0.3)
Flank pain	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	3 (3.3)	5 (0.3)
Bacterial vaginosis [f]	2 (0.3)	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	2 (2.4)	4 (0.2)

BID = twice daily; QD = once daily
Notes:
N = number of participants in the safety population of the treatment group.
n = number of participants in the specific category.
Percentages calculated as 100 x (n/N).
Participants are counted only once within each preferred term.

Long-term Safety Set

AEs were reported for 78.6% of participants in the standard-of-care group and 63.5% of participants in the atogepant 60 mg QD group (64.5% in EM Studies 302 and 309 and 60.8% in CM Studies 306 and 312) in the long-term safety analysis set.

The majority of AEs were mild or moderate in severity, with few severe AEs in either treatment group. AEs that were considered by the investigator to be related to study drug were reported for 36.2% of participants in the standard-of-care group and 13.3% of participants in the atogepant 60 mg QD group.

The most common AEs in the atogepant 60 mg QD group (≥ 5% of participants) were constipation and upper respiratory tract infection.

Table 43: Number and percentage of participants with common AEs (≥ 2% of participants in either treatment group) by preferred term in the long-term safety analysis set

Preferred Term	Standard-of-Care (N=196) n (%)	Atogepant 60 mg QD (N=1662) n (%)
Constipation	6 (3.1)	99 (6.0)
Upper respiratory tract infection	24 (12.2)	99 (6.0)
Nasopharyngitis	10 (5.1)	81 (4.9)
Urinary tract infection	9 (4.6)	72 (4.3)
Nausea	12 (6.1)	71 (4.3)
Pyrexia	1 (0.5)	59 (3.5)
Arthralgia	6 (3.1)	46 (2.8)
Sinusitis	6 (3.1)	44 (2.6)
Back pain	5 (2.6)	37 (2.2)
Dizziness	22 (11.2)	37 (2.2)
Weight decreased	3 (1.5)	37 (2.2)
Gastroenteritis	0 (0.0)	36 (2.2)
Influenza	5 (2.6)	35 (2.1)
Anxiety	11 (5.6)	34 (2.0)
Aspartate aminotransferase increased	5 (2.6)	29 (1.7)
Fatigue	12 (6.1)	29 (1.7)
Alanine aminotransferase increased	4 (2.0)	27 (1.6)
Diarrhoea	6 (3.1)	23 (1.4)
Migraine	6 (3.1)	23 (1.4)
Depression	4 (2.0)	22 (1.3)
Headache	5 (2.6)	20 (1.2)
Gastroenteritis viral	4 (2.0)	18 (1.1)
Insomnia	7 (3.6)	15 (0.9)
Weight increased	11 (5.6)	15 (0.9)
Somnolence	8 (4.1)	13 (0.8)
Contusion	6 (3.1)	9 (0.5)
Paraesthesia	12 (6.1)	8 (0.5)
Dry mouth	8 (4.1)	7 (0.4)
Hypoaesthesia	4 (2.0)	5 (0.3)
Sedation	4 (2.0)	0 (0.0)

QD = once daily

Notes:
N = number of participants in the safety population of the treatment group.
n = number of participants in the specific category.
Percentages calculated as 100 x (n/N).
Participants are counted only once within each preferred term.

Cross reference: ISS (R&D/22/0367) Table 5-2.4.1

Adverse Drug Reactions

Adverse drug reactions (ADRs) were determined by evaluating TEAEs in the placebo-controlled migraine studies (Studies MD-01, 301, and 303) that occurred with a ≥ 2% overall incidence rate in any of the atogepant groups and at a rate at least 2% greater than placebo.

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.

Constipation, decreased appetite, nausea, and fatigue/somnolence were identified as ADRs.

Comparison of Adverse Events in EM versus CM Studies

Placebo-Controlled Studies

The type and frequency of AEs were similar in the placebo-controlled EM and CM studies.

Table 44: Summary of AEs in placebo-controlled EM studies and CM study

	Number (%) Participants								
	Study 3101-301-002 and Study CGP-MD-01: EM						Study 3101-303-002: CM		
		Atogepant						Atogepant	
	Placebo (N = 408)	10 mg QD (N = 314)	30 mg QD (N = 411)	60 mg QD (N = 417)	30 mg BID (N = 86)	60 mg BID (N = 91)	Placebo (N = 255)	30 mg BID (N = 257)	60 mg QD (N = 261)
AEs	218 (53.4)	178 (56.7)	234 (56.9)	231 (55.4)	52 (60.5)	53 (58.2)	126 (49.4)	145 (56.4)	165 (63.2)
Treatment-related AEs	50 (12.3)	68 (21.7)	73 (17.8)	87 (20.9)	18 (20.9)	24 (26.4)	34 (13.3)	52 (20.2)	45 (17.2)
Deaths	0	0	0	0	0	0	0	0	0
SAEs	4 (1.0)	3 (1.0)	2 (0.5)	2 (0.5)	0	0	3 (1.2)	4 (1.6)	7 (2.7)
AEs leading to discontinuation of study drug	11 (2.7)	13 (4.1)	14 (3.4)	12 (2.9)	5 (5.8)	6 (6.6)	10 (3.9)	13 (5.1)	9 (3.4)

AE = adverse event; BID = twice daily; CM = chronic migraine; EM = episodic migraine; QD = once daily; SAE = serious adverse event

Table 45: Number of participants with common AEs (≥ 5% of participants in any treatment group) by preferred term in placebo-controlled EM studies and CM study

	Number (%) Participants								
	Study 3101-301-002 and Study CGP-MD-01: EM						Study 3101-303-002: CM		
		Atogepant						Atogepant	
Preferred Term	Placebo (N = 408)	10 mg QD (N = 314)	30 mg QD (N = 411)	60 mg QD (N = 417)	30 mg BID (N = 86)	60 mg BID (N = 91)	Placebo (N = 255)	30 mg BID (N = 257)	60 mg QD (N = 261)
Fatigue	10 (2.5)	4 (1.3)	10 (2.4)	14 (3.4)	2 (2.3)	9 (9.9)	7 (2.7)	11 (4.3)	8 (3.1)
Nausea	13 (3.2)	16 (5.1)	23 (5.6)	36 (8.6)	8 (9.3)	9 (9.9)	9 (3.5)	20 (7.8)	25 (9.6)
Constipation	5 (1.2)	19 (6.1)	26 (6.3)	25 (6.0)	3 (3.5)	6 (6.6)	8 (3.1)	28 (10.9)	26 (10.0)
Upper respiratory tract infection	25 (6.1)	15 (4.8)	27 (6.6)	19 (4.6)	6 (7.0)	6 (6.6)	6 (2.4)	6 (2.3)	2 (0.8)
Nasopharyngitis	12 (2.9)	7 (2.2)	19 (4.6)	22 (5.3)	1 (1.2)	3 (3.3)	11 (4.3)	10 (3.9)	11 (4.2)
Blood creatine phosphokinase increased	5 (1.2)	9 (2.9)	5 (1.2)	9 (2.2)	6 (7.0)	2 (2.2)	0	1 (0.4)	2 (0.8)

BID = twice daily; CM = chronic migraine; EM = episodic migraine; QD = once daily

Notes: Data are presented by decreasing frequency in the atogepant 60 mg BID group.

Participants counted only once within each preferred term.

MedDRA version 22.0 was used for the EM studies; MedDRA version 24.0 was used for the CM study.

Long-Term Safety Studies

Pyrexia was reported at a higher rate in CM (11.1%) than in EM (0.9%) atogepant-treated participants in the long-term safety analysis set, which was likely related to COVID-19 vaccination in Study 306. Although upper respiratory infection was higher in EM (7.7%) than CM (1.2%) atogepant-treated participants, it is lower than in the standard-of-care group (12.2%); this was likely related to global mask-wearing and social distancing during the COVID-19 pandemic that occurred during the conduct of the CM studies. With the exception of these 2 AEs (pyrexia and upper respiratory infection), the type and frequency of AEs were similar in the long-term safety EM and CM studies.

Table 46: Number of participants with common AEs (≥ 5% of participants in any treatment group) by preferred term in long-term safety EM and CM studies

	Number (%) Participants		
	Study 3101-302-002	Studies 3101-302-002 and 3101-309-002: EM	Studies 3101-306-002 and 3101-312-002: CM
	Standard-of-Care	Atogepant 60 mg QD	
Preferred Term	(N = 196)	(N = 1228)	(N = 434)
Pyrexia	1 (0.5)	11 (0.9)	48 (11.1)
Constipation	6 (3.1)	62 (5.0)	37 (8.5)
Nausea	12 (6.1)	57 (4.6)	14 (3.2)
Fatigue	12 (6.1)	22 (1.8)	7 (1.6)
Upper respiratory infection	24 (12.2)	94 (7.7)	5 (1.2)
Nasopharyngitis	10 (5.1)	57 (4.6)	24 (5.5)
Urinary tract infection	9 (4.6)	64 (5.2)	8 (1.8)
Weight increased	11 (5.6)	15 (1.2)	0
Dizziness	22 (11.2)	34 (2.8)	3 (0.7)
Paraesthesia	12 (6.1)	8 (0.7)	0
Anxiety	11 (5.6)	30 (2.4)	4 (0.9)

CM = chronic migraine; EM = episodic migraine; QD = once daily
Cross reference: ISS (R&D/22/0367) Table 5-2.1.1

Analysis of Adverse Events of Special Interest (AESI)

Cardiovascular events (cardiac arrythmias, central nervous system vascular disorders, embolic and thrombotic, hypertension, and ischaemic heart disease), hepatic AEs, suicide-related events, and abuse-related AEs were identified as AESIs for the placebo-controlled, long-term safety, and Phase 1 analysis sets.

AESI: Cardiovascular Events

Cardiovascular events were examined for reported preferred terms that could be indicative of a potential effect of atogepant on the cardiovascular system because of blockade of calcitonin gene-related peptide (CGRP) receptors (which are expressed widely throughout the vascular system), and which could inhibit vasodilation, with potential effects on vascular tone, blood pressure, and global or regional blood flow. The following 5 AEs of clinical interest categories were evaluated: cardiac arrhythmias, ischaemic heart disease, hypertension, central nervous system vascular disorders, and embolic and thrombotic events.

Placebo-Controlled Analysis Set

A history of hypertension was reported for 10.4% of participants in the placebo group; 10.5%, 10.5%, and 9.6% in the atogepant 10, 30, and 60 mg QD groups, respectively; and 7.9% and 13.2% in the atogepant 30 and 60 mg BID groups, respectively, in the placebo-controlled analysis set.

The incidence of hypertension AEs in the atogepant groups was low and similar to that of placebo in the placebo-controlled analysis set (0.5% in the placebo group; 0.6%, 1.0%, and 0.6% in the atogepant 10, 30, and 60 mg QD groups, respectively; and 1.7% and 1.1% in the atogepant 30 and 60 mg BID groups, respectively).

Table 47: Number and percentage of participants with cardiovascular events in the placebo-controlled analysis set

Category Preferred Term	Placebo (N=663) n (%)	Atogepant 10 mg QD (N=314) n (%)	Atogepant 30 mg QD (N=411) n (%)	Atogepant 60 mg QD (N=678) n (%)	Atogepant 30 mg BID (N=343) n (%)	Atogepant 60 mg BID (N=91) n (%)	Atogepant Overall (N=1837) n (%)
Cardiac arrhythmias TEAE	1 (0.2)	1 (0.3)	1 (0.2)	3 (0.4)	1 (0.3)	0 (0.0)	6 (0.3)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.3)	0 (0.0)	3 (0.2)
Atrioventricular block second degree	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Bundle branch block left	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Supraventricular extrasystoles	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Atrioventricular block first degree	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Central nervous system vascular disorders TEAE	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	3 (0.2)
Hemianaesthesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Hemiparaesthesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Intracranial aneurysm	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Embolic and thrombotic events TEAE	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.3)	0 (0.0)	3 (0.2)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Haemorrhoids thrombosed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Postoperative thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Hypertension TEAE	3 (0.5)	2 (0.6)	4 (1.0)	4 (0.6)	6 (1.7)	1 (1.1)	17 (0.9)
Hypertension	1 (0.2)	1 (0.3)	4 (1.0)	3 (0.4)	5 (1.5)	1 (1.1)	14 (0.8)
Blood pressure diastolic increased	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
Blood pressure increased	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.1)
Blood pressure fluctuation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic heart disease TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

BID = twice daily; QD = once daily; TEAE = treatment-emergent adverse event
Notes:
Participants are counted only once within each category, and preferred term.
Cross reference: ISS (R&D/22/0367) Tables 7-1.1.1 through 7-1.5.1

All hypertension AEs were mild or moderate in severity and non-serious and with the exception of the 1 participant in Study 303 (atogepant 30 BID group) with an AE of blood pressure increased, none were considered by the investigator to be related to study drug. No dose-dependent relationship in the incidence of hypertension events was evident. One participant in the atogepant 30 mg BID group in Study CGP-MD-01 had an AE of hypertension (worsening of) that resulted in discontinuation of study drug; the event was moderate and began on Day 54 and was ongoing at last report.

New antihypertensive medication use and/or increased dose of an existing antihypertensive medication occurred infrequently (0.8% in placebo versus 0.6%, 1.0%, and 0.1% in the atogepant 10, 30, and 60 mg QD groups, respectively, and 1.5% and 2.2% in the atogepant 30 and 60 mg BID groups).

The incidence of other cardiovascular events was low in the placebo-controlled analysis set and no clinically meaningful differences between the placebo group and the atogepant groups were observed. No safety concerns were identified.

AESI: Hepatic Safety

The atogepant clinical development programme incorporated monitoring for any signs of hepatic injury in participants. Hepatic AEs (comprised of the hepatic disorders SMQ [broad] plus the PT of liver transplant) and laboratory data were examined.

A clinical external adjudication committee (an independent panel of liver experts) was established for the blinded surveillance, monitoring, and adjudication of post-baseline elevations of ALT and/or AST ≥ 3 × ULN for participants who received either atogepant or placebo; aminotransferase elevations ≥ 3 × ULN for participants who received standard-of-care were not adjudicated per the adjudication charter. The adjudication charter defined a standardised process for the adjudication of data associated with these events to determine whether the elevation was related to study drug. The relationship of the cases to study drug was adjudicated using a 3-category scale (probable, possible, or unlikely) based on the criteria specified in the hepatic adjudication committee charter.

Post-baseline ALT or AST elevations ≥ 3 × ULN were prospectively defined in the Phase 2/3 study and Phase 3 studies as AESIs and were systematically investigated in accordance with the drug-induced liver injury (DILI) guidance (FDA 2009).

Placebo-Controlled Analysis Set (PCS)

Hepatic Injury Adverse Events (PCS)

The percentages of participants in the placebo-controlled analysis set who had hepatic injury AEs were 1.8% in the placebo group versus 1.5% across atogepant groups. The most common AEs were ALT increased and AST increased.

None of these AEs was serious, and the majority were mild or moderate in severity. Two participants discontinued study drug because of these AEs.

Table 48: Number and percentage of participants with hepatic disorder or liver transplant adverse events in the placebo-controlled analysis set

Category Preferred Term	Placebo (N=663) n (%)	Atogepant 10 mg QD (N=314) n (%)	Atogepant 30 mg QD (N=411) n (%)	Atogepant 60 mg QD (N=678) n (%)	Atogepant 30 mg BID (N=343) n (%)	Atogepant 60 mg BID (N=91) n (%)	Atogepant Overall (N=1837) n (%)
Hepatic Injury TEAE	12 (1.8)	6 (1.9)	6 (1.5)	11 (1.6)	4 (1.2)	1 (1.1)	28 (1.5)
Alanine aminotransferase increased	10 (1.5)	5 (1.6)	4 (1.0)	9 (1.3)	2 (0.6)	1 (1.1)	21 (1.1)
Aspartate aminotransferase increased	9 (1.4)	4 (1.3)	4 (1.0)	7 (1.0)	3 (0.9)	1 (1.1)	19 (1.0)
Blood alkaline phosphatase increased	2 (0.3)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
International normalised ratio increased	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.1)
Hepatitis E antibody positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Liver injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Prothrombin time prolonged	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Blood bilirubin increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic steatosis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

BID = twice daily; QD = once daily; TEAE = treatment-emergent adverse event
Note:
Participants are counted only once within each category and preferred term.

Cross reference: ISS (R&D/22/0367) Table 7-1.8.1

Hepatic Laboratory Values of Special Interest (PCS)

Post-baseline elevations of ALT and/or AST ≥ 3 × ULN were generally similar across atogepant groups and similar to placebo. No participant had concurrent ALT or AST elevations ≥ 3 × ULN and total bilirubin ≥ 1.5 × ULN.

One participant (atogepant 60 mg QD group), with a family history of Gilbert's syndrome, had a post-baseline isolated total bilirubin elevation ≥ 2 × ULN.

Table 49: Number and percentage of participants in the placebo-controlled analysis set with post-baseline hepatic laboratory values of special interest

Hepatic Laboratory Parameter (Unit)	Criterion	Placebo (N=663) n/N1 (%)	Atogepant 10 mg QD (N=314) n/N1 (%)	Atogepant 30 mg QD (N=411) n/N1 (%)	Atogepant 60 mg QD (N=678) n/N1 (%)	Atogepant 30 mg BID (N=343) n/N1 (%)	Atogepant 60 mg BID (N=91) n/N1 (%)	Atogepant Overall (N=1837) n/N1 (%)
ALT (U/L)	>= 1.0 * ULN	85/653 (13.0)	30/312 (9.6)	46/405 (11.4)	59/666 (8.9)	27/339 (8.0)	8/88 (9.1)	170/1810 (9.4)
	>= 1.5 * ULN	33/653 (5.1)	5/312 (1.6)	19/405 (4.7)	19/666 (2.9)	9/339 (2.7)	1/88 (1.1)	53/1810 (2.9)
	>= 2.0 * ULN	15/653 (2.3)	5/312 (1.6)	6/405 (1.5)	9/666 (1.4)	3/339 (0.9)	1/88 (1.1)	24/1810 (1.3)
	>= 3.0 * ULN	6/653 (0.9)	4/312 (1.3)	2/405 (0.5)	4/666 (0.6)	2/339 (0.6)	1/88 (1.1)	13/1810 (0.7)
	>= 5.0 * ULN	2/653 (0.3)	1/312 (0.3)	1/405 (0.2)	2/666 (0.3)	1/339 (0.3)	0/88 (0.0)	5/1810 (0.3)
	>= 10.0 * ULN	0/653 (0.0)	1/312 (0.3)	0/405 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	1/1810 (0.1)
	>= 20.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/405 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1810 (0.0)
AST (U/L)	>= 1.0 * ULN	51/653 (7.8)	16/312 (5.1)	21/405 (5.2)	34/666 (5.1)	14/339 (4.1)	2/88 (2.3)	87/1810 (4.8)
	>= 1.5 * ULN	17/653 (2.6)	5/312 (1.6)	6/405 (1.5)	9/666 (1.4)	6/339 (1.8)	1/88 (1.1)	27/1810 (1.5)
	>= 2.0 * ULN	7/653 (1.1)	3/312 (1.0)	5/405 (1.2)	8/666 (1.2)	4/339 (1.2)	1/88 (1.1)	21/1810 (1.2)
	>= 3.0 * ULN	4/653 (0.6)	1/312 (0.3)	3/405 (0.7)	5/666 (0.8)	2/339 (0.6)	0/88 (0.0)	11/1810 (0.6)
	>= 5.0 * ULN	3/653 (0.5)	1/312 (0.3)	0/405 (0.0)	4/666 (0.6)	0/339 (0.0)	0/88 (0.0)	5/1810 (0.3)
	>= 10.0 * ULN	0/653 (0.0)	1/312 (0.3)	0/405 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	1/1810 (0.1)
	>= 20.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/405 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1810 (0.0)
ALT or AST (U/L)	>= 1.0 * ULN	93/653 (14.2)	36/312 (11.5)	50/405 (12.3)	71/666 (10.7)	32/339 (9.4)	9/88 (10.2)	198/1810 (10.9)
	>= 1.5 * ULN	35/653 (5.4)	7/312 (2.2)	20/405 (4.9)	21/666 (3.2)	10/339 (2.9)	1/88 (1.1)	59/1810 (3.3)
	>= 2.0 * ULN	17/653 (2.6)	6/312 (1.9)	8/405 (2.0)	12/666 (1.8)	5/339 (1.5)	1/88 (1.1)	32/1810 (1.8)
	>= 3.0 * ULN	8/653 (1.2)	4/312 (1.3)	3/405 (0.7)	6/666 (0.9)	3/339 (0.9)	1/88 (1.1)	17/1810 (0.9)
	>= 5.0 * ULN	4/653 (0.6)	1/312 (0.3)	1/405 (0.2)	4/666 (0.6)	1/339 (0.3)	0/88 (0.0)	7/1810 (0.4)
	>= 10.0 * ULN	0/653 (0.0)	1/312 (0.3)	0/405 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	1/1810 (0.1)
	>= 20.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/405 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1810 (0.0)
TBL (umol/L)	>= 1.0 * ULN	18/653 (2.8)	7/312 (2.2)	21/404 (5.2)	27/666 (4.1)	11/339 (3.2)	1/88 (1.1)	67/1809 (3.7)
	>= 1.5 * ULN	4/653 (0.6)	1/312 (0.3)	3/404 (0.7)	6/666 (0.9)	2/339 (0.6)	0/88 (0.0)	12/1809 (0.7)
	>= 2.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/404 (0.0)	1/666 (0.2)	0/339 (0.0)	0/88 (0.0)	1/1809 (0.1)
	>= 3.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/404 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1809 (0.0)
	>= 5.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/404 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1809 (0.0)
	>= 10.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/404 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1809 (0.0)
	>= 20.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/404 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1809 (0.0)
ALP (U/L)	>= 1.0 * ULN	52/653 (8.0)	33/312 (10.6)	44/404 (10.9)	51/666 (7.7)	18/339 (5.3)	3/88 (3.4)	149/1809 (8.2)
	>= 1.5 * ULN	4/653 (0.6)	5/312 (1.6)	2/404 (0.5)	2/666 (0.3)	2/339 (0.6)	0/88 (0.0)	11/1809 (0.6)
	>= 2.0 * ULN	0/653 (0.0)	2/312 (0.6)	0/404 (0.0)	0/666 (0.0)	1/339 (0.3)	0/88 (0.0)	3/1809 (0.2)
	>= 3.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/404 (0.0)	0/666 (0.0)	1/339 (0.3)	0/88 (0.0)	1/1809 (0.1)
	>= 5.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/404 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1809 (0.0)
	>= 10.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/404 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1809 (0.0)
	>= 20.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/404 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1809 (0.0)
Concurrent elevations*	ALT or AST >= 3.0 * ULN AND TBL >= 1.5 * ULN	0/653 (0.0)	0/312 (0.0)	0/404 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1809 (0.0)
	ALT or AST >= 3.0 * ULN AND TBL >= 2.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/404 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1809 (0.0)
Potential Hy's Law*	ALT or AST >= 3.0 * ULN AND TBL >= 2.0 * ULN AND ALP < 2.0 * ULN	0/653 (0.0)	0/312 (0.0)	0/404 (0.0)	0/666 (0.0)	0/339 (0.0)	0/88 (0.0)	0/1809 (0.0)

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BID = twice daily; TBL = total bilirubin; QD = once daily; ULN = upper limit of normal
* Concurrent elevations are from the same day.
Notes:
N = number of participants in the safety population of the treatment group.
N1 = number of participants with at least one postbaseline assessment.
n = number of participants within a specific category.
Percentages are calculated as 100 x (n/N1)

Twenty-four participants in the placebo-controlled analysis set had ALT and/or AST elevations ≥ 3 × ULN that were adjudicated by the clinical adjudication committee; 17 of these cases were in atogepant groups. Of these 17 cases in atogepant-treated participants, 2 cases (1 in the atogepant 30 mg QD group and 1 in the atogepant 60 mg QD group) were adjudicated as probably related to study drug and 2 cases (1 in the atogepant 10 mg QD group and 1 in the atogepant 30 mg QD group) were adjudicated as possibly related. The remaining 13 atogepant cases were adjudicated as unlikely related to study drug.

All 4 atogepant-treated cases that were adjudicated as probably or possibly related to study drug were asymptomatic, non-serious, mild or moderate in severity, without concurrent bilirubin elevations, and resolved with or without atogepant discontinuation; all but one of these cases had potential confounding factors.

Table 50: Number and percentage of participants in the placebo-controlled analysis set with adjudicated cases of post-baseline elevations of ALT and/or AST ≥ 3 × ULN by relationship to study drug

Relationship of Adjudicated Cases to Study Drug	Placebo (N=663)	Atogepant 10 mg QD (N=314)	Atogepant 30 mg QD (N=411)	Atogepant 60 mg QD (N=678)	Atogepant 30 mg BID (N=343)	Atogepant 60 mg BID (N=91)	Atogepant Overall (N=1837)
N1	7	4	3	6	3	1	17
Probable, n(%)	0 (0.0)	0 (0.0)	1 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	2 (11.8)
Possible, n(%)	2 (28.6)	1 (25.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)
Unlikely, n(%)	5 (71.4)	3 (75.0)	1 (33.3)	5 (83.3)	3 (100.0)	1 (100.0)	13 (76.5)
Insufficient data, n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

ALT = alanine aminotransferase, AST = aspartate aminotransferase; BID = twice daily; QD = once daily; ULN = upper limit of normal
Notes:
Includes participants with at least 1 adjudicated case, i.e., ALT >= 3xULN and/or AST >= 3xULN. For participants who had multiple adjudicated cases, the most relevant relationship was counted.
N = Number of participants in the safety population of the treatment group.
N1 = Number of participants with at least 1 adjudicated case (ALT >= 3 x ULN or AST >= 3 x ULN).
n = Number of participants with at least 1 adjudicated case (ALT >= 3 x ULN or AST >= 3 x ULN) and in the specific category.
Percentages are calculated as 100 x (n/N1).

Long-Term Safety Analysis Set (LTS)

Hepatic Injury Adverse Events (LTS)

The number and percentages of participants in the standard-of-care and atogepant 60 mg QD groups who had hepatic injury AEs in the long-term safety analysis were similar (3.1% and 2.5%, respectively). The most common AEs were AST increased and ALT increased. The AE of hepatitis E antibody positive was reported for 6 participants (0.4%) in the atogepant 60 mg QD group; per the protocols all participants from the lead-in studies were to repeat hepatitis E serology tests at the time of enrolment in the long-term extension studies and participants with a positive result were to be discontinued from study drug.

The majority of AEs were mild or moderate in severity and non-serious. Fifteen participants had AEs that led to discontinuation of study drug.

Table 51: Number and percentage of participants with hepatic disorder or liver transplant adverse events in the long-term safety analysis set

Category Preferred Term	Standard-of-Care (N=196) n (%)	Atogepant 60mg QD (N=1662) n (%)
Hepatic Injury TEAE	6 (3.1)	42 (2.5)
Aspartate aminotransferase increased	5 (2.6)	29 (1.7)
Alanine aminotransferase increased	4 (2.0)	27 (1.6)
Hepatitis E antibody positive	0 (0.0)	6 (0.4)
Blood alkaline phosphatase increased	0 (0.0)	4 (0.2)
Hepatic function abnormal	0 (0.0)	1 (0.1)
Hepatic steatosis	0 (0.0)	1 (0.1)
Hepatitis E	0 (0.0)	1 (0.1)
Hypertransaminasaemia	0 (0.0)	1 (0.1)
Prothrombin time prolonged	0 (0.0)	1 (0.1)

QD = once daily; TEAE = treatment-emergent adverse event
Note:
Participants are counted only once within each category, and preferred term.

Hepatic Laboratory Values of Special Interest (LTS)

Post-baseline elevations of ALT and/or AST ≥ 3 × ULN were higher in the standard-of-care group (3.2%) than in the atogepant 60 mg group (1.5%).

One participant (atogepant 60 mg QD group) had concurrent ALT or AST elevations ≥ 3 × ULN and total bilirubin ≥ 1.5 × ULN, in the context of symptomatic cholelithiasis. This case was considered by the investigator to be not related to study drug and adjudicated as unlikely related to study drug by the external adjudication committee.

One participant (atogepant 60 mg QD group), with a history of Gilbert's syndrome, had isolated post-baseline total bilirubin elevations ≥ 2 × ULN.

Table 52: Number and percentage of participants in the long-term safety analysis set with post-baseline hepatic laboratory values of special interest

Hepatic Laboratory Parameter (Unit)	Criterion	Standard-of-Care (N=196) n/N1 (%)	Atogepant 60 mg QD (N=1662) n/N1 (%)
ALT (U/L)	>= 1.0 * ULN	47/190 (24.7)	207/1643 (12.6)
	>= 1.5 * ULN	14/190 (7.4)	73/1643 (4.4)
	>= 2.0 * ULN	8/190 (4.2)	43/1643 (2.6)
	>= 3.0 * ULN	3/190 (1.6)	20/1643 (1.2)
	>= 5.0 * ULN	1/190 (0.5)	10/1643 (0.6)
	>= 10.0 * ULN	0/190 (0.0)	3/1643 (0.2)
	>= 20.0 * ULN	0/190 (0.0)	1/1643 (0.1)
AST (U/L)	>= 1.0 * ULN	34/190 (17.9)	125/1644 (7.6)
	>= 1.5 * ULN	7/190 (3.7)	56/1644 (3.4)
	>= 2.0 * ULN	5/190 (2.6)	29/1644 (1.8)
	>= 3.0 * ULN	4/190 (2.1)	16/1644 (1.0)
	>= 5.0 * ULN	0/190 (0.0)	8/1644 (0.5)
	>= 10.0 * ULN	0/190 (0.0)	3/1644 (0.2)
	>= 20.0 * ULN	0/190 (0.0)	1/1644 (0.1)
ALT or AST (U/L)	>= 1.0 * ULN	55/190 (28.9)	236/1644 (14.4)
	>= 1.5 * ULN	16/190 (8.4)	90/1644 (5.5)
	>= 2.0 * ULN	11/190 (5.8)	50/1644 (3.0)
	>= 3.0 * ULN	6/190 (3.2)	24/1644 (1.5)
	>= 5.0 * ULN	1/190 (0.5)	12/1644 (0.7)
	>= 10.0 * ULN	0/190 (0.0)	4/1644 (0.2)
	>= 20.0 * ULN	0/190 (0.0)	1/1644 (0.1)
TBL (umol/L)	>= 1.0 * ULN	10/190 (5.3)	72/1643 (4.4)
	>= 1.5 * ULN	0/190 (0.0)	9/1643 (0.5)
	>= 2.0 * ULN	0/190 (0.0)	1/1643 (0.1)
	>= 3.0 * ULN	0/190 (0.0)	0/1643 (0.0)
	>= 5.0 * ULN	0/190 (0.0)	0/1643 (0.0)
	>= 10.0 * ULN	0/190 (0.0)	0/1643 (0.0)
	>= 20.0 * ULN	0/190 (0.0)	0/1643 (0.0)
ALP (U/L)	>= 1.0 * ULN	32/190 (16.8)	210/1643 (12.8)
	>= 1.5 * ULN	3/190 (1.6)	17/1643 (1.0)
	>= 2.0 * ULN	0/190 (0.0)	5/1643 (0.3)
	>= 3.0 * ULN	0/190 (0.0)	1/1643 (0.1)
	>= 5.0 * ULN	0/190 (0.0)	0/1643 (0.0)
	>= 10.0 * ULN	0/190 (0.0)	0/1643 (0.0)
	>= 20.0 * ULN	0/190 (0.0)	0/1643 (0.0)
Concurrent elevations*	ALT or AST >= 3.0 * ULN AND TBL >= 1.5 * ULN	0/190 (0.0)	1/1643 (0.1)
	ALT or AST >= 3.0 * ULN AND TBL >= 2.0 * ULN	0/190 (0.0)	0/1643 (0.0)
Potential Hy's Law*	ALT or AST >= 3.0 * ULN AND TBL >= 2.0 * ULN AND ALP < 2.0 * ULN	0/190 (0.0)	0/1642 (0.0)

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal
Notes:
* Concurrent elevations are from the same day.
N = number of participants in the safety population of the treatment group.
N1 = number of participants with at least one postbaseline assessment.
n = number of participants within a specific category.
Percentages are calculated as 100 x (n/N1).

Twenty-four participants (all in the atogepant 60 mg QD group) in the long-term safety analysis set had ALT and/or AST elevations ≥ 3 × ULN. Twenty-two of these cases were adjudicated by the external clinical adjudication committee prior to the 10 January 2022 clinical cutoff date. The remaining 2 cases were adjudicated in April 2022. Three cases were adjudicated as probably related to study drug and 5 cases were adjudicated as possibly related; the remaining 16 atogepant cases were adjudicated as unlikely related to study drug. Aminotransferase elevations in the standard-of-care group were not adjudicated per the adjudication charter.

Among the 8 cases that were adjudicated as probably or possibly related to study drug all were non-serious, mild to moderate in severity, without concurrent bilirubin elevation, and resolved with or without atogepant discontinuation.

Table 53: Number and percentage of participants in the long-term safety analysis set with adjudicated cases of post-baseline elevations of ALT and/or AST ≥ 3 × ULN by relationship to study drug

Relationship of Adjudicated Cases to Study Drug	Standard-of-Care (N=196)	Atogepant 60 mg QD (N=1662)
N1	0	22
Probable, n (%)	0 (NA)	3 (13.6)
Possible, n (%)	0 (NA)	4 (18.2)
Unlikely, n (%)	0 (NA)	15 (68.2)
Insufficient data, n (%)	0 (NA)	0 (0.0)

ALT = alanine aminotransferase, AST = aspartate aminotransferase; NA = not applicable; QD = once daily
Notes:
Includes participants with at least one adjudicated case, i.e., ALT >= 3xULN and/or AST >= 3xULN. For participants who had multiple adjudicated cases, the most relevant relationship was counted.
N = Number of participants in the safety population of the treatment group.
N1 = Number of participants with at least one adjudicated case (ALT >= 3 x ULN or AST >= 3 x ULN).
n = Number of participants with at least one adjudicated case (ALT >= 3 x ULN or AST >= 3 x ULN) and in the specific category.
Percentages are calculated as 100 x (n/N1).
Standard-of-care was not adjudicated for relationship to study drug.
Two cases were adjudicated in April 2022, which was after the data cutoff date; therefore, they are not summarized in this table.

AESI: Suicidal Ideation and Suicidal Behaviour

The potential risk of suicidal ideation and suicidal behaviour was examined because brain-penetrant drugs can cause behavioural or psychiatric side-effects. Atogepant was not associated with an increased risk of suicidal ideation or suicidal behaviour compared with placebo in the placebo-controlled analysis set or with the standard-of-care group in the long-term safety analysis set.

Suicidal ideation was reported via C-SSRS assessment for < 1% of participants in any of the atogepant groups during the treatment period in either the placebo-controlled analysis set or the long-term safety analysis set. The percentage of participants with suicidal ideation or behaviour in the atogepant treatment groups was similar or lower than that of the placebo or standard-of-care groups.

AESI: Abuse

There is no evidence in the literature that CGRP signalling is linked to drug reinforcement or physical dependence and/or withdrawal. Atogepant, a potent CGRP receptor antagonist (Ki = 15-26 pM), did not exhibit significant affinity for a variety of central nervous system targets known to be associated with drugs of abuse, e.g., dopamine, cannabinoid, acetylcholine and opioid receptors, gamma-aminobutyric acid (GABA) or N-methyl-D-aspartate (NMDA) receptor complex, and transporters for dopamine, serotonin, and norepinephrine.

AE PTs potentially predictive of abuse potential were identified based on the FDA Guidance for Industry: Assessment of Abuse Potential of Drugs (2017). The totality of the data support a lack of abuse potential risk with atogepant based on its pharmacological class and properties and its lack of abuse signal in nonclinical and clinical studies.

- ***Serious adverse events, deaths, and other significant events***

Serious Adverse Events (SAEs)

Placebo-controlled Analysis Set

The percentages of participants with SAEs in the atogepant groups in the placebo-controlled analysis set were low and similar to that of placebo with no more than 1.3% of participants in any of the atogepant groups having had SAEs compared with 1.1% of participants in the placebo group. A total of 3.6% of participants in the standard-of-care group and 3.4% of participants in the atogepant 60 mg QD group had SAEs in the long-term safety analysis set. The majority of preferred terms for SAEs were not reported for more than 1 participant. With the exception of an SAE of optic neuritis in the placebo-controlled

analysis set (atogepant 10 mg QD), none of the SAEs was considered by the investigator to be related to study drug. The event of optic neuritis was considered by the sponsor to be not related to study drug as the characteristics of the event were not consistent with the diagnosis of optic neuritis.

Long-term Safety Analysis Set

SAEs were reported for 3.6% of participants in the standard-of-care group and 3.4% of participants in the atogepant 60 mg group in the long-term safety analysis set (2.7.4, Table 22). The majority of preferred terms were not reported for more than 1 participant. None of the SAEs was considered by the investigator to be related to study drug.

Death

No fatal AEs were reported in the placebo-controlled analysis set or in the Phase 1 analysis set; 3 fatal AEs, all in the atogepant 60 mg QD group in the long-term safety analysis set were reported. The causes of death were beta-haemolytic streptococcal infection (toxic shock syndrome), homicide, and asphyxia (by house fire). None of the deaths was considered by the investigator to be related to study drug. Narratives for deaths are provided.

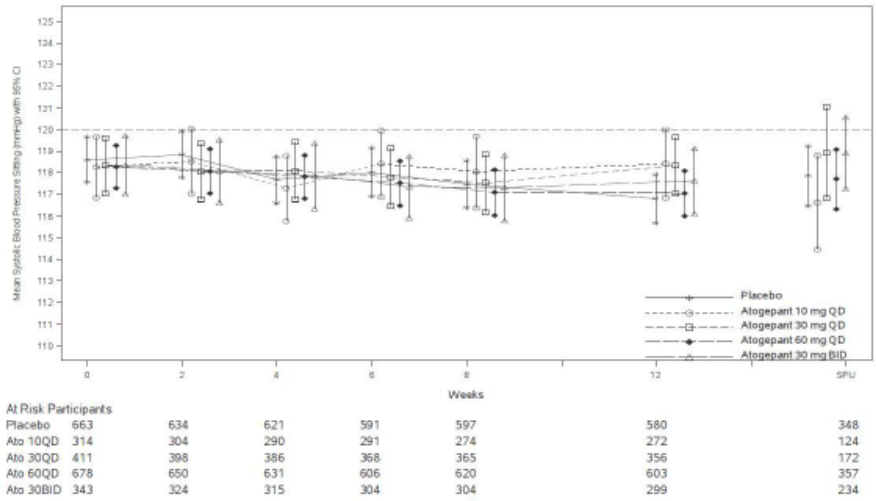
- ***Laboratory findings***

Analysis of laboratory parameters does not suggest any safety concerns. Mean changes from baseline to post-baseline visits were similar across treatment groups in both the placebo-controlled analysis set and the long-term safety analysis set.

Blood Pressure Over Time

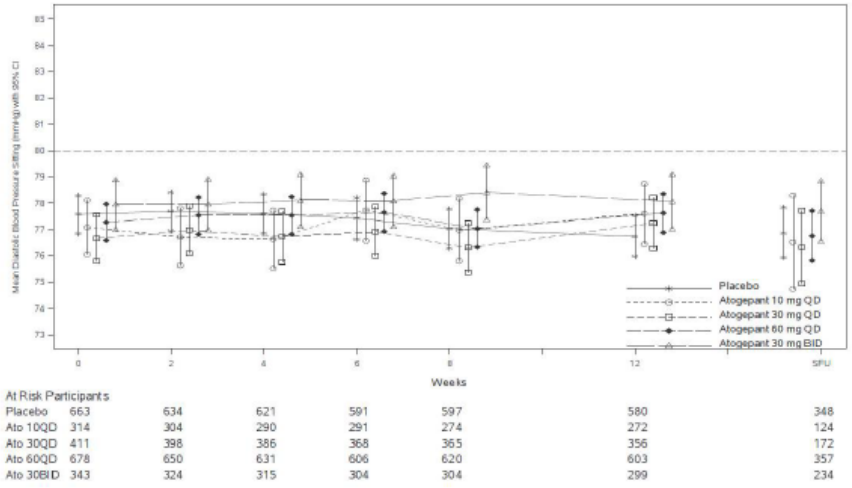
Mean and median changes from baseline to predefined visits and to the end of study for blood pressure parameters in the placebo-controlled analysis set were typically small and similar across treatment groups.

Figure 14: Mean sitting systolic blood pressure in the placebo-controlled analysis set



ATO = atogepant; BID = twice daily; CI = confidence interval; QD = once daily; SFU = safety follow-up

Figure 15: Mean sitting diastolic blood pressure in the placebo-controlled analysis set



ATO = atogepant; BID = twice daily; CI = confidence interval; QD = once daily; SFU = safety follow-up

Weight

A total of 14.1% of participants in the placebo-controlled analysis set had a history of obesity at baseline: 13.9% in the placebo group and 14.2% in the atogepant groups (8.7% to 20.1% across the atogepant groups). Mean weight at baseline for all participants was 79.3 kg, and mean BMI was 28.86 kg/m^2, with 25% of participants weighing between 92.0 and 226 kg and 25% of participants with a BMI between 33.18 and 82.0 kg/m^2.

The change from baseline to end of treatment in mean weight was +0.23 kg in the placebo group versus +0.07, −0.40, and −0.90 kg in the atogepant 10, 30, and 60 mg QD groups, respectively, and −0.86 in both the atogepant 30 and 60 mg BID groups; weight appeared to decrease in a dose-dependent manner across atogepant groups. Decreases in mean weight in the atogepant groups were apparent at Week 2, the first post-dose measurement, and continued to decrease over the 12-week treatment period.

Increases and decreases in weight that met potentially clinically significant (PCS) criteria (≥ 7% change from baseline) were observed in both the placebo and atogepant groups. The percentage of participants with PCS weight decrease was greater in the atogepant groups (4.6%) than in the placebo group (2.5%) and appeared to be dose-dependent. The percentage of participants with PCS weight gain was lower in the atogepant groups (1.6%) than in the placebo group (2.3%).

Figure 16: Potentially clinically significant decreases or increases in weight in the placebo-controlled analysis set

Vital Sign PCS Criterion	Placebo (N=663) n/N1 (%)	Atogepant 10 mg QD (N=314) n/N1 (%)	Atogepant 30 mg QD (N=411) n/N1 (%)	Atogepant 60 mg QD (N=678) n/N1 (%)	Atogepant 30 mg BID (N=343) n/N1 (%)	Atogepant 60 mg BID (N=91) n/N1 (%)	Atogepant Overall (N=1837) n/N1 (%)
Weight (kg)							
Decrease of >= 7%	16/653 (2.5)	12/312 (3.8)	13/404 (3.2)	35/666 (5.3)	18/339 (5.3)	6/88 (6.8)	84/1809 (4.6)
Increase of >= 7%	15/653 (2.3)	7/312 (2.2)	6/404 (1.5)	10/666 (1.5)	6/339 (1.8)	0/88 (0.0)	29/1809 (1.6)

BID = twice daily; PCS = potentially clinically significant; QD = once daily
Notes:
N = of participants in the safety population of the treatment group.
N1 = number of participants with non-PCS baseline values and at least one postbaseline assessment.
n = number of participants within a specific category.
Percentages are calculated as 100 x (n/N1).

In the Long-Term Safety Analysis Set, the change from baseline to end of treatment in mean weight was +0.20 kg in the standard-of-care group and –1.60 kg in the atogepant 60 mg QD group. A decrease in mean weight in the atogepant 60 mg QD group was apparent at Week 4, the first post-dose measurement, and remained generally stable after approximately Week 20.

Increases and decreases in weight that met PCS criteria (≥ 7% change from baseline) were observed in both the standard-of-care and atogepant 60 mg QD groups. The percentage of participants with PCS weight decrease was 23.4% than in the atogepant 60 mg QD group and 14.7% in the standard-of-care group. The percentage of participants with PCS weight gain was 7.4% in the atogepant 60 mg QD group and 12.6% in the standard-of-care group.

Figure 17: Potentially clinically significant decreases or increases in weight in the long-term safety analysis set

Vital Sign PCS Criterion	Standard-of-Care (N=196) n/N1 (%)	Atogepant 60 mg QD (N=1662) n/N1 (%)
Weight (kg)		
Decrease of >= 7%	28/190 (14.7)	385/1644 (23.4)
Increase of >= 7%	24/190 (12.6)	121/1644 (7.4)

Notes:
N = of participants in the safety population of the treatment group.
N1 = number of participants with non-PCS baseline values and at least one postbaseline assessment.
n = number of participants within a specific category.
Percentages are calculated as 100 x (n/N1).

Safety related to drug-drug interactions and other interactions

Drug interactions studies were conducted for concomitant administration of atogepant with ubrogepant, topiramate, sumatriptan, naproxen / acetaminophen, oral contraceptives, esomeprazole, quinidine, rifampin, and itraconazole.

Changes in atogepant exposure were observed after co-administration of strong CYP3A4 inhibitors, OATP inhibitors, and strong CYP3A4 inducers. Appropriate guidance for prescribers and participants was proposed in the labelling with respect to drug-drug interactions.

To examine the potential effects of drug interactions, AE data were examined in the subset of participants who took common classes of concomitant medications (i.e., World Health Organization Drug Dictionary ATC4 medication classes used by ≥ 10% of participants in any treatment group during the treatment period) in the placebo-controlled studies and in the long-term safety studies. Review of AE data showed no appreciable differences in the type of AEs reported in the subsets of participants who took common

classes of concomitant medications for the placebo-controlled and long-term safety analysis sets, respectively.

Discontinuation due to adverse events

Placebo-Controlled Analysis Set

AEs that led to discontinuation of study drug were reported for 3.2% of participants in the placebo group; 4.1%, 3.4%, and 3.1% of participants in the atogepant 10, 30, and 60 mg QD groups, respectively; and 5.2% and 6.6% of participants in the 30 and 60 mg BID groups, respectively, in the placebo-controlled analysis set. AEs that led to discontinuation in more than 1 participant in any treatment group are presented in the table below.

Table 54: Number and percentage of participants (≥ 2 participants in any treatment group) with AEs that led to discontinuation in the placebo-controlled analysis set

Preferred Term	Placebo (N=663) n (%)	Atogepant 10 mg QD (N=314) n (%)	Atogepant 30 mg QD (N=411) n (%)	Atogepant 60 mg QD (N=678) n (%)	Atogepant 30 mg BID (N=343) n (%)	Atogepant 60 mg BID (N=91) n (%)	Atogepant Overall (N=1837) n (%)
Participants with AEs leading to discontinuation	21 (3.2)	13 (4.1)	14 (3.4)	21 (3.1)	18 (5.2)	6 (6.6)	72 (3.9)
Palpitations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.1)
Nausea	2 (0.3)	1 (0.3)	3 (0.7)	3 (0.4)	3 (0.9)	1 (1.1)	11 (0.6)
Constipation	2 (0.3)	1 (0.3)	3 (0.7)	2 (0.3)	3 (0.9)	1 (1.1)	10 (0.5)
Abdominal distension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.9)	0 (0.0)	3 (0.2)
Abdominal pain	3 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.1)
Fatigue	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.3)	3 (3.3)	6 (0.3)
Dizziness	1 (0.2)	0 (0.0)	2 (0.5)	1 (0.1)	1 (0.3)	2 (2.2)	6 (0.3)
Migraine	6 (0.9)	0 (0.0)	1 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	3 (0.2)
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)

BID = twice daily; QD = once daily
Notes:
N = number of participants in the safety population of the treatment group.
n = number of participants in the specific category.
Percentages calculated as 100 x (n/N).
Participants are counted only once within each preferred term.

- ***Post marketing experience***

Atogepant 10, 30, and 60 mg QD was approved in the United States on 28 September 2021 (International Birth Date) for the preventive treatment of EM in adults. The cumulative patient exposure to Qulipta from 28 September 2021 is 35,827 patient treatment years, based on available sales data through 31 October 2022.

A summary of post-marketing reports from 28 September 2021 to 27 March 2022 showed no safety signals.

One spontaneous post-marketing report of acute liver failure with atogepant 60 mg QD that led to liver transplantation was retrieved from the search through 27 March 2022 (described in detail Mod. 2.7.4). AbbVie has performed additional follow-up with due diligence to acquire further information on the case (included in the CIOMS report). The expert opinion was sought to provide causality assessment for the acute liver failure event.

Introduction

On 07 March 2022, AbbVie received follow-up information on a serious spontaneous report of acute liver failure with atogepant that was initially reported as non-serious acute hepatitis.

AbbVie reviewed this case and sought the expert opinion. It was concluded there was insufficient data to assign causality. Additional follow-up with due diligence was performed to acquire further information on the case.

Case Narrative

A female patient experienced acute liver failure on Day 127 after atogepant initiation, that led to liver transplantation. Atogepant 60 mg QD was started for "headache".

The patient's medical history included attention deficit and hyperactivity disorder (ADHD), depression, anxiety, migraine, constipation, and social occasional drinker. No history of obesity (unknown BMI), liver diseases, or alcohol abuse was noted.

The patient's concomitant medications and herbal dietary supplements included paroxetine for depression, clonazepam as needed for anxiety, amphetamine and dextroamphetamine for ADHD, trazodone as needed for anxiety, and linaclotide for constipation. No start date was reported for any of these medications; however, all were discontinued on Day 127. Botulinum toxin type A for migraine prevention was injected on an unknown day approximately 2 months after atogepant initiation.

On Day 76 after atogepant initiation, the patient underwent an outpatient surgical procedure. Cefazoline 2 grams was administered pre-operatively. Fentanyl, rocuronium, succinylcholine, and unspecified steroids (8 mg) were administered intra-operatively. It is unknown whether any inhaled anaesthetics were used or if the patient received inhaled anaesthetics in prior surgeries. A 7-day course of cephalexin was prescribed post-operatively. Acetaminophen and oxycodone were also prescribed as needed; no details on their use after surgery were reported.

Approximately 1 week before the surgery, on Day 68, mild elevations on ALT (86 U/L [ULN not stated]) were noticed with a decreasing trend (ALT 71 U/L on Day 71).

The patient received linaclotide and polyethylene glycol 3350 on unknown days due to aggravation of constipation. On Day 93, the patient received a single dose of fluconazole 150 mg orally due to vaginal yeast infection.

After the surgery, up to Day 127, the patient was observed 6 times by the surgeon, but no details on the clinic visits were provided. No laboratory tests were performed during this period. On Day 127, the surgeon noticed that the patient had jaundice and referred the patient to an internal medicine consultation. Fatigue was also reported on that day and laboratory tests revealed ALT of 1943 IU/L, AST > 2000 IU/L, gamma-glutamyl transferase (GGT) of 174 IU/L, total bilirubin of 12 mg/dL (direct bilirubin not tested), albumin of 4.4 g/dL, creatinine of 1.1 mg/dL (baseline around 0.7 mg/dL), international normalised ratio (INR) of 1.8, prothrombin time (PT) of 19 seconds, and platelet count of 130,000/mm3 (was 220,000/mm3 on Day 71).

The patient discontinued all concomitant medications on Day 127 and went back to the clinic for retesting and supplementary testing on Day 131. Results showed ALT of 1798 IU/L, AST of 1163 IU/L, total bilirubin of 23.9 mg/dL, PT of 21.7 and 25.4 later, INR of 2.1, albumin of 3.6 g/dL, and alkaline phosphatase (ALP) of 255 IU/L. Hepatitis A (HAV IgM), B (HBsAg, anti-HBc), and C (HCV RNA), HIV 1 and 2, and COVID serologies were negative. Reportedly, Epstein-Barr virus (EBV) and hepatitis E virus (HEV) serologies and autoimmune markers were negative. Acetaminophen levels were negative.

An abdominal ultrasound was performed on that day and revealed mild fatty liver and ascites. The patient was hospitalised on the same day in a liver transplant centre. During hospitalisation, a liver biopsy was performed on an unknown day and showed "80% liver necrosis and no evidence of autoimmune hepatitis." The patient developed hepatic encephalopathy and multi-organ failure during hospitalisation and a liver transplantation was performed on Day 141.

No further details on the hospitalisation, tests, treatments, or liver explant results were provided. The patient was discharged on Day 155. Liver test results during the events and evaluation testing results are presented in the table below.

Table 55: Liver test results during the events

Date	Days After Starting Atogepant	ALT (IU/L)	AST (IU/L)	ALP (U/L)	GGT (U/L)	TB (mg/dL)	INR
Normal Range		NR	NR	NR	NR	NR	NR
	68	86	36	68	NR	0.4	NR
	71	71	49	NR	NR	1	NR
	127	1943	> 2000	NR	174	12	1.8
	131	1798	1163	255	NR	23.9	2.1

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;
GGT = gamma-glutamyl transferase; INR = international normalized ratio; NR = not reported; TB = total bilirubin

Table 56: Evaluation testing and results

Test	Test Done After Injury Onset?	Date (Day of Onset) and Result
Hepatitis A IgM antibody	Yes	(Day 131), reportedly negative
Hepatitis B surface antigen	Yes	(Day 131), reportedly negative
Hepatitis B anti-HB core IgM antibody	Yes	(Day 131), reportedly negative
Hepatitis C RNA	Yes	(Day 131), reportedly negative
HIV 1 and 2	Yes	(Day 131), reportedly negative
SARS-CoV-2	Yes	(Day 131), reportedly negative
Hepatitis E IgM antibody	Yes	Unknown date, reportedly negative
EBV capsid antibody IgM	Yes	Unknown date, reportedly negative
Abdominal or liver ultrasound	Yes	(Day 131), mild fatty liver, ascites
Liver histology	Yes	Unknown date, "80% necrosis and no evidence of autoimmune hepatitis"

IgM = immunoglobulin M; EBV = Epstein-Barr virus; HIV = human immunodeficiency virus; RNA = ribonucleic acid;
SARs-CoV-2 = severe acute respiratory syndrome coronavirus 2

Independent DILI Expert Causality Assessment

"*There is insufficient data to assign causality in this case. The event is compatible with DILI and the timing is consistent with a role for Atogepant. However, there was a balance in the incidence of liver chemistry elevations between Atogepant and placebo in the Atogepant clinical trials which is not expected for a drug that can cause liver failure (that is, Atogepant does not fulfill "Temple's Corollary"). In addition, this case is confounded by the surgical procedure this patient underwent that included treatment with potentially hepatotoxic drugs and all relevant data is not available. All efforts should be made to obtain the operative report (to check for inhaled anesthetic administration), the liver biopsy report, serial liver chemistries while hospitalized, and documentation of the full evaluation for alternate. Potential causes should also be sought for the mild elevation in serum ALT observed prior to surgery, including use of over-the-counter medications and herbal/dietary supplements*."

2.7. Discussion on clinical safety

Safety database pools

The overall safety dataset was grouped into 4 distinct Analysis Sets. Of these, the Placebo-controlled Analysis Set (PCS, dose-finding study MD-01, EM study 301, CM study 303 [12-week DBT plus 4-week FU]; N=2500, n=1837 atogepant, n=663 placebo) and the Long-term Safety Analysis Set (LTS, N=1861, n=1665 atogepant, n=196 SOC) are of primary interest. The Long-term Safety Set comprises open label safety data obtained from EM patients (studies 302 and 309) and from CM patients (studies 306 and 312). Safety data from ongoing CM studies 306 and 312 were included as per ISS cutoff date 10 January 2022. Interim Summaries of Efficacy and Safety (Agency Response – EU – Oct 2022) were provided for studies 306 and 312. Study 306 is an open-label, long-term safety extension, conducted in Japanese adults who either completed Study 303 or who were recruited de novo. Per ISS cutoff date, N=155 CM patients were included from study 306 in the Long-term Safety Set. In open-label, long-term safety extension study 312, CM patients were included who completed either Study 303 or Study 304.

Overall exposure to atogepant is sufficiently large. A total of N=3230 unique participants (including 604 healthy volunteers, 656 participants with CM, and 1970 EM patients) were exposed to at least 1 dose of atogepant during clinical development. With regard to the duration of exposure, the minimum requirements as specified per ICH E1 Guidance are fulfilled.

Demographics

In severely affected migraine patients of the PCS set, comorbidity with conditions like anxiety (16.7%), depression (15.9%), or insomnia (13.0%) is considered representative for the target population in clinical practice. Notably, a portion of 14.1% of patients presented with obesity. The mean BMI in the PCS set (N=2500) was 28.86 kg/m^2.

Clinically significant cardiovascular or cerebrovascular disease were excluded, like e.g. ischaemic heart disease (e.g. unstable angina pectoris), cardiac rhythm or conduction abnormalities (e.g. atrial fibrillation, second- or third-degree heart block), myocardial infarction, transient ischaemic attack, or stroke within 6 months prior to Visit 1, Hypertension [systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg]. Subjects with less significant cardiac or vascular conditions were not excluded. About 5% of included subjects presented with cardiac disorders at baseline in studies 301/303. Further 8-10% of subjects presented with less severe forms of hypertension. More than 70% of PCS subjects took concomitant cardiovascular medication. The rates of newly initiated or CV medication dose increases were about equal between placebo (7.2%) and atogepant patients (8.0%).

Most common adverse events

Atogepant preventive migraine treatment was well tolerated. The overall rate of subjects discontinuing due to AE was about equal in the PCS set between participants receiving atogepant 60 mg QD (3.1%) and placebo subjects (3.2%). In the Long-term Safety set, however, more patients discontinued for tolerability reasons in the atogepant arm (4.5%) as compared to SOC (2.6%).

The most common AEs in any atogepant group (≥ 5% of participants) were nausea, constipation, fatigue, and upper respiratory tract infection. Of these, constipation, nausea, and fatigue were considered as related to study drug in the majority of cases. In particular, for nausea (atogepant: 7.5%, placebo 3.3%) and constipation (atogepant: 7.2%, placebo: 2.0%) reporting rates in atogepant patients were higher as compared to placebo. Constipation is also labelled as common adverse reaction to biological CGRP antagonists erenumab and galzanezumab. Of note, the AE of decreased appetite was reported about ten times more often in atogepant patients (2.1%) as compared to placebo (0.2%). There was no clear dose response relation for the rate of TEAEs across the atogepant doses, ranging from atogepant 10 mg QD to supra-therapeutic atogepant 60 mg BID in the PCS set.

In long-term safety study 302, a SOC arm was included to contextualise safety. The rate of patients showing TEAEs was lower for atogepant 60 mg QD (N=1662, 63.5%) as compared to SOC (N=196, 78.6%). However, interpretation is cautioned given the disparity of underlying datasets.

The number and percentage of participants with common AE in the LTS set reveals good tolerability of long-term atogepant 60 mg QD use as compared to the standard of care control arm. Of those AEs observed in the PCS set which were considered related to study drug, only constipation was reported more often for atogepant 60 mg QD (6.0%) as compared to SOC (3.1%). The remaining two "related" AEs were observed more often in the SOC arm (nausea: atogepant 60 mg QD: 4.3%, SOC 6.1%; fatigue: atogepant 60 mg QD: 1.7%, SOC: 6.1%).

There was no indication atogepant would be liable to induce CNS-related AEs. Typical CNS-related AEs like dizziness (atogepant: 2.2%, SOC: 11.2%), anxiety (atogepant: 2.0%, SOC: 5.6%), somnolence (atogepant: 0.8%, SOC: 4.1%), or sedation (atogepant: 0.0%, SOC: 2.0%) were observed more often in patients receiving SOC preventive migraine treatment as compared to atogepant.

In line with reported AE of appetite decreased in the PCS set, after long term treatment with atogepant 60 mg QD more patients were seen with weight decreased (n=37, 2.2%) as compared to SOC (n=3, 1.5%). The inverse effect, i.e. weight increased, were observed more often across SOC patients (5.6%) as compared to atogepant (0.9%). Among commonly used standard of care migraine prevention therapeutics, there are agents for which a potential influence on body weight is established (e.g. topiramate, ß-blockers).

Adverse drug reactions (ADRs) were determined by evaluating TEAEs in the placebo-controlled migraine studies (Studies MD-01, 301, and 303) that occurred with a ≥ 2% overall incidence rate in any of the atogepant groups and at a rate at least 2% greater than placebo. Constipation, decreased appetite, nausea, and fatigue/somnolence were identified as ADRs.

The overall incidence of SAE in the PSC set was low across atogepant treatment arms (≤ 1.3%) and similar to placebo (1.1%). None of the observed SAE was reported in more than 1 participant.

There was one SAE of presumed optic neuritis, which was considered as related to study drug by the Investigator, but was considered not related by the Sponsor. Irrespective of any attempt to retrospectively decide upon potential relatedness of the single SAE of presumed optic neuritis, it is suggested to examine future PSUR reports for potential signals in this regard.

In the LTS set, the overall rate of TESAE was higher in patients receiving SOC (N=196, 3.6%) as compared to patients receiving atogepant 60 mg QD (N=1662, 3.4%). Importantly, there is no accumulation of any SAE. For the vast majority of SAE per preferred term the frequency in atogepant subjects is 0.1%. This includes Hepatobiliary disorders (cholelithiasis, cholecystitis) and Investigations (ALT increased, AST increased). There wasn't any cardiovascular SAE under long-term atogepant treatment.

AEs of special interest

Cardiovascular events (cardiac arrythmias, central nervous system vascular disorders, embolic and thrombotic, hypertension, and ischaemic heart disease), hepatic AEs, suicide-related events, and abuse-related AEs were identified as AESIs for the placebo-controlled, long-term safety, and Phase 1 analysis sets.

Cardiovascular Events

A comprehensive evaluation of cardiovascular safety of atogepant as TEAESI was provided for both the use of atogepant under placebo-controlled conditions and long-term over 52-weeks. There was no incident of ischaemic heart disease. The incidence of arrhythmia-related AEs was low and similar between atogepant (0.3%) and placebo (0.2%). Across the PCS and LTS set, only two cases of hypertension as

reported AE were considered by the Investigator as related to study medication. Based on the narratives, however, there is no clear suspect of atogepant having a causative role given the overall medical conditions of concerned subjects and timing of reporting (resp. persistence of the event) in relation to atogepant treatment.

Hepatic Safety

Historical clinical development programs for other members of the gepant family (telcagepant) were halted when liver toxicity was detected during migraine prophylaxis trials (Ho TW. Neurology 2014). Therefore, AEs related to hepatic toxicity were systematically evaluated as AEs of special interest, including blinded adjudication of post-baseline elevations of ALT and/or AST ≥ 3 × ULN for participants who received either atogepant or placebo by an external expert committee. In the Placebo-controlled Analysis Set, hepatic injury TEAE overall (atogepant: 1.5%, placebo: 1.8%), and hepatic enzyme elevations (ALT increased: atogepant: 1.1%, placebo: 1.5%; AST increased: atogepant: 1.0%, placebo: 1.4%) were observed more often in placebo patients than in participants receiving atogepant. The incidence of ALT or AST increase was independent of the atogepant dose.

A categorised overview was provided of participants in the PCS set with liver enzyme elevations per degree of enzyme elevation (≥ 2 x ULN, ≥ 3 x ULN, ≥ 5 x ULN, ≥ 10 x ULN, ≥ 20 x ULN). In the PCS set, no subject was observed with elevations of ≥ 20 x ULN. In one patient receiving atogepant 10 mg QD, ALT and / or AST were elevated by ≥ 10 x ULN during safety FU. The respective subject never stopped atogepant and completed study 301. Liver enzymes were elevated on Day 1 prior to the first dose of atogepant (ALT: 3.3 x ULN; AST: 4.3 x ULN). The blinded adjudication experts rated the relationship to treatment as unlikely. However, there is concern about the potential role of continued atogepant treatment over 12 weeks in raising liver enzymes from 3.3-4.3 x ULN at study entry to > 10 x ULN during follow-up.

A total of n=24 cases with aminotransferase elevations ≥ 3 x ULN were adjudicated by the external blinded Expert Committee in the PCS set. Of these, n=17 subjects received atogepant (n=7 received placebo). Among the atogepant patients, n=4 subjects (out of N=1837) were adjudicated as either possible (n=2) or probably related (n=2) to atogepant treatment. Narratives were provided. In 3 of these cases, there were confounding factors like intensive weightlifting in the gym, extensive concomitant acetaminophen use for acute headache, or Class III obesity (BMI 39.6 kg/m^2). All 4 atogepant-treated cases that were adjudicated as probably or possibly related to study drug were asymptomatic, non-serious, mild or moderate in severity, without concurrent bilirubin elevations, and resolved with or without atogepant discontinuation.

There was one single case of temporary TBL elevation of 2.08 x ULN. It concerns a 29-year old male participant of study 301 receiving atogepant 60 mg QD. It was reported that his father had Gilbert Syndrome. Prior to receiving the first dose of atogepant on Day 1, total bilirubin was 2.1 mg/dL (1.75 x ULN). Aminotransferases were not relevantly elevated at any stage. Fluctuating bilirubin values were recorded throughout 12-week study 301 and roll-over to open-label extension study 309. Bilirubin elevations are considered not related to atogepant treatment.

Under long term treatment (LTS set), the incidence of hepatic injury overall (atogepant 2.5%, SOC 3.1%), and aminotransferase elevations as TEAE (AST increased: atogepant 1.7%, SOC 2.6%; ALT increased: atogepant 1.6%, SOC: 2.0%) was higher in participants receiving standard-of-care as compared to atogepant.

Analysis of enzyme elevation categories in the long-term analysis set reveals that any aminotransferase elevation (AST or ALT ≥ 1 x ULN) was observed more frequently across SOC patients under long term treatment (28.9%) as compared to atogepant 60 mg QD patients (14.4%). Single cases of very high aminotransferase increases, however, were not reported in SOC patients but only in participants receiving atogepant (ALT or AST ≥ 10 x ULN: n=4 [0.2%], ALT or AST ≥ 20 x ULN: n=1 [0.1%]).

Patients with hepatic enzyme elevations $\geq$ 3 x ULN under long-term atogepant treatment (n=24/1662) were also adjudicated by the external blinded expert committee. In eight cases, the relationship of aminotransferase elevations to study drug was rated as possible or probable. Narratives were provided. In subjects recruited for long-term studies 302 and 309, confounding factors like weightlifting, obesity, history of binge drinking, or transient periods of increased alcohol consumption are reported and subjects completed the study. The remaining cases are reported for long-term study 306 conducted in Japan. Atogepant treatment was discontinued in n=4 subjects from study 306, for which the relationship to study drug was rated possible or probable. In these cases, confounding factors (e.g. concomitant betahistine, cephalosporin, azithromycin) are less clear. There was an increase in any aminotransferase elevations for long-term use of atogepant (LTS: ALT or AST $\geq$ 1 x ULN: 236/1644 [14.4%]) as compared to the 12-week treatment period of the placebo-controlled analysis set (PCS: ALT or AST $\geq$ 1.0 x ULN: 198/1810 [10.9%]). However, the frequency of any aminotransferase increase under long-term atogepant use (14.4%) was lower as compared to participants receiving long-term SOC (28.9%).

Of note, among the 8 cases that were adjudicated as probably or possibly related to study drug all were non-serious, mild to moderate in severity, without concurrent bilirubin elevation, and resolved with or without atogepant discontinuation.

In the clinical trial dataset (placebo-controlled and long-term), there was no case fulfilling criteria for potential Hy's Law (ALT or AST $\geq$ 3 x ULN and TBL $\geq$ 2 x ULN and ALP < 2 x ULN).

Hence, the overall hepatic safety profile of atogepant, as obtained from clinical trials, appears rather favourable. Furthermore, a comprehensive re-evaluation of atogepant's hepatic safety was provided after receipt of one spontaneous post-marketing report of acute liver failure with atogepant 60 mg QD that led to liver transplantation.

The post-marketing case of drug-induced liver injury (DILI) was observed in a female who developed acute liver failure leading to liver transplant on Day 127 of atogepant 60 mg treatment for migraine prophylaxis. An independent Expert confirmed the event to be compatible with DILI and timing as consistent with a role for atogepant. However, the Expert outlines that there was a balance in the incidence of liver chemistry elevations between atogepant and placebo, which is not expected for a drug that can cause liver failure.

A thorough and comprehensive overall evaluation of atogepant's hepatic safety profile was submitted incl. updates of ongoing long-term safety studies 306 /312 and growing post-marketing experience.

The fact that the overall frequency of liver enzyme elevations was not increased in atogepant patients as compared to patients receiving placebo in the PCS dataset, or to subjects receiving SOC in LT study 302 is providing reassurance. In line with results obtained from the DILIsym model (including in vitro tests of mitochondrial dysfunction, oxidative stress, and alterations in bile acid homeostasis) atogepant is not considered to intrinsically induce hepatotoxicity.

A potential idiosyncratic liability, however, may only manifest with temporal latency, and due to its rarity, in larger populations. Across the placebo-controlled (PCS), long-term (LTS) and post-marketing datasets, clinically relevant enzyme elevations were observed in patients receiving atogepant (although mostly asymptomatic across clinical trials). In some of these cases, AST/ALT elevations were adjudicated as possibly or probably related to atogepant treatment based on positive dechallenge and / or absence of clear confounders.

The applicant's proposal is endorsed to address the issue in SmPC section 4.8. Also, the applicant's proposal to extend active surveillance by another year within the scope of ongoing long-term safety study 312 (to a total duration of 3 years) is endorsed.

Suicidal ideation

Atogepant was not associated with an increased risk of suicidal ideation or suicidal behaviour compared with placebo in the placebo-controlled analysis set or compared with the standard-of-care group in the long-term safety analysis set.

Abuse liability

Potential abuse liability of atogepant was systematically evaluated by screening for PTs potentially predictive of abuse potential. It is to be noted that symptoms like dizziness, somnolence, or disturbance in attention may also well occur in the context of migraine attacks, and do not necessarily have to be associated to treatment. Over long-term treatment, all these AEs (dizziness, somnolence, disturbance in attention) were reported more often in SOC patients as compared to participants receiving atogepant 60 mg QD. It is reminded that single standard-of-care migraine preventive agents like e.g. amitriptyline or topiramate may account for respective AEs. No events of euphoria were reported. Overall, examination of abuse-related AEs across all the ISS analysis sets showed no evidence of abuse potential with atogepant.

Vital signs: Blood pressure

Throughout the 12-week DBT period, blood pressure was measured at baseline, scheduled Visits at Week 2, 4, 6, 8, 10, EoT, and Follow-up. Both for placebo and atogepant dose arms, mean systolic BP and diastolic BP remain virtually unaffected. Incidences of BP changes of clinical interest (e.g. systolic BP $\geq$ 180 mmHG or increases by $\geq$ 20 mmHg, or any $\geq$ 10 mmHg increase from baseline in systolic or diastolic BP) were rare and equally distributed across atogepant dose arms and placebo. It is noted that during study Visits BP was measured independent of the time of study medication intake. However, based on phase I population data summarizing vital sign (BP, heart rate) measurements taken per dose (incl. supra-therapeutic doses up to atogepant 300 mg QD) in close timely relation to study medication administration, it could be shown that no clear dose-related effect on BP / heart rate was observed for atogepant in healthy volunteers. This finding goes along with the favourable cardiovascular safety profile, which was monitored throughout the phase II/III trial programme as AE of special interest.

Body weight

Decreases in body weight by $\geq$ 7% from baseline were observed in atogepant patients both under placebo-controlled conditions and under long-term open-label conditions. In both scenarios, the incidence was higher in participants receiving atogepant as compared to the comparator (Body weight decrease by > 7% from baseline: Placebo-controlled Set: atogepant overall: 4.6%, placebo: 2.5%; Long-term Set: atogepant 60 mg QD: 23.4%, SOC: 14.7%). Throughout the 12-week DBT period, the incidence of weight decrease increased with atogepant dose (body weight decrease by > 7%: atogepant 10 mg QD: 3.8%, atogepant 60 mg QD: 5.3%, atogepant 60 mg BID: 6.8%). The tendency for dose-dependent decrease in body weight is adequately reflected in SmPC section 4.8.

It has to be considered that about 14% of participants in the placebo-controlled analysis set had a history of obesity at baseline. Mean weight at baseline for all participants was 79.3 kg, and mean BMI was 28.86 kg/m^2, with 25% of participants weighing between 92.0 and 226 kg and 25% of participants with a BMI between 33.18 and 82.0 kg/m^2. Analysis of a potential relationship between clinically significant weight decrease and obesity (BMI $\geq$ 30 kg/m^2) at baseline revealed that obese patients were not more likely to significantly lose weight under atogepant treatment as compared to normal-weight subjects. Conversely, normal weight subjects (BMI < 30 kg/m^2) appeared to be more liable to significantly lose weight based on comparison with the matched placebo group (atogepant overall [N=1133]: 5.6%, placebo [N=426]: 1.6%).

Transferability between EM and CM population

There were no relevant differences between the EM and CM populations in the PCS set both by the nature and frequency of most common observed AEs. This is considered to provide further assurance regarding

transferability of safety data across populations. Long-term studies in the EM population (302 and 309) were completed and full CSRs were submitted. For the CM population, however, respective long-term studies (306 and 312) are still ongoing and only interim safety data per cutoff date 11 October 2022 could be filed.

2.7.1. Conclusions on the clinical safety

Based on data obtained from the clinical trials, the safety profile of atogepant in preventive migraine treatment appears favourable. Most common ADRs were nausea (7%), constipation (7%), and fatigue/somnolence (5%). No safety concerns for hypertension AEs or other cardiovascular events were identified. Decreases in body weight by $\geq$ 7% from baseline were observed in atogepant patients in a dose-dependent way both under placebo-controlled and long-term treatment conditions.

A thorough and comprehensive overall evaluation of atogepant's hepatic safety profile was submitted incl. updates of ongoing long-term safety studies 306 /312 and growing post-marketing experience.

The proposals to address hepatic safety (inclusion of ALT / AST elevations in SmPC section 4.8, and prolongation of ongoing LT study 312 for another 12 months to an overall duration of 3 years) are endorsed.

2.8. Risk Management Plan

2.8.1. Safety concerns

Table 57: Summary of safety concerns

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

2.8.2. Pharmacovigilance plan

Table 58: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A				
Category 3 - Required additional pharmacovigilance activities				
A Phase 3, multicentre, open label 104-week	To evaluate the long-term safety and		Draft Protocol Submission	10/2020

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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 3101-312-002 (ongoing, will be extended by an additional 1 year for a total of 3 years)	tolerability of atogepant 60 mg once daily in participants when taken for 104 weeks for the prevention of chronic migraine (CM) or episodic migraine (EM).	Long-term safety beyond 1 year	Final Protocol Submission	12/2020
			Study Completion	10/2024
			Final Report Submission	02/2025
Observational Study to Assess Pregnancy Outcomes Following Exposure to Atogepant: PMR 4152-7; Study P22-419 (planned)	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	07/2022
			Final Protocol Submission	05/2023
			Annual Interim Report Submissions	From 02/2024 to 02/2029
			Study Completion	02/2030
			Final Report Submission	04/2031
Atogepant Pregnancy Exposure Registry: PMR 4152-6; Study P22-392 (planned)	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	07/2022
			Final Protocol Submission	05/2023
			Annual Interim Report Submissions	From 02/2024 to 02/2035
			Study Completion	02/2036
			Final Report Submission	04/2037
PASS of atogepant in patients with significant cardiovascular and cerebrovascular diseases	To characterise the safety of atogepant in patients with significant	Use in patients with significant cardiovascular and	Study details will be provided to PRAC post-approval	

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
(planned)	cardiovascular and cerebrovascular diseases.	cerebrovascular diseases		

Overall conclusions on the PhV Plan

The PRAC, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

2.8.3. Risk minimisation measures

Table 59: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Use in patients with significant cardiovascular and cerebrovascular diseases	Other routine RMMs beyond the Product Information: Legal status: Prescription only medicine
Use in pregnant women	Routine risk communication: The risk is communicated through the label in SmPC Section 4.6. Other routine RMMs beyond the Product Information: Legal status: Prescription only medicine
Long-term safety beyond 1 year	Other routine RMMs beyond the Product Information: Legal status: Prescription only medicine

2.8.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.9. Pharmacovigilance

2.9.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28 September 2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Aquipta (atogepant) is included in the additional monitoring list as it includes new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.2. Disease or condition

Migraine is a serious, chronic, disabling neurological disease characterised by attacks of moderate to severe headache (HA) pain associated with other symptoms such as nausea, vomiting, photophobia, and phonophobia. Migraine attacks typically last from 4 to 72 hours if untreated or unsuccessfully treated. People with migraine may experience an aura prior to the onset of their headache.

The indication proposed for Aquipta aligns with standard wordings approved for prophylactic treatment of migraine so far.

3.2.1. Available therapies and unmet medical need

The range of established oral migraine preventive treatment options (ß-blockers, topiramate, antidepressants etc.) most recently was complemented by CGRP antagonist antibodies (ABs, so-called biologicals) targeting circulating CGRP or its receptor (erenumab, fremanezumab, galcanezumab). All three ABs are indicated in the EU for prophylaxis of migraine in adults who have at least 4 migraine days per month. These ABs are injected following 4-week, resp. 12-week dosing intervals. Compliance is a well-documented problem in migraine preventive therapy. The extended dosing intervals of the biologicals may therefore be interpreted as beneficial by increasing compliance of the patients. Irrespective of the compliance aspect, potential advantages for atogepant as a needle-free treatment option may be that it allows flexible treatment if immediate cessation of therapy is required, e.g. in case a serious AE or pregnancy.

Among currently approved preventive treatment options, anticonvulsant topiramate (e.g., Topamax) is indicated in the EU in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Botox (botulinum toxin type A from Clostridium botulinum) is indicated in

the EU for prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine). Preventive treatment of CM with Botox requires multiple bilateral intramuscular injections divided across 7 specific head and neck muscle areas, with a recommended retreatment schedule of every 12 weeks.

These options are not optimal for many patients due to limited effectiveness, poor tolerability, contraindications, and the need for dose titration over multiple visits for some medications. The limitations in conventional oral migraine prevention treatments lead to poor adherence (Berger et al. 2012, Hepp et al. 2017) and reluctance to initiate prophylactic treatment (Silberstein 2015).

Indeed, several epidemiological surveys indicate that available migraine preventive treatments are significantly underutilised in clinical practice (D'Amico et al. 2006), which supports the need for greater dialogue concerning migraine prevention between patients and physicians. Compliance with preventive treatment remains a challenge. Based on a retrospective US claims analysis of N=8707 CM patients, persistence to initial oral preventive medication was only 25% at 6 months and 14% at 12 months follow-up (Hepp et al. 2017). Low adherence to migraine prophylaxis treatment with antidepressants, antiepileptics, or beta blockers at 6 month follow-up was also previously reported (Berger et al. 2012).

3.2.2. Main clinical studies

The clinical data package in support of atogepant comprises phase II/III dose finding, pivotal efficacy/ safety studies in both the EM and CM population, and additional long-term tolerability studies, which also provide data to support maintenance of effect.

Primary evidence for efficacy is derived from 2 pivotal studies, Study 301 ("Advance" study, conducted in the US) for EM prevention and Study 303 ("Progress" study, conducted at 142 sites in the US, Europe, Russia, Japan, Korea and others) for the preventive treatment of CM. Additional supportive data are provided by dose-finding Study CGP-MD-01 for EM prophylaxis.

Furthermore, two long-term open-label studies in EM (Study 3101-302-002) [52-week duration] and Study 3101-309-002 [40-week duration]) were conducted. Persistence of efficacy data in EM were obtained from long term study 302 including de novo participants and patients who completed dose finding Study CGP-MD-01. In long-term study 309, including rollover patients, who completed EM study 301, maintenance of effect was not recorded.

Studies 301 and 303 were 12-week, Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies comparing atogepant with placebo for the preventive treatment of migraine in participants with EM (Study 301; atogepant 10 mg, 30 mg, and 60 mg QD) and in participants with CM (Study 303; atogepant 30 mg BID and 60 mg QD).

Essential features of prevention studies 301 and 303 are accordant with EU Guideline provisions (CPMP/EWP/788/01 Rev.1). The designs of studies 301 and 303 are similar. The major difference between the two studies lies in the target population (EM vs CM) and the atogepant dose range that was tested. While all once daily dose arms examined in dose finding study CGP-MD-01 (10 mg QD, 30 mg QD, 60 mg QD) were taken over into pivotal EM study 301, only the highest total daily dose of 60 mg atogepant (tested for the QD and BID dosing interval) was carried forward to the pivotal CM study 303.

Inclusion criteria applied throughout pivotal studies align with the standard ICHD-3 diagnostic criteria (ICHD-3, 2018). Any medication to be taken for acute migraine attacks (incl. triptans, NSAIDS, acetaminophen etc.) was permissible. As concerns concomitant preventive migraine medication, there were differences between the EM and the CM study. While any medication with demonstrated efficacy for the prevention of migraine (e.g. amitriptyline, topiramate, propranolol etc.) was prohibited in EM study 301, participants of CM study 303 could take one preventive medication with demonstrated

efficacy. At study entry, about 83% of CM subjects reported the use of preventive medication in the past. This is considered to reflect clinical practice in the more severely affected CM population.

Standard and clinically meaningful efficacy endpoints were tested. The primary efficacy endpoint in both pivotal studies was the change from baseline in mean monthly migraine days across the 12-week treatment period (DBT). Further secondary endpoints were tested for superiority of atogepant over placebo while controlling for multiplicity in studies 301/303. The three most relevant was the change from baseline in mean monthly headache days across the 12-week DBT [S1], change from baseline in mean monthly acute medication use days across the 12-week [S2], and ≥ 50% reduction in 3-month average of monthly MDs as responder analysis [S3].

3.3. Favourable effects

Efficacy of atogepant in prevention of episodic and chronic migraine was demonstrated based on statistically significant and clinically relevant results obtained across primary and secondary endpoints in both pivotal trials. The favourable outcome further translates into early onset of effect within the first month of treatment and persistence of effect over 52-week duration. Robustness of data was demonstrated across relevant subgroups per baseline disease burden (mean monthly MDs), and prevalent medication overuse, resp. concomitant prophylactic treatment in CM participants.

Primary: Reduction in MDs

Like it could be observed in previous migraine prevention trials, a considerable placebo response was observed in both populations. Both EM and CM placebo patients reduced the number of mean monthly MDs by up to one third (EM: -2.5 MD [-32.8%], CM: -5.1 MD [-26.9%]). Superiority over placebo was shown for all atogepant treatment arms across the two trials. A numerical dose-response relationship was evident for the change from baseline in mean monthly MDs across the 12-week treatment period in Study 301, with greater reductions seen with increasing atogepant dose from 10 to 60 mg QD (LSMD over placebo: 10 mg QD: -1.22, 30 mg QD: -1.38, 60 mg QD: -1.66). The placebo-corrected mean reduction from baseline in mean monthly migraine days observed with the atogepant 60 mg QD dose was the same in the EM and CM studies (LSMD of –1.66 in both Study 301 and Study 303).

Secondary endpoints

A Headache Day (HD) is defined as any calendar day on which headache pain lasting 2 hours or longer occurs unless an acute headache medication (e.g. ibuprofen, triptan) was used after the start of the headache. As such, a HD captures days with headache irrespective of any other migraine-specific symptoms. In particular in CM patients, where tension type headache and migraine headache often overlap, and who complain about highly frequent or almost continuous headache, measurement of HD is an important parameter for disease burden. Accordingly, reduction of HD from baseline during the 12-week DBT was placed highest in hierarchical multiplicity testing [S1] of secondary endpoints. The results obtained for the S1 secondary endpoint are similar to those obtained for the primary MD reduction endpoint. Statistically significant superiority over placebo after multiplicity adjustment was achieved for each of the atogepant dosages tested in studies 301 and 303. Numerically more favourable results were obtained with increasing doses across the QD (10 mg, 30 mg, 60 mg) dose arms in EM study 301. The net treatment effect over placebo was more favourable for the 30 mg BID dose arm as compared to the 60 mg QD dose arm in study 303 (LSMD for HD reduction from baseline: 30 mg BID: -2.14, 60 mg QD: -1.72).

At baseline, acute medication (incl. both unspecific analgesics and triptans) was used on a mean of 6-7 days among EM patients and on about 15 days per month in the CM population. The change from baseline in mean monthly acute medication use days [S2] was second in hierarchical testing of secondary

endpoints. For both the Acute Medication Use Day and the Triptan Use Day (which was singled out) secondary endpoint significant superiority over placebo could be demonstrated for each atogepant dose arm.

In terms of the ≥ 50% reduction in 3-month average of monthly MDs [S3], statistically significant superiority over placebo was achieved for each atogepant dose arm tested across studies 301 / 303. In study 301, more than 50% of subjects allocated to one of the atogepant dose arms achieved a reduction by ≥ 50% in the 3-month average of monthly MDs (atogepant: 10 mg QD: 54.6%, 30 mg QD: 58.5%, 60 mg QD: 59.3%; placebo 29.2%). This underlines the clinical relevance of the improvement achieved in terms of the primary MD reduction from baseline across all atogepant dose arms. Among the more severely affected CM population of study 303, response rates were slightly lower (30 mg BID: 42.1%, 60 mg QD: 40.1%). Nonetheless, the probability of achieving a ≥ 50% reduction in the 3-month average of monthly MDs was still about twice as high for atogepant as compared to placebo (OR: 30 mg BID: 2.03, 60 mg QD: 1.90).

Time course

The major part of the overall treatment effect is achieved within the first 4-week dosing interval of the 12-week DBT in both the EM and CM population. Thereafter, the reduction of mean monthly MDs is maintained or even slightly increases. The dose response relation across the three QD dose arms of study 301 is consistently observed across the three 28-day intervals of the 12-week DBT. In CM study 303, the more favourable effect of the 30 mg BID dosing regimen as compared to the 60 mg QD dosing scheme gets more pronounced with ongoing treatment duration.

The course of treatment effect was further analysed per week for the first 28-day period of the DBT of studies 301 and 303. In both EM and CM patients, the treatment effect starts within the first week of treatment. There was no clear tendency of increasing or decreasing effect of atogepant over the four 1-week intervals of the first 28-day treatment interval. This is considered to provide valuable information to the prescriber when the treatment effect of atogepant is evaluated within the context of clinical monitoring.

Persistence of effect

In open-label, long-term study 302, the daily use of 60 mg atogepant QD (N=546) was compared to SOC (N=198) over a 52-week treatment period in EM patients, either recruited de novo (85.6%) or taken over from dose finding study MD-01 (14.4%). Participants randomised to oral SOC migraine preventive medication (topiramate: 35.7%, beta-blockers 26.0%, tricyclic antidepressants 25.5%) were included to contextualise safety results.

It was primarily designed to examine safety of long term atogepant use in EM patients. However, efficacy was also monitored in those subjects randomised to atogepant. In atogepant patients, a clinically relevant reduction in mean monthly MDs was achieved within the 1st month and was sustained over the 1-year treatment period. Atogepant treatment led to a reduction in the LS mean number of monthly MDs in the first month (Weeks 1-4) of 3.84 days with continued improvement during the remainder of the 52-week treatment period to a LS mean reduction of -5.19 days in the last month (Weeks 49 to 52).

Overall, it is noted that no efficacy assessment was performed in long-term extension study 309 (in completers of study 301). Nevertheless, the overall number of patients included in the other long-term study 302 in EM patients can be considered sufficient for the evaluation of a long-term efficacy.

3.4. Uncertainties and limitations about favourable effects

Given the overall positive efficacy results, there is little uncertainty about the favourable effects of atogepant in the targeted population. However, there is some concern related to the choice of the dosing

interval proposed for the atogepant 60 mg standard daily dose that is to be taken as a single dose (QD), while numerically more favourable results were obtained for the atogepant 30 mg BID dose arm.

Proposed atogepant 60 mg QD dosing interval

Apart from testing dose response in EM study 301 across the once daily 10, 30, 60 mg dose range, the effect of changing the dosing interval from once daily to twice daily was examined for the highest 60 mg daily dose in the CM population. A noticeable difference was observed in favour of the twice daily dosing schedule in terms of the net difference over placebo for the reduction of mean monthly MDs (Study 303: LSMD over placebo: 30 mg BID: -2.24, 60 mg QD: -1.66). The favourable treatment effect of the 30 mg BID regime (as compared to 60 mg QD) was analogously observed in phase II/III dose finding study MD-01 (reduction in mean monthly MDs from baseline: 30 mg BID: -4.0, 60 mg QD: -3.56). It also translates into most relevant secondary endpoints, like reduction of HDs, reduction of acute medication use, and 50% response rates. Further plausibility for the favourable outcome in the 30 mg BID treatment arm is provided by PK study P002. In study P002, plasma levels were compared for different atogepant doses after repetitive dosing over 10 days. C24 hrs trough values after 30 mg BID dosing were remarkably high, higher than after 100 mg once daily dosing and almost reaching the level of the 170 mg once daily regime. Despite numerically more favourable results for the 30 mg BID dose arm across primary and secondary endpoints, the applicant's posology strategy is to confine to the uniform 60 mg once daily dosing schedule in order to provide a simple and convenient posology scheme. This is assumed to best promote patient compliance, which is an established challenge in migraine prevention.

Potential rebound after treatment cessation.

Both in EM study 301 and CM study 303, subjects were followed up for another 4-week period after termination of the 12-week DBT or early discontinuation. According to the Schedule of Procedures of Study 301, participants' eDiary entries regarding headache were evaluated only in those patients who terminated early, but not in patients who completed the entire 12-week DBT. Hence, no data were provided on potential rebound of migraine after cessation of study medication in (all) participants of studies 301/303. Instead, efficacy endpoint MSQ v2.1 Role function-Restrictive domain scores were collected at the safety follow-up visit (4 weeks after the treatment period). As indicated by smaller Change from Baseline values for MSQ RFR domain scores at 4 weeks Follow-up, the beneficial effect of atogepant treatment weans off after treatment cessation. However, the scores at the 4 week follow-up interview were still higher than baseline values, thereby showing that rebound effects in mean scores were not observed.

3.5. Unfavourable effects

Overall safety data as obtained from RCTs point to a rather favourable safety profile of atogepant. Concerns about hepatic safety of atogepant, however, have arisen after receipt of a post-marketing report of possible DILI that was observed in a female patient during the first months of marketing in the US.

Overall exposure to atogepant is sufficiently large. A total of N=3230 unique participants (including 604 healthy volunteers, 656 participants with CM, and 1970 EM patients) were exposed to at least 1 dose of atogepant during clinical development. With regard to the duration of exposure, the minimum requirements as specified per ICH E1 Guidance are fulfilled.

Most common adverse events

Atogepant preventive migraine treatment was well tolerated. The most common AEs in any atogepant group (≥ 5% of participants) were nausea, constipation, fatigue, and upper respiratory tract infection. Of these, constipation, nausea, and fatigue were considered as related to study drug in the majority of

cases. In particular, for nausea (atogepant: 7.5%, placebo 3.3%) and constipation (atogepant: 7.2%, placebo: 2.0%) reporting rates in atogepant patients were higher as compared to placebo. Constipation is also labelled as common adverse reaction to biological CGRP antagonists erenumab and galzanezumab. Of note, the AE of decreased appetite was reported about ten times more often in atogepant patients (2.1%) as compared to placebo (0.2%). There was no clear dose response relation for the rate of TEAEs across the atogepant doses, ranging from atogepant 10 mg QD to supra-therapeutic atogepant 60 mg BID in the PCS set.

In long-term safety study 302, a SOC arm was included to contextualise safety. The rate of patients showing TEAEs was lower for atogepant 60 mg QD (N=1662, 63.5%) as compared to SOC (N=196, 78.6%). However, interpretation is cautioned given the disparity of underlying datasets.

The number and percentage of participants with common AE in the LTS set reveals good tolerability of long-term atogepant 60 mg QD use as compared to the standard of care control arm. Of those AEs observed in the PCS set which were considered related to study drug, only constipation was reported more often for atogepant 60 mg QD (6.0%) as compared to SOC (3.1%).

Adverse drug reactions (ADRs) were determined by evaluating TEAEs in the placebo-controlled migraine studies (Studies MD-01, 301, and 303) that occurred with a ≥ 2% overall incidence rate in any of the atogepant groups and at a rate at least 2% greater than placebo. Constipation, decreased appetite, nausea, and fatigue/somnolence were identified as ADRs.

Serious Adverse events (SAE)

The overall incidence of SAE in the PSC set was low across atogepant treatment arms (≤ 1.3%) and similar to placebo (1.1%). None of the observed SAE was reported in more than 1 participant.

In the LTS set, the overall rate of TESAE was higher in patients receiving SOC (N=196, 3.6%) as compared to patients receiving atogepant 60 mg QD (N=1662, 3.4%). Importantly, there is no accumulation of any SAE. For the vast majority of SAE per preferred term the frequency in atogepant subjects is 0.1%. This includes Hepatobiliary disorders (cholelithiasis, cholecystitis) and Investigations (ALT increased, AST increased). There wasn’t any cardiovascular SAE under long-term atogepant treatment.

Adverse Events of special interest (AESI)

Cardiovascular events (cardiac arrythmias, central nervous system vascular disorders, embolic and thrombotic, hypertension, and ischaemic heart disease), hepatic AEs, suicide-related events, and abuse-related AEs were identified as AESIs for the placebo-controlled, long-term safety, and Phase 1 analysis sets.

Cardiovascular Events

A comprehensive evaluation of cardiovascular safety of atogepant as TEAESI was provided for both the use of atogepant under placebo-controlled conditions and long-term over 52-weeks. There was no incident of ischaemic heart disease. The incidence of arrhythmia-related AEs was low and similar between atogepant (0.3%) and placebo (0.2%). Across the PCS and LTS set, only two cases of hypertension as reported AE were considered by the Investigator as related to study medication. Based on the narratives, however, there is no clear suspect of atogepant having a causative role given the overall medical conditions of concerned subjects and timing of reporting (resp. persistence of the event) in relation to atogepant treatment.

Hepatic Safety

Historical clinical development programs for other members of the gepant family (telcagepant) were halted when liver toxicity was detected during migraine prophylaxis trials (Ho TW. Neurology 2014).

Therefore, AEs related to hepatic toxicity were systematically evaluated as AEs of special interest, including blinded adjudication of post-baseline elevations of ALT and/or AST ≥ 3 × ULN for participants who received either atogepant or placebo by an external expert committee.

Incidence of hepatic injury, AST/ALT elevations

Absolute figures for the incidence of hepatic injury and/or any liver enzyme elevation (> 1 x ULN) in atogepant patients as compared to placebo appear favourable.

- In the Placebo-controlled Analysis Set, hepatic injury TEAE overall (atogepant: 1.5%, placebo: 1.8%), and hepatic enzyme elevations (ALT increased: atogepant: 1.1%, placebo: 1.5%; AST increased: atogepant: 1.0%, placebo: 1.4%) were observed more often in placebo patients than in participants receiving atogepant. The incidence of ALT or AST increase as TEAE was independent of the atogepant dose.
- Categorical analysis of liver enzyme elevations shows that any aminotransferase elevation (AST or ALT > 1 x ULN) was observed more frequently under placebo (14.2%) as compared to all atogepant patients (10.9%) in the PCS set.
- Likewise, under long term treatment (LTS set), the incidence of hepatic injury overall (atogepant 2.5%, SOC 3.1%), and aminotransferase elevations as TEAE (AST increased: atogepant 1.7%, SOC 2.6%; ALT increased: atogepant 1.6%, SOC: 2.0%) was higher in participants receiving standard-of-care as compared to atogepant.
- Analysis of enzyme elevation categories in the long-term analysis set reveals that any aminotransferase elevation (AST or ALT > 1 x ULN) was observed more frequently across SOC patients under long term treatment (28.9%) as compared to atogepant 60 mg QD patients (14.4%).

Adjudication of relationship to treatment

- In the PCS set, a total of n=24/2500 cases with aminotransferase elevations $\geq$ 3 x ULN were adjudicated by the external blinded Expert Committee. Of these, n=17 subjects received atogepant (n=7 received placebo). Among the atogepant patients, n=4 subjects (out of N=1837) were adjudicated as either possible (n=2) or probably related (n=2) to atogepant treatment. Narratives were provided. In 3 of these cases, there were confounding factors like intensive weightlifting in the gym, extensive concomitant acetaminophen use for acute headache, or Class III obesity (BMI 39.6 kg/m^2). All 4 atogepant-treated cases that were adjudicated as probably or possibly related to study drug were asymptomatic, non-serious, mild or moderate in severity, without concurrent bilirubin elevations, and resolved with or without atogepant discontinuation.
- In the LTS set, a total of n=24/1662 patients with hepatic enzyme elevations $\geq$ 3 x ULN under long-term atogepant treatment were adjudicated. In eight cases, the relationship of aminotransferase elevations to study drug was rated as possible or probable. Narratives were provided. In subjects recruited for long-term studies 302 and 309, confounding factors like weightlifting, obesity, history of binge drinking, or transient periods of increased alcohol consumption are reported and subjects completed the study. The remaining cases are reported for long-term study 306 conducted in Japan. Atogepant treatment was discontinued in n=4 subjects from study 306, for which the relationship to study drug was rated possible or probable. In these cases, confounding factors (e.g. concomitant betahistine, cephalosporin, azithromycin) are less clear. Of note, among the 8 cases that were adjudicated as probably or possibly related to study drug all were non-serious, mild to moderate in severity, without concurrent bilirubin elevation, and resolved with or without atogepant discontinuation.

In the clinical trial dataset (placebo-controlled and long-term), there was no case fulfilling criteria for potential Hy's Law (ALT or AST $\geq$ 3 x ULN and TBL $\geq$ 2 x ULN and ALP < 2 x ULN).

Hence, the overall hepatic safety profile of atogepant, as obtained from clinical trials, appears rather favourable. However, a re-evaluation of atogepant's hepatic safety was required after receipt of one spontaneous post-marketing report of acute liver failure with atogepant 60 mg QD that led to liver transplantation.

3.6. Uncertainties and limitations about unfavourable effects

Hepatic safety

Across the placebo-controlled (PCS), long-term (LTS) and post-marketing datasets, clinically relevant enzyme elevations were observed in patients receiving atogepant (although mostly asymptomatic across clinical trials). In some of these cases, AST/ALT elevations were adjudicated as possibly or probably related to atogepant treatment based on positive dechallenge and / or absence of clear confounders.

For the clinical trial dataset, it is confirmed that the elevations of aminotransferases that are probably or possibly related to atogepant were mostly asymptomatic, all were non-serious, mild to moderate in severity, without concurrent bilirubin elevations and transient in nature. There were no Hy's law cases, coagulopathy, encephalopathy or other organ dysfunction, hospitalisation, liver transplant, acute liver failure, or death due to liver injury in the clinical development programme of atogepant.

Conversely, in the post marketing setting, two cases of serious liver-related events have been reported. The first relates to the female experiencing acute liver failure (on Day 127 after atogepant initiation) leading to liver transplant. With extended post-marketing surveillance (data lock-off 11 October 2022) another suspected case of serious liver-related events (liver cirrhosis) was reported (at the time of first reporting without any further background information). The case of the female patient concerns non-alcoholic fatty liver disease (NAFLD) diagnosed in 2016, i.e. about six years before 30 mg atogepant was initiated (Oct 2022). Hence, the suspected second case of serious post-marketing hepatotoxicity is unlikely to be related to atogepant therapy.

The fact that the overall frequency of liver enzyme elevations was not increased in atogepant patients as compared to patients receiving placebo in the PCS dataset, or to subjects receiving SOC in LT study 302 is providing reassurance. In line with results obtained from the DILIsym model (including in vitro tests of mitochondrial dysfunction, oxidative stress, and alterations in bile acid homeostasis) atogepant is not considered to intrinsically induce hepatotoxicity.

Graphical presentations of Time to onset (TTO) were provided on the cumulative number of atogepant participants with ALT /AST elevations $\geq$ 3 x ULN across the PCS and LTS set to further elucidate the relation between atogepant exposure and liver enzyme elevations. Overall, the TTO of all atogepant-treated cases of aminotransferase elevation ≥ 3 × ULN was wide both in the PCS and LTS studies, ranging from the first week after treatment initiation to the end of the observation period (12+4 weeks for PCS, > 1 year for LTS). Hence, no temporal relation between atogepant exposure and enzyme elevations could be established.

Further issues of uncertainty

There was one SAE of presumed optic neuritis, which was considered as related to study drug by the Investigator, but was considered not related by the Sponsor. Irrespective of any attempt to retrospectively decide upon potential relatedness of the single SAE of presumed optic neuritis, it is suggested to examine future PSUR reports for potential signals in this regard.

3.7. Effects Table

Table 60: Effects Table of Aquipta for prophylaxis of migraine in adults who at least 4 migraine days per month, (data cut-off: Day 80).

Effect	Short Description	Placebo N=216	Atogepant 10 mg QD N=216	Atogepant 30 mg QD N=224	Atogepant 60 mg QD N=226	Strengths / Uncertainties / Limitations
	Favourable Effects: Prevention of episodic migraine (EM), Study 3101-301-002					
Change from Baseline in Mean Monthly Migraine Days (MD) across the 12-week DBT, Primary	Baseline No. of monthly MDs, Mean (SD)	7.53 (2.394)	7.46 (2.466)	7.86 (2.311)	7.75 (2.334)	• Study population representative for clinical practice in preventive therapy of EM •Primary and secondary endpoints [S1-S3] met after multiplicity control • Magnitude of effect clinically relevant • Early onset of effect within the first four weeks • Robust effect across subgroups, e.g. per baseline MDs (< 8 and ≥ 8 monthly MDs) • Maintenance of effect in the EM population shown under long-term open-label conditions over 52 weeks • Most effective dose in dose finding study MD-01 (30 mg BID) not taken over into pivotal EM study 301
	LS Mean (SE) change from baseline	-2.47 (0.210)	-3.69 (0.209)	-3.85 (0.206)	-4.14 (0.205)	
	LSMD (95% CI) Atogepant vs PBO, adjusted p-value		-1.22 (-1.79, -0.65) <0.0001	-1.38 (-1.94, -0.81) <0.0001	-1.66 (-2.23, -1.10) <0.0001	

Effect	Short Description	Placebo N=216	Atogepant 10 mg QD N=216	Atogepant 30 mg QD N=224	Atogepant 60 mg QD N=226	Strengths / Uncertainties / Limitations
Change from Baseline in mean monthly Headache Days (HD) across the 12-week DBT, Secondary [S1]	Baseline No. of monthly HDs, Mean (SD)	8.45 (2.550)	8.43 (2.754)	8.78 (2.615)	8.99 (2.577)	
	LS Mean (SE) change from baseline	-2.52 (0.225)	-3.94 (0.224)	-4.03 (0.220)	-4.17 (0.219)	
	LSMD (95% CI) Atogepant vs PBO, adjusted p-value		-1.42 (-2.03, -0.81) <0.0001	-1.51 (-2.11, -0.91) <0.0001	-1.65 (-2.25, -1.04) <0.0001	
Change from Baseline in mean monthly Acute Medication Use Days across the 12-week DBT, Secondary [S2]	Baseline No. of monthly Acute Mx Use Days, Mean (SD)	6.50 (3.152)	6.58 (2.989)	6.66 (3.050)	6.88 (3.151)	
	LS Mean (SE) change from baseline	-2.34 (0.184)	-3.68 (0.183)	-3.65 (0.181)	-3.78 (0.180)	
	LSMD (95% CI) Atogepant vs PBO, adjusted p-value		-1.34 (-1.84, -0.84) <0.0001	-1.31 (-1.81, -0.82) <0.0001	-1.44 (-1.93, -0.94) <0.0001	
Portion with ≥ 50% reduction in 3-month average of monthly MDs, Secondary [S3]	Responders, n (%)	63 (29.2)	118 (54.6)	131 (58.5)	134 (59.3)	
	Odds ratio (95% CI), Atogepant vs PBO, adjusted p-value		2.91 (1.95, 4.33) <0.0001	3.46 (2.32, 5.14) <0.0001	3.55 (2.39, 5.28) <0.0001	

Effect	Short Description	Placebo N=216	Atogepant 10 mg QD N=216	Atogepant 30 mg QD N=224	Atogepant 60 mg QD N=226	Strengths / Uncertainties / Limitations
Notes	LS = least squares; LSMD = least squares mean difference; Adjusted p-values: using graphical approach to control the overall type I error rate for multiple comparisons					

Effect	Short Description	Placebo N=249	Atogepant 30 mg BID N=254	Atogepant 60 mg QDo N=257	Strengths / Uncertainties / Limitations
	Favourable Effects: Prevention of chronic migraine (CM), Study 3101-303-002				
Change from Baseline in	Baseline No. of monthly MDs, Mean (SD)	19.0 (4.80)	18.6 (5.09)	19.2 (5.29)	• Study population representative for clinical

Effect	Short Description	Placebo N=249	Atogepant 30 mg BID N=254	Atogepant 60 mg QDo N=257	Strengths / Uncertainties / Limitations
Mean Monthly Migraine Days (MD) across the 12-week DBT, Primary	LS Mean (SE) change from baseline	-5.09 (0.409)	-7.33 (0.406)	-6.75 (0.406)	practice in preventive therapy of CM •Primary and secondary endpoints [S1-S3] met after multiplicity control • Magnitude of effect clinically relevant • Early onset of effect within the first four weeks • Robust effect across subgroups, e.g. per baseline MDs (< 18 and ≥ 18 monthly MDs), per concomitant preventive treatment, and per Medication Overuse • Long-term studies in CM are ongoing. No maintenance of effect data in CM available yet • Numerically most favourable results for the 30 mg BID regimen. However, atogepant 60 mg QD proposed as standard dose
	LSMD (95% CI) Atogepant vs PBO, adjusted p-value		-2.24 (-3.31, -1.16) <0.0001	-1.66 (-2.72, -0.59) 0.0024	

Effect	Short Description	Placebo N=249	Atogepant 30 mg BID N=254	Atogepant 60 mg QDo N=257	Strengths / Uncertainties / Limitations
Change from Baseline in mean monthly Headache Days (HD) across the 12-week DBT, Secondary [S1]	Baseline No. of monthly HDs, Mean (SD)	21.4 (4.11)	21.2 (4.15)	21.5 (4.32)	
	LS Mean (SE) change from baseline	-5.17 (0.403)	-7.32 (0.399)	-6.90 (0.399)	
	LSMD (95% CI) Atogepant vs PBO, adjusted p-value		-2.14 (-3.20, -1.09) 0.0002	-1.72 (-2.78, -0.67) 0.0024	
Change from Baseline in mean monthly Acute Medication Use Days across the 12-week DBT, Secondary [S2]	Baseline No. of monthly Acute Mx Use Days, Mean (SD)	15.3 (7.05)	14.5 (7.22)	15.5 (7.36)	
	LS Mean (SE) change from baseline	-4.09 (0.389)	-6.61 (0.388)	-6.19 (0.383)	
	LSMD (95% CI) Atogepant vs PBO, adjusted p-value		-2.52 (-3.52, -1.53) 0.0002	-2.09 (-3.09, -1.10) 0.0024	
Portion with ≥ 50% reduction in 3-month average of monthly MDs, Secondary [S3]	Responders, n (%)	66 (26.5)	107 (42.1)	103 (40.1))	
	Odds ratio (95% CI), Atogepant vs PBO, adjusted p-value		2.03 (1.38, 2.98) 0.0006	1.90 (1.29, 2.79) 0.0024	
Notes	LS = least squares; LSMD = least squares mean difference; Adjusted p-values: using graphical approach to control the overall type I error rate for multiple comparisons				

Effect	Short Description	Atogepant Safety Dataset, of primary interest: ➢ Placebo-controlled Safety (PCS) Pool, N = 2500 incl. n = 663 placebo; ➢ Long-term Safety (LTS) Pool, N = 1665 atogepant, plus N = 196 SOC	Strengths / Uncertainties / Limitations
	Unfavourable Effects		

		• Comprehensive safety evaluation was provided, incl. focus on relevant AEs of Special Interest (AESI)
		• Most common ADRs were nausea (7%), constipation (7%), and fatigue/somnolence (5%).
		• No liability for abuse, no signal for suicidality
		• No safety concerns for hypertension AEs or other cardiovascular events were identified.
		• Decreases in body weight by ≥ 7% from baseline were observed in atogepant patients in a dose-dependent way both under placebo-controlled and long-term treatment conditions.
		• Further elucidation of atogepant's liability to induce liver enzyme elevations is required, based on
		  • One case of possible DILI reported post-marketing
		  • Single cases of particularly high liver enzyme elevations in the PSC and LTS set
		  • Uncertainty about the role of atogepant treatment duration in relation to aminotransferase elevations
		  • Need for updated post-marketing data and long-term treatment data from ongoing studies	

3.8. Benefit-risk assessment and discussion

3.9. Importance of favourable and unfavourable effects

Efficacy

Dose-finding study MD-01 and pivotal studies 301 (EM population) and 303 (CM population) were designed concordant with IHS and EMA guidance and provide a sound database demonstrating evidence for the benefit of atogepant in preventive migraine treatment across the full spectrum of episodic and chronic forms of the disease.

Atogepant in dosages of 10, 30, and 60 mg QD in EM and 60 mg QD and 30 mg BID in CM demonstrated superiority over placebo in reducing the frequency of both migraine days [primary P1], as well as the frequency of headache days [secondary S1] and the associated use of medication for the acute treatment of migraine [S2]. Higher response rates were seen with each atogepant dosage compared with placebo for participants with ≥ 50% reduction in the 3-month average of monthly migraine days [S3].

A numerical dose-response relationship was evident for the change from baseline in mean monthly MDs across the 12-week DBT in EM Study 301, with greater reductions seen with increasing atogepant dose from 10 to 60 mg QD. Only the highest maximum daily dose of 60 mg tested in EM study 301 was taken over in CM Study 303. To explore the potential impact of the once daily vs twice daily dosing regimen, the 60 mg daily dose was examined across a 60 mg QD and a 30 mg BID treatment arm in CM Study 303. The placebo-corrected mean reduction from baseline in mean monthly migraine days observed with the atogepant 60 mg QD dose was the same in the EM and CM studies (LSMD of –1.66 in both Study 301 and 303).

The robustness of the primary and secondary endpoint results [S1-3] after multiplicity adjustment for each of the atogepant dosages tested in studies 301/303 was confirmed across several subgroup analyses, like e.g. prior use of prevention medication, concomitant use of another prophylactic medication (study 303), or prevalent medication overuse (study 303).

The onset of the clinical effect of atogepant is early. In both the EM and CM population, the overall treatment effect in terms of MD reduction is achieved mainly within the first 28-day period of the 12-week DBT of studies 301 and 303.

In terms of persistence of effect, supportive efficacy data are obtained from open-label, long-term study 302 in EM patients for treatment with atogepant 60 QD over 52 weeks. A clinically relevant reduction in mean monthly MDs was achieved within the 1st month and was sustained over the 1-year treatment period.

Overall, efficacy was adequately demonstrated for the proposed use of atogepant in migraine prevention.

Posology

With regard to proposed posology, the numerically most favourable outcome across primary and secondary endpoints in studies MD-01 (EM) and pivotal study 303 (CM) was observed for the 30 mg BID dosing regimen. However, the applicant applies for the 60 mg QD once daily as regular dosing scheme only. It is established that compliance with migraine preventive treatment remains a challenge. Therefore, the potential advantage of a once daily dosing regimen is evident in terms of compliance. On the other hand, administration of the most effective treatment is equally expected to positively impact on patient compliance. A 30 mg tablet formulation was tested in Study 301, i.e. is available. Despite numerically more favourable results for the 30 mg BID dose arm across primary and secondary

endpoints, the applicant's posology strategy is to confine to the uniform 60 mg once daily dosing schedule in order to provide a simple and convenient posology scheme.

Safety

Based on data obtained from the clinical trials, the safety profile of atogepant in preventive migraine treatment appears favourable. Most common ADRs were nausea (7%), constipation (7%), and fatigue/somnolence (5%). No safety concerns for hypertension AEs or other cardiovascular events were identified. Decreases in body weight by $\geq$ 7% from baseline were observed in atogepant patients in a dose-dependent way both under placebo-controlled and long-term treatment conditions.

Concerns about atogepant's hepatic safety profile were raised after receipt of a post-marketing report of a female who developed acute liver failure leading to liver transplant on Day 127 of atogepant 60 mg treatment for migraine prophylaxis. An independent expert confirmed the event to be compatible with DILI and timing as consistent with a role for atogepant.

In-depth evaluation of atogepant's hepatic safety profile was provided based on modelled DILIsym results, the PCS dataset, extended long-term data (from ongoing studies 306 and 312), and further post-marketing experience (cumulative patient exposure / sales data from 28 Sep 2021 to 31 Oct 2022).

The fact that the overall frequency of liver enzyme elevations was not increased in atogepant patients as compared to patients receiving placebo in the PCS dataset, or to subjects receiving SOC in LT study 302 is providing reassurance. In line with results obtained from the DILIsym model (including *in vitro* tests of mitochondrial dysfunction, oxidative stress, and alterations in bile acid homeostasis) atogepant is not considered to intrinsically induce hepatotoxicity.

A potential idiosyncratic liability, however, may only manifest with temporal latency, and due to its rarity, in larger populations. Across the placebo-controlled (PCS), long-term (LTS) and post-marketing datasets, clinically relevant enzyme elevations were observed in patients receiving atogepant (although mostly asymptomatic across clinical trials). In some of these cases, AST/ALT elevations were adjudicated as possibly or probably related to atogepant treatment based on positive dechallenge and / or absence of clear confounders.

3.9.1. Balance of benefits and risks

Efficacy was adequately shown for the proposed use of atogepant for prophylaxis of migraine in adults who have at least 4 migraine days per month. In-depth evaluation of atogepant's hepatic safety profile provided reassurance.

3.9.2. Additional considerations on the benefit-risk balance

NA

3.10. Conclusions

The overall benefit/risk balance of Aquipta is positive, subject to the conditions stated in section Recommendations.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Aquipta is favourable in the following indication(s):

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product on medical prescription for renewable delivery.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that atogepant is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.