Core/EU Risk Management Plan for Atogepant

AbbVie Inc. (AbbVie)

RMP version to be assessed as part of this application:

RMP Version Number: 1.0

Data lock point for this RMP: 11 October 2022

Date of final sign off: June 2023

Rationale for submitting an updated RMP: Not applicable

Summary of significant changes in the RMP: A summary of significant changes is included in RMP Annex 8.

Administrative Information on the RMP

Part Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
Part 1: Product(s) Overview	NA	NA
Part II: Safety Specification		
SI - Epidemiology of the Indication(s) and Target Population(s)	NA	NA
SII - Non-Clinical Part of the Safety Specification	NA	NA
SIII - Clinical Trial Exposure	NA	NA
SIV - Populations Not Studied in Clinical Trials	NA	NA
SV - Post-Authorization Experience	NA	NA
SVI - Additional EU Requirements for the Safety Specification	NA	NA
SVII - Identified and Potential Risks	NA	NA
SVIII - Summary of the Safety Concerns	NA	NA
Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)	NA	NA
Part IV: Plan for Post-Authorization Efficacy Studies	NA	NA
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	NA	NA
Part VI: Summary of the Risk Management Plan	NA	NA
Part VII: Annexes		
Annex 1 - EudraVigilance Interface	NA	NA
Annex 2 - Tabulated Summary of Planned, Ongoing, and Completed PV Study Program	NA	NA
Annex 3 - Protocols for Proposed, Ongoing, and Completed Studies in the PV Plan	NA	NA
Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms	NA	NA
Annex 5 - Protocols for Proposed and Ongoing Studies in RMP Part IV	NA	NA
Annex 6 - Details of Proposed Additional Risk Minimization Activities (If Applicable)	NA	NA
Annex 7 – Other Supporting Data (Including Referenced Material)	NA	NA

Annex 8 – Summary of Changes to the Risk Management Plan Over Time	NA	NA
Annex 9 - Local Currently-Approved Country Labeling	NA	NA
Annex 10 - Local Risk Management/Mitigation Plan	NA	NA

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

QPPV name: Sina Schader

Qualified Person Responsible for Pharmacovigilance oversight declaration: The content of the RMP has been reviewed and approved by the marketing authorization holder (MAH) QPPV through an electronic document system per company standard operating procedure.

Table of Contents

List of Tables

List of Figures

List of Annexes

List of Abbreviations

ADD	average daily dose
ADR	adverse drug reaction
AE	adverse event
aRMMs	additional risk minimization measures
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BSEP	bile salt export pump
CGRP	calcitonin gene-related
CLcr	creatinine clearance
CM	chronic migraine
CNS	central nervous system
CVD	cardiovascular disease
CYP	Cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
EEA	European Economic Area
eGFR	estimate of glomerular filtration rate
EM	episodic migraine
EPAR	European Public Assessment Report
ESRD	end-stage renal disease
EU	European Union
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GI	gastrointestinal
hERG	human ether-a-go-go-related gene
HR	heart rate
INN	International Nonproprietary Name
ISS	Integrated Summary of Safety
MAH	marketing authorization holder
MAST	migraine in America symptoms and treatment
MATE	multidrug and toxin extrusion proteins
MDRD	Modification of Diet in Renal Disease

MedDRA	Medical Dictionary for Regulatory Activities
MRP	multidrug resistance-associated protein
NMDA	N-methyl-D-aspartate
NOAEL	no-observed-adverse-effect level
OATP	organic anion transporting polypeptide
OCT	octamer-binding transcription factor
OR	odds ratio
P-gp	P-glycoprotein
PBPK	physiologically based pharmacokinetic
PIL	patient information leaflet
PND	post-natal day
PTD	patient treatment days
PTY	patient treatment years
PV	pharmacovigilance
QD	once a day
QPPV	Qualified Person Responsible for Pharmacovigilance
RMMs	risk minimization measures
RMP	Risk Management Plan
RR	relative risk
SmPC	Summary of Product Characteristics
TBD	to be determined
TEAE	treatment-emergent adverse event
US	United States
vs.	versus

Part I: Product Overview

Table 1. Product Overview

Active substance(s) (INN or common name)	Atogepant
Pharmacotherapeutic group(s) (ATC Code)	N02CD07
Marketing Authorization	AbbVie Inc.
Medicinal products to which this RMP refers	TRADENAME
Invented name(s) in the European Economic Area (EEA)	AQUIPTA
Marketing authorization procedure	Not applicable
Brief description of the product	Chemical class: CGRP receptor antagonist
	Summary of mode of action: CGRP is a neuropeptide present in the peripheral and CNS. CGRP levels in the cranial circulation are increased during migraine attack, and CGRP itself has been shown to trigger migraine-like headache. Atogepant is a CGRP receptor antagonist that blocks the binding of CGRP to its receptor and antagonizes CGRP receptor function.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	
Indication(s) in the EEA	Current (if applicable): Not applicable
	Proposed (if applicable): The prophylaxis of migraine in adults who have at least 4 migraine days per month.
Dosage in the EEA	Current (if applicable): Not applicable
	Proposed (if applicable): 60 mg once daily (QD)
Pharmaceutical form(s) and strengths	Current (if applicable): Not applicable
	Proposed (if applicable): Oral tablet 10 mg and 60 mg
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC = anatomical therapeutic chemical; CGRP = calcitonin gene-related; CNS = central nervous system; EEA = European Economic Area; EU = European Union; INN = International Nonproprietary Name; QD = once a day; RMP = Risk Management Plan; TBD = to be determined

Part II: Safety Specification

Module SI Epidemiology of the Indication(s) and Target Population(s)

Indication: Migraine prevention

Migraine is a serious, chronic, and disabling neurological disease characterized by recurrent moderate to severe headache attacks with or without aura.

Incidence:

The age-standardized incidence rate of migraine in 2019 for both sexes combined was 11.42 per 1000 population globally, with highest rates in Western Europe (13.86 per 1000) and North America (13.16 per 1000) (Safiri 2022).

Few population studies have been published that estimate incidence rates. A 12-year longitudinal Danish study estimated the overall incidence of migraine to be 8.1 per 1000 person-years (Ashina 2021, Lyngberg 2005). A similar Turkish study reported overall incidence as high as 23.8 per 1000 person-years overall (Baykan 2015).

Prevalence:

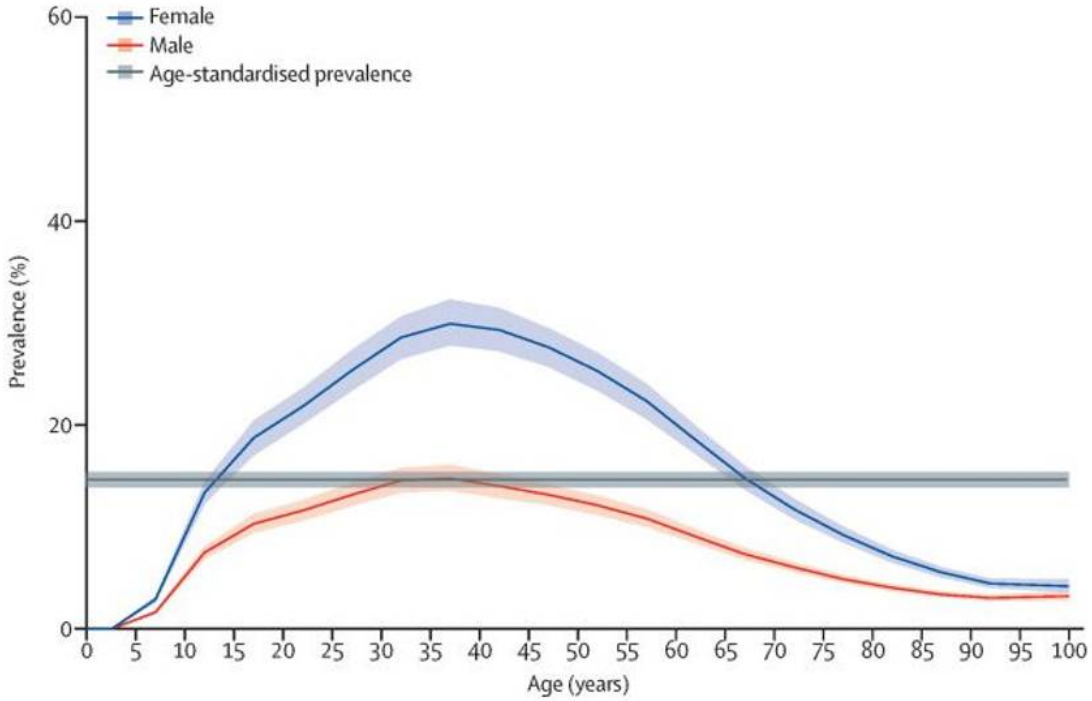
Migraine affects over 1 billion people across all world regions, cultures, and socioeconomic statuses (Ashina 2021). Global 1-year prevalence is estimated as 15% with the highest estimates in southeast Asia (25% to 35%) and the lowest estimates in China (9%) (Ashina 2021, GBD 2018, Saylor 2018). Chronic migraine affects 1% to 2% of the population globally and 2.5% of those with episodic migraine (EM) report progressing to CM each year (Burch 2019). Data collected from 9 European countries as part of the Eurolight project reported a 1-year prevalence of 35% after sex adjustment (Ashina 2021, Steiner 2014). By contrast, the 1-year prevalence of migraine in the United States (US), is reported to occur in 12% to 13% of the population, remaining stable over time (Ashina 2021).

Demographics of the target population:

Age and Gender:

Globally, a peak in migraine prevalence occurs between ages 35 and 39 years. Global age standardized prevalence was 18.9% (18.1% to 19.7%) for women and 9.8% (9.4% to 10.2%) for men (Figure 1) (GBD 2018). In the US the age-adjusted prevalence is 15.9% across all adults and the sex ratio remains stable with 21% of women and 10.7% of men affected (Burch 2021).

Figure 1. Global Prevalence of Migraine by Age and Sex, 2021



Source: Ashina et al. 2021

The American Migraine Prevalence and Prevention study reports a peak incidence rate (migraine onset) at ages 20 to 24 years in women (18.2 per 1000 person-years) and 15 to 19 years in men (6.2 per 1000 person-years). Migraine onset is reported in 75% of both sexes before the age of 35 years (Ashina 2021, Stewart 2008).

Ethnic origin:

Migraine prevalence also varies considerably between races. Migraine or severe headache was more common in American Indian, or Alaska natives (22.1%) compared with white (16.3%), black (15.6%), or Hispanic (16%) populations. The prevalence of migraine or severe headache was lowest in Asian people, with a prevalence of 9.1% (Burch 2021).

Risk Factors:

Females are at higher risk of migraine than males (Gilmour 2001).

Genetic factors are thought to be responsible for around 60% of the clinical features, with the remainder being due to non-genetic factors. Environmental factors identified as potentially triggering or worsening an attack include hormonal fluctuations, comorbid diseases, strong

sensor stimuli (e.g., light, smells, or noises), fatigue, food, and changes in the environment or habits (e.g., weather, sleeping, or eating patterns). Notable comorbid conditions modulating migraine risk or severity include allergies, respiratory illnesses (e.g., sinusitis, asthma, chronic bronchitis), cardiovascular disorders (e.g., high cholesterol, angina, stroke, vascular disorders), psychiatric disorders (e.g., anxiety, depression, stress), arthritis, obesity, noncephalic pain, and ulcers. Comorbidities are more prevalent in patients with CM than those with EM. In patients with EM, comorbidities constitute risk factors for the onset or persistence of CM, e.g., psychiatric disorders, asthma, and noncephalic pain. It has been proposed that higher blood pressure may be inversely correlated with the development of migraine, but these findings need to be further investigated (Agosti 2018).

Currently, the main approved preventive treatment options in European Union (EU) and/or US are:

- Calcitonin gene–related peptide (CGRP) receptor antagonist or monoclonal antibodies: rimegepant, eptinezumab, fremanezumab, galcanezumab, erenumab
- Antiepileptic: divalproex sodium, topiramate
- Tricyclic antidepressants: amitriptyline
- Beta-blockers: metoprolol, nadolol, propranolol
- Calcium channel blocker: flunarizine

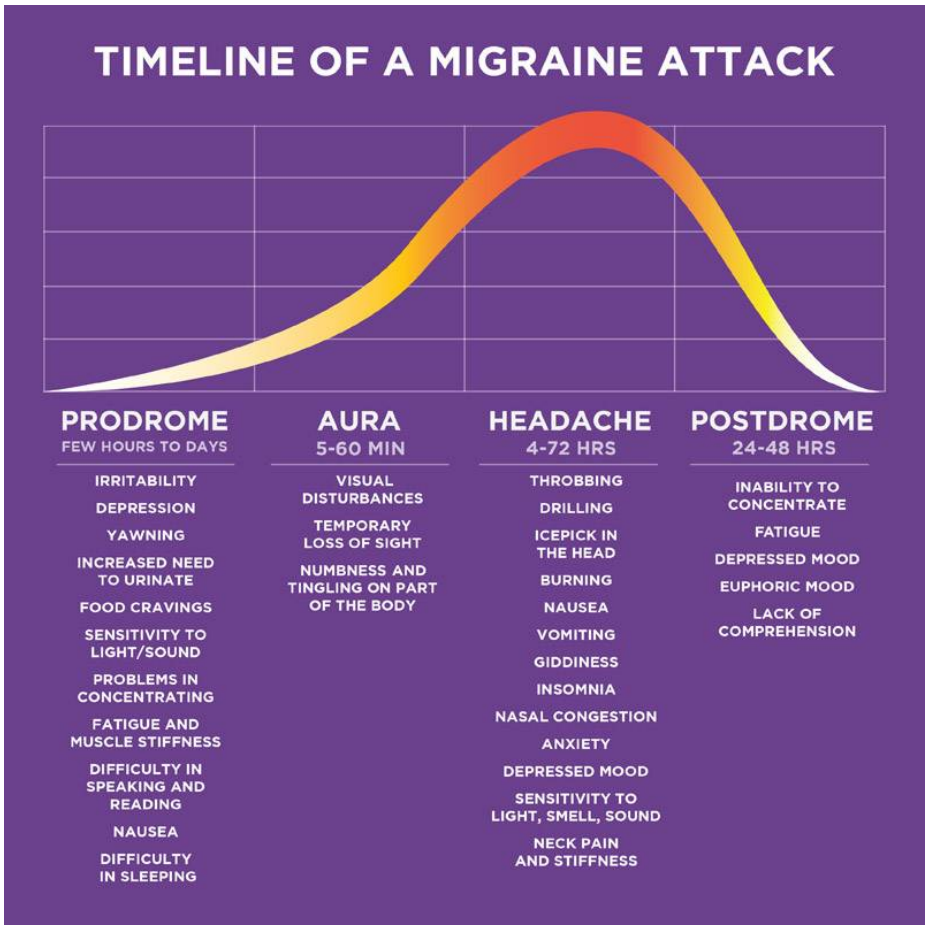
Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity: Migraine remains poorly understood leading to undiagnosed cases and undertreated people with migraine (Agosti 2018).

Migraine is now thought to be a neurological disorder as opposed to the dilation and constriction of blood vessels previously thought to be the main source of migraine pain. Symptoms include severe throbbing recurring pain on one side of the head, with one third of migraine attacks affecting both sides (Russo 2015).

Migraine can occur with or without aura and be classified as acute or chronic. In the revised criteria of International Classification of Headache Disorders-3 (ICHD-3 beta), migraine without aura is classified as recurrent attacks that usually last between 4 and 72 hours (Figure 2). Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia. Migraine with aura is described as recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system (CNS) symptoms that usually develop gradually and are typically followed by headache and other associated migraine symptoms (ICHD-3 2021). Aura occurs in about 25% of migraine sufferers and consist of focal neurologic symptoms (Cutrer 2010).

While most people with migraine experience attacks once or twice a month, more than 4 million people have chronic daily migraine (Foundation 2017). Chronic migraine is classified as a headache occurring on 15 or more days per month for more than 3 months, which, on at least 8 days per month, has the features of a migraine headache (ICHD-3 2021). The most common cause of symptoms suggestive of CM is medication overuse (ICHD-3 2021).

Figure 2. Timeline of a Migraine Attack



Source: https://americanmigrainefoundation.org/resource-library/timeline-migraine-attack/

Migraine is generally considered a non-fatal disease; however neurological disorders such as migraine account for a large and increasing health burden worldwide (Deuschl 2020). Migraine is the second leading cause of disability worldwide, and the leading cause among those under 50 years old. Migraine contributes to 45.1 million years lived with disability. The widespread prevalence and the associated disability of migraine have a range of negative effects not only on those affected but also their families, colleagues, employers, and society (Ashina 2021).

Data from US-based population studies show 32.7% of people with migraine reported that migraine affected their career and 22.8% worried about losing their job because of migraine. Migraine also affects family and friends, 38.6% of people with migraine reported it affected their parenting and 49% indicated they would be a better partner if they did not have headaches (Ashina 2021).

Important co-morbidities: Migraine is associated with multiple comorbidities including neurologic disorders (i.e., epilepsy), respiratory disorders (i.e., emphysema/chronic obstructive pulmonary disease), inflammatory conditions (i.e., asthma, allergic rhinitis), cardiovascular disorders (i.e., stroke, myocardial infarction, hypertension, high cholesterol), psychiatric disorders (i.e., depression, anxiety, panic disorder, bipolar disorder, personality disorders, suicide attempts), sleep conditions (i.e., insomnia, restless leg syndrome, sleep apnea, poor sleep quality and duration), as well as chronic pain conditions such as fibromyalgia (Buse 2020, Vetvik 2017).

The migraine in America symptoms and treatment (MAST) study, a prospective longitudinal cross-sectional web-based survey among US adults with and without migraine calculated the odds ratio (OR) for several comorbid conditions. The analyses included 15,133 people with migraine and 453 controls. Those with migraine were significantly more likely to report insomnia, depression, anxiety, gastric ulcers/gastrointestinal (GI) bleeding, angina, and epilepsy when compared to controls (Buse 2020).

In the untreated migraine population, particularly migraine with aura, an association between migraine and cardiovascular risks is well established in the literature (Bigal 2009, Kurth 2018). Several studies, including five meta-analyses have linked migraine, particularly migraine with aura to an increased risk of ischemic stroke. The relative risk (RR) of ischemic stroke is doubled in people with migraine with aura when compared to those without migraine (Øie 2020).

Among a cohort of 27,858 female health professionals in the US, followed through December 2018, 5.2% had migraine with aura and 94.8% did not. The adjusted incidence rate of major cardiovascular disease (CVD) per 1000 person-years for the cohort was 3.36 for women with migraine versus (vs.) 2.11 for women with migraine without aura or no migraine ($p < 0.001$) (Kurth 2020).

In a nationwide population-based Danish cohort, 51,032 patients with migraine were matched to 510,320 people from the general population. Higher absolute risks of cardiovascular events were observed among incident migraine subjects compared to the general population. In the migraine cohort, 2,451 patients experienced at least 1 cardiovascular event, 575 patients experienced more than 1 event (Adelborg 2018). Following 19 years of follow-up, the cumulative incidence per 1000 people for the migraine cohort compared to the general population were as follows:

- Myocardial infarction: 25 vs. 17
- Ischemic stroke: 45 vs. 25
- Hemorrhagic stroke: 11 vs. 6
- Peripheral artery disease: 13 vs. 11
- Venous thromboembolism: 27 vs. 18
- Atrial fibrillation (or atrial flutter): 47 vs. 34
- Heart failure: 19 vs. 18

Module SII Non-Clinical Part of the Safety Specification

No significant safety findings arising from nonclinical safety studies with atogepant have been identified by MAH.

Key Safety Findings (from Non-Clinical Studies)	**Relevance To Human Usage**
Toxicity	
Repeat dose toxicity The no-observed-adverse-effect level (NOAEL) of 100 mg/kg/day in the 6-month rat chronic study (CGP-TX-02) (average area under the concentration-time curve [AUC] 192.5 μM•hr) represents an exposure multiple of approximately 33-fold. The NOAEL of 300 mg/kg/day for 9-month dosing in the monkey (TT #13-1074) (AUC of 70.7 μM•hr) represents a 12-fold margin. The findings at the high dose (100 mg/kg/day) of the 6-month rat study were a small decrease in body-weight gain and epithelial vacuolation in the jejunum. These findings were not observed in monkeys at any exposure. The vacuolation of the intestinal epithelium was shown to be reversible after discontinuation of the dosing in all recovery animals. No adverse findings were observed in the 9-month monkey study.	Findings of decreased body weight gain in nonclinical studies were observed in rodents only and occurred at exposures at least 33-fold the human dose in the clinic. Epithelial vacuolation is likely a rodent-specific effect and not considered a relevant human risk.
Reproductive toxicity The maternal toxicity identified is consistent with findings from general toxicity studies in rats. Atogepant was transferred into the milk in lactating rats at concentrations that were approximately 2-fold higher than those achieved in maternal plasma (CGP-TX-15).	No effects on reproduction were observed in nonclinical studies at exposures higher than those in the clinic. There is no pregnancy or lactation data from controlled clinical studies. Use during pregnancy will be considered missing information.

Key Safety Findings (from Non-Clinical Studies)	Relevance To Human Usage
Developmental toxicity In embryo-fetal development studies in rat and rabbit (TT #12-7060, TT #12-7070), a fertility and early embryonic development study in rat (TT #12-7380), and a pre/postnatal development study in rat (CGP-TX-15), there were no malformations, fertility findings, or effects on maternal performance, and no effect on sexual development of offspring at doses up to the maximal feasible dose or maximal tolerated dose. Developmental toxicity was observed in the rat and rabbit, consisting of decreased pup weights, and increased skeletal variations in rats and increased visceral and skeletal variations in rabbits at high doses. No developmental effects were observed in rats and rabbits at doses approximately 3 to 4 times the human exposure at 60 mg QD dosing based on AUC (TT #12-7060, TT #12-7070).	Atogepant demonstrated no malformations in rats and rabbits and no effects on fertility in rats at exposures higher than those in the clinic. Developmental toxicity consisting of visceral and skeletal variations was observed in animals at doses higher than 8 times the human exposure. There is no pregnancy data from controlled clinical studies. Use during pregnancy will be considered missing information.
Juvenile Toxicity Atogepant was administered to rats once daily by oral gavage from post-natal day (PND) 28 through PND 70 at 10, 30, or 200 mg/kg/day. Findings were limited to drug-related effects during the dosing period on bone density in males that were considered secondary to reduced individual body weights and on behavior testing (motor activity and Morris water maze). These findings showed full recovery in the off-dose period and were considered not to be adverse. There were increases in liver enzymes and increased bilirubin in urine in females at 200 mg/kg/day on PND 71, but that showed full recovery and had no microscopic correlate. NOAEL for the males and females was considered to be 200 mg/kg/day, approximately 22 times the expected exposure in pediatric population.	No concerns were raised.
Nephrotoxicity No kidney findings were observed in any general toxicity study.	No concerns were raised.

Key Safety Findings (from Non-Clinical Studies)	Relevance To Human Usage
Hepatotoxicity In vitro assays related to known hepatotoxicity mechanisms were conducted with atogepant and 2 predecessor CGRP receptor antagonists that were discontinued for clinical hepatotoxicity: telcagepant and MK-3207. Subsequently, those results were parameterized into the DILIsym® model along with proposed clinical dose, covalent protein binding, and physiologically based pharmacokinetic models for each compound. Results of the DILIsym modeling suggest that atogepant has a significantly reduced risk of causing clinically relevant elevations of alanine aminotransferase in excess of 3-fold the upper limit of normal (≥ 3 × upper limit of normal) compared to the predecessor compounds (CGP-TX-01) (Woodhead 2022).	No hepatotoxicity has been observed clinically that has been adjudicated as related to atogepant.
Genotoxicity Atogepant was neither mutagenic nor genotoxic in assays conducted to detect mutagenicity, deoxyribonucleic acid (DNA) strand breaks, and/or chromosomal aberrations (TT #11-8063, TT #11-8110, TT #11-8565, TT #11-8569).	Atogepant is non-mutagenic nor genotoxic. No concerns were raised.
Carcinogenicity In 2-year carcinogenicity studies in rats and mice, no neoplastic changes were observed at any dose level (CGP-TX-05, CGP-TX-06).	Atogepant was non-carcinogenic in rats and mice. No concerns were raised.
General Safety Pharmacology No toxicologically meaningful changes were observed on cardiovascular function, respiratory performance, or nervous system function.	There were no atogepant-related effects on cardiovascular, respiratory, or nervous system function in nonclinical studies. No concerns were raised.

Key Safety Findings (from Non-Clinical Studies)	Relevance To Human Usage
Cardiovascular Atogepant exhibited minimal human ether-a-go-go-related gene (hERG) current inhibition (23.9% inhibition at 28 µM), which suggests it is unlikely to alter ventricular repolarization in humans at doses required for efficacy. No effects on blood pressure parameters, heart rate (HR), electrocardiogram (ECG) parameters (PR, QRS, RR, and QT intervals), HR-corrected QT interval (QTci interval) or QT:RR interval relationship after single or repeat (3-day) oral dosing in monkeys (up to 75 mg/kg).	No concerns were raised in nonclinical studies.
Nervous system There were no effects on neurological function in conscious mice at a single oral dose of 100 mg/kg and no effects on nervous system function in rats at single doses up to 20 mg/kg.	No concerns were raised.
Mechanisms for drug interactions Atogepant is metabolized primarily by Cytochrome P450 (CYP)3A4 with a minor contribution of CYP2D6, suggesting it could likely be affected by compounds that are known to inhibit or induce CYP3A4. Atogepant was determined to be a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3 and OAT1. Therefore, use of inhibitors of OATP, BCRP, and/or P-gp may increase the exposure of atogepant. It is not a substrate of OAT3, organic cation transporter (OCT)2, or multidrug and toxin extrusion protein (MATE)1. Atogepant inhibits OATP1B1, OATP1B3, OCT1 and MATE1 with concentration producing 50% inhibition (IC_{50}) values of 3.3, 8.4, 1.23, and 2.24 µM, respectively. Atogepant inhibits bile salt export pump (BSEP) by 34% at 20 µM. It does not inhibit multidrug resistance-associated protein (MRP)3 or MRP4 at concentrations up to 15 µM, or MATE2-K at concentrations up to 20 µM.	Clinical drug-drug interaction (DDI) studies with strong CYP3A4 inhibitor, strong CYP3A4 inducer, OATP inhibitor, and P-gp inhibitor were conducted. Dosing adjustments or recommendations are made based on the results of the clinical DDI studies. Atogepant is not anticipated to alter the exposure of concomitantly administered drugs to a significant extent.

Key Safety Findings (from Non-Clinical Studies)	Relevance To Human Usage
Other toxicity-related information or data Abuse liability: Atogepant is not structurally similar to any known drugs of abuse. It also has poor water solubility making intravascular injection difficult, and synthesis of atogepant involves a complex process that would not be feasible for illicit synthesis. Several nonclinical studies were conducted to assess atogepant's abuse potential. In an off target in vitro binding screen, atogepant did not exhibit significant binding affinity for a variety of CNS 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 (Studies PD001 and PD005). Brain penetration of atogepant is poor as it exhibited limited central CGRP receptor occupancy (approximately 25%) in monkeys at plasma concentrations that far exceeded its efficacious concentrations in monkeys (Study PD006). Atogepant was generally without observable behavioral effects in rodents when using a functional observational battery to assess CNS effects of acute and repeated high dose administration (Studies TT# 1106 and TT# 5500). The results of 2 nonclinical abuse potential studies showed no withdrawal signs in male rats exposed for 28 days to atogepant producing approximately 8.5 times higher systemic exposure than that achieved in humans at the highest dose (60 mg) (Study CGP-PH-07). Further, an intravenous self-administration study in heroin-trained rats found no evidence for reinforcing effect at atogepant doses producing plasma concentrations approximately equivalent to the human efficacious dose of 60 mg (Study CGP-PH-08).	Although no human abuse liability studies have been conducted with atogepant, based on its pharmacological properties, its lack of abuse signal in nonclinical and clinical studies, it is expected that atogepant will not have abuse liability in humans.

Non-Clinical Safety Findings that are Included as Safety Concerns

Based on the information above, MAH believes that the nonclinical data satisfactorily support the clinical doses recommended, the indication claimed, and the population targeted, including special populations.

Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Module SIII Clinical Trial Exposure

The following account of clinical trial exposure reflects exposure as of 11 October 2022.

Table 2. Number of Subjects Exposed to Atogepant (Phases 2/3 and 3 Studies)

	Atogepant 60 mg QD		**Atogepant Overall**	
Treatment Duration	**Patients**	**Person Time (Total Person Years)**	**Patients**	**Person Time (Total Person Years)**
≥ 1 dose of atogepant in any clinical study	1822	1248.3	2937	1837.8
Treatment for ≥ 3 months	1332	1164.9	1861	1641.4
Treatment for ≥ 6 months	1185	1112.2	1617	1556.9
Treatment for ≥ 9 months	1027	1014.4	1429	1440.4
Treatment for ≥ 12 months	762	797.3	1125	1189.1
Treatment for ≥ 13 months	160	194.8	287	349.8
Treatment for ≥ 15 months	58	75.4	103	133.0
Treatment for ≥ 18 months	5	7.8	6	9.3

QD = once a day

Based on atogepant clinical safety database Phases 2/3 and 3 studies (Studies CGP-MD-01, 3101-301-002, 3101-302-002, 3101-303-002, 3101-304-002, 3101-309-002, 3101-311-002, and ongoing Studies 3101-306-002 and 3101-312-002 with the interim data cut as of 11 October 2022).

Study CGP-MD-01 completers enrolled into Study 3101-302-002 are counted once based on maximum continuous atogepant exposure from each study. Rollover participants entered into an extension study are counted once with exposure calculated as the sum of exposure from the lead-in and extension studies for rollover at lead-in study completion and as maximum exposure from the 2 studies otherwise.

Source: ISS Table 2.4-2-1.2.1.2

Table 3. Exposure by Age Group and Gender (Phases 2/3 and 3 Studies)

	Atogepant Overall			
	Patients		Person Time (Total Person Years)	
Age Group	**Male**	**Female**	**Male**	**Female**
Less than 40 years	149	1151	88.5	679.6
40 to 64 years	190	1357	118.7	896.7
65 years or older	14	76	11.4	43.0
Total	353	2584	218.5	1619.3

Based on atogepant clinical safety database Phases 2/3 and 3 studies (Studies CGP-MD-01, 3101-301-002, 3101-302-002, 3101-303-002, 3101-304-002, 3101-309-002, 3101-311-002 and ongoing Studies 3101-306-002 and 3101-312-002 with the interim data cut as of 11 October 2022).
Source: ISS Table 2.4-2-1.2.1.2

Table 4. Exposure by Ethnic Origin (Phases 2/3 and 3 Studies)

	Atogepant Overall	
Ethnic Origin	**Patients**	**Person Time (Total Person Years)**
White	2229	1368.3
Black or African American	355	177.1
Asian	299	261.5
American Indian or Alaska Native	11	7.1
Native Hawaiian/Other Pacific Islander	4	2.5
Multiple	38	20.6
Missing	1	0.8

Based on atogepant clinical safety database Phases 2/3 and 3 studies (Studies CGP-MD-01, 3101-301-002, 3101-302-002, 3101-303-002, 3101-304-002, 3101-309-002, 3101-311-002, and ongoing Studies 3101-306-002 and 3101-312-002 with the interim data cut as of 11 October 2022).
Source: ISS Table 2.4-2-1.2.1.2

Module SIV Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Clinical Development Program

Criterion 1: Woman is pregnant, planning to become pregnant during the course of the study, or currently lactating. Women of childbearing potential must have a negative urine pregnancy test at Visit 1 and Visit 2.
Reason for exclusion: Standard precautionary measure for clinical trials due to unknown effect on fetus.
Is it considered to be included as missing information? Yes
Rationale: Safety data on the use of atogepant during pregnancy is very limited.

Criterion 2: Requirement for any medication or diet (i.e., grapefruit juice) that is on the list of prohibited concomitant medications that cannot be discontinued or switched to an allowable, alternative medication.
Reason for exclusion: DDI studies showed that co-administration of atogepant with a strong CYP3A4 inhibitor resulted in a 5.5-fold increase in exposure of atogepant, which might enhance the toxicity of the drug. Co-administration of atogepant with a strong CYP3A4 inducer, resulted in a 60% reduction in atogepant exposure. Efflux transporter assays determined that atogepant is a P-gp and BCRP substrate. Therefore, it could likely be a victim of compounds that are known to inhibit or induce P-gp and/or BCRP. However, a DDI study with quinidine (a strong P-gp inhibitor) revealed no significant effect. In uptake transporter assays, atogepant was determined to be a substrate of OATP1B1 and OATP1B3. It was also a weak inhibitor of OATP1B1 and OATP1B3. A DDI study with single-dose rifampin (a strong OATP inhibitor) increased atogepant exposure by 2.8-fold.
Is it considered to be included as missing information? No
Rationale: Based on DDI studies, concomitant use with strong CYP3A4 inhibitor/inducer drugs is predicated to be associated with DDI. Atogepant 10 mg dose should be used when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin). In patients taking strong and moderate CYP3A4 inducers (e.g., phenytoin, barbiturates, rifampin, St. John's Wort), highest 60 mg dose of atogepant is recommended. In addition, atogepant 10 mg or 30 mg should be used when concomitantly used with inhibitors of OATP transporters (e.g., single-dose rifampin).

Criterion 3: History of hypersensitivity or clinically significant adverse reaction to a CGRP receptor antagonist.
Reason for exclusion: Standard precautionary measure to avoid hypersensitivity reaction to this product.
Is it considered to be included as missing information? No
Rationale: Atogepant should not be used in patients with hypersensitivity to any component of the product.

Criterion 4: An ECG with clinically significant abnormalities as determined by the investigator at Visit 1
Reason for exclusion: To avoid confounding the evaluation of safety outcomes.
Is it considered to be included as missing information? Yes
Rationale: Not applicable since this exclusion criterion is included as missing information.

Criterion 5: A QTcF > 450 msec for males or QTcF > 470 msec for females at Visit 1
Reason for exclusion: To avoid confounding the evaluation of safety outcomes.
Is it considered to be included as missing information? Yes
Rationale: Not applicable since this exclusion criterion is included as missing information.

Criterion 6: Clinically significant cardiovascular or cerebrovascular disease per the investigator's opinion including, but not limited to: • **Clinically significant ischemic heart disease (e.g., unstable angina pectoris)** • **Clinically significant cardiac rhythm or conduction abnormalities (e.g., atrial fibrillation, second- or third-degree heart block) or risk factors for Torsade de Pointes (e.g., heart failure, hypokalemia, bradycardia)** • **Myocardial infarction, transient ischemic attack, or stroke within 6 months prior to Visit 1** • **Heart failure defined as New York Heart Association functional classification system, Class III or IV**
Reason for exclusion: To avoid confounding the evaluation of safety outcomes.
Is it considered to be included as missing information? Yes
Rationale: Data on the use of atogepant in patients with significant cardiovascular and cerebrovascular diseases is limited.

Criterion 7: Hypertension as defined by sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg at Visits 1 or 2. Vital sign measurements that exceed these limits may be repeated only once.
Reason for exclusion: To avoid confounding the evaluation of safety outcomes.
Is it considered to be included as missing information? Yes
Rationale: Not applicable since this exclusion criterion is included as missing information.

Criterion 8: Clinically significant laboratory abnormalities (as determined by the investigator) in physical examination or laboratory safety test at Visit 1 as per guidelines below: • **Alanine aminotransferase or aspartate aminotransferase greater than 1.5 times the upper limit of normal OR** • **Total bilirubin greater than 1.5 mg/dL (except for patients with a diagnosis of Gilbert's disease) OR** • **Serum albumin less than 2.8 g/dL**
Reason for exclusion: Adverse events (AE)s were reported with CGRP receptor antagonists telcagepant and MK-3207, which caused liver toxicity with transient increase of transaminases in a small group of included subjects (n = 13 for telcagepant) upon repeated doses. This led to discontinuation of the development program for these molecules. Other non-peptide CGRP receptor antagonists such as BI44370TA, BMS-927711, and MK-1602 have also been tested. For all 3 molecules, AEs were mild to moderate and the incidence was low and similar to the placebo group. No liver toxicity was reported for these drugs (Deen 2017).
Is it considered to be included as missing information? No
Rationale: In vitro and modeling exercises by DILIsym suggest atogepant does not have a significant increased risk of causing drug induced liver injury (DILI). No evidence of DILI has been observed clinically that has been adjudicated as related to atogepant.

Criterion 9: Any clinically significant hematologic, endocrine, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease. • **If there is a history of such disease but the condition has been stable for more than 1 year prior to Visit 1 and is judged by the investigator as not likely to interfere with the patient's participation in the study, the patient may be included.** • **Patients on dialysis for renal failure are excluded.** **History of acute hepatitis within 6 months of Screening (Visit 1) or chronic hepatitis (including nonalcoholic steatohepatitis) or a positive result on anti-hepatitis A immunoglobulin M antibody, hepatitis B surface antigen, or anti–hepatitis C antibody testing at Screening (Visit 1)**
Reason for exclusion: To avoid confounding the evaluation of safety outcomes
Is it considered to be included as missing information? No
Rationale: In patients with preexisting mild (Child-Pugh Class A), moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C), atogepant exposure was increased by 24%, 15%, and 38%, respectively. However, unbound atogepant exposure was approximately 3-fold higher in patients with severe hepatic impairment. No dose adjustment is required for patients with mild or moderate hepatic impairment. Atogepant use should be avoided in patients with severe hepatic impairment. Atogepant is excreted mostly via the biliary/fecal route, while the renal route is a minor route of elimination. Following single oral dose administration of [^{14}C]-atogepant to healthy male subjects, 42% and 5% of the dose was recovered as unchanged atogepant in feces and urine, respectively. Population pharmacokinetic analysis based on pooled data from Phase 1, Phase 2, and Phase 3 studies did not reveal a difference in the pharmacokinetics of atogepant in patients with mild or moderate renal impairment relative to those with normal renal function. Although use of atogepant in patients with severe renal impairment has not been studied, physiologically based pharmacokinetic (PBPK) modeling suggested a worst-case scenario of 2.3-fold increase in the systemic exposure of atogepant in severe renal impairment. Thus, the lowest 10 mg dose is recommended in patients with severe renal impairment or end-stage renal disease (ESRD). No available evidence suggests that the safety profile will be different in patients with the other preexisting conditions.

Criterion 10: Significant risk of self-harm, based on clinical interview and responses on the Columbia-Suicide Severity Rating Scale (C-SSRS), or of harm to others in the opinion of the investigator; patients must be excluded if they report suicidal ideation with intent, with or without a plan, (i.e., Type 4 or 5 on the C-SSRS) in the past 6 months or report suicidal behavior in the last 6 months prior to Visit 1 or Visit 2 assessments
Reason for exclusion: Routine clinical trial practice.
Is it considered to be included as missing information? No
Rationale: The safety profile is not expected to differ from the known safety profile.

SIV.2 Limitations to Detect Adverse Reactions in the Clinical Development Program

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or adverse reactions caused by prolonged/ cumulative exposure.

Table 5. Limitations to Detect Adverse Reactions in Clinical Development Programs

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are rare	A total of 2937 patients were exposed over the whole clinical trial program.	Adverse drug reaction (ADR) with a frequency greater than 1 in 2937 patients could be detected if there were no background incidences.
Due to prolonged exposure	A total of 1125 patients completed 12 months of treatment with atogepant. During this period there were no adverse reactions reported that could be correlated with prolonged exposure.	These data suggest no increase in treatment-emergent adverse event (TEAE) incidence with longer durations of drug exposure. ADRs due to long term exposure beyond 12 months is classified as a missing information safety concern.
Which have a long latency	The current maximum duration of atogepant exposure was 12 months with a 1-month safety follow-up visit. A long-term safety study up to 104 weeks is ongoing. Therefore, there is a limitation to detect the ADRs with latency beyond 13 months.	Available data suggest no adverse reactions with long latency.

SIV.3 Limitations in Respect to Populations Typically Underrepresented in Clinical Development Program

Table 6. Exposure of Special Populations Included or Not in the Clinical Development Program

Type of special population	Exposure	Implications
Pregnant women	Cumulatively from clinical studies through 11 October 2022, there have been few pregnancy exposure reports on atogepant (n = 23 reports for 22 pregnancies [2 reports for 1 pregnancy]). Among these, there were 3 reports of spontaneous abortion and 3 reports of elective abortion. Ten pregnancies were reported as having normal deliveries and healthy babies. One case reported normal delivery, but fetal outcome was abnormal due to nonserious low blood glucose, low blood potassium, and newborn jaundice. One pregnancy was reported as having preterm delivery; mother had the risk factor of gestational diabetes. The remaining 4 subjects were lost to follow-up.	Since the potential risk in pregnant women and unborn fetus is unknown, safety in pregnancy in patients using atogepant is considered a missing information safety concern.
Breastfeeding women	Not included in the clinical development program.	This population is not considered a missing information safety concern. Although this population has not been studied, studies in lactating rats showed decreased pup body weight at high doses only, no effects were observed at doses 5 times the clinical dose.

Type of special population	Exposure	Implications
Patients with relevant comorbidities:		
Patients with hepatic impairment*	Twenty-four subjects with preexisting mild (8), moderate (8), and severe hepatic impairment (8) were exposed to single dose of 60 mg atogepant (Study CGP-PK-01).	This population is not considered a missing information safety concern. Atogepant is indicated for patients with mild or moderate hepatic impairment with no dose adjustment. Avoid use of atogepant in patients with severe hepatic impairment.
Patients with renal impairment†	In Phase 2/3 and 3 pivotal placebo-controlled episodic and chronic migraine studies, 89 and 1127 patients were considered to have moderate and mild renal impairment, respectively.	This population is not considered to be a missing information safety concern. The product information specifies that atogepant can be administered without dose adjustment in patients with mild and moderate renal impairment. The recommended dose of atogepant for patients with severe renal impairment (creatinine clearance [CLcr]: 15 to 29 mL/min) and ESRD (CLcr < 15 mL/min) is 10 mg. Although patients with severe renal impairment and ESRD have not been studied, renal elimination is minor, and thus, the safety profile is not expected to be different. In addition, the above dosing recommendations for patients with severe renal impairment (CLcr: 15 to 29 mL/min) were based on PBPK modeling.
Patients with cardiovascular and cerebrovascular impairment	Patients with clinically significant cardiovascular or cerebrovascular disease were excluded from the development program (see discussion in important potential risks Section SVII.1.2). Patients with less severe CVD were included in the clinical development program.	Since the potential risk in patients with significant cardiovascular and cerebrovascular diseases is unknown, use in patients with significant cardiovascular and cerebrovascular diseases is considered a missing information safety concern.

Type of special population	Exposure	Implications
Immunocompromised patients	Not included in the clinical development program	This population is not considered a missing information safety concern. Although this population has not been studied, based on general safety pharmacology and carcinogenicity studies in animals, immunocompromised patients who are taking atogepant are not expected to have differences in safety concerns.
Population with relevant different ethnic origin	In atogepant-treated patients in Phase 2/3 and Phase 3 episodic and chronic migraine studies, the number of patients with different race/ethnic origin was as follows: White: 2229 (75.9%) All other races: 708 (24.1%)	Population with relevant different ethnic origin is not considered a missing information of safety concern. There were no differences in the safety profile of atogepant among different ethnic populations. There were no clinically relevant differences in the systemic exposure of atogepant across Caucasians, Japanese, Chinese, and African Americans.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program	There are no known relevant genetic polymorphisms that affect the metabolism, degradation, or pharmacological effects of CGRP receptor antagonists, such as atogepant.

CGRP = calcitonin gene-related; CLcr = creatinine clearance; CVD = cardiovascular disease; ESRD = end-stage renal disease; Min = minimum; PBPK = physiologically based pharmacokinetic

* Mild, moderate, and severe hepatic impairment defined according to Child-Pugh classification (Child-Pugh A, B, and C, respectively).

† Moderate renal impairment defined as estimate of glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease (MDRD) equation between 30 and 59 mL/min/1.73m^2.

Module SV Post-Authorization Experience

SV.1 Post-Authorization Exposure

Atogepant is approved in the US for the preventive treatment of EM in adults.

SV.1.1 Method Used to Calculate Exposure

An estimate of the patient exposure treated with atogepant was calculated from AbbVie sales data. Using the total number of 10 mg, 30 mg, and 60 mg tablets distributed and dividing by the average daily dose (ADD) determined from the product label, an estimate of the number of patient treatment days (PTD) was obtained. The PTD were further divided by 365.25 to obtain the estimated number of patient treatment years (PTY).

SV.1.2 Exposure

It is estimated that there have been approximately 35,827 PTY of atogepant from the international birth date of 28 September 2021 through 31 October 2022.

An estimate of PTY by formulation, age, and gender is presented in the tables below.

Table 7. Post-Marketing Cumulative Patient Exposure

Estimated Cumulative Patient Exposure in US from 28 September 2021 through 31 October 2022 from AbbVie Sales				
Formulation	**Amount Distributed**	**Average Daily Dose (mg)**	**Patient Treatment Days**	**Patient Treatment Years**
10 mg tablets	511,814	1 tablet daily	511,814	1,401
30 mg tablets	1,766,962	1 tablet daily	1,766,962	4,838
60 mg tablets	10,807,183	1 tablet daily	10,807,183	29,588
Total	13,085,959		13,085,959	35,827*

AbbVie = AbbVie Inc.; US = United States

* The numbers may not sum up due to rounding error.

The patient treatments by age and gender available in the table below are based on patterns of usage in the US. In the US, it is estimated that 86.1% of patients are female and 13.8% are male.

Table 8. Post-Marketing Cumulative Patient Exposure by Age and Gender

Total Estimated Number of Atogepant Patient Treatments by Age and Gender (28 September 2021 through 31 October 2022)													
		Total			Females			Males			Unknown		
	Age	%	Patient treatments	Patient-years	%	Patient treatments	Patient-years	%	Patient treatments	Patient-years	%	Patient treatments	Patient-years
10 mg	0 – 19	1.9	9,582	26	1.8	8,059	22	2.2	1,523	4	0.0	0	0
	20 – 39	29.5	150,832	413	30.0	133,007	364	26.0	17,649	48	59.9	176	0
	40-59	49.2	251,922	690	49.7	220,697	604	46.0	31,225	85	0.0	0	0
	60-84	18.6	95,149	261	17.6	78,175	214	25.0	16,943	46	10.5	31	0
	85+	0.3	1,513	4	0.3	1,219	3	0.4	294	1	0.0	0	0
	Unspecified	0.6	2,816	8	0.6	2,494	7	0.3	235	1	29.6	87	0
30 mg	0 – 19	1.9	32,751	90	1.8	27,148	74	2.2	5,603	15	0.0	0	0
	20 – 39	29.5	522,054	1,429	29.5	447,059	1,224	29.8	74,580	204	43.5	415	1
	40-59	50.8	897,448	2,457	51.8	785,663	2,151	44.6	111,609	306	18.4	176	0
	60-84	17.2	303,776	832	16.3	247,010	676	22.6	56,650	155	12.2	116	0
	85+	0.3	6,168	17	0.3	4,376	12	0.7	1,792	5	0.0	0	0
	Unspecified	0.3	4,765	13	0.3	4,288	12	0.1	230	1	25.9	247	1

Total Estimated Number of Atogepant Patient Treatments by Age and Gender (28 September 2021 through 31 October 2022)													
		Total			Females			Males			Unknown		
	Age	%	Patient treatments	Patient-years	%	Patient treatments	Patient-years	%	Patient treatments	Patient-years	%	Patient treatments	Patient-years
60 mg	0–19	1.2	134,536	368	1.2	111,946	306	1.5	22,128	61	12.6	462	1
	20–39	30.2	3,266,980	8,945	30.6	2,849,188	7,801	28.0	417,082	1,142	19.4	710	2
	40-59	52.7	5,697,097	15,598	53.4	4,977,035	13,626	48.3	719,593	1,970	12.8	469	1
	60-84	15.0	1,617,979	4,430	14.0	1,302,515	3,566	21.2	315,434	864	0.8	30	0
	85+	0.2	16,478	45	0.1	11,590	32	0.3	4,888	13	0.0	0	0
	Unspecified	0.7	74,113	203	0.7	61,969	170	0.7	10,146	28	54.5	1,998	5
Total		100	13,085,959	35,827	86.15	11,273,438	30,865	13.81	1,807,604	4,949	0.04	4,917	13

Note: The totals may not sum up due to rounding.

Module SVI Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

MAH is not aware of any existing potential for misuse of atogepant for illegal purposes. Atogepant is used for the prophylaxis of migraine in adults who have at least 4 migraine days per month. Its main pharmacological effects are via CGRP receptor antagonism. CGRP is a neuropeptide present in the peripheral and CNS. CGRP is released from sensory nerve endings during a migraine attack, particularly the nerve endings of sensory trigeminal ganglion neurons. Atogepant is a CGRP receptor antagonist that blocks the binding of CGRP to its receptor and antagonizes CGRP receptor function. Atogepant has minimal central penetration. Based upon the available data and the understanding of the mechanism of action of atogepant, there is no evidence of habit forming and little risk of diversion.

Module SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Table 9. List of Safety Concerns Included in the First Version of the RMP

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

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Known risks that require further characterization and/or HCPs have appropriate awareness and measures as part of routine clinical practice and are followed up via routine pharmacovigilance namely through signal detection and AE reporting:

Constipation

Constipation is one of the most common ADRs observed in clinical trials with atogepant. In the placebo-controlled trials, 7.2% (133/1837) of the overall atogepant group reported

constipation events, compared to 2.0% (13/663) in the placebo group. A trend of potential dose response was noted, with constipation events reported in 6.1% (9/314) in the atogepant 10 mg QD group, 6.3% (26/411) in the atogepant 30 mg QD group, and 7.5% (51/678) in the atogepant 60 mg QD group. All constipation events were nonserious, and most were mild to moderate in severity. There were 2 (0.1%) severe cases in the overall atogepant group, compared to 1 (0.2%) case in the placebo group. However, there were no serious cases of constipation or constipation-related complications. Few cases led to study drug discontinuation (0.5% in the overall atogepant group compared to 0.3% in the placebo group). In the long-term safety studies, similar results were found. Constipation was the most common ADR, reported in 6% (99/1662) of the atogepant 60 mg QD group. All cases were nonserious and all, except 1, were mild to moderate in severity. No serious cases of constipation or constipation-related complications were reported. Constipation led to study drug discontinuation in 0.2% of the atogepant-treated participants.

Constipation with the use of atogepant is listed as Risks not considered important for inclusion in the list of safety concerns to ensure that this risk is proactively monitored via routine pharmacovigilance.

Drug-Induced Liver Injury

In placebo-controlled trials, there was no imbalance in the percentage of participants with alanine transaminase (ALT) or aspartate aminotransferase (AST) elevations ≥ 3 × upper limit of normal (ULN) between the placebo group (1.2%, 8/653) and the overall atogepant group (0.9%, 17/1810). However, there were a few cases with a temporal association between atogepant and the events of ALT/AST elevations ≥ 3 × ULN. The cases were asymptomatic, all were nonserious, without concurrent bilirubin elevations (no Hy's law cases) and resolved with or without atogepant discontinuation. Drug-induced liver injury (DILI) is included in risks not considered important for inclusion in the list of safety concerns to assure that this risk is proactively monitored via routine pharmacovigilance.

SVII.1.2 Risks/Missing Information Considered Important for Inclusion in the RMP

Important Identified Risks

There are no important identified risks.

Important Potential Risks

There are no important potential risks.

Missing information

Information 1: Use in patients with significant cardiovascular and cerebrovascular diseases Reason for Inclusion: Patients with significant cardiovascular and cerebrovascular disease were excluded from the clinical trial program but no contraindications are planned for this patient group. As other common (acute) treatments for migraine such as triptans or NSAIDs have contraindications for patients with cardiovascular/cerebrovascular diseases these patient populations could be preferentially prescribed a CGRP antagonist. CGRP is a potent vasodilator and may have protective effects during cardiac or cerebral ischemia. As there is evidence that migraine itself is a risk factor for ischaemic stroke and other cardiovascular diseases, blocking CGRP in patients with migraine could theoretically put these patients at an increased risk, particularly in long-term treatment. Concomitant use of triptans or NSAR for acute pain relief might further increase the risk. Data to be Collected Post-Authorization: The safety profile for this population will be derived from routine and additional PV activities (including a post authorization safety study [Category 3 PASS]: an observational study to characterize the safety of atogepant in patients with significant cardiovascular and cerebrovascular diseases).
Information 2: Use in pregnant women Reason for Inclusion: Pregnant patients were excluded from clinical trials as standard precaution. Nonclinical studies showed developmental toxicity consisting of visceral and skeletal variations at doses higher than 8 times the human exposure. Studies showed no evidence of fetal malformations. Safety data relating to use of atogepant during pregnancy is very limited. According to the planned SmPC atogepant is not recommended during pregnancy. However, given the epidemiology of migraine, women of childbearing potential are likely to represent a substantial proportion of the product's target population and pregnancy cases are expected to occur. Data to be Collected Post-Authorization: The safety profile for this population will be derived from both routine and additional PV activities including 2 studies in pregnant women to evaluate the atogepant exposure during pregnancy (PMR 4152-6 [Study P22-392] and PMR 4152-7 [Study P22-419], both Category 3 PASS).
Information 3: Long-term safety beyond 1 year Reason for Inclusion: Long-term safety beyond 1 year is currently not available. Data to be Collected Post-Authorization: The safety profile for this population will be derived from additional PV activity via an ongoing open-label long-term safety study up to 104 weeks (Study 3101-312-002). This study will be extended by an additional 1 year (for a total of 3 years).

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

There are no important identified or potential risks for atogepant.

SVII.3.2 Presentation of the Missing Information

Missing information 1:
Use in patients with significant cardiovascular and cerebrovascular diseases.
Evidence sources: Patients with significant cardiovascular and cerebrovascular disease were excluded from the clinical trial program but no contraindications are planned for this patient group. As other common (acute) treatments for migraine such as triptans or NSAIDs have contraindications for patients with cardiovascular/cerebrovascular diseases these patient populations could be preferentially prescribed a CGRP antagonist. CGRP is a potent vasodilator and may have protective effects during cardiac or cerebral ischemia. As there is evidence that migraine itself is a risk factor for ischaemic stroke and other cardiovascular diseases, blocking CGRP in patients with migraine could theoretically put these patients at an increased risk, particularly in long-term treatment. Concomitant use of triptans or NSAR for acute pain relief might further increase the risk.
• Population in need of further characterization: The safety profile for this population will be derived from routine and additional PV activities (including a post authorization safety study [Category 3 PASS]: an observational study to characterize the safety of atogepant in patients with significant cardiovascular and cerebrovascular diseases).

Missing information 2:
Use in pregnant women
Evidence sources: Pregnant patients were excluded from clinical trials as standard precaution. Nonclinical studies showed developmental toxicity consisting of visceral and skeletal variations at doses higher than 8 times the human exposure. Studies showed no evidence of fetal malformations. Safety data relating to use of atogepant during pregnancy is very limited. According to the planned SmPC atogepant is not recommended during pregnancy. However, given the epidemiology of migraine, women of childbearing potential are likely to represent a substantial proportion of the product's target population and pregnancy cases are expected to occur.
• Population in need of further characterization: The risk of use in pregnancy cannot be defined based on available data, and thus, the safety profile will be derived from 2 studies in pregnant women to evaluate atogepant exposure during pregnancy (PMR 4152-6 [Study P22-392] and PMR 4152-7 [Study P22-419] [both Category 3 PASS]).

Missing information 3: Long-term safety beyond 1 year
Evidence sources: Long-term safety beyond 1 year will be included when the data become available.
• Population in need of further characterization: Long-term safety beyond 1 year will be derived from the ongoing open-label long-term safety study up to 104 weeks (Study 3101-312-002). This study will be extended by an additional 1 year for a total of 3 years.

Module SVIII Summary of the Safety Concerns

Table 10. Summary of Safety Concerns

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

Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)

III.1 Routine Pharmacovigilance Activities

Adverse drug reaction reporting, aggregate safety reporting via PSUR/PBRER, and signal detection.

III.2 Additional Pharmacovigilance Activities

Study Short Name and Title:

Observational study to assess pregnancy outcomes following exposure to atogepant: PMR 4152-7; Study P22-419.

Rationale and Study Objectives:

There are no adequate data on the developmental risk associated with the use of atogepant in pregnant women. To fulfill this post-marketing regulatory requirement, a non-interventional, observational cohort study using administrative healthcare claims data will be employed to

assess the risk of pregnancy outcomes and infant outcomes among pregnant women using atogepant.

The objective of the study is to describe and compare the incidence of pregnancy outcomes in women with migraine who are exposed to atogepant during pregnancy compared to comparator groups of women with migraine who are not exposed to atogepant during pregnancy.

Study Design:

Observational cohort study.

Study Population:

The study population consists of pregnant women with migraine, residing in the US and at least 18 years of age.

Milestones:

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

Study Short Name and Title:

Atogepant pregnancy exposure registry: PMR 4152-6; Study P22-392

Rationale and Study Objectives:

The prevalence of migraine in women is highest during childbearing years. Decisions to treat migraine during pregnancy requires clinical judgment to assess the benefits and the potential risks. In 2021, Qulipta® (atogepant) was approved by the Food and Drug Administration (FDA) for the preventive treatment of migraine in adults. However, pregnant women were not systematically included in atogepant clinical trials, and maternal, fetal, and infant effects are unknown. Therefore, this study is designed to fulfill an FDA post-marketing requirement to conduct a prospective pregnancy exposure registry in the US evaluating maternal, fetal, and infant outcomes of women with migraine following atogepant exposure during pregnancy.

The purpose of the study is to prospectively evaluate maternal, fetal, and infant outcomes through 12 months of age among women exposed to atogepant during pregnancy with 2 unexposed control populations: 1) women with migraine who have not been exposed to atogepant before and during pregnancy, and 2) women without migraine.

Study Design:

Prospective observational study.

Study Population:

The study population consists of pregnant women, residing in the US and at least 18 years of age, and live-born infants resulting from enrolled pregnancies.

Milestones:

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: 02/2037

Study Short Name and Title:

A Phase 3, multicenter, open-label, 104-week extension study to evaluate the long-term safety and tolerability of oral atogepant for the prevention of migraine in participants with chronic or EM: Study 3101-312-002 will be extended by an additional 1 year for a total of 3 years.

Rationale and Study Objectives:

The purpose of this study is to evaluate the long-term safety and tolerability of atogepant 60 mg once daily in participants when taken for 104 weeks for the prevention of CM or EM.

Study Design:

This is a multicenter, open-label, 104-week, long-term safety extension study conducted in all eligible participants who complete either lead-in Study 3101-303-002 (Phase 3 CM study) or Study 3101-304-002 (Phase 3 EM study).

Study Population:

Based on expected completion rate from the lead-in Study 3101-303-002 and Study 3101-304-002, approximately 670 participants will be enrolled into this long-term, open-label, safety extension study.

Milestones:

Draft Protocol Submission: 10/2020

Final Protocol Submission: 12/2020

Study Completion: 10/2024

Final Report Submission: 02/2025

Study Short Name:

PASS of Atogepant in Patients with Significant Cardiovascular and Cerebrovascular Diseases Summary

Rationale and Study Objectives:

To characterize the safety of atogepant in patients with significant cardiovascular and cerebrovascular diseases.

Study Design:

Observational study.

Study Population:

Patients with migraine and significant cardiovascular and cerebrovascular diseases.

Milestones:

Study details will be provided to PRAC post-approval.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 11. Ongoing and Planned Additional Pharmacovigilance Activities

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
A Phase 3, multicenter, open-label 104-week extension study to evaluate the long-term safety and tolerability of oral atogepant for the prevention of migraine in participants with chronic or episodic migraine: Study 3101-312-002 is ongoing and will be extended by an additional 1 year for a total of 3 years	To evaluate the long-term safety and tolerability of atogepant 60 mg once daily in participants when taken for 104 weeks for the prevention of chronic migraine (CM) or episodic migraine (EM).	Long-term safety beyond 1 year	Draft Protocol Submission Final Protocol Submission Study Completion Final Report Submission	10/2020 12/2020 10/2024 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 Final Protocol Submission Annual Interim Report Submissions Study Completion Final Report Submission	07/2022 05/2023 From 02/2024 to 02/2029 02/2030 04/2031

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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 Final Protocol Submission Annual Interim Report Submissions Study Completion Final Report Submission	07/2022 05/2023 From 02/2024 to 02/2035 02/2036 02/2037
PASS of atogepant in patients with significant cardiovascular and cerebrovascular diseases Planned	To characterize the safety of atogepant in patients with significant cardiovascular and cerebrovascular diseases.	Use in patients with significant cardiovascular and cerebrovascular diseases	Study details will be provided to PRAC post-approval	

Part IV: Plans for Post-Authorization Efficacy Studies

None are proposed and no efficacy studies have been imposed by competent authorities as a condition of the marketing authorization or as specific obligations in the context of the conditional marketing authorization or marketing authorization under exceptional circumstances.

Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 12. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Use in patients with significant cardiovascular and cerebrovascular diseases	Routine risk communication: None proposed Routine risk minimization activities recommending specific clinical measures to address the risk: None proposed Other routine risk minimization measures: Legal status: Prescription only medicine
Use in pregnant women	Routine risk communication: The risk is communicated through the label in Summary of Product Characteristics (SmPC) Section 4.6. Routine risk minimization activities recommending specific clinical measures to address the risk: None proposed Other routine RMMs beyond the Product Information: Legal status: Prescription only medicine

Safety Concern	Routine Risk Minimization Activities
Long-term safety beyond 1 year	Routine risk communication: None proposed Routine risk minimization activities recommending specific clinical measures to address the risk: None proposed Other routine RMMs beyond the Product Information: Legal status: Prescription only medicine

RMM = risk minimization measures

V.2 Additional Risk Minimization Measures

No additional risk minimization measures (aRMMs) are planned or proposed for atogepant. Routine RMMs as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table 13. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with significant cardiovascular and cerebrovascular diseases	Routine risk minimization measures: None proposed. Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Additional pharmacovigilance activities: PASS: an observational study to characterize the safety of atogepant in patients with significant cardiovascular and cerebrovascular diseases.

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in pregnant women	Routine risk minimization measures: SmPC Section 4.6	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Additional pharmacovigilance activities: Studies P22-419 (PMR 4152-7) and P22-392 (PMR 4152-6)
Long-term safety beyond 1 year	Routine risk minimization measures: None proposed. Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Additional pharmacovigilance activities: Study 3101-312-002

SmPC = Summary of Product Characteristics

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for atogepant

This is a summary of the RMP for atogepant. The RMP details important risks of atogepant, how these risks can be minimized, and how more information will be obtained about atogepant risks and uncertainties (missing information).

Atogepant's Summary of Product Characteristics (SmPC) and its Patient Information Leaflet (PIL) give essential information to healthcare professionals and patients on how atogepant should be used.

This summary of the RMP for atogepant should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of atogepant RMP.

I The Medicine and What it Is Used For

Atogepant is authorized for the prophylaxis of migraine in adults with at least 4 migraine days per month (see SmPC for the full indication). It contains atogepant as the active substance and it is taken by mouth as 10 mg or 60 mg tablets once daily for episodic migraine, or 60 mg once daily for chronic migraine, with or without food.

II Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of atogepant, together with measures to minimize such risks and the proposed studies for learning more about atogepant risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PIL and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorized pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

No aRMMs are planned or proposed for atogepant. Routine RMMs as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

If important information that may affect the safe use of atogepant is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of atogepant are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of atogepant. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
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

II.B Summary of Important Risks

Missing information Risk 1: Use in patients with significant cardiovascular and cerebrovascular diseases	
Risk minimization measures	Routine risk minimization measures: None proposed.
Additional PV activities	PASS: an observational study to characterize the safety of atogepant in patients with significant cardiovascular and cerebrovascular diseases.

Missing information Risk 2: Use in pregnant women	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.6.
Additional PV activities	Additional PV activities: Studies P22-419 (PMR 4152-7) and P22-392 (PMR 4152-6)

Missing information Risk 3: Long-term safety beyond 1 year	
Risk minimization measures	Routine risk minimization measures: None proposed.
Additional PV activities	Additional PV activities: Study 3101-312-002

II.C Post-Authorization Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorization

None.

II.C.2 Other Studies in Post-Authorization Development Plan

A Phase 3, multicenter, open-label, 104-week extension study to evaluate the long-term safety and tolerability of oral atogepant for the prevention of migraine in participants with chronic or episodic migraine: Study 3101-312-002

Purpose of the study: To evaluate the long-term safety and tolerability of atogepant 60 mg once daily in participants when taken for 104 weeks for the prevention of chronic or episodic migraine. Study 3101-312-002 will be extended by an additional 1 year for a total of 3 years.

Atogepant pregnancy exposure registry (PMR 4152-6): Study P22-392

Purpose of the study: To prospectively evaluate maternal, fetal, and infant outcomes through 12 months of age among women exposed to atogepant during pregnancy.

Observational study to assess pregnancy outcomes following exposure to atogepant (PMR 4152-7): Study P22-419

Purpose of the study: To describe and compare the incidence of adverse pregnancy outcomes in women with migraine who are exposed to atogepant during pregnancy compared to comparator groups.

PASS of Atogepant in Patients with Significant Cardiovascular and Cerebrovascular Diseases Summary

Purpose of study: To characterize the safety of atogepant in patients with significant cardiovascular and cerebrovascular diseases.

Part VII: Annexes

Annex 4. Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 6. Details of Proposed Additional Risk Minimization Activities (If Applicable)

Not applicable.