24 February 2022
EMA/CHMP/172260/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vydura

International non-proprietary name: rimegepant

Procedure No. EMEA/H/C/005725/0000

Note

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

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List of abbreviations

AE(s)	Adverse Event(s)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-t}	Area Under the concentration-time Curve from dosing (time 0) to time t
AUC_{0-inf}	Area Under the concentration-time Curve from time zero to infinity
AUC_{0-24hr}	Area Under the concentration-time Curve during 24 hours
AUC_{τ}	Area Under the concentration-time Curve during a dosing interval
ACS	Acute Coronary Syndrome
BA	Bioavailability
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
BQL	Below Quantifiable Limit
BP	Blood Pressure
CAD	Coronary Artery Disease
CIs	Confidence Intervals
C_{max}	maximum concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
(h)CGRP	(human) Calcitonin Gene-Related Peptide
CM	Chronic Migraine
CV	Cardiovascular
CVA	Cerebrovascular Accident
DDI	Drug-Drug Interactions
DBT	Double-Blind Treatment
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
EC50	Half maximal effective concentration
eGRF	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FEED	Fertility and Early Embryonic Development
EFD	Embryofetal Development
EM	Episodic Migraine
EOD	Every Other Day
EOT	End-Of-Treatment
ERA	Environmental Risk Assessment
GI	Gastrointestinal
GLMEM	Generalised Linear Mixed Effect Model
GLP	Good Laboratory Practice
GMR	Geometric Mean Ratios
HR	Heart Rate
ICHD	International Classification of Headache Disorders
IC50	Median Inhibition Concentration
IHS	International Headache Society
IV	Intravenous
LFT	Liver Function Test
LTT	Long-Term Treatment

MAA	Marketing Authorisation Application
MAD	Multiple Ascending Doses
MATE1	Multidrug and Toxin Extrusion protein 1
MATE2-K	Multidrug and Toxin Extrusion protein 2-K
MBS	Most Bothersome Symptom
MD(s)	Migraine Day(s)
MI	Myocardial Infarction
mITT	modified Intention-To-Treat
MIDAS	Migraine Disability Assessment
MoH	Medication overuse Headache
MRHD	Maximum Recommended Human Dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NET	Norepinephrine transporter
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
PRN	As-Needed
OATP1B1	Organic Anion Transport Protein 1b1
OATP1B3	Organic Anion Transport Protein 1b3
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter
OCT2	Organic Cation Transporter 2
ODT	Orodispersible Tablet; Orally Disintegrating Tablet
OLE	Open-Label Extension
OP	Observation Period
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamic
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PPK	Population PK
P-gp	P-glycoprotein
PPND	Prenatal and Postnatal Development
PT(s)	Preferred Term(s)
RGP	Rimegepant
RI	Renal Impairment
RMP	Risk Management Plan
SAD	Single Ascending Doses
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Subcutaneous(ly)
SL	Sublingual(ly)
SmPc	Summary of product characteristics
SOC	System Organ Class
S-STS	Sheehan Suicidality Tracking Scale
TBL	Total Bilirubin Levels
TEAEs	Treatment-Emergent AEs
TIA	Transient Ischemic Attack
TX	Toxicokinetics
t_{max}	time to peak plasma concentrations
t½	elimination half-life

ULN	Upper Limit Normal

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biohaven Pharmaceutical Ireland DAC submitted on 8 February 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Vydura, 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 23 July 2020.

The applicant applied for the following indication:

> VYDURA is indicated for the comprehensive management of migraine in adults, including prophylaxis of migraine and acute treatment of migraine with or without aura.

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 EMA Decision(s) P/0063/2021 and P/0285/2020 on the agreement of a paediatric investigation plan (PIP) for Treatment of migraine headaches and the granting of a (product-specific) waiver for prevention of migraine headaches

At the time of submission of the application, the PIP P/0063/2021 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.

1.4.2. New active substance status

The applicant requested the active substance rimegepant 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.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
31 May 2018 18 July 2018	EMEA/H/SA/3796/1/2018/SME/III EMEA/H/SA/3796/1/2018/SME/III Clarification	Susan Morgan, Mario Miguel Rosa
13 December 2018	EMEA/H/SA/3796/2/2018/SME/II	Livia Puljak, Susan Morgan

The Scientific advice pertained to the following aspects:

The applicant received Scientific Advice on the development of Rimegepant (BHV-3000) for the prophylaxis of acute migraine from the CHMP on 13/12/2018 (EMEA/H/SA/3796/2/2018/SME/II). The Scientific Advice pertained to the following clinical aspects:

Clinical package: Phase 3 study adequately defines the population for the proposed indication of the prophylaxis treatment, appropriate primary and secondary endpoints. Agreement with the statistical plan and the safety and efficacy of the database.

The applicant received Scientific Advice on the development of Rimegepant (BHV-3000) for the treatment of acute migraine from the CHMP on 31/05/2018 *(*EMEA/H/SA/3796/1/2018/SME/III). The Scientific Advice pertained to the following aspects:

Non clinical package was appropriated for MAA.

Clinical package: Phase 3 consistency study is adequate to meet the criteria outlined in the EMA guidance, adequately defines the population for the proposed indication of the acute treatment of migraine in patients who are triptan non responders / or patients who are ineligible for treatment with triptans, appropriate primary and secondary endpoints. Agreement with the statistical plan and the safety and efficacy of the database.

1.6. 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 appointed CHMP co-rapporteur had no such prominent role in scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	8 February 2021
The procedure started on	25 February 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 May 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 May 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 May 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 June 2021
The applicant submitted the responses to the CHMP consolidated List of	10 September 2021

Questions on	
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	18 October 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 October 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	11 November 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 January 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 February 2022
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)	24 February 2022

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 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 (CV) 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 calcitonin gene-related peptide (CGRP). The trigeminal nerve pathway transmits nociception from the meninges via intermediate pathways to the cortex.

The 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). As per inclusion criteria in phase 2/3 trials, the target population, for which treatment with rimegepant (RGP) is claimed, was defined along historical numbers of migraine attacks, resp. migraine days (MDs). While prevention study 305 was ongoing, amendments to the protocol were implemented widening inclusion criteria as to also include subjects with up to 18 headache days per month. Thereby, subjects with CM would potentially be eligible for study participation. Definite ICHD-3 Codes like e.g. 1.1 *Migraine without aura,* 1.2.1 *Migraine with typical aura,* 1.3 *Chronic migraine*, or 8.2 *Medication-overuse headache* (MoH) were not provided at the entry of pivotal RGP studies.

According to diagnostic categories, 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 EM, CM (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

According to current treatment guidelines, unspecific non-steroidal anti-inflammatory drugs (NSAIDS) like acetylic acid, ibuprofen, paracetamol etc. rank among first-line therapies, however, are typically used for less severe migraine attacks. The portion of patients being pain-free 2 hours post-dose is established as the most meaningful measure for efficacy of current migraine therapies. The rates of patients 2-hours pain-free that can be achieved with unspecific NSAIDS in meta-analyses are in the range of 20-25% (Ferrari et al. 2002; Cameron et al. 2015).

Major progress in more specific treatment of acute migraine symptoms was achieved with the advent of the triptans in the nineties. Triptans target 5-HT1B and 5-HT1D receptors and their mechanism is thought to involve cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release (Rizatriptan Summary of product characteristics (SmPC)). As the gold standard for acute treatment of migraine, they represent 28% to 36% of prescribed acute migraine medications (Mafi et al. 2015; Molina et al. 2018). However, triptans are not efficacious for all patients: rates of pain freedom at 2 hours post-dose with triptans in a meta-analysis are in the range of 20% to 40% (Ferrari et al. 2002). Furthermore, efficacy and tolerability vary, both between agents (7 triptans approved so far), and from patient to patient, with about 30-40% of patients not responding adequately to triptan therapy (Viana M et al. 2013).

Not all patients with migraine tolerate triptans. Among those discontinuing triptan therapy, side effects were reported as the reason in 29% of patients (Wells et al. 2014). Also, triptans are contraindicated in patients with coronary artery disease (CAD), peripheral vascular disease, cerebrovascular disease, or uncontrolled hypertension (Dodick et al. 2004; RELPAX SmPC). A large proportion of patients with migraine have CV risk factors, a history of CV events, conditions, or procedures, or a high risk of CV disease (Lipton et al. 2017).

Acute treatment of migraine attacks is to be differentiated from prophylactic treatment of migraine, for which most recently several human / humanised antibodies, selectively binding to the CGRP ligand or its receptor, have been approved (erenumab [Aimovig], fremanezumab [Ajovy], galcanezumab [Emgality], eptinezumab [Vyepti, US].

Although forming the mainstay of current acute migraine therapy, it is concluded that around 30% of patients fail to respond to a particular triptan (Dodick DW 2005). The reasons therefore are not fully understood. On top of considerable inter- and intra-individual attack variability, a large number of other factors modifying responsiveness have been identified, like e.g. concomitant use of preventive medication, MoH, inadequate dosing, the time point of medication intake relative to the onset of the attack, incomplete absorption due to concomitant gastric stasis or vomiting, presence resp. absence of aura symptoms etc. (Viana M 2013). Furthermore, the use of the triptans is limited with regard to their CV risk profile. As evidenced for the leading substance (sumatriptan), triptans are contraindicated in patients with a previous cerebrovascular accident (CVA), transient ischemic attack (TIA), moderately severe or severe hypertension, or untreated mild hypertension, peripheral vascular disease, established CAD, including ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or Prinzmetal's angina.

Overall, in view of incomplete response to currently available acute migraine medications on the one side and limitations to their use due to CV safety concerns on the other side, there is a general need for new therapeutic approaches in acute migraine therapy. Based on its pharmacological profile as an orally-administered CGRP receptor antagonist and the assumed favourable CV risk profile, RGP may potentially constitute a valuable contribution to the currently available therapeutic armamentarium.

2.2. About the product

Rimegepant (BHV-3000; formerly BMS-927711) is presented as a selective, high-affinity, orally administered, small molecule 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).

The indication proposed for Vydura does not align with standard wordings approved for the treatment of migraine so far. Rimegepant is the first substance to claim efficacy both for acute and prophylactic treatment of migraine. Available, orally administered preventive migraine medications (topiramate, ß-blockers) are not effective in acute migraine and their mode of action in migraine prevention is hypothetical.

2.3. Type of application and aspects on development

This is a complete and independent application.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as oral lyophilisate containing 75 mg of rimegepant. The product contains the sulfate salt.

Other ingredients are: gelatin, mannitol (E421), mint flavour and sucralose.

The product is available in blisters made of polyvinyl chloride (PVC), oriented polyamide (OPA) and aluminium foil and sealed with a peelable aluminium foil as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of the active substance is (5*S*,6*S*,9*R*)-5-amino-6-(2,3-difluorophenyl)-6,7,8,9 tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl 4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-

piperidine-1-carboxylate hemisulfate sesquihydrate corresponding to the molecular formula $C_{28}H_{28}F_2N_6O_3 \bullet 0.5\ H_2O \bullet 1.5\ H_2O$. It has a molecular weight of 610.63 g/mol and the following structure:

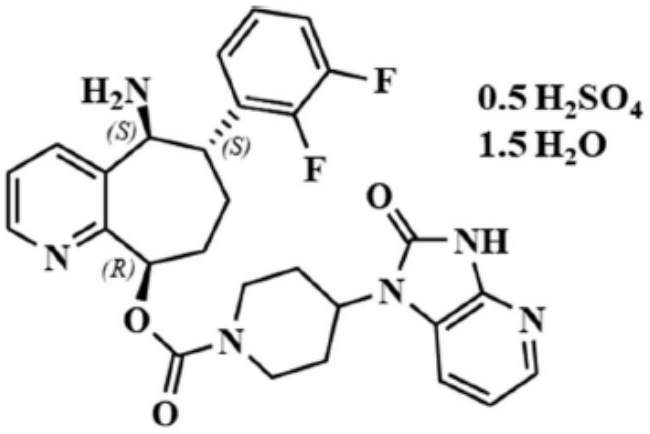


Figure 1: Active Substance Structure

The chemical structure of rimegepant was elucidated by a combination of ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, mass spectrometry, infrared spectroscopy and UV-Visible absorption The solid state properties of the active substance were measured by thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), gravimetric vapor sorption, optical microscopy (for particle morphology) and single crystal X-ray analysis.

The active substance is a white to off-white, slightly hygroscopicity powder, freely soluble in DMSO and DMF, slightly soluble in MeOH and water, very slightly soluble in organic solvents (EtOH, acetone, n-BuOH, THF, acetonitrile) and practically insoluble in ethyl acetate. Its solubility decreases with increasing pH. It has three pKa values at 2.1, 6.5, 9.8.

Rimegepant is a BCS Class 2 substance. It has low aqueous solubility, however excellent permeability provides for consistent and acceptably high oral bioavailability for the formulation.

Rimegepant exhibits stereoisomerism due to the presence of three chiral centres. An acceptable justification for absence of controls on diastereomers is provided.

Control of polymorphic form is included in the active substance specification. No change to polymorphic form has been observed at either long term or accelerated active substance storage conditions. No change to polymorphic form has been observed during manufacture or storage of the finished product either.

2.4.2.2. Manufacture, characterisation and process controls

Two manufacturers are involved in the manufacture of the active substance. Synthesis of the active substance was adequately described.

The synthetic steps carried out at each site are described in detail, indicating either ratio or weight/ volume equivalents for amounts, and tolerance ranges for reaction time and temperature. Low and high proven acceptable ranges (PARs) for process operations together with target set points have been added.

For justification of the three starting materials, contribution as significant structural fragments to the molecular structure of the active substance is claimed, the number of steps to the final active substance, and control/stability as per specifications. The rationale for choice of the starting materials was accepted for regulatory starting material 1. A major objection raised on starting material has been solved by removing the supplier who used a synthetic route with inherent risk of presence of nitrosamines and/or

genotoxic compounds. The risk of presence of nitrosamines or genotoxic compounds has acceptably been ruled out for the actual routes of synthesis. As further requested by the major objection, custom-synthesised, previous starting material 3 used for synthesis of key intermediate II has been re-defined. Reaction is now under GMP control. Binding synthetic are described and suppliers indicated. Acceptable specifications and analytical procedures are provided.

All major objections have been solved. Details of the analytical methodology have been disclosed, as well as sufficient analytical proof that the risk of presence of nitrosamine impurities is negligible. At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. The applicant is reminded that the full active substance manufacturing process has to be validated in line with GMP requirements and this point is put forward and agreed as quality recommendation.

Regarding the different manufacturing sites, the synthetic processes differ slightly with respect to amounts of reagents in terms of ratio and vol/wt equivalents and reaction conditions, as well as the IPC performed at the individual steps. Comparative analytical results and impurity profiles of the key intermediates confirm that the slightly different processes carried out at the proposed manufacturing sites lead to equivalent quality of the key intermediates and final active substance, respectively, in terms of purity and content. Key intermediate specifications have been provided.

Process validation data of commercial scale batches have been made available, according to updated in-process controls, key intermediate specifications and the updated active substance specification.

An overview on manufacturing process history and summary of process changes is provided. The synthetic route remained basically unchanged throughout development, only minor changes were made. Changes introduced have been presented in sufficient detail and have been justified. During process development studies carried out at each site, all operational process parameters were evaluated by an initial risk assessment to identify those which have a negative impact on the critical quality attributes of the active substance. Standard set points were chosen for pre-selected operational parameters based on process experience. Then PAR experiments and one variable at a time OVAT studies were conducted to confirm the operational parameter ranges for their impact on yield and purity. Based on the results obtained, all previous medium risk parameters were reduced to low risk category. Justification of the control strategy for operational process parameters valid for the commercial synthetic process at each site has been provided The PARs and normal operating ranges (NORs) have been set based on process knowledge and development, which is acceptable.

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

Potential and actual impurities were well discussed with regards to their origin and characterised.

2.4.2.3. Specification

The active substance specification includes tests for: appearance (visual), identification (IR, UPLC), assay (UPLC), related substances (UPLC), water content (KF), crystalline form (Ph. Eur.), melting point (Ph. Eur.), residue on ignition (Ph. Eur.), sulfate content (IC), particle size analysis (Ph. Eur.), residual solvents (GC), microbial limits (Ph. Eur.) and specified microorganisms (*E. coli*) (Ph. Eur.).

Elemental impurities were consistently shown to be below the 30% threshold in the final active substance, therefore no routine control is required. Residual solvents are controlled according to ICH Q3C (R6), which has been demonstrated by results on process validation of commercial batches.

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 generated by both manufacturers are provided, respectively, including early toxicology batches and process validation batches. The results and impurity profiles are comparable, complying with specifications. The results consistent from batch to batch.

2.4.2.4. Stability

Stability data from three primary pilot scale batches of active substance from each of the proposed manufacturer stored in the intended commercial package 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. Additional supportive data was provided (on batches used to support clinical studies and process validation batches).

The following parameters were tested: appearance, assay, related substances, water content, solid state form and microbiological limits.

All tested parameters were within the specifications with little or no variability or trending in any of the attributes measured at either condition.

Photostability testing following the ICH guideline Q1B was performed on one batch and demonstrate that the active substance is not sensitive to light.

Results on stress conditions: acid, base, oxidation, high intensity light, and heat stress were also provided on one batch. Forced degradation studies were performed on solid state material (powder) and solutions prepared from the active substance. The active substance showed degradation when exposed to acidic, basic and oxidative conditions. The solid form showed little, or no degradation, when exposed to stress conditions including the photolytic light condition.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as oral lyophilisate containing 75 mg of rimegepant. The product contains the sulfate salt. The oral lyophilisate is designed to rapidly disintegrate in the mouth and does not require a reconstitution diluent. The product is presented as a white to off-white, circular lyophilisate with a diameter of 14 mm and debossed with the symbol .

The pharmaceutical development of the finished product followed QbD principles.

The objective of the development was to provide a stable, oral lyophilisate presentation of rimegepant sulfate of consistent quality, containing 75 mg of rimegepant free base.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards (except for mint flavour). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC a. Compatibility of excipients and the active substance has been verified in stability studies.

Three oral formulations of rimegepant were used during the course of the development programme. A capsule (free base) was developed and used in early development. Two formulations of rimegepant sulfate (hemisulfate sesquihydrate salt), an oral lyophilisate formulation and a tablet formulation, were

then developed for use in pivotal clinical studies. A bioequivalence study was carried out between the tablet and oral lyophilisate formulations. The tablet and oral lyophilisate formulations were shown to be bioequivalent and the decision on what formulation to proceed with was based on patient convenience. Due to its easier administration it was decided to continue development with the oral lyophilisate formulation for commercialisation.

The finished product was developed using Catalent's Zydis technology. The finished product is a rapidly disintegrating oral lyophilisate designed to disperse instantly in the mouth. The manufacturing process development is presented in satisfactory detail and provides information on studies carried out during pilot scale and scale-up campaign.

A major objection on the absence of an appropriate dissolution method was raised. In response, a dissolution method in accordance with Ph. Eur. 2.9.3. was proposed. The discriminatory power of the dissolution method has been. By providing this data the major objection was resolved.

The primary packaging is blisters made of polyvinyl chloride (PVC), oriented polyamide (OPA) and aluminium foil and sealed with a peelable aluminium foil. 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.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of four main steps: mixing/dosing, freezing, freeze-drying, and heat seal/packaging. The process is considered to be a non-standard manufacturing process.

The manufacturing process of the finished product includes three critical processing steps. These critical steps have been monitored during development and manufacture of registration batches through in-process testing and were also monitored during the process validation; they will additionally be monitored during commercial manufacturing.

The manufacturing process has been validated on consecutive commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (UPLC, UV), assay (UPLC), uniformity of dosage units (UPLC), disintegration (Ph. Eur.), water content (KF), related substances (UPLC), dissolution (HPLC), crystalline form (XRPD), microbiological purity (Ph. Eur.), and absence of specified micro-organisms (*E. coli, P. aeruginosa, S. aureus*) (Ph. Eur.).

The disintegration criteria is determined to ensure that the product disintegrates promptly. The limit is consistent with FDA guidance on Orally Disintegrating Tablets, 2008, as well as the 3 minutes limit specified in the Ph. Eur. Monograph for oral lyophilisates.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three pilot scale batches 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 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 for assay and impurities testing has been presented.

Batch analysis results are provided, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

2.4.3.4. Stability of the product

Stability data from four primary pilot scale batches of finished product, manufactured with active substance from both sources, stored for up to 36 months (38 months for one batch) under long term conditions (25ºC / 60% RH), for up to 36 months (38 months for one batch) under intermediate conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of Vydura are identical to those proposed for marketing and were packed in a primary packaging representative of the one proposed for marketing. Further supportive data is provided: at room temperature and 6 months of data at accelerated storage conditions are available for process validation batches at commercial batch size (manufactured with both active substance sources). All the validation batches are scheduled for stability testing as per the stability protocol.

Samples were tested for appearance, water content, assay, related substances and crystalline form. The analytical procedures used are stability indicating.

A photostability study according to the ICH guideline Q1B is not considered necessary as the proposed multi-layered primary packaging has been verified by CHMP and is found to be light-proof. Moreover, the active substance itself is photostable.

Based on available stability data, a shelf-life of 36 months with the storage precautions "Do not store above 30°C; Store in the original package in order to protect from moisture" as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Adventitious agents

Gelatine obtained from fish is used in the product. No other excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Vydura is presented as an oral lyophilisate, a freeze-dried orally administered formulation. The oral lyophilisate is designed to rapidly disintegrate in the mouth and does not require a reconstitution diluent. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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. Major objections on designation of regulatory starting materials and absence of a dissolution method and demonstration of its discriminatory ability have been successfully resolved by providing requested data.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to completion of the validation of the active substance manufacturing process in line with GMP requirements, following the redefinition of the RSM during the MAA evaluation. This point is put forward and agreed as recommendation.

2.4.5. 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 TSE safety.

2.4.6. Recommendation for future quality development

Validation data for the active substance synthesis, using the re-defined starting material should be provided before commercialisation.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical testing strategy was developed consistently with the proposed clinical use of rimegepant, the proposed oral route of administration. The non-clinical pharmacokinetic (PK) /pharmacodynamic (PD) profile of remigepant was evaluated based on studies conducted by the applicant. The non-clinical safety profile of remigepant is described based on a series of non-clinical safety pharmacology and toxicology studies, repeat-dose toxicity studies and reproductive and developmental toxicity studies.

2.5.2. Pharmacology

Rimegepant is a high affinity (Ki = 32.9 pM) oral small molecule antagonist at the human CGRP receptor that is being developed for the treatment of migraine. CGRP is an endogenous 37 amino acid peptide contained within pain signaling nociceptive afferents, and is thought to play a causal role in migraine.

Rimegepant is a CGRP receptor antagonist at the hCGRP receptor with high affinity binding (Ki = 32.9 pM) and functional (Kb = 117.8 pM) activity at the hCGRP receptor. Rimegepant shows rapid onset kinetics and delayed off-rate for binding to the hCGRP receptor, with a 5x tendency to remain bound versus unbound.

Regarding receptor selectivity, rimegepant demonstrates 65- to > 300,000-fold selectivity for the hCGRP receptor over other members of the calcitonin receptor family; binding affinity for amylin 1 was the most similar, with an IC50 of 2.28 nM (compared to 54.3 pM for CGRP). Available data indicate that rimegepant does not have a consequential effect in diabetic patients.

Rimegepant did not significantly alter ligand binding or functional activity against 30 of the 32 unique pharmacological targets at maximum concentrations between 10 and 150 μM, depending on the individual assay. Median Inhibition Concentration (IC50) or Half maximal effective concentration (EC50) values were ⩾10 μM, except for PDE4 (EC50 of 5.8 μM) and the norepinephrine transporter (NET) showing an IC50 of 9.5 uM. As rimegepant does not cross the blood brain barrier, significant interaction

with the NET transporter is not anticipated. Comparing activity across species, rimegepant exhibits similar receptor affinities at both human (Ki of 33 pM) and nonhuman primate (marmoset (92 pM) and cynomolgus monkey (60 pM)) CGRP receptors, with more than 1,300-fold less activity at dog (43 nM), rat (209 nM) and mouse (104 nM) CGRP receptors as compared to human.

Rimegepant does not contract human coronary arteries or intracranial arteries even when *ex vivo* tissues were exposed to high 3-10 µM concentrations.

Rimegepant shows durable efficacy in the marmoset facial blood flow assay against a strong CGRP stimulus (designed to mimic CGRP release during severe migraine). Rimegepant effectively antagonised the hCGRP-induced increases in marmoset facial blood flow showing 75% to 80% inhibition at plasma levels of ~700 nM (or 374 ng/mL).

In studies assessing a core battery of safety pharmacology endpoints, rimegepant demonstrated minimal or no adverse effects on central nervous system (CNS) or respiratory parameters (Sprague-Dawley rat and cynomolgus monkey at oral doses up to 100 and 60 mg/kg, respectively) or on CV parameters *in vitro* (rabbit Purkinje, hERG [IC50 >30 µM] and SCN5A currents in HEK-293 cells) or *in vivo* (cynomolgus monkey, at oral doses up to 60 mg/kg).

2.5.3. Pharmacokinetics

Various *in vitro* and *in vivo* studies were conducted to characterise the PK and metabolism of rimegepant in the non-clinical setting. Further data on toxicokinetics (TK) were obtained within the different studies conducted to investigate the toxicology of rimegepant.

Single dose PK studies were performed in male rats, dogs and monkeys. Absolute oral bioavailability of rimegepant given as a solution in rats and monkeys was 45% and 67% respectively. When rimegepant was dosed as a suspension in monkeys, bioavailability was 48%. After oral administration, time to peak plasma concentrations (t_{max}) was 1.7 to 3.3 hours in rats and monkeys, respectively. Rimegepant has a significant pH-effect in dogs and oral dosing of the hemisulfate salt reduces the impact of higher gastric pH. Accordingly, all clinical phase III studies were conducted with the hemisulfate formulation.

Rimegepant does not readily distribute into red blood cells, is moderately bound to plasma proteins and is highly distributed into tissues. Brain distribution was studied as a part of a 2-week exploratory study in male and female rats. Brain-to-plasma concentration ratio 24 hours after the last dose was 0.02 to 0.08 in all groups, except for low dose males. The same brain exposure was observed, but 50% lower plasma exposure resulting in brain-to-plasma ratios below 0.19.

In humans and different animal species investigated, unchanged rimegepant was the most prominent circulating component in plasma. Rimegepant was metabolised to a wide variety of different metabolites. No major metabolite (>10%) was detected in human plasma as well as in plasma of animal species. All metabolites detected in humans were also observed in at least one animal species. Based on data from animals and humans, rimegepant undergoes multiple pathways of metabolism: carbamoylation followed by glucuronidation, hydrolysis and oxidative metabolism.

Faecal excretion was the major elimination pathway for [14C]-rimegepant in humans and animals (mice, rats, monkeys).

Whether rimegepant transfers into breast milk was not investigated in animal studies. However, a clinical study was performed to evaluate rimegepant concentrations in plasma and breast-milk of breast-feeding women.

When assessed *in vitro*, the metabolism of rimegepant was primarily mediated via CYP3A4 and to a lesser extent by CYP2C9. No turnover was detected with the CYP2C9 variant forms, CYP2C9*2 and

CYP2C9*3. A time-dependent inhibition was observed for CYP3A4 in recombinant CYP expression systems as well as in liver microsomes which lowered the exposure margin to the therapeutic maximum concentration (C_{max} of rimegepant to 3.5-times. However, rimegepant was not likely an CYP3A4 inducer. Other CYP enzymes or Phase II enzymes do not seem to play a major role in rimegepant metabolism. Interactions of rimegepant with CYP3A4 inducers or inhibitors were also investigated clinically and are labelled in section 4.5 and 5.2 of the SmPC.

Rimegepant is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BRCP) efflux transporters in vitro. Transporter interactions of rimegepant with P-gp inhibitors were observed in a clinical drug interaction study assessing the effect of both P-gp and BCRP inhibition. However, no clinically significant interaction due to BCRP inhibition was observed. Respective statements are given in sections 4.5 and 5.2 of the SmPC.

Rimegepant is not a substrate of OATP1B1 (Organic Anion Transport Protein 1b1) or OATP1B3 (Organic Anion Transport Protein 1b3). Considering its low renal clearance, it was not evaluated as a substrate of the OAT1 (Organic anion transporter 1), OAT3 (Organic anion transporter 3), OCT2 (Organic Cation Transporter 2), MATE1 (multidrug and toxin extrusion protein 1), or MATE2-K (multidrug and toxin extrusion protein 2-K). Rimegepant is not an inhibitor of P-gp, BCRP, OAT1, or MATE2-K at clinically relevant concentrations. It is a weak inhibitor of OATP1B1 and OAT3. Rimegepant inhibited OCT2, MATE1 and OATP1B3. IC50 values of OCT2 and MATE1 are near the therapeutic C_{max} level of rimegepant (1.4 µM). Considering 91-96 % of plasma protein binding, the free C_{max} value results in an exposure margin below the in vitro IC50s.Concomitant administration of rimegepant with the MATE1 transporter substrate metformin showed no clinically significant impact on metformin PK or on glucose utilisation which is accordingly labelled in section 5.2 of the SmPC.

2.5.4. Toxicology

A full nonclinical toxicology testing was performed in mice (carcinogenicity), rats (single- and repeat-dose toxicity, *in vivo* genotoxicity, reproductive and developmental toxicity, carcinogenicity), rabbits (reproductive and developmental toxicity) and monkeys (single- and repeat-dose toxicity). Phototoxicity testing was performed *in vitro* and qualification of the impurity profile of rimegepant was investigated in a 3-month chronic toxicity study in rats. The impurity profiles of the batches used in the non-clinical studies tested was comparable to that used in clinic.

No stand-alone local tolerance studies were performed with rimegepant because the intended therapeutic route (oral) was assessed in the repeat-dose general toxicity studies. Pivotal studies were conducted in compliance with GLP regulations and according to the ICH guidelines. All studies used rimegepant as the free base with the exception of the 6- and 9-repeat toxicity studies (rat, monkey), Segment I and III reproductive/developmental (rat), juvenile toxicity (rat), and carcinogenicity studies (mouse, rat) that used rimegepant sulfate, which is the form of this compound for human use. All studies used the oral application, the intended clinical route of administration of rimegepant. TK data for rimegepant was determined in all studies.

Repeat dose toxicity

Repeat-dose toxicity studies were performed in rats and monkeys.

In the two week exploratory studies, rimegepant exposures of males and females were similar. However, in longer term studies (3 month and 6 month) exposures in females were around 2-times higher than in males. No accumulation of rimegepant was observed as well as a dose-proportional increase in C_{max} and AUC in all rat studies.

Safety margins in rats at No-observed-effect level (NOEL) / No-observed-adverse-effect level (NOAEL) to the exposure at the clinical dose (based on AUC) were obtained at ≥ 20 x for males and ≥ 27 x for females.

The toxicity of rimegepant in monkeys was limited to dose dependent sporadical emesis (≥ 50 mg/kg) and transient, partly intermittent body weight loss and food consumption (≥ 50 mg/kg). Emesis was also a finding observed in clinical trials. Increased liver weight (≥ 50 mg/kg) and histopathologic findings (Kupffer cell hypertrophy with accumulated intracellular material, phagocytised cytoplasmic organelles, ≥ 200 mg/kg) were transient, reversible and likely physiological adaptive responses related to the metabolism of the test article. Reversible minimal to mild intravascular hemolysis and reversible minimal to slight changes in clinical chemistry parameters showed no microscopic changes, were generally of low magnitude or had no dose relationship.

No drug-induced liver injury or hemolysis were observed in clinical studies.

In general, TK data is comparable between all pivotal monkey studies with respect to dose and systemic exposures. Safety margins to exposures (based on AUC) at the the clinical dose were obtained at ≥ 16 x for males and ≥ 24 x for females.

Rimegepant-related effects at higher doses in repeat-dose studies (hepatic lipidosis in mice and rats, intravascular hemolysis in rats and monkeys, and emesis in monkeys) were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use (≥ 12 times [mice] and ≥ 49 times [rats] for hepatic lipidosis, ≥ 95 times [rats] and ≥ 9 times [monkeys] for intravascular hemolysis, and ≥ 37 times for emesis [monkeys]) as represented in section 5.3 of the SmPC.

Genotoxicity

Genotoxicity testing of rimegepant was carried out in two *in vitro* (bacterial and mammalian mutation assay, chromosome aberration assay) and an *in vivo* (rat micronucleus tests) study in compliance with GLP. Rimegepant was negative in *in vitro* Ames tests, chromosome aberration assays in CHO cells and in an oral *in vivo* micronucleus test performed in the rat.

Carcinogenicity

Rimegepant was not carcinogenic in a short-term study in hemizygous Tg.rasH2 mice and a 2 year lifespan study in Crl:CD(SD) rats. Despite the even lower binding affinity (Ki) for the CGRP receptors compared to humans (≥ 1300 x) the exposures (C_{max} unbound) in rodents exceeded the Ki 269 x in mice (Ki 0.104 µM) respectively 14 x in rats (Ki 0.209 µM) at the NOAEL (300 and 45 mg/kg) for carcinogenicity. Therefore, both the on-target and off-target effects of rimegepant were appropriately evaluated in the carcinogenicity studies. The calculated safety margins based on AUC compared to the clinical exposure (75 mg/d) were 379x in mice and 45x in rats. Additionally, the applicant submitted a comprehensive weight of evidence risk assessment for carcinogenicity of rimegepant based on literature and study data. Rimegepant has generally minimal off-target binding, was negative for genetic toxicity, showed no proliferative (hypertrophic/hyperplastic) or preneoplastic/neoplastic changes or persistent tissue injury or chronic inflammation in repeat dose toxicity studies up to the highest doses tested independent of species and study duration. Further, no hormonal perturbation, histopathological changes in endocrine or reproductive organs or effects on the immune system were observed in pivotal non-clinical studies.

Therefore, it can be assumed that rimegepant has no carcinogenic potential under the conditions of the studies.

Reproductive and juvenile toxicity

In line with the proposed indication for comprehensive management of migraine in adults a full range of reproductive toxicity studies at different laboratory sites were conducted. Overall, the parameters studied meet the requirements of ICHS5 and compliance with GLP regulations was confirmed for all studies.

The species used for the reproductive toxicity studies were considered adequate to evaluate both on-target and off-target reproductive/developmental effects of rimegepant, as pharmacological activity at inhibiting CGRP binding to both rabbit and rat CGRP receptors was demonstrated.

Two fertility and early embryonic development (FEED) studies were submitted. As pregnancy rate was significantly decreased following treatment of male and female rats with rimegepant at 150 mg/kg/d, a subsequent study with comparable design but much lower doses up to 25 mg/kg/d was conducted. This study showed no impact on pregnancy rate.

In the first study, uterine atrophy was diagnosed for almost all non-pregnant high dose females at 150 mg/kg/d as well as in single non-pregnant rats in the second study, respectively. However, external experts (Pathological Working Group / PWG) did not confirm this finding later. Instead, these experts identified deficiencies in the histopathologic evaluation resulting in significant artefacts microscopically. Furthermore, in the second study, uterine weights of several animals in each group were excluded due to wrong handling of gravid uteri prior to weighing. Nevertheless, when considering the results of both studies, it can be concluded that reproductive parameters including early embryonic development were not adversely affected in rats following treatment with rimegepant up to 60 mg/kg/d. TK values which were only obtained in the second study, revealed exposure margins of 12-13 and 16-24 times the human exposure at the NOAEL of 25 mg/kg/day for male and female rats, respectively. Using exposure levels from other rat studies for a dose of 60 mg/kg/d, exposure margins were 29 times and 46 times the human exposure at the MRHD.

Embryofetal development (EFD) studies are considered adequate to conclude that embryofetal development was affected neither in rats at doses $\leqslant$ 60 mg/kg /d nor in rabbits at $\leqslant$ 50 mg/kg/d, respectively.

Rimegepant did neither induce maternal nor developmental toxicity when administered to pregnant rats during the period of organogenesis at doses up to 60 mg/kg/day (46 times the human exposure at the Maximum Recommended Human Dose (MRHD)). Rimegepant-related developmental toxicity (reduced fetal body weights and delayed ossification) was limited to fetuses of dams treated with 300 mg/kg/day, a dose associated with mild maternal toxicity. In rabbits, rimegepant was neither embryolethal nor teratogenic when administered to pregnant rabbits over the period of organogenesis at doses up to 50 mg/kg/day (10 times the human exposure at the MRHD), a dose associated with maternal toxicity.

As some deficits were identified in an initial prenatal and postnatal development (PPND) study another study using the same strain of rats and identical dosages was conducted. Overall, the parameters evaluated in both of the studies are considered adequate to meet the requirements of ICHS5 for comprehensive assessment of possible rimegepant induced effects on postnatal development. Treatment of female rats during the period of gestation and lactation did not affect growth, reflex, sensory and neuromuscular development, learning and memory or the capability for reproduction in the offspring at doses up to 60 mg/kg/day (≥ 24 times the human exposure at the MRHD).

No data are available on placental transfer or the secretion of rimegepant into the milk in lactating animals. However, the applicant included into section 4.6 of the SmPC preliminary PK data obtained in a Phase 1 study in 12 breastfeeding women following a single dose of rimegepant. It was estimated that less than 1% of the maternal dose will reach the breast fed infant. At present, the information proposed for the section "Breast feeding" is considered sufficient for the prescriber. Following finalisation of the study report, specific PK data may be included in section 5.2 of the SmPC with cross reference to section 4.6 "Breast feeding" and vice versa in the course of variation procedure.

Juvenile toxicity studies in rats were submitted. However, as there is no paediatric indication yet, these studies were not assessed in detail in the course of this assessment.

Phototoxicity

Rimegepant absorbs light in the UVB range. At the absorbance maxima of 293 nm the molar extinction coefficient of rimegepant (13500 Lmol-1/cm) was greater than the threshold (1000 Lmol-1/cm).

A single-dose tissue distribution study in pigmented and albino rats demonstrated that rimegepant is widely distributed extravascularly and likely binds to melanin. However, as outlined in ICH S10 guideline, penetration of UVB light into human skin is mainly limited to the epidermis and thus the clinical relevance of photochemical activation by UVB is considered less important than activation by UVA for systemic drugs.

An *in vitro* phototoxicity testing of rimegepant free base was submitted. Rimegepant free base revealed no phototoxic potential in the *in vitro* neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts. Also rimegepant (substance and medicinal product) is photostable. Phototoxic reactions are unlikely based on the above finding.

2.5.5. Ecotoxicity/environmental risk assessment

At present the environmental risk assessment (ERA) cannot be finalised. A post-authorisation measure need to be addressed.

The applicant has submitted the report detailing the experimental determination of the log Kow of rimegepant sulfate in accordance with OECD Test Guidelines (determined using the Shake Flask method).

The estimated log (P) Kow value for rimegepant sulfate has been experimentally determined to be 0.806. Therefore, there is no PBT risk. The applicant used a default Fpen value resulting in a $PEC_{surfacewater}$ of 0.375 µg/l that clearly exceeds the action limit of 0.01 µg/L. Therefore, a phase II risk assessment is deemed necessary.

Table 1: Summary of Main Study Results

Substance (INN/Invented Name): rimegepant			
CAS-number (if available): 1289023-67-1 (free base)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log *K*ow	OECD 107	0.806	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PECsurfacewater, default Fpen 0.01	0.375	µg/L	> 0.01 threshold (Y)

As a result of the above considerations, the available data do not allow to conclude on the potential risk of rimegepant sulfate to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacodynamic data of rimegepant were sufficiently discussed by the applicant.

Pharmacokinetic data of rimegepant were sufficiently discussed by the applicant. Pharmacokinetic findings on possible drug-drug interactions (DDIs) of rimegepant are labelled in section 5.2 of the SmPC.

Repeat-dose toxicity studies were performed in rats (up to 6-month) and monkeys (up to 9-month). The toxicity profile of rimegepant in both species seems to be low and approximately similar. All findings were transient and reversible after recovery.

Major toxicity findings [rat (hepatic lipidosis, intravascular hemolysis), monkey (emesis, intravascular hemolysis)] with safety margins based on exposure were represented in section 5.3 of the SmPC.

Rimegepant was negative for genetic toxicity *in vitro* and *in vivo* and was not carcinogenic in a 6 months study in hemizygous Tg.rasH2 mice and a 2 years study in rats.

Reproductive toxicity studies conducted and rats and rabbits were considered adequate for assessment of possible rimegepant-induced effects on reproduction. There were no adverse findings on reproductive parameters in rats up to exposure levels of least 24 times the human exposure in rats and at 10 times the human exposure at the MRHD, respectively. No embryotoxicity was noted in rabbits.

Rimegepant absorbs light in the UVB range. Rimegepant free base revealed no phototoxic potential in the *in vitro* neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts. Also rimegepant (substance and medicinal product) is photostable. Phototoxic reactions are unlikely based on the above finding.

At present the ERA cannot be finalised. As a result of the above considerations, the available data do not allow to conclude on the potential risk of rimegepant sulfate to the environment. The applicant has been requested to conduct a phase II ERA for the active ingredient and submit the full study reports as post-authorisation measure.

2.5.7. Conclusion on non-clinical aspects

Overall, the PD and PK data presented in the nonclinical package was sufficiently discussed by the applicant. The toxicity profile of RGP is expected to be low, transient and reversible. RGP was not genotoxic *in vitro* and *in vivo* and was not carcinogenic in studies in mice and rats. RGP did not exert any embryotoxic or phototoxic effects.

The available data do not allow to conclude on the potential risk of RGP sulfate to the environment. Therefore, the applicant has been requested to conduct a phase II ERA for the active ingredient.

Based on the available non-clinical data regarding PD, PK and toxicology profile, the application was considered approvable.

The CHMP considers the following measures necessary to address the non-clinical issues:

> The applicant is asked to conduct a phase II ERA for the active ingredient rimegepant sulfate and submit the full study reports by June 2023.

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 2: Rimegepant Biopharmaceutics Studies

Study	Study Primary Objective	Population PK[a]
Phase 1 Clinical Studies: Biopharmaceutics Bioavailability		
BHV3000-102[35]	Relative bioavailability study of rimegepant capsule and tablet	X
BHV3000-110[2]	Bioequivalence study of rimegepant 75 mg tablets and sublingual ODT	X
BHV3000-112[36]	Food effect study for rimegepant 75 mg tablet and sublingual ODT	X
BHV3000-113[3]	Bioequivalence study of rimegepant 75 mg tablet and ODT on top of the tongue and effect of food on ODT on top of tongue	---
BHV3000-117[37]	Dose proportionality of rimegepant 10, 25, and 75 mg ODT dose strengths	X
BHV3000-120[38]	Food effect study for rimegepant 75 mg ODT	---

[a] "X" identifies the studies that were used to support population pharmacokinetic modeling.
[b] Population PK validation dataset only
Abbreviations: ^{14}C-ADME = ^{14}C-labeled absorption, distribution, metabolism; and excretion; IV = intravenous; MTD = maximum tolerated dose; ODT = orodispersible tablet; PK = pharmacokinetics

Table 3: Rimegepant Clinical Pharmacology Studies in Normal Healthy Subjects

Phase 1 Clinical Studies: Pharmacokinetics in Normal Healthy Subjects		
CN170001[39]	Safety, tolerability, MTD, PK, food effect, pH and gender effects	---
CN170006[42]	Safety, tolerability, absolute bioavailability, IV PK, ^{14}C-ADME	---

Table 4: Rimegepant Pharmacokinetics in Target Population

Phase 1 Clinical Studies: Pharmacokinetics in Subjects with Migraine		
CN170004[11]	Safety, tolerability, single dose PK in migraine and non-migraine state	---

Table 5: Rimegepant Pharmacokinetics in Special Populations

Phase 1 Clinical Studies: Intrinsic Factor Pharmacokinetics		
BHV3000-106[35]	Effects of renal impairment of PK of rimegepant	X
BHV3000-107[36]	Effects of hepatic impairment of PK of rimegepant	X
BHV3000-108[37]	PK of rimegepant in non-elderly versus elderly population	X
BHV3000-111[38,39]	PK of rimegepant in Japanese vs Caucasian subjects	X
BHV3000-115[40] (concluded)	PK of rimegepant in lactating women	---

Table 6: Rimegepant, Extrinsic Factor Pharmacokinetics

Phase 1 Clinical Studies: Extrinsic Factor Pharmacokinetics		
CN170002[40]	Effects of single and multiple doses of rimegepant (600 mg and 450 mg) on PK, safety, and tolerability of rimegepant + oral contraceptive	---
BHV3000-101[44]	Effects of single and multiple doses of rimegepant 75 mg on PK, safety and tolerability of rimegepant + an oral contraceptive	---
CN170007[43]	Effects of single- and multiple-dose rimegepant (300 mg and 150 mg) on single dose PK of midazolam	---
BHV3000-103[45]	Effects of multiple-dose administration of itraconazole on single-dose PK of rimegepant	X
BHV3000-104[46]	Effects of multiple-dose administration of rifampin on single-dose PK of rimegepant	---
BHV3000-105[47]	Effects of multiple-dose administration of fluconazole on single-dose PK of rimegepant	X
BHV3000-114[54]	Effects of rimegepant and concomitant sumatriptan on blood pressure, PK, safety, tolerability	---
BHV3000-119[55]	Effects of rimegepant on steady-state pharmacokinetics of metformin after oral administration, safety, tolerability	---
BHV3000-122[33] (concluded)	Effect of P-gp and BCRP inhibition of the PK of rimegepant	---

Table 7: QT Assessment

Phase 1 QT Assessment in Healthy Subjects		
BHV3000-109[51]	Thorough QT study	X[b]

Table 8: Rimegepant, Supportive Phase 2b Dose-ranging Study CN170003

Supportive Phase 2b Clinical Study – Acute Treatment					
CN170003[12] Supportive Study Completed CSR available FPFV: 27-Oct-2011 LPLV: 04-May-2012	Adaptive, double-blind, randomized, multicenter, outpatient, dose-ranging study to evaluate the efficacy and safety of rimegepant for the acute treatment of moderate to severe migraine	Single dose/ Free base capsule/ Administered orally	Rimegepant 10 mg Rimegepant 25 mg Rimegepant 75 mg Rimegepant 150 mg Rimegepant 300 mg Rimegepant 600 mg Sumatriptan 100 mg Placebo	811/799 72/71 62/61 86/86 86/85 112/111 84/82 100/100 209/203	Freedom from pain at 2 hours postdose

Table 9: Summary of Acute Treatment of Migraine Studies Presented in the Summary of Clinical Efficacy

Study No. Status	Study Description	Dosing	Treatment Groups	No. of Subjects Treated/Evaluable[a]	Primary Endpoint(s)
Pivotal Phase 3 Clinical Studies – Acute Treatment					
BHV3000-303[8] Pivotal Study Completed CSR available FPFV: 27-Feb-2018 LPLV: 15-Oct-2018	Double-blind, randomized, placebo-controlled safety and efficacy study of rimegepant 75 mg ODT for the acute treatment of migraine	Single dose/ ODT/ Administered sublingually	Rimegepant 75 mg Placebo	1,375/1,351 682/669 693/682	Freedom from pain at 2 hours postdose Freedom from the most bothersome symptom associated with migraine at 2 hours postdose
BHV3000-302[10] Pivotal Study Completed CSR available FPFV: 27-Jul-2017 LPLV: 31-Jan-2018	Double-blind, randomized, placebo-controlled safety and efficacy study of rimegepant 75 mg tablet for the acute treatment of migraine	Single dose/ Tablet/ Administered orally	Rimegepant 75 mg Placebo	1,083[b]/1,072 543/537 540[b]/535	Freedom from pain at 2 hours postdose Freedom from the most bothersome symptom associated with migraine at 2 hours postdose
BHV3000-301[9] Pivotal Study Completed CSR available FPFV: 18-Jul-2017 LPLV: 26-Jan-2018	Double-blind, randomized, placebo-controlled safety and efficacy study of rimegepant 75 mg tablet for the acute treatment of migraine	Single dose/ Tablet/ Administered orally	Rimegepant 75 mg Placebo	1,095/1,084 546/543 549/541	Freedom from pain at 2 hours postdose Freedom from the most bothersome symptom associated with migraine at 2 hours postdose

[a]Subjects were evaluable for efficacy if they were randomized only once, took study medication, had a baseline migraine of moderate to severe intensity, and provided at least 1 postbaseline efficacy data point.
[b]Three subjects in the placebo group of BHV3000-302 were treated twice (both times with placebo) but are only counted once each.
Abbreviations: CSR = clinical study report; FPFV = first patient first visit; LPLV = last patient last visit; ODT = orodispersible tablet

Table 10: Summary of Migraine Prophylaxis Studies Presented in the Summary of Clinical Efficacy

Study No. Status	Study Description	Dosing	Treatment Groups	No. of Subjects Treated/Evaluable[a]	Efficacy Endpoints
Pivotal Phase 2/3 Clinical Study – Migraine Prophylaxis					
BHV3000-305[11] Pivotal Study DBT phase Completed CSR available FPFV: 14-Nov-2018 DBL: 21-Mar-2020	Double-blind, randomized, placebo-controlled safety and efficacy study of rimegepant 75 mg tablet for migraine prophylaxis	Tablet/ Administered orally EOD for 12 weeks	Overall Rimegepant 75 mg Placebo	741/695 370/348 371/347	Primary: Reduction from baseline in the mean number of migraine days per month in the last 4 weeks of the 12-week DBT phase. Key Secondary: (1) ≥ 50% Reduction from baseline in mean number of moderate or severe migraine days per month in the last 4 weeks of the DBT phase (2) Change from baseline in mean number of total migraine days per month during the entire 12-week DBT phase (3) Rescue medication days per month in the last 4 weeks of the 12-week DBT phase
Supportive Phase 2/3 Clinical Study – Migraine Prophylaxis					
BHV3000-201[13] Supportive Study Completed CSR available FPFV: 30-Aug-2017 LPLV: 15-Jul-2019	Open-label, long-term, safety study in subjects with migraine	75 mg tablet/ Administered orally	Overall (PRN plus scheduled EOD+PRN) EOD + PRN	1,800/1,769 286/278	Exploratory efficacy assessments conducted in this safety study were related to the effect of repeated rimegepant 75 mg dosing on the frequency and severity of migraine attacks during the up to 1-year LTT period.

[a]Subjects were evaluable for efficacy in BHV300-305 if they had ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and at least 1 month (i.e., 4-week interval) in the DBT phase. Subjects were evaluable in BHV3000-201 if they had ≥ 14 days of data (not necessarily consecutive) in both the OP analysis period and at least one 4-week interval in the LTT analysis period.
Abbreviations: CSR = clinical study report; FPFV = first patient first visit; LPLV = last patient last visit; LTT = long-term treatment period; DBT = double-blind treatment; OP = observation period; PRN = as needed for up to 52 weeks; EOD = every other day for up to 12 weeks.

2.6.2. Pharmacokinetics

Formulation development

Three oral formulations of rimegepant, all claimed to be similar in bioavailability, were used during the course of the rimegepant development programme. A capsule (free-base) was developed and used in early development. Two formulations of rimegepant sulfate, an orodispersible tablet (ODT drug formulation using Zydis® technology and a tablet formulation, have been developed for use in pivotal clinical studies. The ODT drug formulation has been developed for commercialisation.

Mass balance

Mass balance study CN170006 followed an open-label, non-randomised, 2-period, 3-treatment, single-sequence, sequential cross-over design in healthy male subjects and was conducted

- To determine the absolute bioavailability (BA of rimegepant from the immediate release capsule in healthy male subjects.
- To determine the mass balance recovery of radioactivity following the oral administration of [14C]-rimegepant (300 mg).
- To describe the metabolism and elimination of [14C]-rimegepant after oral administration and
- To define the IV pharmacokinetics (PK) of rimegepant.

A total of 24 subjects were enrolled (i.e., signed the consent form) and 8 subjects were administered study treatment. All 8 subjects (all male, mean age 38.9 [range 30-55] years old, mean body mass index (BMI) 25.80 kg/m^2 [range 19.9-29.9]) completed the study and were included in the safety and PK analyses.

Rimegepant was administered in 2 periods as follows:

Period 1: rimegepant reference oral formulation (150 mg capsule × 2) in the fasted state, and a 15-minute infusion of [14C] -rimegepant (100 µg, containing not more than 10 kBq [270 nCi] ^{14}C) ending at 1 hour after the oral dose was administered.

Period 2: [^{14}C]-rimegepant oral suspension (300 mg, containing not more than 3.29 MBq [89 µCi] ^{14}C) in the fasted state.

In Period 1, the absolute BA of rimegepant was determined by administration of a rimegepant reference oral formulation (2 x 150 mg capsule) in the fasted state, accompanied by an additional 15-minute infusion of [^{14}C]-rimegepant (100 µg, 270 nCi) ending at 1 hour after the oral dose was administered. Absolute bioavailability was determined by using dose-normalised area under the concentration time-curves from time zero to infinity ($AUC_{0\text{-}inf}$ values following oral and IV administration. The geometric mean absolute bioavailability was 64% (90% CI: 53%, 77%).

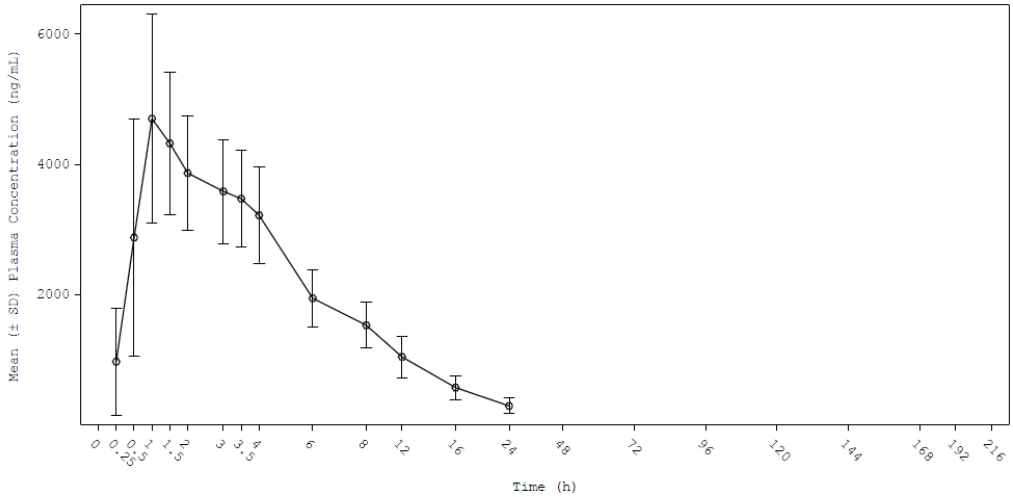
Table 11: Statistical Analysis of Rimegepant $AUC_{0\text{-}inf}$ to Assess Absolute Oral Bioavailability – Period 1 (PK Population), Study CN170006

Parameter	Treatment	n	Adjusted Geometric Mean of Dose-Normalized Values	Treatment Comparison	Ratio of Adjusted Geometric Mean (90% CI)
$AUC_{0\text{-}inf}$ (hr*ng/mL)	Rimegepant (Oral Capsules)	8	0.070	Oral/IV	0.637 (0.525, 0.773)
	[^{14}C]-Rimegepant (IV Solution)	8	0.110		

$AUC_{0\text{-}inf}$ = area under the curve 0 to infinity; IV = intravenous; CI = confidence interval
Period 1: rimegepant reference oral formulation (150 mg capsule × 2) in the fasted state, and a 15-minute infusion of [^{14}C]-rimegepant (100 ug, containing not more than 10 kBq [270 nCi] ^{14}C) ending at 1 hour after oral dosing.
The statistical model was performed on the logarithm of dose-normalized $AUC_{0\text{-}inf}$, with treatment as a fixed effect and measurements within subject as repeated measures.
PK parameters were determined using actual infusion start times as some T_{max} values occurred during the infusion.
Source: Table 14.2-12

In Period 2, the peak concentration of total radioactivity occurred shortly after administration, with concentrations declining in a biphasic manner and was not quantifiable after 24 hours post-dose. The mean plasma concentration-time profiles for rimegepant and total radioactivity were comparable over the first 24 hours after study drug administration.

Figure 2: Radioactivity Period 2 Mean (±SD) Plasma Conc. -Time Profiles, Study 170006 (Linear)



Rimegepant was the primary circulating component in plasma with 88% to 92% unchanged parent present throughout the first 4 hours. Over longer periods of time, compared to metabolites, unchanged rimegepant represented approximately 77% of the total administered dose with only low levels of circulating metabolites of rimegepant quantifiable.

Radioactivity representing rimegepant and its metabolites after oral dosing was mainly excreted in the feces (78%), with approximately 24% excreted in the urine. The $AUC_{0\text{-}inf}$ ratio of rimegepant to total radioactivity was 77%, which indicated that although there were metabolites in the circulation, rimegepant was not extensively metabolised. Unchanged rimegepant was the major component found within faeces (42%) and urine (51%).

Bioequivalence between ODT sublingual (SL) and Tablets, Study BHV3000-110

PK Study 110 was an open-label, randomised, crossover, replicate-design study conducted in 2 Parts. Part 1 assessed the definitive bioequivalence of the rimegepant 75 mg tablet and 75 mg ODT formulation administered sublingually in healthy adult men and women. Part 2 assessed the relative BA of the ODT when administered on top of the tongue or sublingually.

Part 1

For ln-transformed AUC_{0-t} and C_{max}, the within subject coefficient of variation was 30% and the 90% confidence intervals (CI) for the sublingual ODT/Tablet (test/reference) ratio, using MIXED procedures in SAS, was within the acceptance limits of 0.80 and 1.25 for both parameters, indicating bioequivalence of the rimegepant formulations.

Table 12: Ln-transformed Rimegepant PK Parameters Bioequivalence Comparison Between Rimegepant Sublingual ODT and Rimegepant Tablet Treatments in Part I (EMA) (PK Population) Study 110

Parameter	Treatment	N	Estimate	CV_{WR}	90% CI	Acceptance Limits
AUC_{0-t}	Sublingual ODT (Test)	34	4977.19			
	Tablet (Reference)	34	5143.88	15.69		
	Test/Reference	34	0.97		(0.93, 1.01)	(0.80, 1.25)
AUC_{0-inf}	Sublingual ODT (Test)	34	4991.95			
	Tablet (Reference)	34	5158.49			
	Test/Reference	34	0.97		(0.93, 1.01)	
C_{max}	Sublingual ODT (Test)	34	856.94			
	Tablet (Reference)	34	819.17	23.74		
	Test/Reference	34	1.05		(0.98, 1.12)	(0.80, 1.25)

AUC_{0-inf} = area under the curve 0 to infinity; AUC_{0-t} = area under the curve zero to time t; CI: Confidence interval; CV_{WR} = within subject coefficient of variation; C_{max} = maximum concentration; ODT = orally disintegrating tablet
Source: Table 14.2.5-1

The median untransformed rimegepant t_{max} values were 1.50 hours for the sublingual ODT and 1.93 hours for the tablet.

Part 2

In Part 2 of Study 110, two ways of administration of ODT tablets were compared, i.e. either placed sublingually or on top of the tongue. In both cases, the ODT tablet should remain until completely dissolved and was then swallowed without water. Comparative BA points to similar AUC values with 90% CIs within the 80-125% acceptance range, however, C_{max} was about 10% higher after SL administration (ratio 1.10 [0.96, 1.27]).

Table 13: Summary Statistics for the Plasma Pharmacokinetic Parameters of Rimegepant Sublingual ODT or On Top of the Tongue (Part 2) – PK Population, Study 110

Parameter	Treatment	N	Estimate	90% CI
AUC_{0-t}	Sublingual ODT (Test)	24	4896.85	
	Top of tongue ODT (Reference)	24	4748.71	
	Test/Reference	24	1.03	(0.96 -1.11)
AUC_{0-inf}	Sublingual ODT (Test)	24	4910.09	
	Top of tongue ODT (Reference)	24	4762.64	
	Test/Reference	24	1.03	(0.96 -1.11)
C_{max}	Sublingual ODT (Test)	24	902.21	
	Top of tongue ODT (Reference)	24	823.75	
	Test/Reference	24	1.10	(0.96 -1.27)

Source: BHV3000-110 CSR[16]
Abbreviations: AUC = area under the concentration-time curve; $AUC_{(0-t)}$ = AUC from time zero to the last non-zero concentration; AUC(0-inf) = AUC from time zero to infinity

Median t_{max} was about 30 min earlier when the ODT tablet was administered sublingually (median t_{max}: SL 1.50 hr, on top of tongue 1.99 hour).

Bioequivalence between ODT on top of the tongue and tablets, Study BHV3000-113

Bioequivalence study 113 was conducted from Aug 2018 to Dec 2018. It was an open-label, randomised, single-dose study to compare the rate and extent of absorption of 75 mg rimegepant ODT administered on top of the tongue versus 75 mg rimegepant tablet under fasting conditions, and to evaluate the effect of food on the PK properties of rimegepant 75 mg ODT, administered on top of the tongue in healthy subjects.

Part 1 - Bioequivalence

The 90% CIs of the observed geometric mean ratios (GMR) of rimegepant 75 mg ODT administered on top of tongue / rimegepant 75 mg tablet for the AUC_{0-t}: GMR = 98.45%, (93.68, 103.47), AUC_{0-inf}: GMR = 98.45%, (93.69, 112.01), and C_{max}: GMR = 102.82, (94.38, 112.01), thereby demonstrating bioequivalence under fasting conditions in healthy subjects for each parameter.

Table 14: Plasma PK Parameters of Rimegepant after SD Administration of Rimegepant 75 mg ODT Top of Tongue or Rimegepant 75 mg Tablet Under Fasting Conditions, Study 113

		90% Geometric CI[b]						p-values		
Parameter (unit)	Treatment Comparison	Ratio[a] (%)	Lower (%)	Upper (%)	S^b_{WR}	CV_{WR} (%)	Acceptance Range for 90% CI[c]	Sequence	Period	Treatment
AUC_{0-t} (h*ng/mL)	Treatment A – Treatment B	98.45	93.68	103.47	0.03123	17.81	80.00% to 125.00%	0.9322	0.5788	0.6037
AUC_{0-inf} (h*ng/mL)	Treatment A – Treatment B	98.45	93.69	103.46	0.03096	17.73	NA	0.9361	0.5655	0.6024
C_{max} (ng/mL)	Treatment A – Treatment B	102.82	94.38	112.01	0.10845	33.85	77.86% to 128.44%	0.8687	0.5955	0.5914

[a] Calculated using least-squares means according to the formula: exp (DIFFERENCE) * 100
[b] 90% Geometric confidence interval using ln-transformed data
[c] If CV_{WR} was ≤ 30% for C_{max}, the acceptance range for the 90% geometric CI was 80.00% to125.00%. If CV_{WR} was > 30% for C_{max}, the acceptance range for the 90% CI was widened based upon the reference within-subject variability to a maximum of 69.84 to 143.19%; it was calculated as exp [±k·SWR], where k is the regulatory constant set to 0.760 and S_{WR} is the within-subject standard deviation of the ln transformed values of C_{max} of the reference product.
Treatment A: 1 x 75 mg rimegepant ODT fasting conditions; Treatment B (Reference): 1 x 75 mg rimegepant tablet fasting conditions
Abbreviations: AUC = area under the concentration-time curve; $AUC_{(0-t)}$ = AUC from time zero to the last non-zero concentration; AUC(0-inf) = AUC from time zero to infinity; CI = confidence interval; C_{max} = maximum observed concentration; CV = coefficient of variable; LSM: least square mean; ODT = orodispersible tablet
Source: BHV3000-113 CSR[17]

Median t_{max} values were similar between the two modes of administration (median t_{max}: ODT top of tongue 2.0 hour, tablet 2.3 hour).

Part 2 – Food effect

For the rimegepant 75 mg ODT (placed on top of tongue), the GMRs (fed/fasted) and associated 90% CIs for AUC_{0-t}: GMR = 62.18%, (55.48, 69.68), AUC_{0-inf}: GMR = 62.29%, (55.60, 69.77), and C_{max}: GMR = 46.57%, (40.94, 52.97), were reduced in the presence of a high fat meal, as compared to administration in the fasted state.

Table 15: Plasma PK Parameters of Rimegepant after SD Administration of Rimegepant 75 mg ODT Top of the Tongue Under Fed and Fasting Conditions, Study 113

	Geometric LSM		90% Geometric CI[b]					p-values		
Parameter (unit)	Trt C	Trt D	Ratio[a] (%)	Lower (%)	Upper (%)	Intra-subject CV (%)[c]	Inter-subject CV (%)[d]	Sequence	Period	Treatment
AUC_{0-t} (h*ng/mL)	2,860.20	4,600.12	62.18	55.48	69.68	17.71	22.69	0.2478	0.5487	< 0.0001
AUC_{0-inf} (h*ng/mL)	2,875.63	4,616.85	62.29	55.60	69.77	17.64	22.57	0.2449	0.5439	< 0.0001
C_{max} (ng/mL)	429.98	923.27	46.57	40.94	52.97	20.07	30.53	0.8823	0.5542	< 0.0001

[a] Calculated using least-squares means according to the formula: exp (DIFFERENCE) * 100
[b] 90% Geometric confidence interval calculated according to the formula: exp (DIFFERENCE ± $t_{(dfResidual)}$* $SE_{(DIFFERENCE)}$
[c] Calculated according to formula: SQRT (exp (MSE) - 1) * 100
[d] Calculated according to formula: SQRT (exp ((MSSUBJECT(SEQ) - MSE)/2) - 1) * 100
Probability (p) values are derived from Type III sums of squares. p-value for the sequence effect (SE) was tested using the Subject (Sequence) effect as the error term.
Abbreviations: AUC = area under the concentration-time curve; $AUC_{(0-t)}$ = AUC from time zero to the last non-zero concentration; AUC(0-inf) = AUC from time zero to infinity; CI = confidence interval; C_{max} = maximum observed concentration; CV = coefficient of variable; LSM: least square mean; ODT = orodispersible tablet; Trt = treatmentSource: BHV3000-113 CSR[17]

Rimegepant ODT administered on top of the tongue has a lower rate and extent of absorption under fed conditions when compared to fasting conditions as seen from the GMR for AUC and C_{max} reduced by 38% and 53%, respectively.

Food effect on PK after ODT sublingual and per oral tablet, Study BHV3000-112

Food effect study 112 was conducted at inVentiv Health Clinique Inc. (« inVentiv »), Québec, Canada from June 2018 to July 2018. It was a randomised, single-dose, open-label, parallel-group, 2-

sequence, crossover, study to evaluate the safety, tolerability, and effect of food on the PK properties of rimegepant tablet (not shown here in detail) and rimegepant ODT administered sublingually in healthy subjects, both under fed (high fat meal) and fasting conditions.

Part 1 - ODT 75 mg Food Effect

For the rimegepant 75 mg ODT administered sublingually, the GMRs (fed/fasted) and associated 90% CIs for AUC_{0-t}: GMR = 68.26%, (61.56, 75.70), AUC_{0-inf}: GMR = 68.31, (61.65, 75.69), and C_{max}: GMR = 58.78, (51.51, 67.08), were reduced in the presence of a high fat meal, compared to the fasted state.

Table 16: Statistical Comparisons for the Plasma PK Parameters of Rimegepant 75 mg ODT Under Fed and Fasting Conditions, Study 112

	Geometric LSM		90% Geometric CI[b]					p-values		
Parameter (unit)	Trt A	Trt B	Ratio[a] (%)	Lower (%)	Upper (%)	Intra-subject CV (%)[c]	Inter-subject CV (%)[d]	Sequence	Period	Treatment
$AUC_{(0-t)}$ (h*ng/mL)	3,214.86	4,709.45	68.26	61.56	75.70	16.05	30.62	0.9236	0.1163	< 0.0001
AUC_{0-inf} (h*ng/mL)	3,227.70	4,725.06	68.31	61.65	75.69	15.94	30.58	0.9272	0.1153	< 0.0001
C_{max} (ng/mL)	460.82	783.97	58.78	51.51	67.08	20.58	29.22	0.4264	0.5060	< 0.0001

[a] Calculated using least-squares means according to the formula: $\exp^{(DIFFERENCE)} * 100$
[b] 90% Geometric confidence interval calculated according to the formula: $\exp(DIFFERENCE \pm t_{(dfResidual)} * SE_{(DIFFERENCE)})$
[c] Calculated according to formula: SQRT (exp (MSE) - 1) * 100
[d] Calculated according to formula: SQRT (exp ((MSSUBJECT(SEQ) - MSE)/2) - 1) * 100
Probability (p) values are derived from Type III sums of squares. p-value for the sequence effect (SE) was tested using the Subject (Sequence) effect as the error term.
Abbreviations: AUC = area under the concentration-time curve; $AUC_{(0-t)}$ = AUC from time zero to the last non-zero concentration; AUC(0-inf) = AUC from time zero to infinity; CI = confidence interval; C_{max} = maximum observed concentration; CV = coefficient of variable; LSM: least square mean; ODT = orodispersible tablet; Trt = treatment
Source: BHV3000-112 CSR[18]

Rimegepant ODT administered sublingually has a lower rate and extent of absorption under fed conditions when compared to fasting conditions as seen from the GMRs for AUC and C_{max}, reduced by 32% and 41%, respectively. Under fed conditions, maximum plasma concentration are achieved about one hour later as compared to the fasted state (mean t_{max}: fed 3.4 hour, fasted 2.4 hour).

Effect of low-fat meal on PK of rimegepant ODT, sublingual, BHV3000-120

Study 120 was conducted at Syneos Health, Québec, Canada from Oct 2019 to Dec 2019. It was an open-label, randomised, single-dose, 2-period, 2-sequence, crossover study to evaluate the effect of a low-fat meal on the PK of rimegepant 75 mg ODT, administered sublingually in healthy volunteers.

For Treatment A (sublingual, fed), after a supervised fast of at least 10 hours, subjects will be served a low-fat, low-calorie meal of approximately 400 to 500 calories (approximately 25% of total caloric content of the meal derived from fat).

The so-called low-fat, low-calorie meal contains exactly half the calorie amount (400-500 calories) and half the percent fat content (25%) as compared to the standardised high-fat, high-calorie meal.

For the rimegepant 75 mg ODT administered sublingually, the GMRs, fed/fasted) and associated 90% CIs for AUC_{0-t}: GMR = 71.8%, (66.6, 77.4), AUC0-inf: GMR = 71.8% (66.6, 77.4), and C_{max}: GMR = 63.9% (56.9, 71.8), indicate a reduction of exposure in the presence of a low fat meal, compared to the fasted state. These findings can also be expressed as reductions in AUC_{0-t} of 28%, in AUC_{0-inf} of 28%, and in C_{max} of 36% in the presence of a low fat meal as compared to the fasted state. The median t_{max} increased from 2.0 hours under the fasting condition to 3.5 hours under the fed condition.

Dose proportionality of 10 mg, 25 mg, and 75 mg rimegepant ODT, BHV3000-117

Comparative bioavailability Study 117 was conducted at Syneos Health, Miami, Florida, US from Oct 2019 to Dec 2019. Rimegepant 10, 25, and 75 mg ODT were administered as a single oral dose on top of the tongue in HV under fasting conditions following a 3-period, 6-sequence, dose-proportionality crossover design.

The rate (C_{max}) and extent (AUC) of rimegepant ODT absorption increased with dose over the range of 10 to 75 mg when administered on top of the tongue under fasting conditions. The mean t_{max} at 10 and 25 mg was similar (1.5 hours) and earlier relative to the 75 mg dose (3 hours). The mean $t_{½}$ el increased with dose across the explored dose range ($t_{1/2}$: 10 mg: 5.5 hour, 75 mg: 8.5 hour).

Following a single oral dose of rimegepant ODT administered on top of the tongue under fasting conditions, a greater than dose-proportional exposure of rimegepant was observed over the rimegepant ODT dose range of 10 to 75 mg. The power model slope estimates for AUC_{0-t}, AUC_{0-inf}, C_{max} (1.197, 1.181, and 1.164, respectively) and their corresponding 90% CI ([1.156, 1.238], [1.140, 1.222], and [1.107, 1.221], respectively) were each above and outside the interval criteria range of (0.889, 1.111).

Table 17: Results of Power Model to Assess Dose Proportionality Across SD of Rimegepant ODT 10, 25, and 75 mg Administered on Top of the Tongue Under Fasting Conditions, Study 117

Parameter	N	Slope Estimate	90% CI for the Slope	Interval Criterion	Criterion Satisfied[1]
AUC_{0-t} (h•ng/mL)	42	1.197	(1.156,1.238)	(0.889,1.111)	No
AUC_{0-inf} (h•ng/mL)	42	1.181	(1.140,1.222)	(0.889,1.111)	No
C_{max} (ng/mL)	42	1.164	(1.107,1.221)	(0.889,1.111)	No

AUC = area under the concentration-time curve; AUC_{0-t} = AUC from time zero to the last non-zero concentration; AUC_{0-inf} = AUC from time zero to infinity; CI = confidence interval; C_{max} = maximum observed concentration; N = number of subjects dosed; ODT = orally disintegrating tablet
[1] Criteria: If the reported 90% CI is entirely contained within the interval criterion of (0.889, 1.111), then dose proportionality is supported across the investigated dose range, for the particular dosing regimen.
Source: Table 14.2.3A

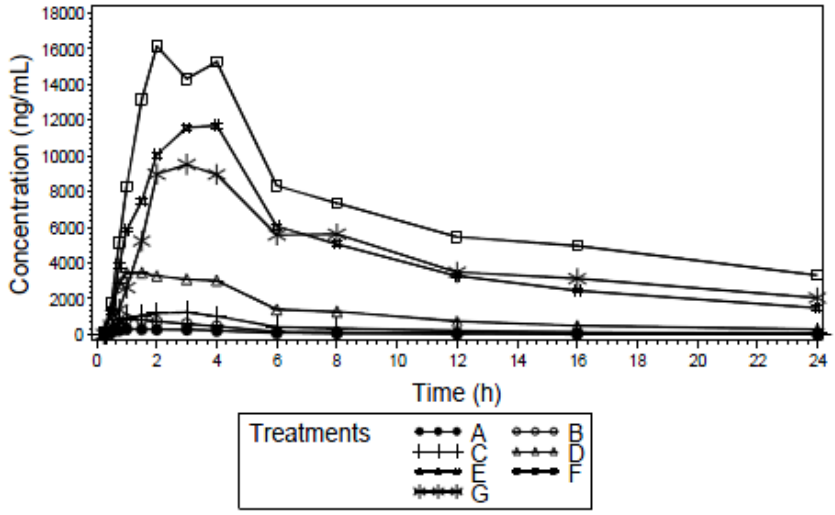
Single (SAD) and multiple ascending doses (MAD) of BMS-927711

Early (first-in-human) Phase I study CN170001 was conducted at Comprehensive Neuroscience Inc., Miami, Florida, US from Dec 2010 to Sep 2011.

Part A (SAD)

Four (4) men and 4 women of non-childbearing potential, 18 to 55 years, were enrolled in each of the 7 sequential panels (25, 75, 150, 300, 600, 900, and 1500 mg). In each panel, subjects were randomly assigned to receive either a SD of BMS-927711 or placebo in a 3 to 1 ratio, stratified by gender. In addition, a second period was conducted as a crossover on 2 panels (150 and 300 mg) to assess the effect of pH (40 mg famotidine 2 hour prior to RGP dose) and food (RGP dose within 5 min of completing a standard high-fat meal) on the PK of BMS-927711.

Figure 3: Mean Plasma Concentration-Time Profiles for BMS-927711 Following Single Oral Doses to Healthy Subjects, up to 24 h, Linear, Part A, Study CN170001



Source: Table S.8.2.1

Treatment Codes: A = 25-mg Single Dose; B = 75-mg Single Dose; C = 150-mg Single Dose; D = 300-mg Single Dose; E = 600-mg Single Dose; F = 900-mg Single Dose; G = 1500-mg Single Dose

Note: LLOQ = 0.5 ng/mL; N = 6 for all treatments.

Table 18: Summary Statistics for BMS-927711 PK Parameters after Single Oral Doses, Study CN170001, Part A

	Treatment								
Pharmacokinetic Parameter	**25 mg (n=6)**	**75 mg (n=6)**	**150 mg (n=6)**	**150 mg + Famotidine (n=6)**	**300 mg (n=6)**	**300 mg Fed (n=6)**	**600 mg (n=6)**	**900 mg (n=6)**	**1500 mg (n=6)**
Cmax (ng/mL)- Geometric Mean (CV%)	311.1 (44.13)	862.9 (42.97)	990.7 (84.75)	259.3 (34.94)	3724.8 (49.20)	3717.3 (25.24)	12221.8 (22.62)	19350.7 (26.70)	8029.2 (65.82)
Tmax (h)- Median (Min, Max)	1.000 (0.750, 3.00)	1.000 (1.00, 2.00)	2.500 (0.750, 3.00)	3.000 (2.00, 4.00)	1.000 (0.750, 2.00)	4.000 (3.00, 4.00)	3.500 (0.750, 4.00)	2.500 (1.50, 4.00)	3.000 (2.00, 4.00)
AUC(0-T) (ng*h/mL)- Geometric Mean (CV%)	1667.0 (68.99)	3643.3 (35.04)	6779.0 (75.11)	2878.4 (26.32)	25553.3 (54.47)	31163.1 (30.55)	113273.8 (32.40)	189006.1 (46.86)	84715.7 (79.51)
AUC(INF) (ng*h/mL)- Geometric Mean (CV%)	1685.7 (68.69)	3668.5 (34.57)	6850.2 (74.70)	2915.8 (25.82)	25585.9 (54.43)	31203.8 (30.50)	113461.0 (32.30)	189263.1 (47.17)	85064.3 (79.31)
T-HALF (h)- Median (Min, Max)	7.721 (6.93, 14.4)	10.02 (6.86, 13.0)	12.35 (8.75, 18.6)	12.66 (8.48, 20.5)	8.849 (8.05, 15.1)	8.895 (7.55, 17.6)	9.395 (8.46, 22.1)	9.055 (7.66, 12.6)	9.969 (7.46, 13.3)
CLT/F (mL/min)- Geometric Mean (CV%)	247.2 (65.89)	340.7 (28.94)	365.0 (77.24)	857.4 (27.58)	195.4 (71.95)	160.2 (30.11)	88.14 (32.32)	79.25 (27.12)	293.9 (91.72)
C30min (ng/mL)- Geometric Mean (CV%)	49.80 (97.29)	67.49 (80.66)	61.06 (187.7)	8.121 (109.6)	1078.6 (56.87)	4.555 (130.3)	635.1 (130.6)	1100.5 (92.50)	106.0 (105.3)
C2h (ng/mL)- Geometric Mean (CV%)	233.9 (47.14)	693.0 (35.32)	788.4 (79.84)	189.5 (56.29)	2900.0 (44.21)	1783.6 (26.11)	9961.1 (15.29)	14806.8 (46.85)	6650.2 (71.27)

Source: Table S.8.2.2

BMS-927711 was rapidly absorbed with the median t_{max} ranging from 1h (75 mg dose) to 4 h (300 mg dose, fed conditions). A large range of inter-subject variability (22-85%) was seen in the PK parameters for BMS-927711 across different doses. BMS-927711 exposures, as measured by C_{max}, AUC_{0-t}, and AUC_{0-inf} increased with increase in dose over the single dose range of 25 to 900 mg under fasting conditions. The dose of 1500 mg had exposure values less than those following the 600 and 900 mg doses.

The t½ of BMS-927711 ranged from 8-12 h after a single oral dose. Co-administration of a single oral dose of 150-mg BMS-927711 with famotidine decreased the C_{max} (to 26%) and AUC (to 43%) when compared to BMS-927711 administered alone.

Due to small sample size and high PK variability, there was no consistent pattern of gender difference in exposure across dose groups. However, female subjects had higher exposure (~2.5 fold) than male subjects in the 300-mg dose group.

Part B (MAD)

Four (4) men and 4 women of non-childbearing potential, age 18 to 55 years, were randomised within each dose panel to receive BMS-927711 or placebo in a ratio of 3:1 (stratified by gender). Five (5) sequential dose panels were planned (75, 150, 300, 450 and 600 mg). BMS-927711 or placebo was administered in the fasted state once daily for 14 days as a capsule. In addition, 300 mg (Panel 12) was administered twice daily in the fasted state 2 h apart for 14 days based on the tolerability of the previous 600 mg once-daily dose.

The accumulation index (AIs) remained constant at approximately 1.4 over the 75, 150, and 300 mg QD dose range, while increasing with the 450 (1.6) and 600 mg (2.3) QD doses. A similar trend was seen in the effective $t_{1/2}$ of BMS-927711 where the values were similar (13-19 h) in the 75, 150, 300, and 450 mg QD dose groups and longer effective $t_{1/2}$ were seen at the 600 (31 h) QD mg dose.

To assess the dose-systemic exposure relationship over the multiple dose range of 75 to 600 mg QD, the power model was used.

Table 19: Summary of Dose Proportionality Assessment on Day 14, Part B, Study CN170001

PK parameter	Estimated Slope, beta	90% CI of Slope
AUC(TAU) (ng*h/mL)	1.939	(1.695, 2.184)
Cmax (ng/mL)	1.559	(1.301, 1.816)

Pharmacokinetics in target population

Phase I study CN170004 was conducted from 17-Nov-2011 to 14-Sep-2012 at four US sites. It examined the SD PK profile of rimegepant (300 mg and 600 mg) in the target population of migraine subjects during a migraine attack as compared to the interictal period.

Rimegepant exposures (C_{max} and AUC) following migraine were generally higher than exposures in non-migraine subjects at both the 300 mg and 600 mg single doses.

Table 20: Comparison of Non-migraine to Migraine Pharmacokinetics, Study CN170004

Dose (Number participants; Migraine / Non-migraine)	Parameter	Non-migraine / Migraine 90% Geometric CI (%)		
		Ratio (%)	Lower	Upper
300 mg (N = 23 / N =23)	$AUC_{0\text{-}24hr}$ (hr•ng/mL)	66	51	86
	C_{max} (ng/mL)	58	45	73
600 mg (N = 25 / N = 19)	$AUC_{0\text{-}24hr}$ (hr•ng/mL)	79	60	103
	C_{max} (ng/mL)	79	61	102

Source: Table 14.2.6 and Table 14.2.7 of CN170004 CSR[11]

Renal impairment

Renal impairment study BHV3000-106 was conducted at inVentiv Health Clinical Research Services LLC., Miami, Florida, US and at the Division of Clinical Pharmacology, University Miami, Florida, US from 17-Oct-2017 to 27-Mar-2018.

It examined the effect of various categories of severity of renal impairment (RI) on the PK of rimegepant following a single dose of 75 mg (administered as tablet) in subjects with normal renal function, mild, moderate, or severe RI.

Healthy controls with normal renal function (Group 1, estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 $m^{2)}$ were matched to subjects with RI (mild, moderate, or severe) according to gender, age (± 10 years), and BMI (± 15%) to the extent possible.

Subjects with RI (Groups 2-4) included:

- 60 - 89 mL/min/1.73 m² (Group 2 – mild group);
- 30 – 59 mL/min/1.73 m² (Group 3 – moderate group);
- < 30 mL/min/1.73 m² (Group 4 – severe group) not requiring dialysis.

The ratios of AUC for mild RI and severe RI compared to their respective matched controls were approximately 100%. For the moderate RI group, the AUCs were increased compared with the matched controls, with ratios of approximately 140%. However, C_{max} was increased in the mild RI group and decreased in the moderate and severe RI groups vs control.

Table 21: Comparison of Renal Impairment States to Matched Controls after SD administration of 75 mg Rimegepant, Study BHV3000-106

Group Comparison	Parameter	Renal Impairment (RI) / Control 90% Geometric CI (%)		
		Ratio (%)	Lower	Upper
Mild RI (N = 6) vs Control (N = 6)	$AUC_{0\text{-}inf}$ (hr•ng/mL)	106.48	74.76	151.67
	C_{max} (ng/mL)	120.22	75.44	191.56
Moderate RI (N = 6) vs Control (N = 6)	$AUC_{0\text{-}inf}$ (hr•ng/mL)	140.04	96.95	202.29
	C_{max} (ng/mL)	76.35	42.48	137.25
Severe RI (N = 6) vs Control (N = 6)	$AUC_{0\text{-}inf}$ (hr•ng/mL)	104.42	69.51	156.88
	C_{max} (ng/mL)	89.66	49.68	161.83

Source: Table 14.2.1-17 of BHV000-106 CSR[35]

Although a less than 50% increase in total rimegepant exposure was observed following a single 75 mg dose, the unbound AUC of rimegepant was approximately 40% 2.57-fold higher in subjects with severe renal impairment. Caution is recommended in patients with severe renal impairment and frequent rimegepant use.

Hepatic impairment

Hepatic impairment study BHV3000-107 was conducted at inVentiv Health Clinical Research Services LLC., Miami, Florida, US and at the Division of Clinical Pharmacology, University Miami, Florida, US from 05-Sep-2017 to 19-Feb-2018.

It examined the effect of various categories of severity of hepatic impairment on the PK of rimegepant following a 75 mg single dose (administered as tablet) in subjects with normal hepatic function, mild, moderate, or severe hepatic impairment.

Healthy subjects with normal hepatic function (Group 1) were matched to subjects with hepatic impairment (mild, moderate, or severe) according to gender, age (± 10 years), and BMI (± 15%). Subjects were assigned to a group according to their degree of hepatic impairment based on Child-Pugh score, as follows:

- Group 1: 18 healthy subjects with normal hepatic function (control group)
- Group 2: 6 subjects with mild hepatic impairment (Child-Pugh Group A: score 5-6 points)
- Group 3: 6 subjects with moderate hepatic impairment (Child-Pugh Group B: score 7-9 points)
- Group 4: 6 subjects with severe hepatic impairment (Child-Pugh Group C: score 10-15 points)

For the mild and moderate hepatic impairment groups, there were no significant differences in AUC or C_{max} compared with the matched control groups. But there was an increase in AUC and C_{max} in the severe hepatic impairment group compared with the matched control group, with ratios for the severe HI group compared to the matched control group of 202% for AUC ($p < 0.001$) and 190% for C_{max} ($p = 0.009$). Changes to median t_{max} in subjects with hepatic impairment were modest as compared to normal healthy subjects.

Table 22: Comparison of Hepatic Impairment States to Matched Controls, Study BHV3000-107

Group Comparison	Parameter	Hepatic Impairment (HI) / Control 90% Geometric CI (%)		
		Ratio (%)	Lower	Upper
Mild HI (N = 6) vs Control (N = 6)	$AUC_{0\text{-}inf}$ (hr•ng/mL)	83.57	58.25	119.90
	C_{max} (ng/mL)	92.28	64.15	132.74
Moderate HI (N = 6) vs Control (N = 6)	$AUC_{0\text{-}inf}$ (hr•ng/mL)	107.11	69.31	165.50
	C_{max} (ng/mL)	86.21	45.29	164.12
Severe HI (N = 6) vs Control (N = 6)	$AUC_{0\text{-}inf}$ (hr•ng/mL)	202.21	154.20	265.17
	C_{max} (ng/mL)	189.14	132.11	270.80

Source: Table 14.2.1-17 of BHV3000-107 CSR[36]

Pharmacokinetics in the elderly

PK study BHV3000-108 was conducted at Syneos (formerly) inVentiv Health Clinique Inc. Québec, Canada from 30-Sep-2017 to 30-Jan-2018.

It examined the PK of a SD of 75 mg rimegepant (administered as tablet) in healthy elderly (aged ≥ 65 years) as compared to non-elderly (≥ 18 and ≤ 45 years of age) following a parallel group design. A total of 28 subjects were administered study treatment, and all 28 subjects completed the study. All 28 subjects were included in the safety and PK analyses.

Administration of a single 75 mg dose of rimegepant resulted in small increases in AUC (< 5%) and a decrease in C_{max} (< 5%) in elderly subjects as compared to non-elderly subjects. For rimegepant $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} values, there were no statistically significant differences between the elderly and non-elderly groups of subjects. The ratio (elderly/non-elderly) for $AUC_{0\text{-}t}$ was 104.5 (90% CI: 81.40, 134.19, p=0.766), for $AUC_{0\text{-}inf}$ was 104.6 (90% CI: 81.59, 134.15, p=0.759), and for C_{max} was 96.6 (90% CI: 70.71, 131.83, p=0.849). The results for the secondary PK endpoints showed a statistically significant increase of 4.9 hours in untransformed $t_{1/2}$ el in elderly subjects (p=0.016).

Table 23: Comparison of Elderly to Non-elderly Pharmacokinetics, Study 108

Parameter Comparison	Parameter	Elderly / Non-elderly 90% Geometric CI (%)		
		Ratio (%)	Lower	Upper
Elderly (N = 14) vs Non-elderly (N = 14)	$AUC_{0\text{-}inf}$ (hr•ng/mL)	104.62	81.59	134.15
	C_{max} (ng/mL)	96.55	70.71	131.83

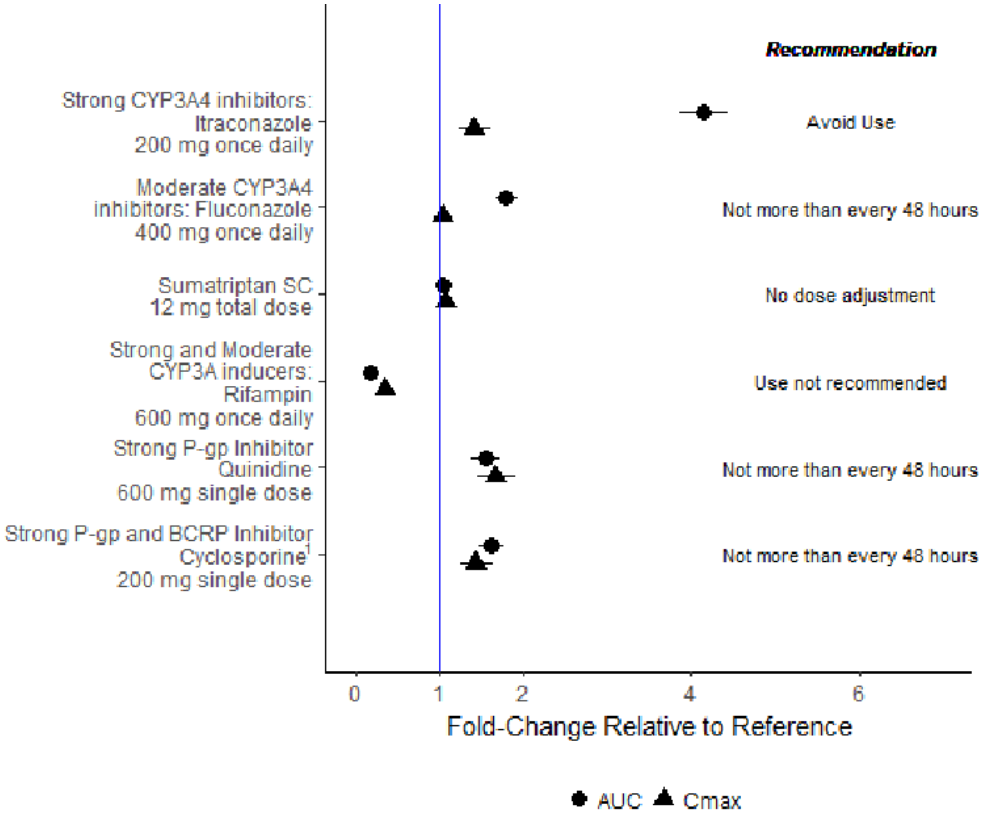
Source: Table 14.2.1-13 of BHV3000-108 CSR[37]

Drug-Drug Interactions

Effect of Co-administered Drugs on Rimegepant (Rimegepant as Victim)

The change in rimegepant PK parameters (AUC and C_{max}) after co-administration with various drugs relative to rimegepant administered alone (test/reference) for studies evaluating rimegepant as a victim and dose frequency recommendations based on the results are summarised below.

Figure 4: Effect of Co-administered Drugs on the Exposure of Rimegepant

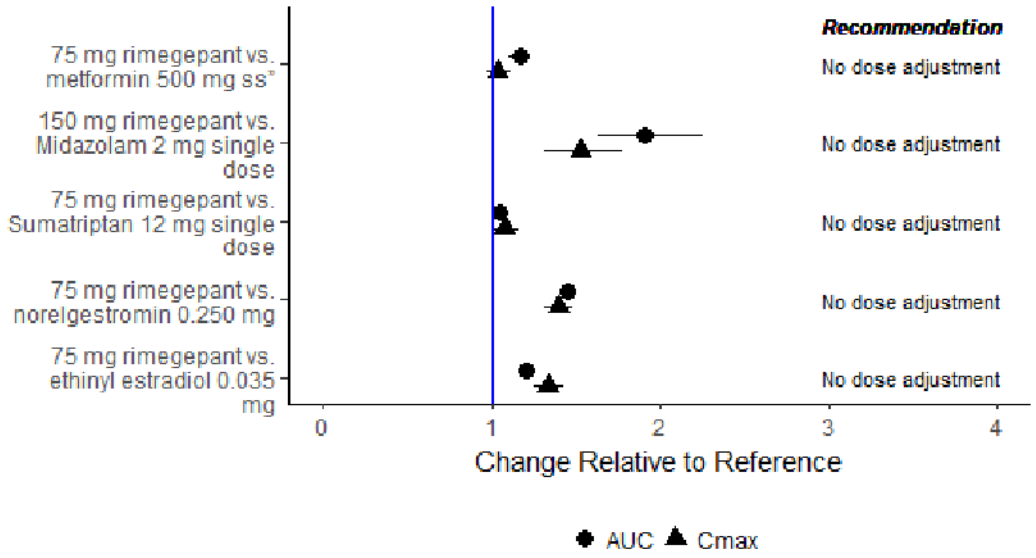


[1] Observed inhibition is ascribed to P-gp only. Strong BCRP inhibitors do not require dose frequency adjustment. Source: BHV3000-103 CSR, BHV3000-104 CSR, BHV3000-105 CSR, BHV3000-112 CSR, and BHV3000-122 Preliminary PK analysis memo

Effect of Rimegepant on Co-administered Drugs (Rimegepant as Perpetrator)

The change in rimegepant PK parameters (AUC and C_{max}) after co-administration of an oral contraceptive, midazolam, or sumatriptan with rimegepant relative to the drug administered alone (test/reference) for studies evaluating rimegepant as a perpetrator and dose regimen recommendations based on the results are summarised below.

Figure 5: Effect of Rimegepant on the Exposure of Co-administered Drugs



Source: CN170007 CSR, BHV3000-114 CSR, BHV3000-101 CSR, BHV3000-119 CSR

Population pharmacokinetics

A PPK model has been developed with data of eight studies in healthy volunteers including subjects with different degrees of renal and hepatic impairment and elderly people. A two-compartment disposition model for rimegepant with 4 transit compartments of absorption into the central compartment was identified to best describe the time course of the plasma concentration-time course of rimegepant. The following statistically significant covariates were identified in the final model: Allometric weight scaling on clearance and volume parameters, Fluconazole and itraconazole use (moderate and strong CYP3A4 inhibitor, respectively), and severe/moderate hepatic impairment on elimination clearance, fed status, itraconazole use, capsule formulation, and ODT on transit absorption rate constant (ktr), fed status on bioavailability. Impacts on exposure by the statistically significant parameters were not clinically relevant with the exception of strong CYP3A inhibitors. SmPC sections 4.4 and 4.5 specify that rimegepant is not recommended for concomitant use with strong inhibitors of CYP3A4.

2.6.3. Pharmacodynamics

The following studies will be discussed in this section:

Primary pharmacology

- Phase IIb Dose-ranging study CN170003

  Double-blind, randomised, placebo-controlled dose ranging study of BMS-927711 in acute migraine

Secondary pharmacology

- Pharmacodynamic Interaction Study BHV3000-114

  To evaluate the effect of RGP and concomitant sumatriptan on blood pressure (BP) in healthy adult subjects

- QTc Study BHV3000-109

Partially double-blind, randomized, crossover study to assess the effects of rimegepant on QTc interval

Relationship between plasma concentration, PD and clinical effect

- Early data obtained from literature, animal testing, and modelling to develop a relationship between RGP plasma levels and levels of CGRP signalling inhibition required for clinical anti-migraine effect

Acute Treatment of migraine attacks – Dose ranging study

Phase 2b dose ranging study CN170003 was conducted from Oct-2011 to May-2012 at 41 sites in the US. CN170003 was a response-adaptive, double-blind, randomised, multi-centre, outpatient evaluation of the safety, efficacy, and dose-response of BMS-927711, as compared to placebo, in the treatment of moderate to severe migraine headache. Subjects were randomised to receive placebo, sumatriptan 100 mg active control, or 1 of 6 doses of BMS-927711: 10 mg, 25 mg, 75 mg, 150 mg, 300 mg, or 600 mg.

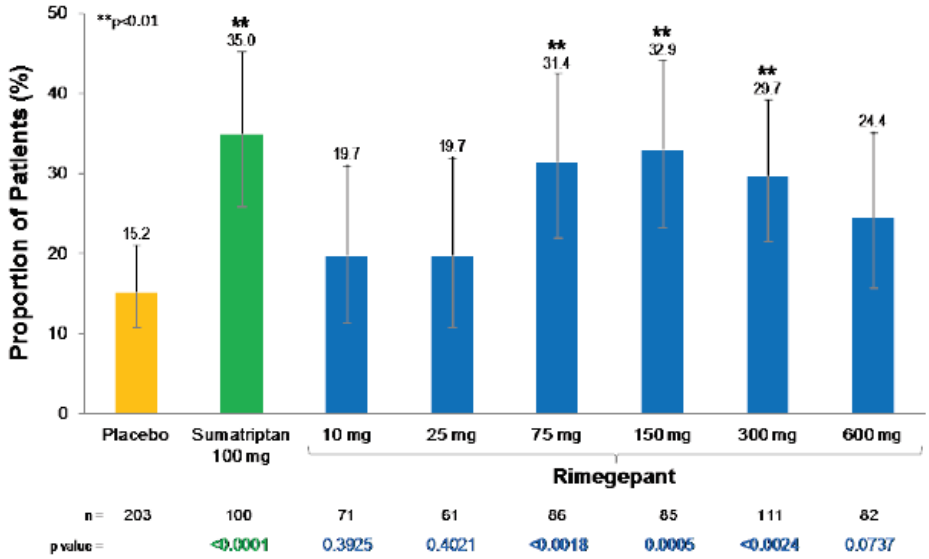
The study was divided into 3 phases: a screening/baseline phase (3-28 days), an acute treatment phase (up to 45 days during which time subjects treated 1 migraine headache of moderate to severe intensity), followed by an EOT visit within 7 days of administration of study medication.

Subjects were included if presenting with at least a 1-year history of migraines (with or without aura), age of onset prior to 50 years, migraine attacks (on average) lasting about 4 - 72 hours if untreated, and not more than 8 attacks of moderate to severe intensity per month within the last 3 months.

Eligible subjects had to report less than 15 days with headache (migraine or non-migraine) per month in each of the 3 months prior to the screening visit and maintained this requirement during the screening period. Prophylactic migraine medication was permitted while on study therapy provided the dose was stable dose for at least 3 months prior to study entry. A total of 1,026 subjects were enrolled in the study, and 86.3% (885) of these were randomised to treatment. Of the 885 randomised subjects, 812 (79.1%) completed the study.

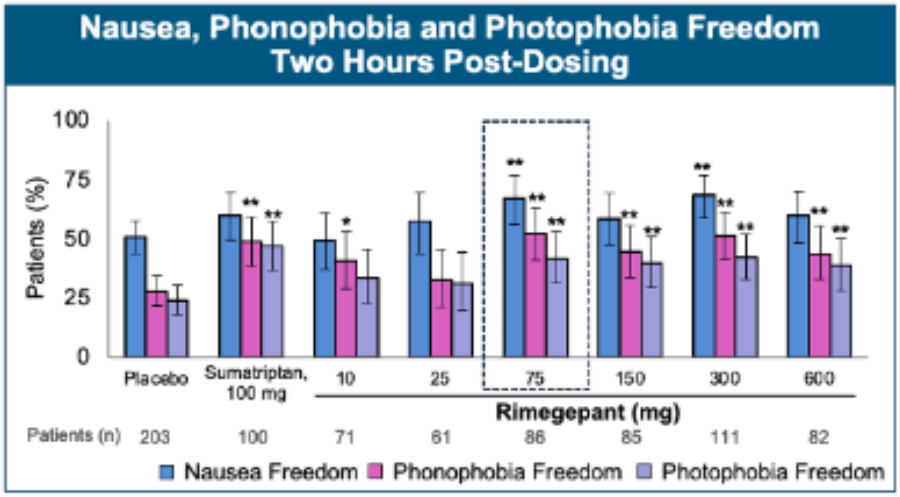
Efficacy was measured as the portion of subjects achieving pain freedom at 2 hours post-dose, i.e. headache pain intensity reported as "no pain" using a four point rating scale (no pain, mild pain, moderate pain, severe pain). Additionally, total migraine freedom was measured (composite endpoint consisting of headache pain freedom coupled with no symptoms of photophobia, phonophobia, and nausea at 2 hours post-dose).

Figure 6: Phase 2b Primary Endpoint: Rimegepant Pain Freedom at 2 hours Post Dose (+/- 95% Confidence), Study CN170003



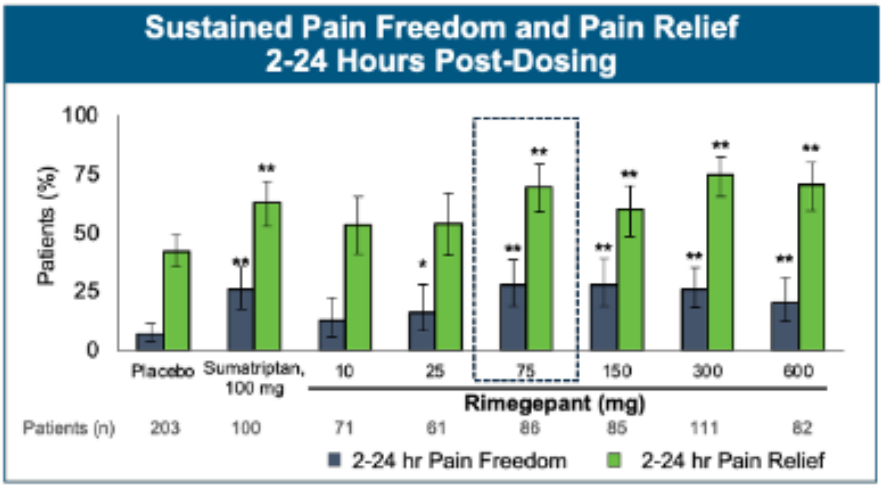
Results of the Bayesian model showed that among the BMS-927711 doses, the 150 mg dose was the most effective with 32.9% of subjects achieving pain freedom at 2 hours post-dose. The 75 mg, 150 mg and 300 mg doses of BMS-927711 were similar, with response rates of 31.4% (p = 0.0018), 32.9% (p = 0.0005) and 29.7% (p = 0.0024), respectively. All 3 doses were significantly better than placebo (15.2%). The efficacy of the 600 mg dose (response rate of 24.4%) was not significantly better than placebo. The difference in the percentage of pain-free subjects at 2 hours post-dose between sumatriptan (35%) and placebo (15.3%) was statistically significant (p < 0.0001) and consistent with historical norms.

Figure 7: Dose-ranging Study CN170003, Freedom from associated symptoms at 2 hours post-dose



Result of analyses of the migraine-related symptoms of photophobia, phonophobia, and nausea show that several doses of BMS-927711 were significantly more effective than placebo in relieving these symptoms at 2 hours post-dose.

Figure 8: Phase 2b Dose-ranging Study CN170003, Sustained Pain Freedom and Pain Relief from 2-24 hours post-dose



Sumatriptan and several dose levels of BMS-927711 had a significantly greater percentage of subjects with sustained pain freedom from 2 to 24 hours post-dose as compared with placebo: 26.0% for sumatriptan, 28.2% for 150 mg, 27.9% for 75 mg, 26.1% for 300 mg, 20.7% for the 600 mg, and 16.4% for the 25 mg dose groups.

Pharmacodynamic interaction with sumatriptan on blood pressure

The primary objective of Study 114 (Oct-2018 to Nov-2018) was to evaluate the effect of rimegepant on resting BP when administered concomitantly with sumatriptan in healthy subjects. As a secondary objective, the PK of sumatriptan when administered alone and concomitantly with rimegepant in healthy subjects were assessed.

Sumatriptan succinate injection was administered as two subcutaneous (SC injections of 6 mg/0.5 mL separated by approximately 1 hour for a total dose of 12 mg on Days 1 and 5. Rimegepant 75 mg (tablet) or placebo was administered once daily for 4 consecutive days from Day 2 to Day 5. Since sumatriptan was administered as a SC injection, only rimegepant and placebo were administered in a double-blinded fashion. Subjects were randomly assigned to receive either rimegepant or matching placebo in a 6 to 1 ratio.

The safety and tolerability of rimegepant, sumatriptan, and placebo were evaluated through the assessment of adverse events (AEs), clinical laboratory parameters (biochemistry, haematology, and urinalysis), 12-lead electrocardiogram (ECG), vital signs, Sheehan Suicidality Tracking Scale (S-STS, and physical examination.

Automated Blood Pressure Analyses

Following a manual recording at pre-dose, a total of 37 automated BP recordings were performed over a 15-hour period at pre-determined time points just after the first sumatriptan injection on Day 1 and rimegepant administration on Days 4 and 5 as follows:

- Every 10 minutes for the first 4 hours
- Every 30 minutes for the next 2 hours
- Every 60 minutes for the last 9 hours

A manual BP recording was also performed approximately 24 hours post-dose in the morning of Day 3. BP at 24 hour post dose using the ambulatory blood pressure monitoring system was collected in the mornings of Days 2, 5, and 6.

Table 24: Comparisons of Time Weighted Average Median Arterial BP, SBP and DBP Between Rimegepant and Sumatriptan Co-administration and Sumatriptan Alone, Study 114

Parameter	Ratio of Time Weighted Average	Sumatriptan + Rimegepant 75 mg / Sumatriptan Only 90% Geometric CI (%)	
		Lower	Upper
MAP	-0.21	-1.61	1.19
SBP	-0.80	-3.07	1.48
DBP	-0.06	-0.93	0.82

Abbreviations: DBP = diastolic blood pressure; MAP = mean arterial blood pressure; SBP = systolic blood pressure
Source: Table 11.3.2-2 of BHV3000-114 CSR[44]

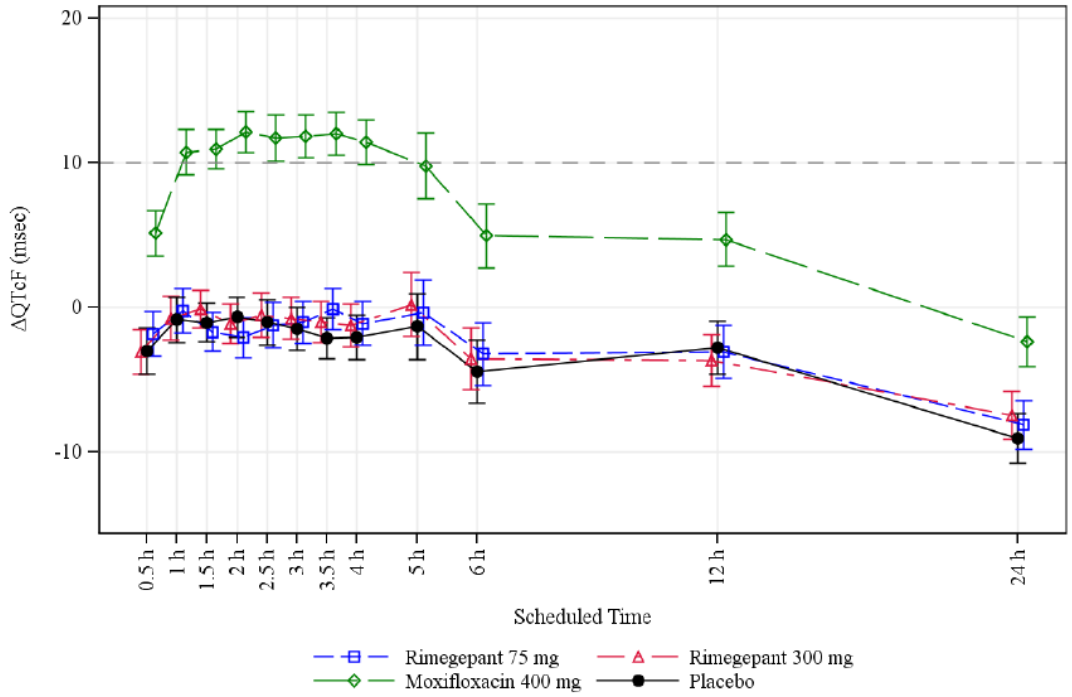
No relevant differences were observed for vital signs measurements over time. No significant difference was detected in time weighted average BP measures of mean arterial pressure, systolic (SBP) or diastolic pressures (DBP) between co-administration of rimegepant and sumatriptan as compared to sumatriptan administration alone.

TQTc study

Study 180099 (Aug 2018 to Oct 2018) was a randomised, partially double-blind, placebo- and positive-controlled, 4-way crossover, single-centre study of oral Rimegepant at therapeutic (75 mg) and supratherapeutic (300 mg) doses, administered as single doses, in healthy adults. Moxifloxacin (a single 400-mg oral dose) was used as a positive control.

The following figure illustrates the time course of QTcF changes from baseline in the four treatment groups.

Figure 9: Change-from-Baseline QTcF (ΔQTcF) Across Time Points (QT/QTc Population)



Source: CSR Study 180099 (BHV300-109) dated 22 Mar 2020, Figure 11.3.2-1

Mean change-from-baseline QTcF (ΔQTcF) on rimegepant followed closely the placebo pattern and did not suggest an effect on cardiac repolarisation. Mean ΔQTcF values on rimegepant were negative at all post-dose time points, with the exception a ΔQTcF value of 0.2 msec at 5 hours post-dose in subjects dosed with 300 mg rimegepant. As a result, mean placebo-corrected ΔQTcF (ΔΔQTcF) was also very small and ranged from -1.4 msec at 2 hours post-dose to 2.0 msec at 3.5 hours post-dose, both after dosing with 75 mg rimegepant and ΔΔQTcF was within ± 1.6 msec upon treatment with 300 mg rimegepant. After dosing with moxifloxacin, a clear increase of mean ΔΔQTcF was observed with a peak value of 14.1 msec (90% CI: 12.10 to 16.20) at 3.5 hours post-dose. There were no treatment-emergent T-wave or U-wave morphology changes.

Relationship between plasma concentration and effect

Targeted ≥ 90% inhibition of CGRP-signalling

Primate CGRP PD and human PK identified rimegepant 75 mg as the human dose where ≥ 90% inhibition of CGRP-signalling would occur (the predicted target for efficacy).

Dose selection for rimegepant in migraine was supported from preclinical and phase 1 safety data as well as PD data in primates (marmosets) using the CGRP-induced dermal blood flow assay. This assay employs a strong agonist dose of human-αCGRP (10 µg/kg, IV) that is designed to mimic waves of CGRP release during a migraine attack (human plasma levels of CGRP rise substantially during migraine, reflecting CGRP release from trigeminal afferents). Rimegepant was expected to inhibit CGRP-induced increases in dermal blood flow.

In early studies, rimegepant 0.3 mg/kg SC produced ≤ 17% inhibition, 1 mg/kg produced up to 46% inhibition, 3 mg/kg produced up to 66% inhibition, and 7 mg/kg produced up to 80% inhibition of CGRP-induced increases in dermal blood flow. Based on these data and multispecies allometric scaling, it was predicted that a human single dose of 70 to 140 mg would be efficacious in migraine with a C_{max} target

of 750 nM (400 ng/mL) to provide ≥ 90% inhibition of CGRP-signalling (the predicted PD inhibition target for efficacy). Based on clinical exposures from Phase 1 (CN1700018), rimegepant 75 mg was identified as the lowest dose to achieve this Cmax target, and the next lowest dose 25 mg was shown to fail to reach the target.

Previously, four injectable CGRP mAbs (erenumab, fremanezumab, galcanezumab and eptinezumab) and one other orally-administered CGRP receptor antagonist (atogepant), have all demonstrated clinical efficacy in migraine prevention, with a common mechanism of inhibiting CGRP signalling. (Goadsby et al. 2017) Two of these agents, erenumab and eptinezumab, conducted pharmacodynamic inhibition efficacy-exposure studies to guide clinical dose selection in prevention. Both agents showed that a C_{max} with ≥ 90% inhibition was required for efficacy in migraine prevention. Clinical doses that failed to achieve a C_{max} with ≥ 90% inhibition were ineffective and dosing higher did not provide added therapeutic benefit.

Table 25: Comparison of Migraine Clinical Activity to Pharmacodynamic Inhibition

C. Rimegepant	Ineffective Doses		Clinically Active Doses			
Dose (mg)	10	25	75	150	300	600
PD inhibition	19.0%	79.8%	91.5%	92.7%	99.2%	99.8%
Prevention efficacy			++			
Acute efficacy	-	-	++	++	++	++

Source: Rimegepant: CN170001,8 CN170003,10 BHV3000-303,62 BHV3000-305;51 PD = marmoset CGRP-induced laser Doppler blood flow data on file)

Rationale for Dose Selection from Human PK Modelling of EOD (every other day) Expected Exposures and CGRP Inhibition

Rimegepant has consistently shown sustained benefits through 48 hours after a single rimegepant 75 mg dose was administered for the treatment of migraine (CN170003, BHV3000-301, BHV3000-302, and BHV3000-303). Most recently, single dose rimegepant 75 mg showed statistically significant effects over 2 to 48 hour on four measures of durable efficacy: sustained pain freedom 2 to 48 hour, sustained freedom from MBS 2 to 48 hour, sustained ability to function normally 2 to 48 hour and sustained pain relief 2 to 48 hour. These comprehensive and durable benefits through 48 hours from a single dose suggest that daily dosing would not be required for a clinically meaningful preventive effect.

It has not been established that constant high blockade of CGRP-signalling is required for efficacy in the preventive treatment of migraine. Other CGRP signal-blocking agents, including a long-acting injectable CGRP mAb (erenumab) and daily dosing of another oral CGRP receptor antagonist (atogepant), have shown an unwanted signal of constipation when administered for the preventive treatment of migraine. Therefore, as part of the rimegepant dose selection process the expected exposure profile and its potential effects on providing a more favourable safety/tolerability profile was considered. Rimegepant has a favourable PK profile with a $t_{1/2}$ of ~11 hours. In this regard, the PK profile of oral rimegepant has the potential to provide both effective therapy (with periods of maximal CGRP inhibition ≥ 90%) and a respite from prolonged blockade (by planned regular excursions into periods of lower CGRP inhibition) when administered in an EOD regimen.

A population PK model utilizing 10 clinical studies and 337 healthy subjects given doses ranging from 10 to 150 mg was used to simulate single-dose and steady-state rimegepant exposures (e.g., C_{max}, AUC, and overall PK profiles) from dosing scenarios of interest. A representative population of virtual subjects (n = 1,000) were resampled from the analysis dataset demography.

Simulations over 48 hours for single and steady-state EOD dose of rimegepant 25 mg (anticipated ineffective dose) and 75 mg (anticipated effective dose) were generated. There is little accumulation with the EOD dosing regimen, and consequently the simulated C_{max} and 48 hour AUC are similar whether given as a single dose or at steady-state (ss) after EOD for both rimegepant 25 mg and 75 mg. Comparing the exposure profiles of the two doses there is minimal overlap in the 90% CI for C_{max} and 48 hour AUC between the 25 mg and 75 mg doses.

The clinical exposure required for efficacy in migraine was predicted based on PK-PD modelling data from a primate pharmacodynamic in vivo efficacy assay measuring CGRP inhibition. A target of ≥ 90% CGRP inhibition was established for the acute treatment of migraine and also for the preventive treatment of migraine. The aim was to provide both effective therapy (with periods of maximal CGRP inhibition ≥ 90%) and support safety/tolerability with repeated use (by planned regular excursions into periods of lower CGRP inhibition). The target for prevention was further supported by analysis of publicly available PK-PD data from two previously approved competitor CGRP signal-inhibiting agents which indicated that a Cmax with ≥ 90% CGRP inhibition was required for therapeutic benefit in the preventive treatment of migraine. A Phase 2b dose-ranging study in the acute treatment of migraine confirmed rimegepant 75 mg as the minimum fully efficacious dose that provided 48 hour comprehensive and durable efficacy on multiple outcome measures (with no clinical benefit observed by dosing up to 8x higher). The initial clinical data from Study BHV3000-201, showing reductions in monthly migraine days (MMD) in a cohort of patients treated every other day (EOD), was confirmed in a subsequent pivotal clinical trial (BHV3000-305) demonstrating that rimegepant 75 mg dosed EOD was effective in the preventive treatment of migraine (without a signal for constipation seen with other CGRP blocking agents). Discussion on clinical pharmacology

Pharmacokinetics

A comprehensive PK study programme was provided to delineate the PK profile of rimegepant (RGP) 75 mg ODT. The ODT tablet formulation is proposed to be administered either sublingually or on top of the tongue. For the treatment of acute migraine attacks, one 75 mg ODT tablet is to be taken as needed without the option of a second dose within the same day. If taken for migraine prevention, one 75 mg ODT tablet is proposed to be regularly taken EOD).

The pivotal phase III studies were partly conducted with the rimegepant per oral tablet formulation (single attack studies 301/302, prevention study 305), and with the ODT formulation intended to be marketed (single attack study 303). Therefore, demonstration of bioequivalence across the ODT and tablet formulations is essential to mutually bridge the existing clinical safety and efficacy data. Bioequivalence between the tablet and the ODT formulation could be shown in two dedicated studies, Study 110 for the sublingual ODT application, and Study 113 for the ODT to be placed on top of the tongue. The was around 8 hours for both ODT and per oral tablet. After (and on top of tongue) placement of the ODT tablet, the subject has to wait until completely dissolved and then swallow without water. Notably, t_{max} was earlier for ODT sublingual (1.5 hour) as compared to the per oral tablet (1.9 hour), despite the fact that the tablet was swallowed with water. The portion of transmucosal absorption of RGP after oromucosal placement of ODT tablets is assumed to be negligible. ODT tablets (either on top of or under the tongue, as recorded during PK studies) disintegrate within seconds after contact with saliva.

In Part 2 of Study 110, the two ways of administration of ODT tablets were directly compared, i.e. either placed sublingually or on top of the tongue. In both cases, the ODT tablet should remain until completely dissolved and was then swallowed without water. Comparative BA points to similar AUC values with 90% CIs within the 80-125% acceptance range, however, C_{max} was about 10% higher after SL administration (ratio 1.10 [0.96, 1.27]). Median t_{max} was about 30 min earlier when the ODT tablet was administered sublingually (median t_{max}: SL 1.50 hour, on top of tongue 1.99 hour). In pivotal single attack Study 303, the ODT tablet was placed sublingually. Hence, there are no clinical data obtained for the on top of

tongue ODT application. The posology section of the proposed SmPC specifies that the ODT may be placed on the tongue or under the tongue.

In the treatment of acute migraine attacks, the onset of effect of medication is of critical importance. The rimegepant tablets were compared with ODT in two separate studies for sublingual (Study 110), resp. on top of tongue placement (Study 113). In Study 110, the median untransformed rimegepant t_{max} values were 1.50 hours for the SL ODT and 1.93 hours for the tablet. If placed on top of tongue, the median t_{max} was 2.0 hours for ODT, as compared to 2.3 hours for the tablets (Study 113). Hence, the benefit of the ODT formulation as compared to tablets in terms of rapid increase in blood levels is not evident. However, it is acknowledged that due to associated symptoms of nausea / vomiting it may be advantageous for some patients to administer the ODT tablet without water in acute migraine attacks.

A considerable food effect was observed for the ODT formulation. Rimegepant ODT, administered either sublingually or on top of tongue, has a lower rate and extent of absorption after ingestion of a standard high-fat meal when compared to fasting conditions. The GMRs for AUC and C_{max} reduced by 32% and 41% after sublingual administration (Study 112), and by 38% and 53%, if placed on top of tongue (Study 113). Under fed conditions, maximum plasma concentration are achieved about one hour later as compared to the fasted state (mean t_{max}: fed 3.4 hour, fasted 2.4 hour). In clinical trials, rimegepant was administered irrespective of any meals taken or not. By its nature as a medication designed for acute treatment of migraine attacks, which are often accompanied by nausea and/or vomiting, any recommendation in terms of food intake may hardly reflect clinical practice. In any way, given the magnitude of food effect, SmPC section 5.2 gives due account about the food effect on the PK of rimegepant. It is important for transferability of pivotal clinical data obtained with the RGP tablet, that the food effect observed for the tablet formulation was similar in nature (decrease of AUC, C_{max}; delay of t_{max} by about one hour) and magnitude as compared to ODT.

Study 120 further examined the food effect observed in studies 112/113 by measuring the exposure of rimegepant (75 mg ODT, sublingual) after ingestion of a low-fat, low calorie (exactly half the calorie amount [400-500 calories] and fat content [25%], as compared to a standard high-fat meal). In general, PK results obtained from Study 120 (low-fat, low-calorie meal) confirm those previously obtained from Study 112, which examined the food effect of a high-fat, high-calorie standard meal. While ingestion of a high-fat meal lead to about 32% resp, 41% decrease of AUC and C_{max} (Study 112) after SD sublingual administration of rimegepant 75 mg ODT, AUC was reduced by 28% and C_{max} was reduced by 36% if the respective meal contained half as much fat / calories (Study 120). Under both conditions, t_{max} was delayed by 1-1.5 hours under fed conditions.

Along the same line as the food effect observed for rimegepant, the availability of RGP (if administered as free base) appears to be dependent on pH conditions in the GIT. In Part A of study CN170001, pre-treatment with histamine-2 antagonist famotidine (150 mg, 2 hour prior to rimegepant dosing) lead to markedly reduced rimegepant exposure (C_{max} and AUC reduced by 75% resp. 57%). The decreased availability of rimegepant after prior treatment with antacids is in line with RGP's pH solubility profile revealing an about 100-fold decrease in solubility if the pH is increased from pH 1.4 to pH 6.8.

In [^{14}C] mass balance Study CN170006, radio-chromatographic profiling of plasma, urine and faecal samples revealed that in plasma, unchanged parent was the most prominent drug-related circulating component, no major metabolite (i.e., representing >10% of drug-related material) was present in plasma. The $AUC_{0\text{-}inf}$ ratio of rimegepant to total radioactivity was 77%, which indicated that although there were metabolites in the circulation, rimegepant was predominant. On the other side, rimegepant was extensively metabolised to a wide variety of minor metabolites with an overall low rate of metabolic clearance prior to elimination. The primary biotransformation pathway was the cleavage of the carbamate bond of the RGP molecule, apart from hydroxylation and formation of a number of minor secondary oxidative metabolites. Rimegepant and its metabolites were primarily eliminated in the faeces

(appr. 78%) and the secondary route is via renal excretion (appr. 24%). Unchanged rimegepant was the major component found within faeces (42%) and urine (51%). Hence, around 32% of the initial oral rimegepant dose is found unchanged in the faeces and about 12% of the rimegepant dose is found unchanged in the urine. The absolute BA of an oral 300 mg RGP dose (administered as 2 x 150 mg capsules) was 64% (90% CI: 53%,77%).

When increasing doses of rimegepant are administered, it was a consistent finding across 3 studies (117, CN170001, 111) that more than dose proportional increases in RGP exposure result. In Part B of Study CN170001 multiple ascending (supra) therapeutic doses of 75, 150, 300, 450 and 600 mg were administered once daily over a period of 14 days. More than dose proportional increases in RGP exposure were observed with increasing doses (estimated slope: area under the concentration-time curve during a dosing interval (AUC_T 1.94, C_{max} 1.56). At the same time, oral clearance decreases from 297 mL/min for 75 mg to 37 mL/min for 600 mg once daily. The decrease in oral clearance translates into increasing accumulation of RGP with dose (AI: 75 mg: 1.48, 600 mg 2.25), which points to non-linear disposition with increasing doses. In migraine prophylaxis, RGP is proposed to be taken EOD, with a maximum daily dose of 75 mg, in case RGP should be used for an acute migraine attack on top of regular preventive treatment. Study CN170001 does not inform about plasma levels after EOD dosing proposed for preventive treatment.

In order to further investigate the more than dose proportional increases with increasing doses, bioavailability (relative to the 75 mg dose) was modelled across the 10-150 mg dose range. PPK Modelling reveals the administered dose as a factor impacting on bioavailability. Mechanistic explanations for this finding are hypothetical. It was specified that the absolute oral BA of rimegepant is approximately 64%. Respective absolute BA data are derived from ^{14}C-ADME study CN170006 based on a 300 mg oral RGP dose as compared to IV.

As concerns PK in the target population, there have been literature reports describing decreased absorption of medication, if taken during acute attacks, e.g. zolmitriptan (Thomsen et al. 1996). The phenomenon was generally attributed to gastric stasis during a migraine attack. In the case of rimegepant, however, a migraine attack appeared to increase RGP exposure. In Study CN170004, the potential effect of an acute migraine attack on the PK profile of RPG was examined by comparing RPG blood levels after SD administration of 300 mg resp. 600 mg rimegepant taken within 4 hours after the onset of an acute attack with an inter-ictal period. For both dose levels examined (300 and 600 mg), the rate and extent of RGP absorption were greater during an attack as compared to the control period. The area under the concentration-time curve during 24 hours (AUC_{0-24hr}) and C_{max} values were 34-21% resp. 42-21% lower during the non-migraine control period as compared to administration during an acute attack. As concerns t_{max} (mean), results are not consistent. While for the 300 mg dose peak RGP concentrations were achieved about 30 min earlier during an acute attack, it took about 35 min longer for the 600 mg dose. Median t_{max} values, however, were equal for the 600 mg dose under both conditions (2.0 hour). In essence, although Study CN170004 did not examine the 75 mg RGP dose, it can be concluded that an acute migraine attack does not appear to negatively impact the rate and extent of rimegepant absorption.

Pharmacokinetics in special populations

Dedicated studies were conducted in renally and hepatically impaired subjects and the elderly were undertaken to characterize the PK profile of rimegepant in special populations.

In hepatic impairment study 107, a SD of 75 mg rimegepant was administered to subjects with mild, moderate, or severe hepatic impairment as compared to matched healthy controls. Administration of a single 75 mg dose of rimegepant to subjects with mild or moderate hepatic impairment resulted in similar C_{max} and AUC_{0-inf} values compared to matched controls, whereas both rate and extent of RGP absorption in subjects with severe hepatic impairment were elevated approximately 2-fold. The applicant's

conclusion is endorsed that in patients with mild or moderate hepatic impairment no dose adaption is required. For subjects with severe hepatic impairment, however, it is specified in the SmPC that the use of rimegepant should be avoided.

ADME-Study CN170006 revealed that the primary route of elimination is through the faeces, with approximately 78% of the radioactivity from a [^{14}C]-rimegepant dose recovered in the faeces compared to only 24% recovered in the urine. Accordingly, administration of a single 75 mg dose of rimegepant to subjects with mild, moderate, or severe resulted in largely similar C_{max} and AUC values compared to normal healthy matched controls. However, there are some inconsistencies in observed changes of rimegepant availability relative to the various degrees of renal impairment. While AUC values were almost unchanged in subjects with mild (AUC ratio 106%) resp. severe (AUC ratio 104%) RI as compared to controls, a 40% increase in AUC was observed in subjects with moderately impaired renal function. Also, C_{max} values do not change consistently to the degree of RI. While C_{max} values increased by 20% in mild RI, C_{max} was decreased by about 10% in severely impaired subjects. Since there is no other plausible clinical explanation, these inconsistencies may be due to the low number of subjects included in study 106 (n=6 per renal impairment level). Importantly, in renally impaired subjects no delay in t_{max} was observed. Overall, it is concluded that changes in RGP availability as function of RI do not require dose adaptions of rimegepant. The minor impact of renal function on rimegepant's PK is consistent with the expectation of renal clearance as a secondary elimination mechanism to overall elimination. The results of study 106 are adequately reflected in the SmPC.

The effect of age was examined in study 108 comparing the exposure of rimegepant after SD administration of a 75 mg tablet in healthy elderly (aged $\geq$ 65 years) with non-elderly ($\geq$ 18 and $\leq$ 45 years of age) subjects following a parallel group design. Bioequivalence between the two age groups could not be shown, however, the ratio (elderly/non-elderly) resp. associated 90% CIs did not point to a statistically significant differences between the elderly and non-elderly subjects (AUC_{0-t}: 104.5 [81.40, 134.19], C_{max}: 96.6 [70.71, 131.83]). The increased extent of exposure in terms of AUC goes along with a statistically prolonged $t_{1/2}$ value (increase of 4.9 hour) in elderly subjects. In pivotal phase III studies no upper age limit was defined for study participation. The applicant's conclusion that no dose adjustment is required in the elderly subpopulation is acceptable.

Pharmacokinetic Interactions

The PK interaction potential of rimegepant was thoroughly characterised by a number of *in vivo* DDI studies.

The prevalence of migraine peaks in women of childbearing potential, hence, any potential IA with oral contraceptives is of critical importance. DDI Study CN170002 was conducted early during clinical development and examined the impact of supra-therapeutic rimegepant doses (600 mg, 450 mg o.d.) on plasma levels of once daily oral contraceptive (norgestimate [NGM], 250 ng; ethinyl estradiol [EE], 35 ng, Ortho Cyclen™). Clinically relevant increases of hormone concentrations were observed. The EE estrogen component increased by 70% (C_{max}) resp. 78% (AUC_{τ}). An even greater increase in systemic exposure was observed for NGMN, an active metabolite of NGM (C_{max} increased by 87%, AUC_{τ} increased 2.3-fold relative to control).

Given the magnitude of effect, further insight was required from subsequent IA study BHV3000-101, where the same oral contraceptive was combined with single resp. multiple therapeutic 75 mg rimegepant doses. Co-administration of a single 75 mg dose of RGP with Ortho-Cyclen™ did not have any clinically relevant effects on estrogen resp. gestagen levels. However, co-administration of 8 consecutive 75 mg daily doses of RPG with Ortho-Cyclen™ (0.250 mg NGM, 0.035 mg EE) resulted in a significant increase in the exposure of EE (1.2- to 1.3-fold increase in AUC and C_{max}) and NGMN (1.4- to 1.5-fold increase in AUC and C_{max}). Hence, the increasing effect on estrogen / gestagen levels was less pronounced than observed in preceding IA study CN170002 (when supra-therapeutic rimegepant doses

were tested). The observed increases in AUC and C_{max} of the estrogen and gestagen components of combined oral contraceptives fulfil the criteria for weak enzyme inhibition by rimegepant according to the EMA Guideline on the investigation of drug interactions. Hence, no particular labelling is required.

Non-clinical *in vitro* studies revealed that rimegepant is primarily metabolised by CYP3A4 and to a lesser extent by CYP2C9. Study CN170007 was conducted to evaluate the impact of single and multiple doses of rimegepant on the PK of the sensitive CYP3A4 substrate, midazolam. Both single dose (300 mg) and multiple once daily doses (150 mg) of rimegepant significantly increased exposure of co-administered CYP3A4 substrate midazolam (2 mg). However, even after administration of supra-therapeutic rimegepant doses, AUC and C_{max} values of of co-administered CYP3A4 substrate midazolam (2 mg) increased by (only) 86-91% and 38-53%. Hence, the criteria for weak enzyme inhibition according to the EMA Guideline on the investigation of drug interactions are fulfilled. In section 5.2 of the proposed SmPC rimegepant is identified as a weak inhibitor of CYP3A4 with time-dependent inhibition.

In vivo DDI Study 103 further identifies rimegepant as a substrate of CYP3A4 metabolism. If co-administered with the strong CYP3A4 inhibitor itraconazole, the extent of rimegepant exposure increases by more than 4-fold. SmPC sections 4.4 and 4.5 specify that rimegepant is not recommended for concomitant use with strong inhibitors of CYP3A4.

The inverse effect was observed in Study 104, examining DDI between therapeutic 75 mg doses of rimegepant and the strong CYP3A4 inducer rifampin (600 mg o.d. over 11 consecutive days). Exposure of rimegepant was decreased to a degree, which may lead to a loss of efficacy (AUC reduced by 81%, and C_{max} by 64%). Therefore, SmPC sections 4.4 and 4.5 do not recommend the concomitant use of rimegepant with strong or moderate CYP3A4 inducers.

The contribution of CYP2C9 to rimegepant's metabolism was further characterised in Study 105, which examined the impact of fluconazole, a strong CYP2C9 and moderate CYP3A4 inhibitor, on rimegepant PK. Administration of a single 75 mg dose of rimegepant concurrent with steady state fluconazole (400 mg QD) increased rimegepant AUC by approximately 1.8-fold. An effect on RPG's peak plasma concentrations (C_{max}) was not observed. Fluconazole is a strong inhibitor of CYP2C9, and a moderate inhibitor of CYP3A4. Non-clinical *in vitro* studies indicated that rimegepant is predominantly metabolised by CYP3A4, and to a lesser extent by CYP2C9. The relative contribution of either CYP2C9 or CYP3A4 inhibition to the 80% increase in AUC, if rimegepant is co-administered with fluconazole, is therefore not evident. SmPC section 4.5 specifies that only one rimegepant dose should be administered within 48 hours, if co-administered with moderate CYP3A4 inhibitors.

Available *in vitro* data revealed that rimegepant has the potential to inhibit human MATE1 and OCT2, with a more potent inhibition of MATE1 than OCT2. Interaction Study 119 examined the PK and PD interaction between regular administration of the antidiabetic metformin (2 x 500 mg/d) with once daily rimegepant 75 mg tablets. Metformin is a known substrate of renal cationic transporter systems. This suggested the potential for an interaction between rimegepant and metformin to occur in the kidney, where inhibition of MATE1 by rimegepant would cause an increase in plasma metformin concentrations and a decrease in metformin clearance in urine. *In vivo* data confirmed preliminary theoretical considerations. Co-administered rimegepant increased steady state $AUC_{0\tau}$ values of metformin by 16%. The increase in metformin exposure goes along with an approx. 10% decrease of metformin's renal clearance. These pharmacokinetic interactions, however, did not translate into inhibition of metformin's antidiabetic activity. The oral glucose tolerance in healthy adult subjects was almost unaffected by co-administered rimegepant as compared to regular metformin administration alone. The issue is adequately addressed in the SmPC.

Rimegepant has also been shown to be a substrate of P-gp and BCRP efflux transporters *in vitro*. Study 122 was designed to assess the effect of cyclosporine (strong nonselective inhibitor of P-gp, and BCRP) on the PK of rimegepant 75 mg in healthy subjects (Part I). Dependent on the results obtained in Part I,

the effect of a specific, strong P-gp inhibitor quinidine on rimegepant PK was planned to be analysed in Part II.

The strong nonselective P-gp and BCRP transporter inhibitor cyclosporine increased rimegepant AUC and C_{max} by 1.62-fold, resp. by 1.44-fold, suggesting an increased rate and extent of rimegepant absorption through the inhibition of intestinal efflux transporters (P-gp and/or BCRP). Given the magnitude of effect observed in Part I, it was required to further elucidate the relative contribution of the P-gp resp. BCRP transporter inhibition to the observed increase in rimegepant exposure.

In Part II of Study 122, the strong selective P-gp transporter inhibitor quinidine (2 x 300 mg) was co-administered with rimegepant (75 mg). A higher rate and extent of rimegepant absorption was observed suggesting inhibition of P-gp by quinidine at the intestinal level. The similarity in magnitude of the quinidine (selectively inhibits P-gp) results with those of cyclosporine (inhibits both P-gp and BCRP) indicates that the effects of BCRP inhibition on rimegepant exposure may be inconsequential. Additionally, unlike cyclosporine, quinidine has not shown *in vivo* inhibition of either CYP3A or CYP2C9, further demonstrating that the increase in rimegepant exposures by both cyclosporine and quinidine is primarily due to inhibition of P-gp. Overall, strong P-gp inhibitors such as cyclosporine and quinidine have the potential to increase the exposure of rimegepant by > 50% but <2-fold. The applicant specifies in the SmPC that strong P-gp inhibitors may be co- administered with rimegepant no more frequently than once every 48 hours.

Taken together, a number of clinically relevant interactions were explored. These mainly relate to changes in rimegepant exposure if co-administered with strong or moderate inhibitors / inducers of CYP3A4 metabolizing enzymes, but also to concomitant administration with strong P-gp transporter inhibitors. The pH-related IA with acid-modifying agents did not lead to rimegepant's loss of efficacy, as shown be retrospective subgroup analysis of phase 3 data. Hence, co-administration with antacids and rimegepant does not need to be explicitly discouraged in the label.

TQTc Study

The submitted thorough QTc study 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 rimegepant could prolong the QT interval in a relevant way. However, a gender-related evaluation is currently missing. As most of the migraine patients are females, subgroup analysis by gender (ΔQTcF and ΔΔQTcF estimates incl. 90% CI per time-point) should be presented.

Dose ranging and PK/PD

Dose ranging phase 2b study CN170003 examined a dose range of 10 mg to 600 mg rimegepant single doses and demonstrated efficacy for the 75 mg dose in acute treatment of migraine attacks. Lower doses (10 mg, 25 mg) did not separate from placebo. Higher than 75 mg doses (150 mg, 300 mg) did not lead to clinically relevant increased benefit as compared to the 75 mg dose.

Analysis of PK-PD data published for competitor CGRP antagonists, approved for migraine prevention, suggested that clinical activity is connected to a $\geq$ 90% inhibition of CGRP signalling. A target C_{max} of 750 nM (400 ng/mL) for efficacious migraine therapy with rimegepant was derived from PD testing in primates (marmosets) using the CGRP-induced dermal blood flow assay.

Based on efficacy data obtained from pivotal trials in acute migraine (studies 301/302/303), it was shown that the beneficial effect of rimegepant is maintained for up to 48 hours post-administration. This finding lead to the rationale of testing rimegepant in subsequent migraine prevention trial 305 following an EOD dosing schedule. PK-PD modelling data from a primate pharmacodynamic assay and human PK data demonstrated that rimegepant 75 mg single dose and the EOD dosing regimen both achieved the PD

target of ≥ 90% CGRP inhibition established for the acute and preventive treatment of migraine. The aim was to provide both effective therapy (with periods of maximal CGRP inhibition ≥ 90%) and support safety/tolerability with repeated use (by planned regular excursions into periods of lower CGRP inhibition).

In summary, it is concluded that classical dose finding data obtained in acute treatment of migraine attacks (study CN170003) substantiate the use of the 75 mg rimegepant in pivotal trials for abortive migraine treatment (301/302/303). The rationale for the use of 75 mg rimegepant doses to be taken every other day in migraine prevention is based on PK/PD modelling on one side, and on the other side, on the observation from acute RCTs that the beneficial effect of rimegepant in acute attacks is maintained over 48 hours post-administration. The latter aspect illustrates the difference in the migraine prevention approach between rimegepant and available per oral migraine preventive agents like ß-blockers, topiramate and others. For these, efficacy in acute migraine attacks is not established and administered doses in migraine prevention are similar to the doses administered for their primary field of clinical use (hypertension, epilepsy etc.). In the case of rimegepant, however, the same dose is applied in abortive and preventive treatment, only the dosing interval was adapted for prevention, based on the period for which beneficial effects were demonstrated in acute trials.

Irrespective of PK-PD modelling, the adequacy of the 75 mg dose of rimegepant to be taken EOD in migraine prevention is to be assessed based on randomised, placebo-controlled data provided from study 305.

2.6.4. Conclusions on clinical pharmacology

Taken together, it is concluded that a comprehensive PK data package was provided. The PK of rimegepant in special populations was adequately characterised. The rationale for EOD dosing of 75 mg rimegepant to achieve a 90% inhibition of CGRP signalling in migraine prevention was based on nonclinical testing in marmosets, published data for other CGRP antagonists, and PK/PD modelling.

There are principle differences in the way migraine "prophylaxis" is achieved between rimegepant and other orally administered preventive agents, like ß-blockers, topiramate, antidepressants or others.

2.7. Clinical efficacy

2.7.1. Dose response study

Dose ranging has been established on the basis of study CN170003 described in section above.

2.7.2. Main study(ies)

The rimegepant marketing authorisation application (MAA) dossier includes efficacy data from 4 pivotal studies for the treatment of migraine conducted in the US (three pivotal Phase 3 studies for the acute treatment of migraine [BHV3000-303 with ODT; BHV3000-301 and BHV3000-302 with tablet], and a pivotal Phase 2/3 study for migraine prophylaxis [BHV3000-305 with tablet]). Supportive studies include a Phase 2/3, open-label, long-term safety study where subjects could receive rimegepant 75 mg doses for up to 52 weeks, including nearly 300 subjects who received scheduled dosing with rimegepant 75 mg EOD as well as needed (PRN) up to once per calendar day for up to 12 weeks (BHV3000-201 with tablet).

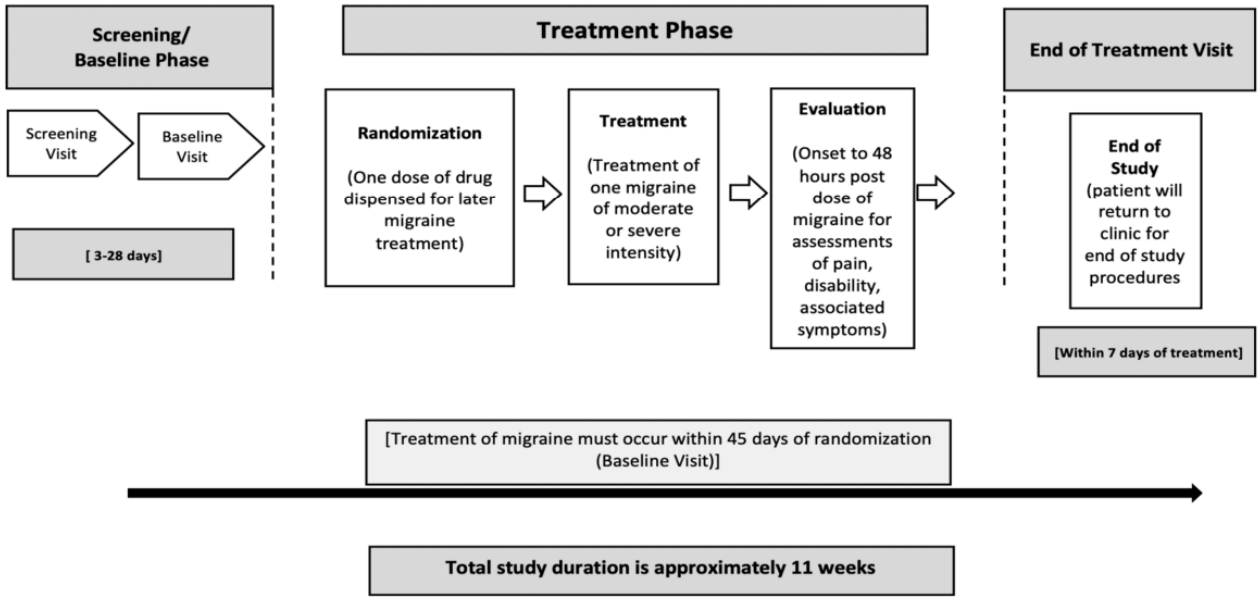
Treatment of acute single attack studies 301/302/303

The 3 pivotal acute treatment studies had similar study designs and requirements: Study 303 was a phase 3, double-blind, randomised, placebo-controlled, multi-centre, outpatient evaluation of the safety

and efficacy of a single dose of rimegepant 75 mg ODT compared to placebo in the treatment of migraine with moderate or severe pain intensity.

Participants were randomised in a 1:1 ratio and dispensed 1 dose of study medication consisting of rimegepant 75 mg ODT or matching placebo. The total duration of the study was up to 11 weeks. This included a 3- to 28-day screening period; an acute treatment phase that could last up to 45 days, during which the subject could treat one migraine that reached moderate or severe pain intensity; and an end-of-treatment (EOT) visit within 7 days after the administration of the study medication. The overall study design, eligibility, and requirements of studies 302 and 301 were identical, apart from the fact that the tablet study drug formulation was used instead of the ODT tablet for studies 301 and 302.

Figure 10: BHV3000-303/302/301 Study Design Schematic



Migraine prevention study 305

BHV3000-305 was a multi-centre study to assess the safety and efficacy of rimegepant 75 mg in migraine prophylaxis. The study consists of 4 phases: a 28-day screening phase, a 12-week double-blind treatment (DBT) phase, a 52-week open-label extension (OLE) phase, and an 8-week follow-up safety phase.

Screening Phase

The screening phase included a Screening visit and a 28-day observation period (OP). The subject's migraine history and medical history were collected at the Screening visit. Upon completion of the Screening visit, subjects were provided an electronic diary (eDiary) to document each day of the 28-day OP if a migraine occurred and the migraine intensity and characteristics. Subjects recorded the standard of care migraine treatment received on a paper diary and female subjects recorded their menstrual period information on a paper log.

Double-blind Treatment Phase

After completing the 28-day OP, subjects returned to the clinic for the baseline visit, during which their eligibility for continued participation in the study was assessed. If eligible, subjects were randomised and entered the 12-week DBT phase (Weeks 1 through 12), during which they were instructed to take 1 tablet of blinded study drug (rimegepant 75 mg or placebo) EOD. If subjects had a migraine during the

DBT phase of the study, if needed, they could treat the migraine with their standard of care medication and were instructed to continue to take study medication on their regular schedule (scheduled dosing days only).

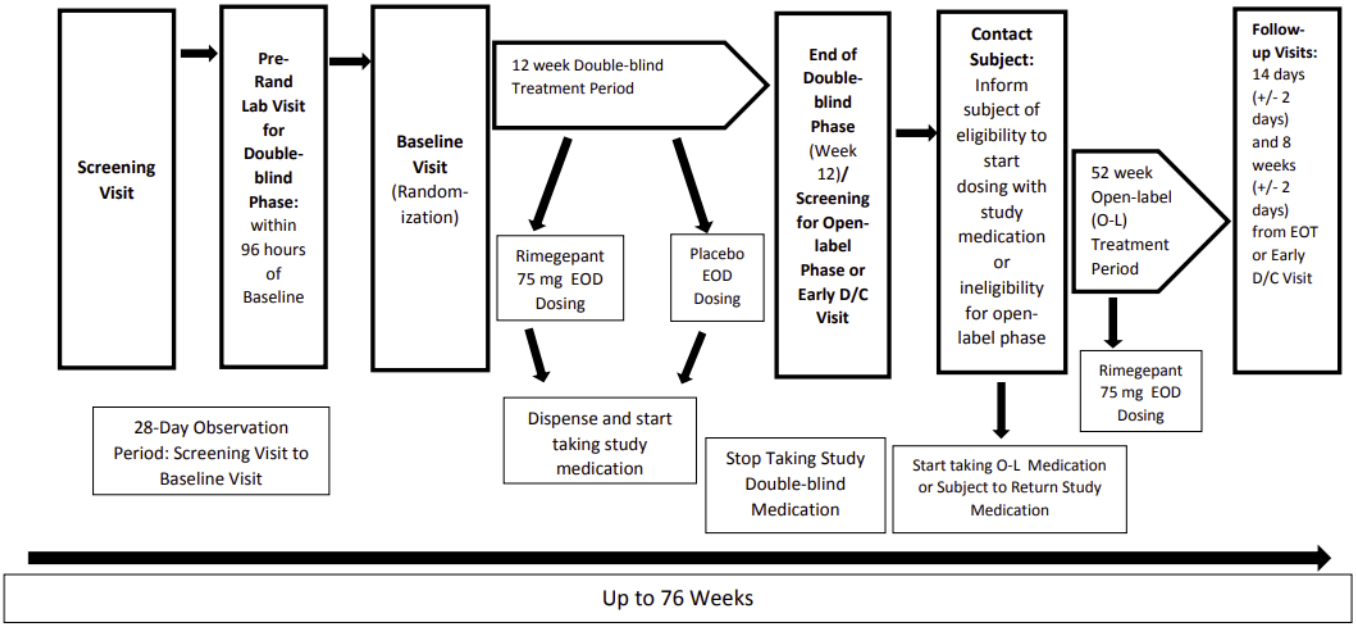
Open-label Extension Phase

At the completion of the 12-week DBT phase, subjects could enter into the 52-week OLE phase (Weeks 13 through 64) if they continued to meet study entry criteria and laboratory test results were acceptable per protocol. During the OLE phase, subjects were instructed to take 1 tablet of rimegepant 75 mg EOD. If subjects had a migraine on a day that they were not scheduled to dose with rimegepant, they could take 1 tablet of rimegepant 75 mg on that calendar day to treat a migraine. Therefore, during the OLE phase, subjects could take a maximum of 1 rimegepant 75 mg tablet per calendar day for this 52-week period.

Follow-up Safety Phase

After completing the OLE phase, subjects were to return to the clinic for an EOT visit. There were follow-up safety visits 2 and 8 weeks after the EOT visit for assessment of liver function tests (LFTs). Subjects who did not complete the DBT phase and/or did not enter or complete the OLE phase were to complete the EOT visit, the 2-week follow-up safety visit, and the 8-week follow-up safety visit after their early discontinuation

Figure 11: BHV3000-305 Study Design Schematic



Methods

Study Participants

Single attack studies 301, 302, 303

Key inclusion criteria included women or men who were 18 years of age and older and had at least a 1-year history of migraines (with or without aura) consistent with a diagnosis according to the ICHD, 3rd edition beta version and including the following:

- Migraine attacks present for more than 1 year with the age of onset prior to 50 years of age
- Migraine attacks, on average, lasting about 4 - 72 hours if untreated
- Not more than 8 attacks of moderate or severe intensity per month within last 3 months
- Patients must be able to distinguish migraine attacks from tension/cluster headaches.
- Consistent migraine headaches of at least 2 migraine headache attacks of moderate or severe intensity in each of the 3 months prior to the screening visit and maintains this requirement during the screening period
- Less than 15 days with headache (migraine or non-migraine) per month in each of the 3 months prior to the Screening Visit and maintains this requirement during the Screening Period
- Patients on prophylactic migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry.
- Patients with contraindications for use of triptans may be included provided they meet all other study entry criteria.

Exclusion Criteria included

- Patient has a history of basilar migraine or hemiplegic migraine
- Patient history with current evidence of uncontrolled, unstable or recently diagnosed CV disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Patients with Myocardial Infarction (MI), Acute Coronary Syndrome (ACS), Percutaneous Coronary Intervention, cardiac surgery, stroke or TIA) during the 6 months prior to screening.
- Uncontrolled hypertension (high BP), or uncontrolled diabetes (however patients can be included who have stable hypertension and/or diabetes for 3 months prior to being enrolled)
- Patient has a current diagnosis of major depression, other pain syndromes, psychiatric conditions (e.g, schizophrenia), dementia, or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments
- The patient has a history or current evidence of any significant and/or unstable medical conditions (e.g, history of congenital heart disease or arrhythmia, known suspected infection, hepatitis B or C, or cancer)
- History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months
- ECG and Laboratory Test Findings
  a) eGFR according to the re-expressed abbreviated (four-variable) Modification of Diet in Renal Disease Study equation $\leq$ 40 ml/min/1.73m^2
  b) Corrected QT interval > 470 msec (QTc by method of Frederica), during the screening/baseline Phase
  c) Left Bundle Branch block
  d) Right Bundle Branch Block with a QRS duration $\geq$ 150msec.
  e) Intraventricular Conduction Defect with a QRS duration $\geq$ 150msec.
  f) Serum bilirubin (Total, Direct and Indirect) > 1 x upper limit normal (ULN) (only abnormal values of between 1-1.5x ULN may be repeated once for confirmation during the screening period.)
  g) Neutrophil count $\leq$ 1000/μL (or equivalent).
  h) AST (Aspartate aminotransferase) or ALT (Alanine aminotransferase) > 1 x ULN (Only abnormal values of between 1-1.5x ULN may be repeated once for confirmation during the screening period.)

Prevention study 305

Inclusion Criteria for the Target Population correspond to subjects has at least 1 year history of migraine (with or without aura) consistent with a diagnosis according to the ICHD, 3rd Edition2, including the following:

- Age of onset of migraines prior to 50 years of age
- Migraine attacks, on average, lasting 4 - 72 hours if untreated
- Per subject report, 4-18 migraine attacks of moderate or severe intensity per month within the last 3 months prior to the Screening Visit (month is defined as 4 weeks for the purpose of this protocol)
- 6 or more **MDs** during OP
- Not more than 18 **headache days** during the OP
- Ability to distinguish migraine attacks from tension/cluster headaches
- Subjects on prophylactic migraine medication are permitted to remain on therapy if the dose has been stable for at least 3 months (12 weeks) prior to the OP, and the dose is not expected to change during the course of the study.
    i. Subjects may remain on one (1) medication with possible migraine prophylactic effects, excluding CGRP antagonists [biologic or small molecule], during the DBT phase.
    ii. Concomitant use of a CGRP antagonist, such as erenumab or fremanezumab, is prohibited.
    iii. Subjects who previously discontinued prophylactic migraine medication must have done so at least 90 days prior to the Screening Visit.
- Subjects with contraindications for use of triptans may be included provided they meet all other study entry criteria

Treatments

Rescue Mx (Single attack studies 301/302/303)

In single attack studies 301/302/303, rescue medication is prohibited until the 2-hour post-dose assessment for the primary endpoint. Thereafter, the subject is allowed to take unspecific analgesics or antiemetics for rescue, if pain relief was not achieved or pain recurs. The efficacy assessment time spans over 48 hours post-dose to record sustained pain relief from 2-48 hours post-dose. Thereafter, the subject is allowed to also administer triptans as individual rescue, if not contraindicated. Once rescue Mx was taken, any subsequent efficacy assessment is classified as failure.

Rescue MX: Prevention study 305

During the 12-week DBT period rimegepant is to be taken EOD for prevention, but is prohibited to be taken as rescue in case an acute attack occurs. During the DBT period subjects may take their usual rescue medication for acute attacks, incl. triptans. During the subsequent OLE phase, however, triptans are prohibited. Instead, subjects are allowed to take 1 rimegepant dose for an acute attack (on top of regular EOD dosing) on days for which rimegepant EOD for prevention is not scheduled, i.e. taken acute and preventive rimegepant together, a MDD of 1 dose per day (75 mg) is to be observed.

Prohibited Concomitant Medication (Single attack studies 301/302/303)

The below medications are prohibited prior to randomisation and during the course of this study.

- St. John's Wort, Butterbur root or extracts
- Barbiturate-containing products
- Modafinil (PROVIGIL®)
- History of use of ergotamine medications on greater than/equal 10 days per month on a regular basis for greater than/equal 3 months.
- History of non-narcotic analgesic intake on greater than/equal 15 days per month for greater than/equal 3 month (e.g. acetaminophen, NSAIDs, gabapentin etc.) ***for other pain indications***.

- Use of narcotic medication, such as opioids (e.g. morphine, codeine, oxycodone and hydrocodone) for at least 2 days prior to randomisation.
- Use of all acetaminophen or acetaminophen containing products must be discontinued at least 2 days prior to randomisation (acetaminophen < 1000mg/day is allowed as rescue). During the screening phase (3-28 days) use of acetaminophen or acetaminophen containing products at daily dosing levels of greater than 1000mg/day is prohibited.
- Concomitant use of strong CYP3A4 inhibitors or inducers with rimegepant

Subjects on prophylactic migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry. Low dose aspirin (e.g. 81 mg or less) for documentedcardiovascular prophylaxis is allowed.

Prohibited Concomitant Medication (Prevention study 305)

(where divergent from studies 301/302/303)

- triptans are prohibited during the OLE phase
- CGRP antagonists (biologic [e.g. Aimovig™ and Ajovy™] or small molecule) other than rimegepant
- Concomitant use of CYP2C9 inhibitors or inducers
- Concomitant use of atypical antipsychotics or Depakote/Depakene (valproic acid/valproate)
- Concomitant use of LAMICTAL (lamotrigine)
- Use of analgesics (e.g. nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) on ≥ 15 days per month is prohibited during the study.

Prophylactic Medications (Prevention 305)

Throughout preventive trial 305, subjects were allowed to continue 1 (but not 2) of their usual prophylactic medications, if administered in stable doses within 3 months (12 weeks) prior to the start of the OP and throughout the study.

Objectives

The primary objective of SD studies 301/302/303 was to evaluate the efficacy of rimegepant 75-mg ODT (or tablet) compared to placebo in the acute treatment of migraine as measured by the co-primary endpoints freedom from pain and from the most bothersome symptom (MBS) associated with migraine at 2 hours post-dose.

The primary objective of prevention study 305 was to compare the efficacy of rimegepant 75 mg to placebo as a preventive treatment for migraine, as measured by the reduction from baseline (i.e., the 4-week OP) in the mean number of MDs per month in the last 4 weeks of the 12-week DBT phase.

Outcomes/endpoints

Single attack studies 301/302/303

Single attack studies 301/302/303 had 2 co-primary endpoints:

- Freedom from Pain at 2 Hours Post-dose

  Freedom from pain was assessed using the number of modified intention-to-treat (mITT) subjects that reported pain levels of "none" at 2 hours post-dose on a 4-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

- Freedom from MBS at 2 Hours Post-dose

Freedom from each subject's MBS was assessed using the number of mITT subjects who reported that their MBS (reported prior to dosing) was absent at 2 hours post-dose. The symptoms that could have been nominated as the MBS (phonophobia, photophobia, or nausea) were measured using a binary scale (0 = absent, 1 = present).

A number of secondary endpoints were defined. These were hierarchically arranged. The order of hierarchy differs between most recent study 303 (conducted with ODT) and previous single attack studies 301/302 (conducted with tablets). The secondary endpoints in 302/301 are a subset of the secondary endpoints in study 303.
Relevant secondary endpoints include pain relief at 2 hours post-dose, sustained pain relief from 2 to 24 hours, sustained pain freedom from 2 to 24, resp. from 2 to 48 hours post-dose, freedom from photophobia / phonophobia / nausea, and others.

Prevention study 305

The primary efficacy endpoint of study 305 was the change from the OP in the mean number of MDs per month in the last month (Weeks 9 to 12) of the DBT phase.

There were six secondary efficacy endpoints in this study (hierarchically arranged), which were evaluated in the following manner:

1. Percentage of subjects who have a ≥ 50% reduction from OP in the mean number of moderate or severe MDs per month on treatment in the last month of the DBT phase. Evaluable mITT subjects with ≥ 50% reductions were compared between treatment groups using a CMH test, stratified by prophylactic migraine medication use at randomisation (yes, no).
2. Change from baseline in the mean number of MDs per month over the entire DBT phase (Weeks 1 to 12)
3. Mean number of rescue medication days per month on treatment in the last month of the DBT phase
4. Change from OP in the mean number of MDs per month on treatment in the first month (Weeks 1 to 4) of the DBT phase
5. Change from baseline in the Migraine Specific Quality of Life Questionnaire restrictive role function domain score at Week 12 in the DBT phase
6. Change from baseline in the Migraine Disability Assessment (MIDAS) total score at Week 12 in the DBT phase

Type 1 error was controlled through the use of hierarchical testing.

Definition of a Migraine Day

A migraine day is defined as any calendar day that the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 30 minutes, and meeting at least one of the following criteria (A and/or B):

A) At least two of the following pain features:

- Unilateral location
- Pulsating quality (throbbing)
- Moderate or severe pain intensity
- Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

B) At least 1 of the following associated symptoms:

- Nausea and/or vomiting
- Photophobia and phonophobia

Randomisation and blinding (masking)

Single attack studies 301/302/303

After completion of all screening evaluations, all eligible subjects were randomised in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomisation was stratified by the use of prophylactic migraine medications (yes or no).

Prevention study 305

At the baseline visit for the DBT phase, eligible subjects were randomised in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomisation was stratified by the use of prophylactic migraine medications (yes or no).

Blinding was critical to the integrity of clinical studies. However, in the event of a medical emergency or pregnancy in an individual subject, the blind for that subject could be broken by the treating physician.

Statistical methods

Studies 301/302/302

Efficacy evaluations were based on mITT subjects: randomised subjects who were randomised only once, took study medication, had a baseline migraine of moderate to severe pain intensity and who provided at least 1 post-baseline efficacy data point.

Rimegepant was tested for superiority to placebo, at a 2-sided alpha level of 0.05, on both co-primary endpoints of freedom from pain at 2 hours postdose and freedom from MBS at 2 hours postdose. Both endpoints were evaluated using Cochran-Mantel-Haenszel tests stratified by the use of prophylactic migraine medication (yes or no). The population summary, the between group difference in the percentage of pain free subjects, is assessed by computing the "risk difference" between treatment groups.

Secondary endpoints are analysed using the same methods as for the co-primary endpoints. Type I error was controlled in this study by using a hierarchical gate-keeping procedure.

Sensitivity analyses were conducted to assess the influence of missing data.

Study 305

Efficacy evaluation were based on evaluable mITT subjects: subjects with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and at least one month (i.e., 4-week interval) in the DBT phase.

The principal analysis of the primary endpoint (change from the OP in the mean number of MDs per month in the last month (Weeks 9 to 12) of the DBT phase) used a generalised linear mixed effect model (GLMEM) with the following variables: change from the OP in number of total MDs per month as the dependent variable; subject as a random effect; number of total MDs per month in the OP as a covariate; treatment group, prophylactic migraine medication use at randomisation, month (i.e., months 1 to 3 of the DBT phase), and the month-by-treatment group interaction as fixed effects. MDs per month are based on data from the previous visit to the current visit (i.e., 4-week interval), and were prorated to account for missing migraine reports.

A sensitivity analysis of the primary endpoint used the same GLMEM as the principal analysis, but with jump to reference to impute missing data in months 1 to 3.

There were 6 secondary efficacy endpoints in this study. Type 1 error was controlled through the use of hierarchical testing. The significance of the primary endpoint was evaluated at the 0.05 level. If the

primary endpoint was significant, then the following secondary endpoints were tested hierarchically in a pre-specified order.

Results

Participant flow

Studies 301/302/303

Study completion was high across the 3 single attack studies 301/302/303 and dose arms (around 99% for rimegepant 75 mg and placebo). Subjects were given a 45-day period to treat 1 acute migraine attack. A migraine attack of moderate to severe intensity was not experienced in only very isolated cases during that time.

Table 26: Subject Disposition - Treated Subjects in Single-Dose Studies with Rimegepant 75 mg and Placebo - Phase 3 Studies BHV3000-301/302/303

	BHV3000-301		BHV3000-302		BHV3000-303	
Disposition: n (%)	Rimegepant 75mg (N=546)	Placebo (N=549)	Rimegepant 75mg (N=543)	Placebo (N=540)	Rimegepant 75mg (N=682)	Placebo (N=693)
Completed	541 (99.1)	540 (98.4)	538 (99.1)	539 (99.8)	679 (99.6)	689 (99.4)
Discontinued	5 (0.9)	9 (1.6)	5 (0.9)	1 (0.2)	3 (0.4)	4 (0.6)
Reason for discontinuation						
Lost to Follow-Up	4 (0.7)	7 (1.3)	2 (0.4)	1 (0.2)	3 (0.4)	1 (0.1)
Never Experienced Migraine (of Moderate to Severe Intensity)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Technical Problems	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by Subject	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)

Prophylaxis Study 305

Overall, 747 subjects were randomised, and 741 subjects were treated with rimegepant (370 subjects) or placebo (371 subjects) in the DBT phase. The reasons that 6 subjects were randomised but not treated were due to protocol deviations (2 rimegepant subjects and 2 placebo subjects) and lost to follow-up (1 rimegepant subject and 1 placebo subject).

There are no ongoing subjects in the DBT phase. The majority of treated subjects (626/741, 84.5%) completed the DBT phase. The most common reasons for the 115 treated subjects not completing the DBT phase were withdrawal by subject (11 rimegepant subjects and 22 placebo subjects), lost to follow-up (19 rimegepant subjects and 12 placebo subjects), and eligibility failure due to baseline laboratory values (8 rimegepant subjects and 13 placebo subjects).

Table 27: Subject Disposition in the Double-Blind Treatment Phase, Treated Subjects, Study 305

Disposition: n (%) Reason: n (%)	Rimegepant (N=370)	Placebo (N=371)	Overall (N=741)
Ongoing in double-blind treatment phase	0	0	0
Completed double-blind treatment phase	316 (85.4)	310 (83.6)	626 (84.5)
Did not complete double-blind treatment phase	54 (14.6)	61 (16.4)	115 (15.5)
Adverse event	5 (1.4)	2 (0.5)	7 (0.9)
Eligibility failure due to baseline laboratory values	8 (2.2)	13 (3.5)	21 (2.8)
Lack of efficacy	1 (0.3)	1 (0.3)	2 (0.3)
Lost to follow-up	19 (5.1)	12 (3.2)	31 (4.2)
Non-compliance	6 (1.6)	5 (1.3)	11 (1.5)
Physician decision	0	1 (0.3)	1 (0.1)
Protocol deviation	4 (1.1)	5 (1.3)	9 (1.2)
Withdrawal by subject	11 (3.0)	22 (5.9)	33 (4.5)
Continuing to open-label extension phase	302 (81.6)	302 (81.4)	604 (81.5)
Continuing to follow-up phase	34 (9.2)	25 (6.7)	59 (8.0)
Not continuing to follow-up phase	35 (9.5)	46 (12.4)	81 (10.9)
Lost to follow up	21 (5.7)	14 (3.8)	35 (4.7)
Not applicable; randomized, did not take study medication	0	1 (0.3)	1 (0.1)
Screen failure due to inclusion/exclusion criteria	0	2 (0.5)	2 (0.3)
Not Reported	0	2 (0.5)	2 (0.3)
Subject withdrew consent	14 (3.8)	29 (7.8)	43 (5.8)
Completed double-blind treatment phase and not continuing to open-label extension phase	16 (4.3)	11 (3.0)	27 (3.6)
Adverse event	1 (0.3)	0	1 (0.1)
Non-compliance	3 (0.8)	1 (0.3)	4 (0.5)
Other	0	4 (1.1)	4 (0.5)
Physician decision	0	1 (0.3)	1 (0.1)
Withdrawal by subject	11 (3.0)	5 (1.3)	16 (2.2)
Not Reported	1 (0.3)	0	1 (0.1)

Baseline data

Demographics – Single attack studies 301/302/303

In mITT subjects, the median age ranged from 38.9 to 41.5 years across treatment groups. Most subjects were female (84.9% to 89.2% across treatment groups) and white (73.4% to 82.1%). About 1% of subjects in all treatment groups had a CV risk contraindicating triptan use (range 0.4% to 1.2%). Almost half of the subjects (range 41.4% to 52.7% across treatment groups) had a BMI $\geq$ 30 kg/m^2. Aura symptoms were experienced by about one third of patients. About 14-17% of all subjects used concomitant non-study prophylactic migraine medication.

Table 28: Demographic and Baseline Characteristics – mITT Subjects in BHV3000-301, BHV3000-302, and BHV3000-303

	BHV3000-301		BHV3000-302		BHV3000-303	
	Rimegepant 75mg (N=543)	Placebo (N=541)	Rimegepant 75mg (N=537)	Placebo (N=535)	Rimegepant 75mg (N=669)	Placebo (N=682)
Age [years] at informed consent						
n	543	541	537	535	669	682
Mean (SD)	41.9 (12.33)	41.3 (12.14)	40.2 (11.87)	40.9 (12.12)	40.3 (12.08)	40.0 (11.87)
Median	41.5	41.3	39.1	40.4	39.7	38.9
Min, Max	19, 73	19, 71	18, 72	18, 84	18, 76	18, 72
Age [years] category at informed consent: n (%)						
< 40	249 (45.9)	253 (46.8)	287 (53.4)	263 (49.2)	343 (51.3)	368 (54.0)
>= 40	294 (54.1)	288 (53.2)	250 (46.6)	272 (50.8)	326 (48.7)	314 (46.0)
< 65	529 (97.4)	525 (97.0)	528 (98.3)	518 (96.8)	657 (98.2)	665 (97.5)
>= 65	14 (2.6)	16 (3.0)	9 (1.7)	17 (3.2)	12 (1.8)	17 (2.5)
Sex: n (%)						
Female	464 (85.5)	463 (85.6)	479 (89.2)	472 (88.2)	568 (84.9)	579 (84.9)
Male	79 (14.5)	78 (14.4)	58 (10.8)	63 (11.8)	101 (15.1)	103 (15.1)
Race: n (%)						
White	417 (76.8)	444 (82.1)	394 (73.4)	399 (74.6)	496 (74.1)	521 (76.4)
Black or African-American	107 (19.7)	80 (14.8)	111 (20.7)	118 (22.1)	141 (21.1)	125 (18.3)
Other Including Asian	19 (3.5)	17 (3.1)	32 (6.0)	18 (3.4)	30 (4.5)	36 (5.3)
BMI [kg/m2]						
n	543	541	537	535	668	680
Mean (SD)	30.15 (7.644)	29.77 (7.659)	30.94 (7.881)	31.87 (8.436)	31.12 (8.168)	30.64 (8.033)
Median	29.20	28.30	29.60	30.80	29.85	29.25
Min, Max	16.9, 61.1	15.8, 71.0	14.7, 67.6	17.7, 75.7	16.5, 63.8	15.1, 69.7
Aura at treated migraine attack onset: n (%)						
Presence	189 (34.8)	180 (33.3)	173 (32.2)	165 (30.8)	207 (30.9)	252 (37.0)
Absence	354 (65.2)	361 (66.7)	364 (67.8)	370 (69.2)	462 (69.1)	430 (63.0)
Historical number of moderate or severe migraine attacks per month: n (%)						
< 4	137 (25.2)	148 (27.4)	190 (35.4)	165 (30.8)	205 (30.6)	236 (34.6)
>= 4	406 (74.8)	393 (72.6)	347 (64.6)	370 (69.2)	464 (69.4)	446 (65.4)
Triptan non-responder: n (%)						
Yes	31 (5.7)	31 (5.7)	20 (3.7)	39 (7.3)	27 (4.0)	34 (5.0)
No	512 (94.3)	510 (94.3)	517 (96.3)	496 (92.7)	642 (96.0)	648 (95.0)
CV risk contraindicating triptans: n (%)						
Yes	5 (0.9)	2 (0.4)	4 (0.7)	5 (0.9)	8 (1.2)	5 (0.7)
No	538 (99.1)	539 (99.6)	533 (99.3)	530 (99.1)	661 (98.8)	677 (99.3)
Prophylactic migraine medication use: n (%)						
Yes	90 (16.6)	92 (17.0)	89 (16.6)	89 (16.6)	93 (13.9)	94 (13.8)
No	453 (83.4)	449 (83.0)	448 (83.4)	446 (83.4)	576 (86.1)	588 (86.2)

At screening, about one third of subjects was currently using triptans for the treatment of acute attacks. Triptans were prohibited as rescue in single attack studies 301/302/303 until the subject had completed all e-diary entries at 48 hours post-dose.

In terms of migraine history, mITT treatment groups both within and across studies were well balanced. The median number of moderate or severe pain intensity migraine attacks per month was 4.0 for all treatment groups. Across treatment groups, most subject's primary migraine type was migraine without aura (range 65.0% to 71.7%), and their MBS was photophobia (range 55.1% to 58.9%). The median onset of migraine was at about 19 years of age. Given the mean age of 40 years of included subjects, the mean duration of migraine history is about 20 years at study entry.

Prevention study 305

Of the 741 subjects treated in this study, 15 (2.0%) had been previously treated in one of the single-dose rimegepant acute treatment studies (BHV3000-301, BHV3000-302, or BHV3000-303): 2 subjects were from BHV3000-301 and 13 subjects were from BHV3000-303.

The median age was 40.0 years, the majority of subjects were female (83.0%), and most subjects were white (81.2%). With respect to their migraine disease history, evaluable mITT subjects of study 305 presented with a disease history of about 20 years (mean age about 40 years, age of onset about 18 years). The median number of moderate to severe migraine attacks per month was 8.0 (range: 4 to 18), and the median average duration of untreated migraine attacks was 24.0 hours. The typically MBS was photophobia (57.1%) and the primary migraine type was migraine without aura (60.1%). Of the evaluable subjects, 22.7% reported history of CM.

Table 29: Migraine History, Evaluable mITT Subjects, Study 305

History	Rimegepant (N=348)	Placebo (N=347)	Overall (N=695)
Age (years) at migraine onset			
n	348	347	695
Mean (SD)	21.5 (10.97)	21.1 (11.18)	21.3 (11.07)
Median	18.0	18.0	18.0
Min, Max	2, 48	2, 49	2, 49
Number of moderate to severe migraines per month			
n	348	347	695
Mean (SD)	7.8 (2.78)	7.9 (2.66)	7.8 (2.72)
Median	7.0	8.0	8.0
Min, Max	4, 16	4, 18	4, 18
Number of moderate to severe migraines per month category: n (%)			
< 6	81 (23.3)	68 (19.6)	149 (21.4)
>= 6	267 (76.7)	279 (80.4)	546 (78.6)
< 8	177 (50.9)	157 (45.2)	334 (48.1)
>= 8	171 (49.1)	190 (54.8)	361 (51.9)
< 12	296 (85.1)	309 (89.0)	605 (87.1)
>= 12	52 (14.9)	38 (11.0)	90 (12.9)
< 15	343 (98.6)	341 (98.3)	684 (98.4)
>= 15	5 (1.4)	6 (1.7)	11 (1.6)
Average duration of untreated migraine attacks (hours)			
n	348	347	695
Mean (SD)	29.9 (21.74)	28.0 (20.54)	28.9 (21.16)
Median	24.0	24.0	24.0
Min, Max	4, 72	4, 72	4, 72
Primary migraine type: n (%)			
Migraine without aura	206 (59.2)	212 (61.1)	418 (60.1)
Migraine with aura	142 (40.8)	135 (38.9)	277 (39.9)
Most bothersome symptom: n (%)			
Nausea	73 (21.0)	98 (28.2)	171 (24.6)
Photophobia	207 (59.5)	190 (54.8)	397 (57.1)
Phonophobia	68 (19.5)	59 (17.0)	127 (18.3)
History of chronic migraine: n (%)			
Yes	71 (20.4)	87 (25.1)	158 (22.7)
No	160 (46.0)	143 (41.2)	303 (43.6)
Not Reported	117 (33.6)	117 (33.7)	234 (33.7)

* Based on imputed last migraine date up to 1 year before informed consent date
\# Percentages are based on the number of subjects with a history of migraine with aura.
Evaluable subjects are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period and >= 1 month (4-week interval) in the Double-Blind Treatment Phase.

Numbers analysed

In the 3 pivotal acute treatment studies 303, 302, and 301, 1.771 subjects were treated with the proposed single rimegepant dose of 75 mg and 1.782 were treated with placebo. Of these, 1.749 rimegepant subjects and 1.758 placebo subjects were evaluable for efficacy (i.e., were mITT subjects).

Of the 747 randomised subjects in study 305 (6 of these were randomised twice), 695 were included in the evaluable mITT population. Reasons for exclusion from the evaluable mITT population include < 14 days of efficacy data in all 3 months in DBT phase (46 subjects) and not treated with DBT (6 subjects). Most (624/695; 89.8%) of evaluable mITT subjects completed the DBT phase.

Table 30: Inclusion and Exclusion from the Evaluable mITT Population Sample Randomised Subjects, Study 305

Reason: n (%)	Rimegepant (N=373)	Placebo (N=374)	Overall (N=747)
Inclusion in the evaluable mITT population sample	348 (93.3)	347 (92.8)	695 (93.0)
Exclusion from the evaluable mITT population sample	25 (6.7)	27 (7.2)	52 (7.0)
Not mITT	3 (0.8)	3 (0.8)	6 (0.8)
Not treated with DBT	3 (0.8)	3 (0.8)	6 (0.8)
Treated with DBT but randomized more than once	0	0	0
mITT but not evaluable	22 (5.9)	24 (6.4)	46 (6.2)
< 14 days of efficacy data in OP only	0	0	0
< 14 days of efficacy data in all 3 months in DBT Phase only	22 (5.9)	24 (6.4)	46 (6.2)
< 14 days of efficacy data in both OP and in all 3 months in DBT Phase	0	0	0

Evaluable subjects are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period (OP) and >=1 month (4-week interval) in the Double-Blind Treatment (DBT) Phase.

Outcomes and estimation

Single attack studies 301/302/303

Co-Primary Efficacy Endpoints

Significant efficacy was demonstrated on both of the co-primary endpoints of freedom from pain and freedom from MBS at 2 hours post-dose across the 3 single attack studies.

Table 31: Co-primary Efficacy Endpoints - mITT Subjects in Phase 3 Single-Dose Migraine Studies BHV3000-303, BHV3000-302, and BHV3000-301 with Rimegepant 75 mg and Placebo

		BHV3000-303		BHV3000-302		BHV3000-301	
Coprimary Endpoints	Statistic	Rimegepant 75 mg N = 669	Placebo N = 682	Rimegepant 75 mg N = 537	Placebo N = 535	Rimegepant 75 mg N = 543	Placebo N = 541
Pain freedom at 2 hours postdose	n/N	142/669	74/682	105/537	64/535	104/543	77/541
	Risk[a] (%)	21.2	10.9	19.6	12.0	19.2	14.2
	(95% CI)	(18.1, 24.3)	(8.5, 13.2)	(16.2, 22.9)	(9.2, 14.7)	(15.8, 22.5)	(11.3, 17.2)
	Risk difference[a,b] (%)	10.37	---	7.59	---	4.91	---
	(95% CI)	(6.5, 14.2)	---	(3.3, 11.9)	---	(0.5, 9.3)	---
	p-value	< 0.0001*	---	0.0006*	---	0.0298*	---
Freedom from most bothersome symptom at 2 hours postdose	n/N	235/669	183/682	202/537	135/535	199/543	150/541
	Risk[a] (%)	35.1	26.8	37.6	25.2	36.6	27.7
	(95% CI)	(31.5, 38.7)	(23.5, 30.2)	(33.5, 41.7)	(21.6, 28.9)	(32.6, 40.7)	(24.0, 31.5)
	Risk difference[a,b] (%)	8.29	---	12.38	---	8.90	---
	(95% CI)	(3.4, 13.2)	---	(6.9, 17.9)	---	(3.4, 14.4)	---
	p-value	0.0009*	---	< 0.0001*	---	0.0016*	---

*Statistically significant
[a]Risks (percentages) are calculated using Cochran-Mantel-Haenszel weights, stratified by use of prophylactic migraine medication.
[b]Risk difference is the difference in the percentage of subjects with a positive result for the rimegepant minus the placebo treatment groups.

Freedom from associated symptoms

The endpoint freedom from photophobia reflects complete relief of photophobia at 2 hours post-dose, irrespective of its categorisation as most bothersome relative to other associated symptoms that might have also been present. Across treatment arms, photophobia was reported to be present by 86-91% of

subjects. Phonophobia was reported to be present at the onset of a migraine attack by 63-70% of subjects. Consistent superiority over placebo could be shown for freedom of photophobia and phonophobia at 2 hours post-dose across the 3 single attack studies.

Nausea is the least common of the cardinal associated symptoms of migraine and, as a result, power for detecting differences in nausea freedom in individual clinical trials is relatively low. Results from the 3 pivotal studies show a consistent advantage of rimegepant over placebo, with the therapeutic gains in those studies ranging from 4.76% to 5.87%. Since nausea is only analysed in subjects that present with that symptom at the start of the treated migraine, the sample size is limited to roughly 60% of the mITT population. Hence, tests on nausea were underpowered in the individual pivotal studies. After statistical significance could not be shown for freedom from nausea at 2 post-dose, all endpoints listed afterwards in the hierarchy were not considered statistically significant in either study.

Table 32: Summary of Secondary endpoint, Freedom from nausea at 2 hours post-dose, mITT Subjects, Single attack studies 301/302/303

Secondary endpoint	Statistic	BHV3000-301		BHV3000-302		BHV3000-303	
		Rimegepant 75 mg N=543	Placebo N=541	Rimegepant 75 mg N=537	Placebo N=535	Rimegepant 75 mg N=669	Placebo N=682
Freedom from nausea at 2 hours post-dose	n/N	149/318	134/322	171/355	145/336	203/397	194/430
	Risk[a] (%)	46.9	41.6	48.1	43.3	51.0	45.2
	(95% CI)	(41.4, 52.3)	(36.2, 47.0)	(42.9, 53.3)	(38.0, 48.6)	(46.1, 55.9)	(40.5, 49.9)
	Risk difference[a,b](%)	5.24	--	4.76	--	5.87	--
	(95% CI)	(-2.4, 12.9)	--	(-2.7, 12.2)	--	(-0.9, 12.7)	--
	p-value	0.1815	--	0.2084	--	0.0898	--

* = Statistically significant; [a]Risks (percentages) are calculated using Cochran-Mantel-Haenszel weights, stratified by use of prophylactic migraine medication. [b]Risk difference is the difference in the percentage of subjects with a positive result for the rimegepant minus the placebo treatment groups.

Sustained pain freedom from 2-24 hours, and from 2-48 hours post-dose

Table 33: Summary of Secondary endpoint, Sustained Pain freedom from 2 to 24 hours post-dose, mITT Subjects, Single attack studies 301/302/303

Secondary endpoint	Statistic	BHV3000-301		BHV3000-302		BHV3000-303	
		Rimegepant 75 mg N=543	Placebo N=541	Rimegepant 75 mg N=537	Placebo N=535	Rimegepant 75 mg N=669	Placebo N=682
Sustained Pain freedom from 2 to 24 hours post-dose	n/N	76/543	44/541	66/537	38/535	105/669	38/682
	Risk[a] (%)	14.0	8.1	12.3	7.1	15.7	5.6
	(95% CI)	(11.1, 16.9)	(5.8, 10.4)	(9.5, 15.1)	(4.9, 9.3)	(12.9, 18.4)	(3.9, 7.3)
	Risk difference[a,b](%)	5.86	--	5.19	--	10.12	--
	(95% CI)	(2.1, 9.6)	--	(1.7, 8.7)	--	(6.9, 13.4)	--
	p-value	0.0020	--	0.0040	--	<0.0001*	--

* = Statistically significant; [a]Risks (percentages) are calculated using Cochran-Mantel-Haenszel weights, stratified by use of prophylactic migraine medication. [b]Risk difference is the difference in the percentage of subjects with a positive result for the rimegepant minus the placebo treatment groups.

Table 34: Summary of Secondary endpoint, Sustained Pain freedom from 2 to 48 hours post-dose, mITT Subjects, Single attack studies 301/302/303

Secondary endpoint	Statistic	BHV3000-301		BHV3000-302		BHV3000-303	
		Rimegepant 75 mg N=543	Placebo N=541	Rimegepant 75 mg N=537	Placebo N=535	Rimegepant 75 mg N=669	Placebo N=682
Sustained Pain freedom from 2 to 48 hours post-dose	n/N	63/543	39/541	53/537	32/535	90/669	37/682
	Risk[a] (%)	11.6	7.2	9.9	6.0	13.5	5.4
	(95% CI)	(8.9, 14.3)	(5.0, 9.4)	(7.3, 12.4)	(4.0, 8.0)	(10.9, 16.0)	(3.7, 7.1)
	Risk difference[a,b](%)	4.39	--	3.89	--	8.02	--
	(95% CI)	(0.9, 7.8)	--	(0.7, 7.1)	--	(4.9, 11.1)	--
	p-value	0.0130	--	0.0181	--	<0.0001*	--

* = Statistically significant; [a]Risks (percentages) are calculated using Cochran-Mantel-Haenszel weights, stratified by use of prophylactic migraine medication. [b]Risk difference is the difference in the percentage of subjects with a positive result for the rimegepant minus the placebo treatment groups.

Prevention study 305

Primary efficacy endpoint

Subjects are instructed to report headache status (yes, no), severity (mild, moderate, severe, none), and characteristics (e.g., aura, nausea, vomiting), as well as medication taken to treat headache or during aura, in the eDiary evening report headache log or follow-up headache log recorded every day in the OP, DBT, and OLE phases.

Migraine days per month will be assessed as "migraine days per 4 weeks" to correspond with the 4-week visit schedule. Migraine days per month are based on data from the previous visit to the current visit (i.e., 4-week interval), and are prorated to account for missing migraine reports.

The number of migraine days per month in the DBT phase will be examined relative to the number of migraine days per month in the OP for evaluable mITT subjects, i.e., subjects with $\geq$ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP analysis period and $\geq$ 1 month (i.e., 4-week interval) in the on-DBT analysis period.

Rimegepant at a dose of 75 mg EOD demonstrated superiority to placebo on the primary endpoint of change from the OP in the mean number of migraine days per month on treatment in the last month (Weeks 9 to 12) of the DBT phase in evaluable mITT subjects. The difference (therapeutic gain) between treatment groups (i.e., rimegepant – placebo) was -0.8 days (- 4.3 days for rimegepant and – 3.5 days for placebo; p = 0.0099) (principal analysis using GLMEM).

Table 35: Primary Endpoint on Double blind Treatment – Evaluable mITT Subjects, Study BHV3000-305

	Rimegepant N = 348	Placebo N = 347
Primary Endpoint		
Change from OP in Mean Number of Total Migraine Days per Month in the Last Month of the DBT Phase (Weeks 9 through 12)[a]		
n	348	347
Least-squares mean (95% CI)	- 4.3 (- 4.83, - 3.87)	- 3.5 (- 4.00, - 3.04)
Difference from placebo (95% CI)	- 0.8 (- 1.46, - 0.20)	---
p-value	0.0099*	---

Evaluable subjects were those with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and ≥ 1 month (4-week interval) in the DBT phase.

* Significant p-value in hierarchical testing

[a] GLMEM: change from OP in number of total migraine days per month is dependent variable; subject is random effect; number of total migraine days per month in OP is covariate; treatment group, prophylactic migraine medication use at randomization, month, and month-by-treatment group interaction are fixed effects.

If the sensitivity analysis applying GLMEM but with Jump-to-Reference to impute missing data, the net difference between rimegepant and placebo in evaluable mITT subjects in terms of MD reduction throughout the last 4 weeks (wk 9-12) of the DBT is diminished to -0.7 MDs (p=0.0400), as compared to the primary GLMEM analysis yielding a net difference of -0.8 MDs (p=0.0099).

Table 36: Total Migraine Days per Month Changes from the Observation Period Over Time on Double-Blind Treatment Estimated Using GLMEM: Sensitivity Analysis (Jump to Reference), Evaluable mITT Subjects, Study 305

Randomization Stratum Time Interval	Statistic	Rimegepant (N=348)	Placebo (N=347)	Difference (Rimegepant - Placebo)
Overall	n	348	347	
Month 1 (<= 4 weeks) *	Least-squares mean (SE)	-3.5 (0.59)	-2.4 (0.58)	-1.2 (0.29)
	95% CI	(-4.69, -2.40)	(-3.50, -1.22)	(-1.74, -0.62)
	P-value			<.0001
Month 2 (> 4 to <= 8 weeks) *	Least-squares mean (SE)	-3.7 (0.65)	-3.3 (0.64)	-0.5 (0.32)
	95% CI	(-5.00, -2.47)	(-4.54, -2.02)	(-1.08, 0.17)
	P-value			0.1553
Month 3 (> 8 to <= 12 weeks) *	Least-squares mean (SE)	-4.7 (0.65)	-4.0 (0.65)	-0.7 (0.32)
	95% CI	(-5.94, -3.39)	(-5.27, -2.73)	(-1.29, -0.03)
	P-value			0.0400

Evaluable subjects are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period (OP) and >= 1 month (4-week interval) in the Double-Blind Treatment Phase.
* Subjects must have >= 14 days of eDiary efficacy data (not necessarily consecutive) in the month.
Generalized linear mixed effects model (GLMEM): change from OP in number of total migraine days per month is dependent variable; subject is random effect; number of total migraine days per month in OP is covariate; treatment group, age, sex, race, prophylactic migraine medication use at randomization, month, and month-by-treatment group interaction are fixed effects.

During the OP subjects experienced 10.3 (rimegepant) resp. 9.9 (placebo) MDs. In both arms, the number of MDs per 28-day assessment period decreases constantly per month throughout the 12-week DBT period. In terms of percent reduction, the number of MDs was reduced by -50.3% in rimegepant subjects, while placebo subjects achieved to reduce the mean number of MDs from week 9-12 by -41.7%. The overall net difference of -0.7 MDs per month between rimegepant and placebo corresponds to less than 10% of the number of MDs experienced at baseline.

The applicant specified that subjects must have $\geq$ 14 days of efficacy data (not necessarily consecutive) in the specified month to be counted as mITT evaluable. The portion of subjects not considered mITT evaluable due to less than 14 days of eDiary efficacy data in any of the 3 treatment months (28 day intervals) was about equally distributed across arms (rimegepant 5.9%, placebo 6.5%).

Table 37: Missing Migraine Efficacy Data on Double-Blind Treatment, mITT Subjects, Study 305

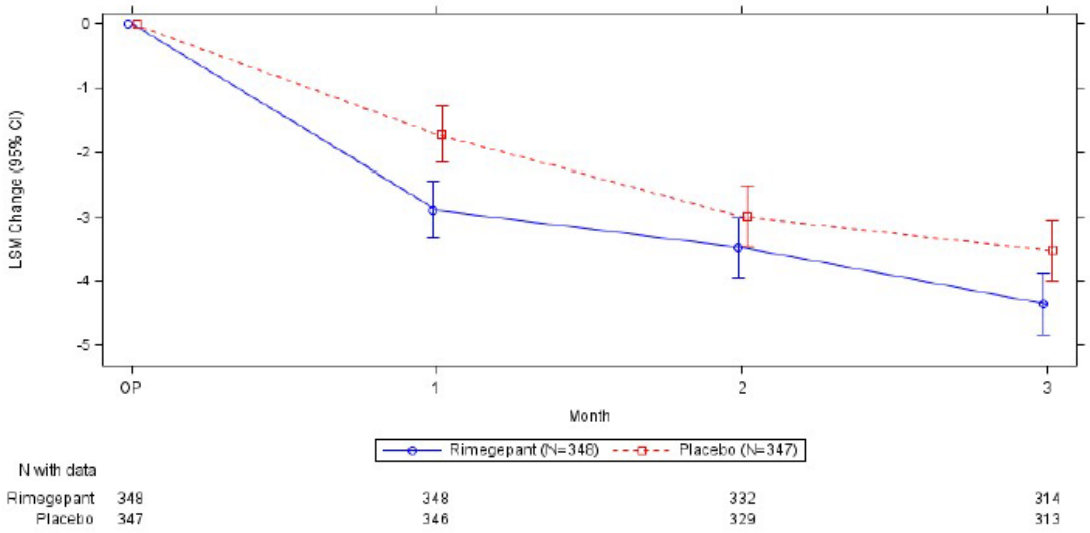
Category: n (%)	Rimegepant (N=370)	Placebo (N=371)
Evaluable	348 (94.1)	347 (93.5)
Month 1 (<= 4 weeks) *	348 (94.1)	346 (93.3)
Month 2 (> 4 to <= 8 weeks) *	332 (89.7)	329 (88.7)
Month 3 (> 8 to <= 12 weeks) *	314 (84.9)	313 (84.4)
Not evaluable	22 (5.9)	24 (6.5)
< 14 days of efficacy data in OP only	0	0
< 14 days of efficacy data in all 3 months in the DBT Phase only	22 (5.9)	24 (6.5)
< 14 days of efficacy data in both OP and all 3 months in the DBT Phase	0	0

Evaluable subjects are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period (OP) and >= 1 month (4-week interval) in the Double-Blind Treatment (DBT) Phase.
* Subjects must have >= 14 days of eDiary efficacy data (not necessarily consecutive) in the month.

Total Migraine Days over time

Consistent with the primary analysis demonstrating the efficacy of rimegepant during the last month of the DBT phase, rimegepant also displayed statistically significant superiority over placebo on the reduction in MDs per month over the entire 12-week DBT phase (- 3.6 days for rimegepant and – 2.7 days for placebo; p = 0.0017).

Figure 12: Longitudinal Plot of Total Migraine Days per Month LS Mean Change From the Observational Period Over Time on Double-Blind Treatment - Evaluable mITT Subjects, Study 305



Evaluable subjects are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period (OP) and >= 1 month (4-week interval) in the Double-Blind Treatment Phase.

Use of rescue

Throughout the 12-week DBT period, subjects could use their individual rescue medication (incl. triptans, NSAIDs, antiemetics) in case an acute migraine attack occurred despite preventive study medication. Across arms and the three 28-day treatment intervals of the DBT, subjects used rescue on a mean of about 4-5 days per month. Rimegepant did not significantly separate from placebo in any of the three 28-day intervals of the DBT in terms of rescue medication use.

Table 38: Rescue Medication Days per Month Over Time on Double-Blind Treatment Estimated Using GLMEM Evaluable mITT Subjects, Study 305

Randomization Stratum Time Interval	Statistic	Rimegepant (N=348)	Placebo (N=347)	Difference (Rimegepant - Placebo)
Overall	n	348	347	
Month 1 (<= 4 weeks) *	Least-squares mean (SE)	4.6 (0.22)	5.0 (0.22)	-0.4 (0.29)
	95% CI	(4.21, 5.08)	(4.58, 5.45)	(-0.94, 0.19)
	P-value			0.1973
Month 2 (> 4 to <= 8 weeks) *	Least-squares mean (SE)	4.2 (0.23)	4.4 (0.23)	-0.2 (0.30)
	95% CI	(3.74, 4.64)	(3.94, 4.83)	(-0.78, 0.40)
	P-value			0.5209
Month 3 (> 8 to <= 12 weeks) *	Least-squares mean (SE)	3.7 (0.22)	4.0 (0.22)	-0.2 (0.28)
	95% CI	(3.29, 4.15)	(3.53, 4.39)	(-0.80, 0.31)
	P-value			0.3868
Overall Double-Blind Treatment Mean	Least-squares mean (SE)	4.2 (0.20)	4.5 (0.20)	-0.3 (0.26)
	95% CI	(3.78, 4.58)	(4.06, 4.85)	(-0.78, 0.24)
	P-value			0.2998

Evaluable subjects are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period and >= 1 month (4-week interval) in the Double-Blind Treatment Phase.
* Subjects must have >= 14 days of eDiary efficacy data (not necessarily consecutive) in the month.
Generalized linear mixed effects model (GLMEM): number of rescue medication days per month is dependent variable; subject is random effect; treatment group, prophylactic migraine medication use at randomization, month, and month-by-treatment group interaction are fixed effects.

50% Reduction in MDs Responder analysis

A responder analysis was conducted to examine the portion of subjects achieving a 50% reduction in monthly MDs. It could be shown that 49.1% of rimegepant subjects achieved a ≥ 50% reduction in the mean number of moderate or severe MDs per month in the last month of the DBT phase, compared to 41.5% of placebo subjects, which was statistically significant (p = 0.0438).

Table 39:≥ 50% Reduction in moderate or severe MDs per month in week 9-12 of double-blind Treatment – Evaluable mITT Subjects, Study 305

≥ 50% Reduction from OP in Mean Number of Moderate or Severe Migraine Days per Month in the Last Month of the DBT Phase (Weeks 9 – 12)		
Response rate (n/N)	171/348	144/347
Stratified risk[b] (95% CI)	49.1 (43.9, 54.3)	41.5 (36.3, 46.7)
Difference from placebo (95% CI)	7.6 (0.2, 14.9)	---
p-value	0.0438*	---

Evaluable subjects were those with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and ≥ 1 month (4-week interval) in the DBT.

* Significant p-value in hierarchical testing

[b] Stratified by prophylactic migraine medication use at randomization using Cochran-Mantel Haenszel weighting.

MIDAS Score

The MIDAS Migraine Disability Assessment score retrospectively reflects on how many days a patient was negatively affected by migraine throughout the preceding 3 months period. Results are presented for those subjects reporting the MIDAS score at baseline and at the end of the 3 months DBT. Baseline mean MIDAS scores were 36.9 in the rimegepant group and 35.3 in placebo patients. Rimegepant numerically hardly separated from placebo in reducing migraine-related disability (MIDAS: rimepgepant: -11.8, placebo -11.7, p=0.9616).

Table 40: MIDAS Total Score and Change from Baseline at Week 12 on Double-Blind Treatment Estimated Using GLM Evaluable mITT Subjects with MIDAS Total Scores at Both Baseline and Week 12, Study 305

Randomization Stratum	Statistic	Rimegepant (N=269)	Placebo (N=266)	Difference (Rimegepant - Placebo)
Overall				
	n	269	266	
	Least-squares mean (SE)	-11.8 (1.83)	-11.7 (1.83)	-0.1 (2.35)
	95% CI	(-15.41, -8.21)	(-15.29, -8.10)	(-4.74, 4.51)
	P-value			0.9616
Prophylactic Migraine Medication Use: Yes				
	n	60	62	
	Least-squares mean (SE)	-9.6 (4.53)	-12.7 (4.45)	3.1 (6.42)
	95% CI	(-18.55, -0.61)	(-21.50, -3.86)	(-9.61, 15.81)
	P-value			0.6300
Prophylactic Migraine Medication Use: No				
	n	209	204	
	Least-squares mean (SE)	-14.8 (1.68)	-12.7 (1.70)	-2.0 (2.39)
	95% CI	(-18.08, -11.48)	(-16.09, -9.41)	(-6.73, 2.66)
	P-value			0.3954

Evaluable subjects are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period and >= 1 month (4-week interval) in the Double-Blind Treatment Phase.
* Generalized linear model (GLM): Week 12 change from baseline in total score is dependent variable; baseline total score is covariate; treatment group and prophylactic migraine medication use at randomization are fixed effects.

Subgroup analyses

A number of subgroup analyses were conducted. Factors like age, sex, BMI, number of baseline MDs (<14 or ≥ 14 MDs), history of CM did not impact on the outcome for the primary endpoint. However, subjects recruited for study 305 were stratified according to concomitant prophylactic migraine medication yes or no. In the subgroup of subjects receiving concomitant non-study migraine prophylactic medication (rimegepant arm: 75/348, 21.6%), rimegepant numerically hardly separated from placebo. Throughout the last period of the DBT (week 9-12) subjects with non-study preventive medication reduced the mean number of MDs by -3.5 in the rimegepant arm as compared to a reduction of -3.4 (p=0.8993) in the placebo arm.

Table 41: Total Migraine Days per Month Changes from the Observation Period Over Time on Double-Blind Treatment Estimated Using GLMEM: Sensitivity Analysis (Jump to Reference), Evaluable mITT Subjects stratified according to prophylactic medication, Study 305

Randomization Stratum Time Interval	Statistic	Rimegepant (N=348)	Placebo (N=347)	Difference (Rimegepant - Placebo)
Prophylactic Migraine Medication Use: Yes	n	75	78	
Month 1 (<= 4 weeks) *	Least-squares mean (SE) 95% CI P-value	-3.6 (1.31) (-6.19, -1.06)	-1.8 (1.28) (-4.33, 0.68)	-1.8 (0.65) (-3.09, -0.50) 0.0067
Month 2 (> 4 to <= 8 weeks) *	Least-squares mean (SE) 95% CI P-value	-4.0 (1.33) (-6.63, -1.42)	-3.2 (1.30) (-5.71, -0.63)	-0.9 (0.67) (-2.19, 0.48) 0.2057
Month 3 (> 8 to <= 12 weeks) *	Least-squares mean (SE) 95% CI P-value	-3.5 (1.40) (-6.26, -0.75)	-3.4 (1.37) (-6.10, -0.73)	-0.1 (0.72) (-1.52, 1.33) 0.8993
Prophylactic Migraine Medication Use: No	n	273	269	
Month 1 (<= 4 weeks) *	Least-squares mean (SE) 95% CI P-value	-3.7 (0.61) (-4.93, -2.53)	-2.7 (0.61) (-3.89, -1.50)	-1.0 (0.32) (-1.66, -0.41) 0.0013
Month 2 (> 4 to <= 8 weeks) *	Least-squares mean (SE) 95% CI P-value	-4.1 (0.69) (-5.43, -2.72)	-3.7 (0.69) (-5.06, -2.35)	-0.4 (0.37) (-1.09, 0.35) 0.3147
Month 3 (> 8 to <= 12 weeks) *	Least-squares mean (SE) 95% CI P-value	-5.2 (0.68) (-6.49, -3.82)	-4.3 (0.68) (-5.65, -2.99)	-0.8 (0.36) (-1.54, -0.12) 0.0216

Evaluable subjects are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period (OP) and >= 1 month (4-week interval) in the Double-Blind Treatment Phase.
* Subjects must have >= 14 days of eDiary efficacy data (not necessarily consecutive) in the month.
Generalized linear mixed effects model (GLMEM): change from OP in number of total migraine days per month is dependent variable; subject is random effect; number of total migraine days per month in OP is covariate; treatment group, age, sex, race, prophylactic migraine medication use at randomization, month, and month-by-treatment group interaction are fixed effects.

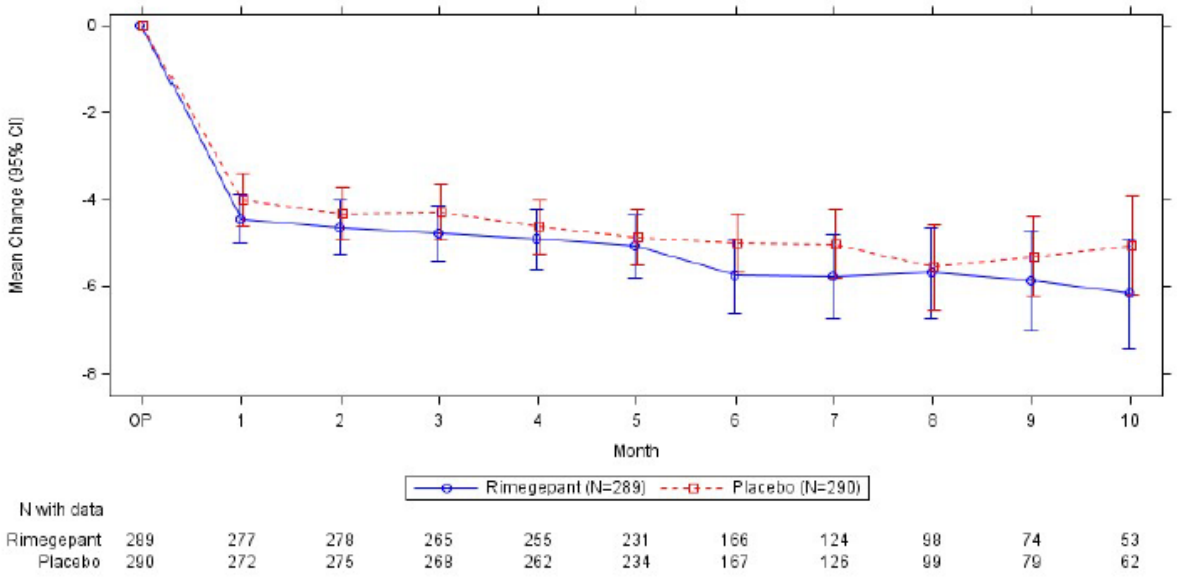
Open-label Extension Phase, Study 305 OLE

At the completion of the 12-week DBT phase, subjects could enter into the 52-week OLE phase (Weeks 13 through 64) if they continued to meet study entry criteria and laboratory test results were acceptable per protocol. The 52-week OLE period of study 305 was still ongoing at the time of dossier submission. Carry-over to OLE from the DBT period was high. The vast majority of evaluable mITT subjects (rimegepant: 302/348 [86.8%], placebo: 301/347 [86.7%]) continued treatment and entered the OLE period.

During the OLE phase, subjects were instructed to take one tablet of rimegepant 75 mg every other calendar day. If subjects had a migraine on a day that they were not scheduled to dose with rimegepant, they could take one tablet of rimegepant 75 mg on that calendar day to treat a migraine. Therefore, during the OLE phase, subjects could take a maximum of one rimegepant 75 mg tablet per calendar day for this 52-week period. Contrary to the DBT, triptans were not allowed as rescue during the OLE.

The figure below displays the mean change in total MDs per month data for open-label evaluable rimegepant mITT subjects.

Figure 13: Longitudinal Plot of Total Migraine Days per Month Mean Change From the Observational Period Over Time on Open-Label Rimegepant - Open-Label Rimegepant Evaluable mITT Subjects



Evaluable subjects are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period (OP) and >= 1 month (4-week interval) in the Open-Label Extension Phase.
Rimegepant and placebo groups based on double-blind treatment assignment

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 42: Summary of efficacy for Study 301

Title: A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine			
Study identifier	BHV3000-301 clinicaltrials.gov: NCT 03235479		
Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel study of a single migraine attack that assessed rimegepant 75 mg (administered as tablet) vs placebo. Patients were to take study drug when they had a migraine headache of at least moderate severity that was not improving. There was no option of a second dose of study medication. If required, subjects could take allowed rescue medication per Protocol.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment period could last up to 45 days or until the subject had a migraine attack of at least moderate severity not applicable not applicable	
Hypothesis	Superiority		
Treatments groups Total N=1.095 / 1084 (treated / evaluable)	Placebo (PBO)	541 evaluable	
	Rimegepant (RGP) 75mg	543 evaluable	
Endpoints and definitions	Primary endpoint	Pain freedom	Proportion of patients who were pain free at 2 hours following initial dose
	Co-Primary endpoint	Freedom from most bothersome symptom (MBS; as identified by the individual from the associated symptoms of nausea, phonophobia, and photophobia)	Proportion of patients who were MBS free at 2 hours following initial dose
	Secondary endpoints	Pain relief	Proportion of patients with pain relief at 2 hours following initial dose
		Sustained pain freedom at 24 hours or 48 hours	Proportion of patients who were pain free at 2 hours following initial dose and again at 24 hours or 48 hours without use of any rescue medication
Database lock	01 March 2018		

<u>Results and Analysis</u>

Analysis description	**Primary endpoint: Pain freedom at 2 hours after dose**		
Population/time point	Modified Intent to treat (mITT)		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg, N=543	Placebo, N=541
	Patients pain free at 2h, Risk[a], % (95% CI)	19.2 (15.8, 22.5)	14.2 (11.3, 17.2)
	Risk difference[a,b] (95% CI) vs PBO	4.91 (0.5, 9.3)	-
	P-value	0.0298*	-
Analysis description	**Co-primary endpoint: MBS freedom at 2 h after dose**		

Population/time point	Modified Intent to treat (mITT)		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg, N=543	Placebo, N=541
	Patients MBS free at 2h, Risk[a], % (95% CI))	36.6 (32.6, 40.7)	27.7 (24.0, 31.5)
	Risk difference[a,b] (95% CI) vs placebo	8.90 (3.4, 14.4)	-
	P-value	0.0016*	-
Notes	* = Statistically significant [a]Risks (percentages) are calculated using Cochran-Mantel-Haenszel weights, stratified by use of prophylactic migraine medication. [b]Risk difference is the difference in the percentage of subjects with a positive result for the rimegepant minus the placebo treatment groups.		
Analysis description	**Secondary endpoint: Pain relief at 2 hours after dose**		
Population/time point	Modified Intent to treat (ITT)		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg, N=543	Placebo, N=541
	Patients with pain relief at 2 h, Risk[a] %	56.0 (51.8, 60.2)	45.7 (41.5, 49.9)
	Risk difference[a,b] (95% CI) vs placebo	10.30 (4.4, 16.2)	-
	P-value vs PBO	0.0006*	-
Analysis description	**Other secondary endpoint: Sustained pain freedom**		
Population/time point	Modified Intent to treat (mITT)		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg N=543	Placebo N=541
	Patients with sustained pain freedom at 24 hours, Risk[a], % (95% CI)	14.0 (11.1, 16.9)	8.1 (5.8, 10.4)
	Risk difference[a,b] (95% CI) vs placebo	5.86 (2.1, 9.6)	-
	P-value	0.0020	-
	Patients with sustained pain freedom at 48 hours, Risk[a] (%)	11.6 (8.9, 14.3)	7.2 (5.0, 9.4)
	Risk difference[a,b] (95% CI) vs placebo	4.39 (0.9, 7.8)	-
	P-value vs PBO	0.0130	-
Notes	* = Statistically significant [a]Risks (percentages) are calculated using Cochran-Mantel-Haenszel weights, stratified by use of prophylactic migraine medication. [b]Risk difference is the difference in the percentage of subjects with a positive result for the rimegepant minus the placebo treatment groups.		

Table 43: Summary of efficacy for Study 302

Title: A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine	
Study identifier	BHV3000-302 clinicaltrials.gov: NCT 03237845

Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel study of a single migraine attack that assessed rimegepant 75 mg (administered as tablet) vs placebo. Patients were to take study drug when they had a migraine headache of at least moderate severity that was not improving. There was no option of a second dose of study medication. If required, subjects could take allowed rescue medication per Protocol.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment period could last up to 45 days or until the subject had a migraine attack of at least moderate severity not applicable not applicable	
Hypothesis	Superiority		
Treatments groups Total N=1.083 / 1.072 (treated / evaluable)	Placebo (PBO)	535 evaluable	
	Rimegepant (RGP) 75mg	537 evaluable	
Endpoints and definitions	Primary endpoint	Pain freedom	Proportion of patients who were pain free at 2 hours following initial dose
	Co-Primary endpoint	Freedom from most bothersome symptom (MBS; as identified by the individual from the associated symptoms of nausea, phonophobia, and photophobia)	Proportion of patients who were MBS free at 2 hours following initial dose
	Secondary endpoints	Pain relief	Proportion of patients with pain relief at 2 hours following initial dose
		Sustained pain freedom at 24 hours or 48 hours	Proportion of patients who were pain free at 2 hours following initial dose and again at 24 hours or 48 hours without use of any rescue medication
Database lock	06 March 2018		

Results and Analysis

Analysis description	**Primary endpoint: Pain freedom at 2 hours after dose**		
Population/time point	Modified Intent to treat (mITT)		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg, N=537	Placebo, N=535
	Patients pain free at 2h, Risk[a], % (95% CI)	19.6 (16.2, 22.9)	12.0 (9.2, 14.7)
	Risk difference[a,b] (95% CI) vs PBO	7.59 (3.3, 11.9)	-
	P-value	0.0006*	-
Analysis description	**Co-primary endpoint: MBS freedom at 2 h after dose**		
Population/time point	Modified Intent to treat (mITT)		
	Treatment group	Rimegepant 75 mg, N=537	Placebo, N=535

Descriptive statistics, estimate variability, and estimate of effect	Patients MBS free at 2h, Risk[a], % (95% CI))	37.6 (33.5, 41.7)	25.2 (21.6, 28.9)
	Risk difference[a,b] (95% CI) vs placebo vs PBO	12.38 (6.9, 17.9)	-
	P-value	<0.0001*	-
Notes	* = Statistically significant [a]Risks (percentages) are calculated using Cochran-Mantel-Haenszel weights, stratified by use of prophylactic migraine medication. [b]Risk difference is the difference in the percentage of subjects with a positive result for the rimegepant minus the placebo treatment groups.		
Analysis description	**Secondary endpoint: Pain relief at 2 hours after dose**		
Population/time point	Modified Intent to treat (ITT)		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg, N=537	Placebo, N=535
	Patients with pain relief at 2 h, Risk[a] %	58.1 (53.9, 62.3)	42.8 (38.6, 47.0)
	Risk difference[a,b] (95% CI) vs placebo	15.29 (9.4, 21.2)	-
	P-value vs PBO	<0.0001*	-
Analysis description	**Other secondary endpoint: Sustained pain freedom**		
Population/time point	Modified Intent to treat (mITT)		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg N=537	Placebo N=535
	Patients with sustained pain freedom at 24 hours, Risk[a], % (95% CI)	12.3 (9.5, 15.1)	7.1 (4.9, 9.3)
	Risk difference[a,b] (95% CI) vs placebo	5.19 (1.7, 8.7)	-
	P-value	0.0040	-
	Patients with sustained pain freedom at 48 hours, Risk[a] (%)	9.9 (7.3, 12.4)	6.0 (4.0, 8.0)
	Risk difference[a,b] (95% CI) vs placebo vs PBO	3.89 (0.7, 7.1)	-
	P-value vs PBO	0.0181	-
Notes	* = Statistically significant [a]Risks (percentages) are calculated using Cochran-Mantel-Haenszel weights, stratified by use of prophylactic migraine medication. [b]Risk difference is the difference in the percentage of subjects with a positive result for the rimegepant minus the placebo treatment groups.		

Table 44: Summary of efficacy for Study 303

Title: A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Migraine

Study identifier	BHV3000-303 clinicaltrials.gov: NCT 03461757		
Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel study of a single migraine attack that assessed rimegepant 75 mg (administered as ODT, sublingually) vs placebo. Patients were to take study drug when they had a migraine headache of at least moderate severity that was not improving. There was no option of a second dose of study medication. If required, subjects could take allowed rescue medication per Protocol.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment period could last up to 45 days or until the subject had a migraine attack of at least moderate severity not applicable not applicable	
Hypothesis	Superiority		
Treatments groups Total N=1.375 / 1.351 (treated / evaluable)	Placebo (PBO)	682 evaluable	
	Rimegepant (RGP) 75mg	669 evaluable	
Endpoints and definitions	Primary endpoint	Pain freedom	Proportion of patients who were pain free at 2 hours following initial dose
	Co-Primary endpoint	Freedom from most bothersome symptom (MBS; as identified by the individual from the associated symptoms of nausea, phonophobia, and photophobia)	Proportion of patients who were MBS free at 2 hours following initial dose
	Secondary endpoints	Pain relief	Proportion of patients with pain relief at 2 hours following initial dose
		Sustained pain freedom at 24 hours or 48 hours	Proportion of patients who were pain free at 2 hours following initial dose and again at 24 hours or 48 hours without use of any rescue medication
Database lock	21 Nov 2018		

Results and Analysis

Analysis description	**Primary endpoint: Pain freedom at 2 hours after dose**		
Population/time point	Modified Intent to treat (mITT)		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg, N=669	Placebo, N=682
	Patients pain free at 2h, Risk[a], % (95% CI)	21.2 (18.1, 24.3)	10.9 (8.5, 13.2)
	Risk difference[a,b] (95% CI) vs PBO	10.37 (6.5, 14.2)	-
	P-value	<0.0001*	-
Analysis description	**Co-primary endpoint: MBS freedom at 2 h after dose**		
Population/time point	Modified Intent to treat (mITT)		

Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg, N=669	Placebo, N=682
	Patients MBS free at 2h, Risk[a], % (95% CI))	35.1 (31.5, 38.7)	26.8 (23.5, 30.2)
	Risk difference[a,b] (95% CI) vs placebo vs PBO	8.29 (3.4, 13.2)	-
	P-value	<0.0009*	-
Notes	* = Statistically significant [a]Risks (percentages) are calculated using Cochran-Mantel-Haenszel weights, stratified by use of prophylactic migraine medication. [b]Risk difference is the difference in the percentage of subjects with a positive result for the rimegepant minus the placebo treatment groups.		
Analysis description	**Secondary endpoint: Pain relief at 2 hours after dose**		
Population/time point	Modified Intent to treat (ITT)		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg, N=669	Placebo, N=682
	Patients with pain relief at 2 h, Risk[a] %	59.3 (55.6, 63.1)	43.3 (39.5, 47.0)
	Risk difference[a,b] (95% CI) vs placebo	16.09 (10.8, 21.3)	-
	P-value vs PBO	<0.0001*	-
Analysis description	**Other secondary endpoint: Sustained pain freedom**		
Population/time point	Modified Intent to treat (mITT)		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg N=669	Placebo, N=682
	Patients with sustained pain freedom at 24 hours, Risk[a], % (95% CI)	15.7 (12.9, 18.4)	5.6 (3.9, 7.3)
	Risk difference[a,b] (95% CI) vs placebo	10.12 (6.9, 13.4)	-
	P-value	<0.0001*	-
	Patients with sustained pain freedom at 48 hours, Risk[a] (%)	13.5 (10.9, 16.0)	5.4 (3.7, 7.1)
	Risk difference[a,b] (95% CI) vs placebo vs PBO	8.02 (4.9, 11.1)	-
	P-value vs PBO	<0.0001*	-
Notes	* = Statistically significant [a]Risks (percentages) are calculated using Cochran-Mantel-Haenszel weights, stratified by use of prophylactic migraine medication. [b]Risk difference is the difference in the percentage of subjects with a positive result for the rimegepant minus the placebo treatment groups.		

Table 45: Summary of efficacy for Study 305

Title: A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention			
Study identifier	BHV3000-305 clinicaltrials.gov: NCT03732638		
Design	Phase 2/3, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of rimegepant 75 mg EOD in migraine prevention. The study enrolled subjects with both EM and CM), where chronic migraine was defined as a headache occurring on 15 or more days/month and met other IHS criteria for CM. The study consists of 4 phases: a 28-day screening phase, a 12-week DBT) phase, a 52-week OLE) phase, and an 8-week follow-up safety phase. During the 28-day OP) subjects were to document each day if a migraine occurred and the migraine intensity and characteristics. If eligible, the OP subjects were randomised and entered the 12-week DBT phase (Weeks 1-12), during which they were instructed to take 1 tablet of blinded study drug (rimegepant 75 mg or placebo) every other calendar day. If subjects had a migraine during the DBT, if needed, they could treat the migraine with their standard of care medication (incl. triptans) and were instructed to continue to take study medication on their regular schedule. At the completion of the 12-week DBT phase, subjects could enter into the 52-week OLE phase (Weeks 13-64), during which subjects were instructed to take 1 tablet of rimegepant 75 mg EOD. If subjects had a migraine on a day that they were not scheduled to dose with rimegepant, they could take 1 tablet of rimegepant 75 mg on that calendar day to treat a migraine. Therefore, during the OLE phase, subjects could take a maximum of one rimegepant 75 mg tablet per calendar day for this 52-week period. During the OLE phase, triptans were not allowed as rescue.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12-week DBT 28-day OP 52-week OLE	
Hypothesis	Superiority		
Treatments groups Total N=741 / 695 (treated / evaluable)	Placebo	347 evaluable	
	Rimegepant 75mg tablet	348 evaluable	
Endpoints and definitions	Primary endpoint	Change from the OP in the mean number of MDs per month in the last month (Weeks 9 to 12) of the DBT phase	Generalised linear mixed effect model (GLMEM) with the following variables: change from the OP in number of total migraine days per month as the dependent variable; subject as a random effect; number of total MDs per month in the OP as a covariate; treatment group, prophylactic migraine medication use at randomisation, month (i.e., months 1 to 3 of the DBT phase), and the month-by-treatment group interaction as fixed effects

	Secondary endpoints	Percentage of subjects who have a ≥ 50% reduction from OP in the mean number of moderate or severe MDs per month on treatment in the last month of the DBT phase	The percentages of evaluable mITT subjects with ≥ 50% reductions were compared between treatment groups using a CMH test stratified by prophylactic migraine medication use at randomisation (yes, no).
		Change from baseline in the mean number of MDs per month over the entire DBT phase (Weeks 1 to 12)	The same analysis method was used as for the principal analysis of the primary efficacy endpoint, however, the average effect over the 3 months of DBT were compared between the groups.
		Mean number of rescue medication days per month on treatment in the last month of the DBT phase	The mean number of rescue medication days per month were compared using GLMEM with the following variables: number of rescue medication days per month as the dependent variable; subject as a random effect; treatment group, prophylactic migraine medication use at randomisation, month (i.e., months 1 to 3 of the DBT phase), and the month-by-treatment group interaction as fixed effects.
		Change from baseline in the MIDAS total score at Week 12 in the DBT phase	The change from baseline in the Migraine Disability Assessment (MIDAS) total scores were compared using a GLM with the following variables: Week 12 change from baseline in the total score as the dependent variable; baseline total score as a covariate; treatment group and prophylactic migraine medication use at randomisation as fixed effects.
Database lock	12 Mar 2020 (for the 12-week DBT phase)		

Results and Analysis

Analysis description	**Primary endpoint: Change from the OP in the mean number of MDs per month in the last month (Weeks 9 to 12) of the DBT phase**		
Population/time point	Evaluable mITT subjects: enrolled subjects who were randomised only once and received at least 1 dose of double-blind study medication (rimegepant or placebo), and had ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and at least 1 month (i.e., 4-week interval) in the DBT phase.		
	Treatment group	Rimegepant 75 mg, N=348	Placebo, N=347

Descriptive statistics, estimate variability, and estimate of effect	Change from the OP in the mean number of MDs per month in the last month (Weeks 9 to 12) of the DBT phase Least squares mean (95% CI)	-4.3 (-4.83, -3.87)	-3.5 (-4.00, -3.04)
	Difference vs placebo (95% CI)	-0.8 (-1.46, -0.20)	-
	P-value	0.0099*	-
Analysis description	**Secondary endpoint: Percentage of subjects who have a ≥ 50% reduction from OP in the mean number of moderate or severe MDs per month on treatment in the last month of the DBT phase**		
Population/time point	Evaluable mITT		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg, N=348	Placebo, N=347
	Percentage of subjects who have a ≥ 50% reduction from OP in the mean number of moderate or severe migraine days per month on treatment in the last month of the DBT phase Stratified risk 95% CI	49.1 (43.9, 54.3)	41.5 (36.3, 46.7)
	Difference vs placebo (95% CI)	7.6 (0.2, 14.9)	-
	P-value	0.0438*	-
Analysis description	**Secondary endpoint: Change from baseline in the mean number of MDs per month over the entire DBT phase (weeks 1 to 12)**		
Population/time point	Evaluable mITT		
Descriptive statistics, estimate variability and estimate of effect	Treatment group	Rimegepant 75 mg, N=348	Placebo, N=347
	Change from baseline in the mean number of MDs per month over the entire DBT phase (Weeks 1 to 12) Least squares mean 95% CI	-3.6 (-3.97, -3.17)	-2.7 (-3.14, -2.34)
	Difference vs placebo (95% CI)	-0.8 (-1.34, -0.31)	-
	P-value vs PBO	0.0017*	-
Analysis description	**Secondary endpoint: Mean number of rescue medication days per month on treatment in the last month of the DBT phase**		

Population/time point	Evaluable mITT		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg N=348	Placebo, N=347
	Mean number of rescue medication days per month on treatment in the last month of the DBT phase Least squares mean 95% CI	3.7 (3.29, 4.15)	4.0 (3.53, 4.39)
	Difference vs placebo (95% CI)	-0.2 (-0.80, 0.31)	-
	P-value	0.3868†	-
Analysis description	**Secondary endpoint: Change from baseline in the MIDAS total score at Week 12 in the DBT phase**		
Population/time point	Evaluable mITT		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	Rimegepant 75 mg N=269	Placebo, N=266
	Change from baseline in the MIDAS total score at Week 12 in the DBT phase Least squares mean 95% CI	-11.8 (-15.41, -8.21)	-11.7 (-15.29, -8.10)
	Difference vs placebo (95% CI)	-0.1 (-4.74, 4.51)	-
	P-value	0.9616†	-
Notes	* Statistically significant as determined by hierarchical testing. † Nominal p-value in hierarchical testing. Type 1 error was controlled through the use of hierarchical testing. The significance of the primary endpoint was evaluated at the 0.05 level. If the primary endpoint was significant, then the secondary endpoints were tested hierarchically in a fixed sequence in the order shown above (list not exhaustive), each at the 0.05 level. Thus, a secondary endpoint was tested only if the preceding secondary endpoint in the hierarchy was determined to be significant. Descriptive p-values were provided for any non-significant secondary endpoints.		

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Supportive study

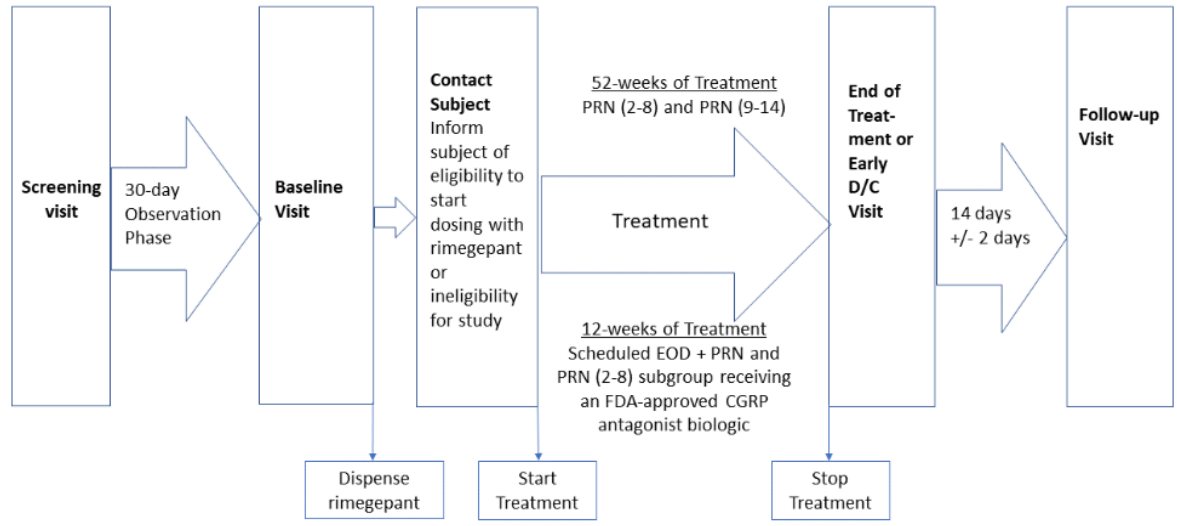
A Multicenter, Open-Label Long-Term Safety Study of BHV-3000 in the Acute Treatment of Migraine (Protocol No. BHV3000-201, NCT03266588)

The primary objective of phase 2/3, open-label, study 201 (Aug-2017 to Jul-2019, conducted at 103 US sites) was to evaluate the safety and tolerability of long-term use of rimegepant tablets in migraine patients.

There were no primary or secondary efficacy objectives in this study. For the key exploratory endpoint, the number of migraine headache days and severity of migraine attacks during the period that subjects were treated with rimegepant relative to the OP were analysed from data collected using the eDiary. In study 201, a migraine day was defined as a day of eDiary data with a "yes" response to having a migraine without any further quantification criteria in terms of duration.

After a 1-month OP, subjects were entered into long-term treatment (LTT) with rimegepant 75 mg. The majority of subjects were assigned to one of two 52-week enrolment groups, where they could take rimegepant on an as-needed (PRN) basis for the acute treatment of migraine. However, in one of the LTT enrolment groups (lasting 12 weeks), subjects were scheduled to dose with rimegepant EOD, regardless of whether or not they were experiencing a migraine.

Figure 14: BHV3000-201 Study Design Schematic



Abbreviations: D/C = discontinuation.

In open-label, long-term safety study 201, subjects were not randomised, but allocated to three different enrolment groups according to the self-reported historical rate of migraine attacks per month for the subjects preceding enrolment in the cohort: PRN (2-8) [N=1033], PRN (9-14) [N=481], and EOD+PRN (4-14) [N=286]. In PRN groups rimegepant could be taken as needed (max. 1 tablet 75 mg RPG per day) over 52 weeks, in the EOD+PRN group, which was treated for 12 weeks, rimegepant was administered prophylactically EOD plus the option to take rimegepant on non-scheduled days for acute attacks.

Subject demographics do not inform about MDs prior to study entry, hence, do not specify whether subjects suffered episodic or CM. The self-reported number of migraine attacks per month was 4.9 (PRN 2-8 group), 10.8 (PRN 9-14 group), resp. 6.8 in the EOD+PRN (4-14) group.

Subjects with analgesic overuse (history of non-narcotic analgesic intake on ≥ 15 days per month for ≥ 3 months) were initially excluded. However, this restriction was removed with Revised Protocol v2.0.

Importantly, the use of triptans was prohibited during LTT, however, triptans were allowed for acute migraine attack treatment during the OP.

Across the N=1800 treated subjects, overall completion was about 66.5% (PRN2-8: 66.1%, PRN9-14: 56.3%, EOD+PRN4-14: 85.0%). The higher completion rate in the EOD+PRN group is to be seen in the context, that the scheduled study duration for this group was 12 weeks only, as opposed to the PRN groups with a planned treatment duration of 52 weeks. About half of included subjects (51%) participated in one of the previous rimegepant single attack studies 301/302/303. Since the single attack studies 301/302/303 were placebo-controlled (1:1 randomisation), about a quarter of subjects recruited for study 201 actually has pre-knowledge of acute migraine treatment with rimegepant.

Study 201 Exposure

Overall, the mean time in the LTT period, based on eDiary records, was 36.1 weeks (PRN groups ([2-8]: 42.1 weeks; [9-14]: 38.0 weeks; Scheduled EOD + PRN group: 11.3 weeks). Within the enrolment groups, the median time in the LTT period was consistent with the protocol-specified treatment durations.

Overall, 112,014 doses of rimegepant 75 mg were administered among the 1,800 subjects treated in the study.

The median cumulative rimegepant exposure (number of tablets) was 50.0 tablets overall (PRN groups [2-8]: 52.0 tablets and [9-14]: 73.0 tablets; and 43.0 tablets in the Scheduled EOD + PRN group). Within the Scheduled EOD + PRN group, the mean average exposure was slightly less than 14 tablets per 4 weeks (13.7 tablets).

Table 46: Time in Long-term Treatment Period, and Cumulative and Average Rimegepant Exposure (Tablets per 4 Weeks): Treated Subjects, Study 201

	n (%)			
	Enrollment Group			
	PRN (2-8) (N = 1,033)	PRN (9-14) (N = 481)	Scheduled EOD + PRN (N = 286)	Overall (N = 1,800)
Time in LTT period (weeks)				
Mean (SD)	42.1 (16.47)	38.0 (18.61)	11.3 (2.87)	36.1 (19.20)
Median	52.0	51.6	12.1	51.1
Cumulative rimegepant exposure (tablets)				
Mean (SD)	59.9 (45.34)	80.8 (60.09)	39.6 (12.70)	62.2 (48.42)
Median	52.0	73.0	43.0	50.0
Average rimegepant exposure (tablets per 4 weeks)[a]				
Mean (SD)	5.6 (3.50)	8.5 (4.20)	13.7 (2.90)	7.7 (4.63)
Median	4.9	7.8	14.2	6.5

Source: Table 14.5.2.1

[a] Tablets per 4 weeks are based on 4-week (28-day) intervals in the LTT period. Number of 4-week intervals are not necessarily consecutive.

Exploratory analysis of MDs during LTT vs OP

The mean overall change from OP over the long-term treatment period was -0.5 MDs per 4-week interval across all evaluable treated subjects of study 201. However, exploratory efficacy results are divergent between enrolment groups. While in the biggest enrolment group PRN (2-8) [N=1023] with historical 2-8 migraine attacks per month the mean number of MDs per 4-week interval increased by 0.1 as compared to OP, the mean number of MDs decreased by -2.2 in the EOD+PRN group [N=278].

Table 47: Number of Migraine Days per 4 Weeks on Long-Term Treatment: Values, Changes and Percent Changes from Observational Period by Severity over Time, Evaluable Treated Subjects, Study 201

	PRN Dosing (2-8) (N=1023)	PRN Dosing (9-14) (N=468)	EOD+PRN Dosing (4-14) (N=278)	Overall (N=1769)
Overall Long-Term Treatment Average				
n	1023	468	278	1769
Mean (SD)	5.2 (3.42)	8.4 (4.81)	4.3 (3.15)	5.9 (4.08)
Median	4.6	7.6	3.5	5.1
Min, Max	0.0, 27.0	0.0, 27.8	0.0, 18.1	0.0, 27.8
Change from Observational Period				
n	1023	468	278	1769
Mean (SD)	0.1 (3.08)	-0.9 (4.16)	-2.2 (3.05)	-0.5 (3.49)
[95% CI]	[-0.10,0.28]	[-1.28,-0.52]	[-2.55,-1.83]	[-0.69,-0.37]
Median	-0.1	-0.9	-2.2	-0.5
Min, Max	-12.0, 17.9	-15.9, 15.5	-20.8, 8.3	-20.8, 17.9
Percent Change from Observational Period#				
n	1014	468	277	1759
Mean (SD)	17.0 (82.47)	-1.3 (60.18)	-27.3 (55.32)	5.1 (74.97)
[95% CI]	[11.90,22.06]	[-6.79,4.15]	[-33.85,-20.76]	[1.63,8.64]
Median	-3.1	-10.9	-40.0	-9.7
Min, Max	-100.0, 825.7	-100.0, 365.2	-100.0, 414.3	-100.0, 825.7

Note: Number of migraine days per 4 weeks is prorated to 28 days.
* Subjects must have >= 14 days of data (not necessarily consecutive) in the 4-week interval (n).
# Subjects must have >= 1 total number of migraine days of appropriate severity during the observational period.
Evaluable subjects are those with >= 14 days of data (not necessarily consecutive) in both the observational period and at least one 4-week interval in the long-term treatment period.

Evaluable treated subjects taking concomitant non-study prophylactic medication

Across the three enrolment groups, a subgroup of 14.0% (252/1.800) subjects took concomitant non-study prophylactic migraine medication. In the subgroup of subjects with concomitant prophylactic medication, the mean overall change from OP over the long-term treatment period was -0.1 MDs per 4-week interval across all enrolment groups of study 201. In the subgroup of patients with concomitant prophylactic medication of the PRN(2-8) enrolment group, the mean number of MDs increased by +0.2 MDs in the course of the 52-week open label treatment period.

Table 48: Number of Migraine Days per 4 Weeks on Long-Term Treatment: Values, Changes and Percent Changes from Observational Period by Severity over Time Evaluable Treated Subjects Taking Concomitant Prophylactic Migraine Medication, Study 201

	PRN Dosing (2-8) (N=142)	PRN Dosing (9-14) (N=83)	EOD+PRN Dosing (4-14) (N=27)	Overall (N=252)
Overall Long-Term Treatment Average				
n	142	83	27	252
Mean (SD)	5.4 (3.16)	8.6 (5.37)	5.5 (4.94)	6.5 (4.44)
Median	5.0	7.1	3.3	5.4
Min, Max	0.0, 18.0	0.6, 26.4	0.3, 16.9	0.0, 26.4
Change from Observational Period				
n	142	83	27	252
Mean (SD)	0.2 (3.12)	-0.3 (4.01)	-0.9 (2.45)	-0.1 (3.39)
[95% CI]	[-0.31,0.73]	[-1.15,0.60]	[-1.84,0.10]	[-0.49,0.35]
Median	0.0	-0.5	-1.3	-0.3
Min, Max	-7.2, 11.9	-8.5, 12.6	-4.3, 4.6	-8.5, 12.6
Percent Change from Observational Period#				
n	141	83	27	251
Mean (SD)	17.7 (72.98)	4.0 (60.88)	-16.9 (47.16)	9.4 (67.47)
[95% CI]	[5.51,29.82]	[-9.29,17.29]	[-35.59,1.72]	[1.04,17.81]
Median	0.0	-8.9	-19.1	-6.1
Min, Max	-100.0, 298.2	-86.3, 242.4	-82.1, 72.8	-100.0, 298.2

Note: Number of migraine days per 4 weeks is prorated to 28 days. Concomitant medications are those taken on or after enrollment date - 14 days.
* Subjects must have >= 14 days of data (not necessarily consecutive) in the 4-week interval (n).
# Subjects must have >= 1 total number of migraine days of appropriate severity during the observational period. Evaluable subjects are those with >= 14 days of data (not necessarily consecutive) in both the observational period and at least one 4-week interval in the long-term treatment period.

2.7.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The sponsor introduces RGP as the first orally administered CGRP antagonist to demonstrate benefit for both the acute treatment and prophylaxis of migraine. Accordingly, Vydura™ is proposed to be indicated for *the comprehensive management* of migraine in adults, including prophylaxis of migraine and acute treatment of migraine with or without aura.

The wide indication proposed by the applicant does not differentiate between EM or CM subtypes. The present assessment of the clinical dossier was based on currently valid diagnostic criteria (IHCD-3) and most recent European resp. IHS treatment Guidance, which make a clear distinction between both the EM and CM target population, and the acute vs preventive treatment approach.

The clinical dossier of rimegepant includes efficacy data from two separate sets of clinical studies that were provided for the acute (single attack studies 301 [N=1.084] / 302 [N=1.072] / 303 [N=1.351]) and preventive treatment (study 305 [N=695]) of migraine under randomised, placebo-controlled conditions. Supportive data include phase 2b dose-ranging study CN170003 ([N=811], with capsule) establishing rimegepant 75 mg as the minimum effective dose, and a phase 2/3, open-label, long-term safety study where subjects could receive rimegepant 75 mg doses for up to 52 weeks (201 [N=1.800]). All studies were conducted in the US.

Single aspects of the phase III programme were designed according to current IHS resp. EMA guideline provisions, like e.g. the choice of efficacy endpoints. However, a number of uncertainties resp. shortcomings were also identified, which will be further explored in the following.

With regard to acute treatment of migraine, single attack studies 301, 302 and 303 followed standard guidance and were almost identical in design, apart from the study drug formulation (study 303 with final ODT formulation, studies 301/302 with intermediate tablet formulation). Bioequivalence between the tablet and ODT formulation was established.

As concerns migraine attack frequency, subjects were required to have suffered not more than 8 attacks of moderate / severe intensity per month, and have suffered less than 15 days with headache (migraine

or non-migraine) per month in each of the 3 months prior to screening. Hence, the study population is inferred to correspond to the EM type, however, specific IHS diagnostic codes were not provided at study entry. Subjects with MoH were not included.

The inclusion criteria specify that subjects with contraindications to triptans may be eligible, provided they meet all other study entry criteria. Contraindications to triptans mainly concern CV safety. However, patients with uncontrolled, unstable or recently diagnosed CV disease, such as ischemic heart disease, coronary artery vasospasm, cerebral ischemia, MI, ACS etc. were excluded from 301/302/303. Overall, subjects with CV risk factors that would contraindicate triptan use were relatively uncommon. In mITT subjects, 17 of 1,749 rimegepant subjects (1.0%) and 12 of 1,758 placebo subjects (0.7%) reported risk factors that would contraindicate triptan use. There is no statement in the proposed rimegepant SmPC highlighting or claiming a potential advantage of RGP as compared to triptans in terms of the CV risk profile.

Participants were randomised in a 1:1 ratio and dispensed 1 dose of study medication consisting of rimegepant 75 mg ODT or matching placebo. Notably, subjects did not have the option to take a second tablet for rescue or recurrence of pain. Concomitant prophylactic migraine medication was permitted, if stable for at least 3 months prior to study entry. In single attack studies 301/302/303, rescue medication is prohibited until the 2-hour post-dose assessment for the primary endpoint. Thereafter, subjects were allowed to take unspecific analgesics (at 2-hours post-dose), triptans (earliest 48 hours post-dose) or antiemetics for rescue, if pain relief was not achieved or pain recurs. The efficacy assessment time spans over 48 hours post-dose to record sustained pain relief from 2-48 hours post-dose. Once rescue Mx was taken, any subsequent efficacy assessment is classified as failure.

The most relevant efficacy endpoints in single attack studies 301/302/303 are adequately chosen and are in line with guideline provisions. These include pain resp. MBS freedom at 2 hours post-dose (co-primary), sustained freedom from pain / MBS from 2-24 or 2-48 hours post-dose, and pain relief at early assessment time points.

The co-primary efficacy endpoints for the 3 pivotal studies, i.e. pain and MBS freedom at 2 hours following initial dose, are fully concordant with current IHS Guidance. Prior to dosing, patients were asked to assess and record their pain severity using the IHS 4-point pain severity rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain). Pain freedom was defined as a reduction in pain severity from mild, moderate, or severe at baseline to none. At the same time, subjects also recorded presence or absence (yes or no) of each of the following associated symptoms of migraine: nausea, phonophobia, and photophobia. From the list of present associated symptoms the subjects identified which ONE was most bothersome to them as the MBS. Improvement of other associated symptoms (nausea, photophobia, phonophobia,) at 2 hours post-dose was also recorded as further secondary endpoint. Other endpoints included sustained freedom from pain / MBS from 2-24 or 2-48 hours post-dose, and pain relief at early assessment time points

Rimegepant was tested for superiority over placebo, at a 2-sided alpha level of 0.05, on both co-primary endpoints. Both endpoints were evaluated using CMH tests stratified by the use of prophylactic migraine medication (yes or no). The population summary, the between group difference in the percentage of pain free subjects, is assessed by computing the "risk difference" between treatment groups. This analysis is appropriate.

As concerns baseline demographics, the mITT population is considered as typically representative of the migraine target population in terms of age (mean of 40-42 years, 96.8% < 65 years), gender (85-89% female), history of migraine with aura (30-37%), and the portion of subjects receiving preventive medication (13-17%). At screening, about one third of subjects was currently using triptans for the treatment of acute attacks. The mean duration of migraine history is about 20 years at study entry. The

median number of moderate to severe migraine attacks per month is 4.0 across treatment arms. The majority of subjects is considered moderately to severely affected by the disease.

The EMA Guideline recommends that single attack studies are supplemented with studies on consistency of effect with regard to general variability of migraine attacks. A consistency study 304 across 4 acute migraine attacks was originally planned (along EMA guideline provisions) and discussed within the scope of EMA SA from May 2018, however, no consistency data were submitted.

As concerns prophylactic migraine treatment, essential features of pivotal prevention study 305 are accordant with EU Guideline provisions. The frequency of migraine attacks is documented during an initial prospective 1-month OP. The DBT period covers a 12 week duration. During DBT, subjects were randomised 1:1 to receive either RGP or placebo.

Based on efficacy data obtained from pivotal trials in acute migraine (studies 301/302/303), it was assumed that the beneficial effect of rimegepant was maintained for up to 48 hours post-administration. This finding lead to the rationale of testing rimegepant in subsequent migraine prevention trial 305 following an every-other-day (EOD) dosing schedule.

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 contextualize the clinical effect of the test medication, however, is not considered essential from the regulatory perspective. Throughout the 12-week DBT period, subjects had to treat acute attacks (if any occurred) using their usual standard medication, i.e. PRN rimegepant was not allowed. On the contrary, during the subsequent 1-year open-label extension (OLE) period (wk 13-64) PRN rimegepant could be used in case an acute migraine attack occurred. However, a maximum daily dose of 75 mg rimegepant had to be observed, i.e. PRN rimegepant could only be taken on days for which every-other-day (EOD) rimegepant for prevention was not scheduled.

It is inherent to claimed *comprehensive management* of migraine that rimegepant may be taken as needed for acute migraine attacks on top of regular preventive RGP administration. The lack of controlled data to demonstrate the efficacy and safety of combined acute and prophylactic use of rimegepant is considered a major limitation of the present clinical data package. The efficacy of RGP, taken for acute migraine attacks, was not demonstrated under placebo-controlled conditions in subjects already receiving regular preventive RGP. On the other side, it is noted that exclusion of additional rimegepant doses to be taken PRN for acute attacks during the 12-wk DBT period, allows for proper and focussed evaluation of rimegepant's effect in migraine prevention.

To be eligible for participation in prevention study 305, subjects had to present with 4-18 migraine attacks per month, respectively at least 6 MD and not more than 18 headache days. IHS diagnostic code 1.3 for CM 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. Hence, the inclusion criteria of study 305 may include both EM and CM patients. The applicant did not provide respective IHS codes 1.1, 1.2.1, or 1.3 of included subjects.

Subjects could remain on their stable prophylactic treatment, as long as these do not belong to the group of CGRP antagonists (either biological or small molecule). There is no objection to exclusion of other CGRP antagonists since existing CGRP antagonist therapy leaves little (virtually no) space for further improvement through rimegepant. During the DBT period subjects may take their usual rescue medication for acute attacks, incl. triptans. Throughout the subsequent OLE period, however, triptans were prohibited.

The primary efficacy endpoint of study 305 was the change from the OP in the mean number of MD) per month in the last month (Weeks 9 to 12) of the DBT phase. Initially, study 305 was planned for EM patients, with implementation of the 4th Protocol Amendment inclusion criteria were widened to also

include subjects with a history of CM. In the context of recruiting a mixed of EM/CM population in study 305, implications result as concerns definition of a migraine day. The IHS 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). 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 and meeting ICHD-3 criteria for migraine or probable migraine, the guidance for CM requires the headache to last at least 4 hours (all other criteria identical). Since reduction from baseline in the mean number of MDs per month in the last 4 weeks of the 12-week DBT period is defined as primary efficacy endpoint, the definition of a MD is of critical importance. In the present study 305, the sponsor defined a MD along the provisions for an EM population.

The principal analysis of the primary endpoint used a GLMEM, subject as a random effect with number of total MDs per month in the OP as a covariate, and treatment group, prophylactic migraine medication use at randomisation, month (i.e., months 1 to 3 of the DBT phase), and the month-by-treatment group interaction as fixed effects. However, this analysis targets the hypothetical effect 'if all patients were fully adherent to treatment' that is not of primary regulatory interest. Therefore, the jump to reference analysis, that was provided as sensitivity analysis targeting the effect regardless of treatment discontinuation (treatment policy), should be considered of primary relevance for efficacy assessment.

Subjects included in prevention study 305 experienced a median number of 8.0 migraine attacks per month. A portion of 12.9% was severely affected experiencing $\geq$ 12 attacks per month. With the 4th of 8 amendments implemented to the Protocol of study 305, eligibility criteria were expanded to also include subjects with CM, which were previously excluded. The number of allowed days per month with headache was increased to 18. However, the actual number of subjects fulfilling CM diagnostic criteria at baseline is not fully clear, since only "History of CM" is reported. For a subgroup of subjects, that previously participated in studies 301/302/303 (and therefore had pre-knowledge of study medication), participation in study 305 was opened with Protocol Amendment No.6. With regard to maintenance of the blind, the applicant asserts that subjects remained blinded to randomised study drug.

Primary and secondary efficacy endpoints were analysed using *evaluable mITT subjects,* i.e. enrolled subjects who were randomised only once, received at least 1 dose of double-blind study medication (rimegepant or placebo), and had $\geq$ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and at least 1 month (i.e., 4-week interval) in the DBT phase. The portion of subjects not considered mITT evaluable due to less than 14 days of eDiary efficacy data in any of the 3 treatment months (28 day intervals) was low (rimegepant 5.9%, placebo 6.5%) and equally distributed across arms. Additional analyses in *treated* subjects were presented.

Supportive, exploratory efficacy data are obtained from open-label, LTT safety study 201. Subjects were not randomised, but allocated to three different enrolment groups according to the self-reported historical rate of migraine attacks per month: PRN (2-8) [N=1033], PRN (9-14) [N=481], and EOD+PRN (4-14) [N=286]. In PRN groups, rimegepant could be taken as needed (max. 1 tablet 75 mg RGP per day) over 52 weeks, in the EOD+PRN group, which was treated for 12 weeks, rimegepant was administered prophylactically EOD plus the option to take rimegepant on non-scheduled days for acute attacks. Subject demographics do not inform about migraine or headache days prior to study entry, hence, do not specify whether subjects suffered EM or CM. The self-reported number of migraine attacks per month was 4.9 (PRN 2-8 group), 10.8 (PRN 9-14 group), resp. 6.8 in the EOD+PRN (4-14) group.

Exploratory efficacy assessments conducted in study 201 related to the effect of repeated rimegepant 75 mg dosing on the frequency of MDs during the up-to-1-year long-term treatment (LTT) period as compared to the 28-day OP, based on daily eDiary entries. In study 201, a migraine day was defined as a day of eDiary data with a "yes" response to having a migraine without any further quantification criteria

in terms of duration etc. Accurate comparability between the OP and 4-week LTT treatment intervals was compromised by the fact that the use of triptans as rescue medication was prohibited during LTT, however, subjects were permitted to use triptans during the 4-week OP.

Efficacy data and additional analyses

In terms of subject disposition, study completion was very high across the 3 single attack studies 301/302/303 and dose arms (around 99% for rimegepant 75 mg and placebo), which does not surprise, given the shortness of intervention. Subjects were given a 45-day period to treat 1 acute migraine attack. A migraine attack of moderate to severe intensity was not experienced in only very isolated cases during that time.

Equally, a high portion of subjects completed the 12-week DBT period of prevention study 305 (84.5%, equally distributed across arms: rimegepant 85.4%, placebo 83.6%). Only very few subjects discontinued due to AE on DBT or subsequent OLE period (n=13 [3.5%] rimegepant, n=5 [1.7%] placebo patients). About equal portions of subjects continued to the OLE phase after terminating the DBT period (rimegepant: 81.6%, placebo: 81.4%).

Across the 3 pivotal single attack studies, superiority over placebo could consistently be shown for both co-primary endpoints, i.e. portions of patients achieving pain freedom resp. MBS freedom at 2 hours post-dose. Despite statistical significance, the overall effect size is rather modest (net risk difference over placebo for 2-hour pain freedom: 301: 4.91%, 302: 7.59%, 303: 10.37%).

As concerns the co-primary rate of MBS freedom at 2-hours post-dose, both rimegepant and placebo response rates were higher as compared to response rates for pain freedom. The net risk difference over placebo, however, remains modest (net risk difference over placebo for 2-hour MBS freedom: 301: 8.90%, 302: 12.38%, 303: 8.29%). However modest with regard to the magnitude of the effect size, it is noted that placebo superiority could be reproduced in terms of the two co-primary endpoints across 3 independent single attack studies.

The co-primary endpoints are based on data entry into the e-diary at the 2 hours post-dose assessment time point. If data at 2 hours were missing, these were imputed as failures for the primary CMH analysis. The portion of imputed data was low, in the range of 3.0-7.8% across the two co-primary endpoints and single attack studies. As long as the rate of imputed data is about equal between the arms, or even higher in the rimegepant arm, the approach taken for the primary analysis is considered conservative. The LOCF, Complete case, and multiple imputation sensitivity analyses did not change the overall results across studies. In several cases, the sensitivity analyses even yielded higher risk differences in favour of rimegepant as compared to risk difference resulting from the primary CMH analysis.

A multitude of secondary efficacy endpoints were tested hierarchically in studies 301 and 302. Freedom of associated symptoms (photophobia, phonophobia, nausea) was placed high in the hierarchy. After statistical significance could not be shown for freedom from nausea at 2 post-dose, all endpoints listed afterwards in the hierarchy were not considered statistically significant in either study. From the CHMP perspective, there was no imminent necessity to arrange the hierarchical order of testing the secondary endpoints in the way it was conducted in studies 301/302. In study 303, the hierarchical order was modified. In line with EMA Guideline provisions, demonstration of sustained freedom of pain from 2-24 hours and/or from 2-48 hours post-dose are considered meaningful endpoints. In line with results obtained for the co-primary endpoints, net differences over placebo were modest for sustained effect-related endpoints. However, across all single attack studies, numerical differences in favour of rimegepant could be shown (risk difference (%) / p-values: pain freedom 2-24 hour: 301: 5.86 / 0.002, 302: 5.19 / 0.004, 303: 10.12 / <.0001*; pain freedom 2-48 hour: 301: 4.39 / 0.013, 302: 3.89 /

0.018, 303: 8.02 / <.0001*). Due to hierarchical testing, however, statistical superiority over placebo could only be shown for sustained pain freedom in study 303.

Contrary to freedom from photophobia and phonophobia at 2 hours post-dose, for which consistent superiority over placebo could be shown, rimegepant did not significantly separate from placebo for the freedom from nausea as associated symptom. The differential effect of rimegepant, on the associated symptoms, photophobia/phonophobia on the one side, and nausea/vomiting on the other side, could be explained by different pathophysiological mechanisms causing the symptoms, with the ones being affected by rimegepant's CGRP antagonism, while the others aren't.

Throughout single attack studies 301/302/303, subjects were instructed not to use rescue medication until the 2-hours post-dose assessment time point for the co-primary endpoints. Thereafter, the use of rescue medication rises fairly steeply. Within the course of 24 hours, about 14-20% of subjects receiving rimegepant as first dose took additional rescue medication.

Concerns about lacking proof of consistency of rimegepant's effect across multiple acute attacks are to be seen in the context of the modest net treatment effect shown in single attack studies 301/302/303 and the poor outcome of exploratory efficacy data in PRN enrolment groups of long-term study 201. The applicant's assertion that consistency would have been shown by long-term data (e.g. study 201) does not address consistency as specified in the guideline.

In terms of migraine prevention, subjects receiving prophylactic EOD 75 mg rimegepant tablets reduced the mean number of MDs by -4.3, as opposed placebo subjects who achieved a reduction of MD by -3.5 days throughout the last 4 weeks (week 9-12) of the DBT. Although statistical superiority over placebo could be demonstrated (p=.0099) using the primary GLMEM analysis, the net difference of 0.8 MD per month is considered modest. However, the applied GLMEM analysis is not considered as the analysis that targets the effect of primary regulatory interest. The jump to reference analysis targeting the treatment policy estimand, which was provided as sensitivity analysis, is considered as the adequate analysis. If the sensitivity analysis Jump-to-Reference is applied, the net difference between rimegepant and placebo in evaluable mITT subjects in terms of MD reduction throughout the last 4 weeks (wk 9-12) of the DBT is further diminished to -0.7 MDs (p=0.0400).

In order to more accurately describe the clinical relevance of the net difference over placebo, the change of MDs from the OP over the 12-week DBT is to be taken into account. During the OP, subjects experienced 10.3 (rimegepant) resp. 9.9 (placebo) MDs. In both arms, the number of MDs per 28-day assessment period decreases constantly per month throughout the 12-week DBT period. In terms of percent reduction, the number of MDs was reduced by -50.3% in rimegepant subjects, while placebo subjects achieved to reduce the mean number of MDs from week 9-12 by -41.7%. The overall net difference of -0.7 MDs per month between rimegepant and placebo corresponds to less than 10% of the number of MDs experienced at baseline.

Reduction in monthly MDs starts early after initiation of EOD rimegepant 75 mg treatment. The difference over placebo is largest during the first month of the 3 months DBT (-1.2 MDs). Thereafter, the net difference over placebo diminished in line with increasing placebo response in the course of the 12-week treatment period.

A number of subgroup analyses were conducted. Subjects recruited for study 305 were stratified according to concomitant prophylactic migraine medication. In the subgroup of subjects receiving concomitant non-study migraine prophylactic medication (rimegepant arm: 75/348, 21.6%), rimegepant numerically hardly separated from placebo. Throughout the last period of the DBT (wk 9-12) subjects with non-study preventive medication reduced the mean number of MDs by -3.5 in the rimegepant arm as compared to a reduction of -3.4 (p=0.8993) in the placebo arm. Subjects without concomitant preventive treatment reduced MDs to the same degree (-0.8 MDs net difference over control, Jump to

Reference) as observed in the total mITT population of study 305. The benefit of the use of rimegepant in migraine prevention in subjects already receiving individual prophylactic medication is unclear.

Throughout the 12-week double blind treatment period, subjects could use their individual rescue medication (incl. triptans, NSAIDs, antiemetics) in case an acute migraine attack occurred despite preventive study medication. Across arms and the three 28-day treatment intervals of the DBT, subjects used rescue on a mean of about 4-5 days per month. Rimegepant did not significantly separate from placebo in any of the three 28-day intervals of the DBT in terms of rescue medication use.

Borderline significance (net effect over placebo: 7.6%, p=0.0438) could be shown for the responder analysis of subjects achieving a 50% reduction in moderate or severe MDs during week 9-12 of the DBT.

The MIDAS Migraine Disability Assessment score retrospectively reflects on how many days a patient was negatively affected by migraine throughout the preceding 3 months period. Results are presented for those subjects reporting the MIDAS score at baseline and at the end of the 3 months DBT. Baseline mean MIDAS scores were 36.9 in the rimegepant group and 35.3 in placebo patients. Rimegepant numerically hardly separated from placebo in reducing migraine-related disability (MIDAS: rimepgepant: -11.8, placebo -11.7, p=0.9616) during the 12-week DBT period. However, meaningful reductions in MIDAS scores were achieved over time (week 24, week 64) over the 1-year OLE period of study 305.

According to study 305 demographics, subjects reported at study entry whether there was a history of CM (yes 22.7%, no 43.6%, not reported 33.7%). The applicant did not pre-specify stratified analysis of migraine prevention results in EM vs CM. Only *ad hoc* exploratory results are presented, not yielding statistical significance for the subgroup of "historical CM" in terms of the primary efficacy endpoint (Total MD reduction from OP to week 9-12 of DBT). In preceding MAAs concerning the use of biologicals in migraine prevention, separated studies in properly defined EM vs CM populations were conducted in line with IHS Guidance.

Supportive, exploratory, efficacy results were obtained from open-label, long-term safety study 201. Subjects were not randomised, but allocated to three different enrolment groups according to the self-reported historical rate of migraine attacks (range specified in parentheses) per month for the subjects preceding enrolment in the cohort: PRN (2-8) [N=1033], PRN (9-14) [N=481], and EOD+PRN (4-14) [N=286]. In PRN groups rimegepant could be taken as needed (max. 1 tablet 75 mg RPG per day) over 52 weeks, in the EOD+PRN group, which was treated for 12 weeks, rimegepant was administered prophylactically EOD plus the option to take rimegepant on non-scheduled days for acute attacks. The number of MDs experienced per 28-day interval during the LTT period was compared with the OP.

Exploratory efficacy results of study 201 demonstrate that the long-term overall effect in acute migraine treatment is modest in the PRN (9-14) group (-0.9 MDs) and virtually no beneficial effect was observed in terms of reduced mean MDs per month as compared to OP in the largest enrolment group PRN (2-8) of subjects historically experiencing 2-8 attacks per month (+0.1 MDs).

As concerns exposure in study 201, the median duration of study continuation corresponded to the scheduled duration for the respective enrolment groups (52 weeks for PRN groups and 12 weeks for EOD+PRN). In PRN enrolment groups, subjects were free to take rimegepant as needed (MDD 1 tablet of 75 mg rimegepant) and did so on a mean of 5.6 (PRN 2-8), resp. 8.5 (PRN 9-14) days. In the EOD+PRN enrolment group, planned to be treated for 12 weeks, subjects were instructed to take 1 rimegepant tablet EOD (corresponding to 14 tablets per 4-week interval) plus 1 tablet on non-scheduled dosing days as needed. Usage of as needed rimegepant was very low, as illustrated by median 14.2 tablets per 4 weeks. Full EOD treatment compliance would translate into 14 tablets. The low use of rimegepant in the EOD+PRN group (median 14.2 tablets per 4-week interval), hardly corresponding to compliant EOD administration, may support the preventive use of rimegepant in migraine prevention under open-label

conditions, however, does not allow any conclusions to be drawn on the effect of acute (as needed) use of rimegepant under open-label regular EOD dosing conditions.

2.7.4. Conclusions on clinical efficacy

To support the claimed *comprehensive management* of migraine in adults, including prophylaxis and acute treatment, four pivotal RCTs were provided to demonstrate the efficacy of rimegepant in acute migraine treatment (single attack studies 301/302/303) and migraine prevention (study 305). Statistical significant effects along primary efficacy endpoints could be shown, however, the following considerations need also to be taken into account.

- The placebo-subtracted treatment effect observed across the 3 pivotal single attacks studies (net risk difference over placebo for 2-hour pain freedom: 301: 4.91%, 302: 7.59%, 303: 10.37%) is modest.
- A guideline-conforming prospective, placebo-controlled proof of within-patient consistency in acute migraine is lacking. Exploratory data obtained from acute migraine treatment during OLE of study 305 on unscheduled EOD dosing days were provided *post hoc*. These provide some insight into reproducibility of treatment success in consecutive acute attacks, however, have severe limitations. They reflect uncontrolled open-label conditions in patients with maintenance EOD preventive dosing that could only take rimegepant for acute migraine on non-scheduled dosing days. A focused analysis in subgroups of patients with > 3 moderate to severe MDs (N=350) and those with > 4 MDs (N=310) was provided on the first 3 resp. 4 attacks, detailing the number of patients achieving 2-hours pain freedom in 0, 1, 2, 3, (4) of the first attacks and calculating the portion of subjects achieving pain freedom in at least 2 out of first 3, resp. 3 out of first 4 attacks.

  The profile obtained largely corresponds to the modest treatment effect already observed across the single attack studies 301/302/303. In both subgroups of patients with > 3, respectively > 4 moderate to severe migraine attacks, more than half of patients could not successfully treat a single attack of the first three resp. four attacks (0 out of 3: 58.4%; 0 out of 4: 52.4%). Only a very small minority of patients achieved pain freedom at 2 hours post-dose in every single of the first 3 resp. 4 attacks (3 out of 3: 5.3%; 4 out of 4: 3.4%).

  As could be expected, the magnitude of requested within-patient consistency parameter (2 out of 3: 16.5%, resp. 3 out 4: 9.7%) is considerably smaller than the average absolute responder rates observed across the three single attack studies 301/302/303 of 19-21% (placebo 10.9 – 14.2%).
- In study 305, the net difference over placebo in terms of MD reduction was limited (-0.8 MDs for the primary GLMEM analysis; -0.7 MDs for the relevant Jump-to-Reference sensitivity analysis over a 28-day treatment period (week 9-12) of DBT), corresponding to less than 10% of the mean number of MD at baseline (10.3-9.9 MDs).
- The modest treatment effect for the primary endpoint goes along with non-significant treatment effects in relevant subgroups of patients (e.g. CM history, subjects with less than 8 attacks per month, subjects > 65 years of age, subjects continuing their non-study prophylactic medication).

The applicant claimed a broad indication of migraine prevention irrespective of EM or CM classification. However, the CM subgroup was too small to be able to show any effect independently. Furthermore, data does not allow a precise estimation on the treatment effect in this subgroup

2.8. Clinical safety

Patient exposure

As of 03-Sep-2020, more than 7,200 subjects have participated in Phase 1 studies in healthy subjects or Phase 2 and 3 studies in subjects with migraine in the rimegepant clinical development programme. Among these subjects, more than 3,800 unique subjects have received the rimegepant clinical dose of 75 mg in Phase 2 and 3 studies, including 1,857 unique subjects who received rimegepant 75 mg in single-dose studies: 1,771 unique subjects in the three pivotal Phase 3 single-dose, placebo-controlled acute treatment studies (i.e., BHV3000-303, BHV3000-302, and BHV3000-301), and 86 subjects in the Phase 2b dose-ranging study CN170003. Safety data are also available for the 2,471 subjects who received rimegepant 75 mg in the Phase 2/3 multiple-dose studies (BHV3000-201 and BHV3000-305).

In the pivotal migraine prophylaxis study (BHV3000-305), the OLE phase remains ongoing as of the safety snapshot for this summary and a total of 527 subjects received rimegepant (EOD or EOD + PRN up to QD) for at least 6 months, and 311 subjects received rimegepant for at least 1 year.

Overall, among the 1,800 subjects treated in BHV3000-201 with an average rimegepant exposure of $\geqslant$ 2 tablets per 4 weeks, 954 (53.0%) were in the LTT period for $\geqslant$ 1 year. In the long-term, open-label safety study 201, the median time in the LTT period overall was 51.1 weeks. Overall, 1,154 (64.1%) subjects had at least 6 months of rimegepant exposure, and 368 (20.4%) subjects had 1 year of rimegepant exposure. A total of 112,014 doses of rimegepant 75 mg were administered among the 1,800 subjects treated in the study.

Table 49: Study Pools for Analyses of Safety Data: Treated Subjects

	Rimegepant												
	QD administration									BID			
Population: n Study: n	10 mg	25 mg	75 mg	150 mg	300 mg	450 mg	600 mg	900 mg	1500 mg	300 mg	Overall	Placebo	Sumatriptan 100 mg	Total[a]
Single-dose Migraine: Rimegepant 75 mg and Placebo														
BHV3000-301			546								546	549		1,095
BHV3000-302			543								543	540		1,083
BHV3000-303			682								682	693		1,375
CN170003			86								86	209		295
Subtotal[a]			1,857								1,857	1,991		3,846
Single-dose Migraine: Other Rimegepant Doses and Sumatriptan														
CN170003	72	62		86	112		84				416	209	100	725
Multiple-dose Migraine														
BHV3000-201[b]			1,800								1,800			1,800
BHV3000-305[c]			671								671	371		741
Subtotal[a]			2,471								2,471	371		2,541
Healthy Subjects														
BHV3000-102			18								18			18
BHV3000-109[d]			37		38						38	36		38
BHV3000-110			59								59			59
BHV3000-112			32								32			32
BHV3000-113			52								52			52
BHV3000-117	41	42	41								42			42
BHV3000-120			23								23			23
CN170001		6	12	12	12	6	12	6	6	6	78	26		104
CN170006					8						8			8
Subtotal[a]	41	48	274	12	58	6	12	6	6	6	350	62		376
Total[a]	**113**	**110**	**4,136**	**98**	**170**	**6**	**96**	**6**	**6**	**6**	**4,628**	**2,421**	**100**	**6,354**

Abbreviations: BID = twice daily; EOD = every other day; PRN = as needed; QD = once daily

[a] Unique subjects

[b] A total of 1,800 subjects were treated in the long-term, open-label safety study (BHV3000-201), including 890 subjects who were not treated in BHV3000-301, BHV3000-302, or BHV3000-303 and 910 subjects who were treated in Studies BHV3000-301, BHV3000-302, or BHV3000-303 (456 with rimegepant and 454 with placebo). A total of 286 subjects were treated in the long-term, open-label safety study (BHV3000-201) in the EOD + PRN group, including 181 subjects who were not treated in BHV3000-301, BHV3000-302, or BHV3000-303 and 105 subjects who were treated in Studies BHV3000-301, BHV3000-302, or BHV3000-303 (55 with rimegepant, and 50 with placebo).

[c] A total of 741 subjects were treated in the multiple-dose, pivotal migraine prophylaxis study (BHV3000-305), including 726 subjects who were not treated in BHV3000-301, BHV3000-302, or BHV3000-303 and 15 subjects who were treated in Studies BHV3000-301, BHV3000-302, or BHV3000-303. A total of 671 subjects received double-blind or open-label rimegepant, 370 as double-blind study drug and 301 as open-label study drug after receiving placebo.

[d] Cross-over study: 38 unique subjects received rimegepant 75 mg, rimegepant 300 mg, placebo, and/or moxifloxacin. Thirty-eight unique subjects received rimegepant 75 mg or 300 mg.

In study 305, a total of N=747 subjects were randomised, and 741 subjects were treated with rimegepant (370 subjects) or placebo (371 subjects) in the DBT phase.

The DBT phase of prevention study 305 is complete; there are no treated subjects ongoing in this phase. The majority of treated subjects (626/741, 84.5%) completed the DBT phase.

Table 50: Summary of eDiary Exposure in the Pivotal Phase 2/3 Migraine Prophylaxis Study (BHV3000-305) and in the Phase 2/3 Long-term, Open-label Safety Study (BHV3000-201)

	Pivotal Migraine Prophylaxis Study: BHV3000-305			Supportive Safety Study: BHV3000-201
	Double-blind Treatment (12 weeks)		≥ 1 dose Rimegepant in DB or OLE (up to 64 weeks)	Scheduled EOD + PRN (up to 12 weeks)
	Rimegepant (N = 370)	Placebo (N = 371)	(N = 671)[a]	(N = 286)
Time on study drug (weeks)				
Mean (SD)	11.2 (2.77)	11.1 (3.26)	41.8 (19.14)	10.3 (3.03)
Median	11.9	11.9	48.7	11.3
Cumulative exposure (tablets)				
Mean (SD)	38.3 (10.29)	37.9 (11.53)	151.4 (74.20)	39.6 (12.70)
Median	42.0	42.0	172.0	43.0
Average exposure (tablets per 4 weeks)[b]				
Mean (SD)	13.8 (1.55)	13.9 (1.82)	14.3 (2.17)	13.7 (2.90)
Median	14.2	14.2	14.2	14.2
Total exposure (tablets) summed across all subjects	14,174	14,049	101,585	11,336

Abbreviations: CSR = clinical study report; DB = double-blind; DBT = double-blind treatment; EOD = every other day; OLE = open-label extension; PRN = as needed; SD = standard deviation.

Shaded column for each study includes subjects whose data are also reported in the unshaded column(s) for that study.

[a] Number of subjects includes 370 subjects who were treated with rimegepant in the double-blind or open-label phase and 301 subjects who were treated with placebo in the double-blind treatment phase and rimegepant in the open-label phase (Appendix 1.1).

[b] Average exposure is shown in tablets per month (defined as 4 weeks) for BHV3000-305 and tablets per 4 weeks for BHV3000-201.

Adverse events

Acute treatment – On-treatment adverse events – SD studies

On-treatment AEs were specified as those occurring from the study drug first dose through the study drug last dose + 7 days. Notably, on-treatment AEs were differentiated from treatment-emergent AEs (TEAEs) (defined as those occurring, worsening, or becoming serious during treatment relative to pre-treatment).

Across the single-dose studies, on-treatment AEs were reported in 192 (10.8%) subjects in the rimegepant group and 154 (8.6%) subjects in the placebo group. The most frequently (⩾ 1.0% in either treatment group) reported on-treatment AE was nausea (rimegepant 1.2%, placebo 0.8%), followed by urinary tract infections (rimegepant 0.8%, placebo 0.3%).

Table 51: Summary of On-treatment Adverse Events Reported in at Least One Percent of Subjects Overall: Treated Subjects in the Phase 2/3 Single-dose Studies, Acute Treatment of Migraine (301, 302, 303, CN170003)

	Pivotal Placebo-controlled Single-dose Studies						Supportive Single-dose Study	
	Pooled Tablet Studies: BHV3000-301/ -302		ODT Study: BHV3000-303		Pooled Single-dose Phase 3 Studies		CN170003 (75-mg Group)	
System Organ Class Preferred Term	Rimegepant (N = 1,089)	Placebo (N = 1,089)	Rimegepant (N = 682)	Placebo (N = 693)	Rimegepant (N = 1,771)	Placebo (N = 1,782)	Rimegepant (N = 86)	Placebo (N = 209)
On-treatment AEs	**121 (11.1)**	**95 (8.7)**	**71 (10.4)**	**59 (8.5)**	**192 (10.8)**	**154 (8.6)**	**18 (20.9)**	**30 (14.4)**
Reported in ≥ 1% in any group								
Infections and Infestations								
Urinary tract infection	6 (0.6)	5 (0.5)	8 (1.2)	1 (0.1)	14 (0.8)	6 (0.3)	1 (1.2)	1 (0.5)
Gastrointestinal Disorders								
Nausea	15 (1.4)	11 (1.0)	11 (1.6)	3 (0.4)	26 (1.5)	14 (0.8)	3 (3.5)	5 (2.4)
Vomiting	1 (0.2)	1 (0.2)	2 (0.3)	3 (0.4)	3 (0.2)	5 (0.3)	2 (2.3)	5 (2.4)
Nervous System Disorders								
Dizziness	5 (0.5)	6 (0.6)	6 (0.9)	7 (1.0)	11 (0.6)	13 (0.7)	1 (1.2)	2 (1.0)
On-treatment severe AEs	**5 (0.5)**	**2 (0.2)**	**2 (0.3)**	**1 (0.1)**	**7 (0.4)**	**3 (0.2)**	**1 (1.2)**	**5 (2.4)**
Reported in > 1 subject								
Gastrointestinal Disorders								
Diarrhoea	2 (0.2)	0	0	0	2 (0.1)	0	0	0
On-treatment AEs related to study drug	**69 (6.3)**	**51 (4.7)**	**44 (6.5)**	**34 (4.9)**	**113 (6.4)**	**85 (4.8)**	**8 (9.3)**	**15 (7.2)**
Reported in ≥ 1% in any group								
Gastrointestinal Disorders								
Nausea	13 (1.2)	11 (1.0)	9 (1.3)	3 (0.4)	22 (1.2)	14 (0.8)	1 (1.2)	4 (1.9)
Vomiting	1 (0.1)	1 (0.1)	1 (0.1)	0	2 (0.1)	1 (0.1)	1 (1.2)	3 (1.4)
Dry mouth	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.3)	2 (0.1)	4 (0.2)	0	2 (1.0)
Enlarged uvula	0	0	0	0	0	0	1 (1.2)	0
Nervous System Disorders								
Somnolence	5 (0.5)	4 (0.4)	2 (0.3)	1 (0.1)	7 (0.4)	5 (0.3)	0	2 (1.0)
Investigations								
Glomerular filtration rate decreased	1 (0.1)	0	1 (0.1)	0	2 (0.1)	0	1 (1.2)	0
Laboratory test abnormal	0	0	0	0	0	0	1 (1.2)	0
Skin and Subcutaneous Tissue Disorders								
Rash maculo-papular	0	0	1 (0.1)	0	1 (0.1)	0	1 (1.2)	0
Psychiatric Disorders								
Agitation	0	0	0	0	0	0	1 (1.2)	0
Respiratory, Thoracic and Mediastinal Disorders								
Rhinorrhoea	0	0	0	0	0	0	1 (1.2)	0
On-treatment severe AEs related to study drug	**3 (0.3)**	**0 (0.0)**	**1 (0.1)**	**1 (0.1)**	**4 (0.2)**	**1 (0.1)**	**0**	**3 (1.4)**
Reported in > 1 subject								
Gastrointestinal disorders								
Diarrhoea	2 (0.2)	0	0	0	2 (0.1)	0	0	0

Abbreviations: AE = adverse event; CSR = clinical study report; ODT = orodispersible tablet.

Source: Appendix A: Appendix 3.2.1.1A (AEs Phase 3 BHV3000-303 ODT); Appendix 3.2.1.1C (AEs BHV3000-301/302 Tablet); Appendix 3.2.1.1D (AEs Phase 3 studies overall); Appendix 3.2.1.1B (AEs CN170003); Appendix 3.2.3.1A (AEs ≥ 1% Phase 3 BHV3000-303 ODT); Appendix 3.2.3.1C (AEs ≥ 1% BHV3000-301/302 Tablet); Appendix 3.2.3.1D (AEs ≥ 1% Phase 3 studies overall); Appendix 3.2.5.1A (Related AEs Phase 3 BHV3000-303 ODT); Appendix 3.2.5.1C (Related AEs BHV3000-301/302 Tablet); Appendix 3.2.5.1D (Related AEs Phase 3 studies overall); Appendix 3.2.5.1B (Related AEs CN170003)

Shaded numbers represent values of < 1% included because another study or pooled dataset had ≥ 1% for that preferred term.

Acute treatment – On-treatment AEs – Long-term study 201

Overall, on-treatment AEs were reported in 1,088 (60.4%) treated subjects of study 201. The most frequently (≥ 2.0% overall) reported on-treatment AEs were upper respiratory tract infections, nasopharyngitis, sinusitis, influenza, bronchitis, urinary tract infections, nausea, dizziness, back pain, and arthralgia. In general, the frequencies of AEs were comparable between the PRN groups and lower in the Scheduled EOD + PRN group. These differences likely reflected the longer treatment durations in the PRN groups.

Table 52: Summary of On-treatment Adverse Events Reported in at Least Two Percent of Subjects Overall: Treated Subjects in the Long-term, Open-label Safety Study Supporting the Acute Treatment of Migraine (BHV3000-201)

	n (%)			
	Enrollment Group			
System Organ Class Preferred Term	PRN (2-8) (N = 1,033)	PRN (9-14) (N = 481)	Scheduled EOD + PRN (N = 286)	Overall (N = 1,800)
Subjects with at least 1 on-treatment AE	**664 (64.3)**	**315 (65.5)**	**109 (38.1)**	**1,088 (60.4)**
Reported in ≥ 2% overall				
Infections and Infestations	306 (29.6)	127 (26.4)	37 (12.9)	470 (26.1)
Upper respiratory tract infection	108 (10.5)	38 (7.9)	12 (4.2)	158 (8.8)
Nasopharyngitis	72 (7.0)	41 (8.5)	9 (3.1)	122 (6.8)
Sinusitis	57 (5.5)	28 (5.8)	7 (2.4)	92 (5.1)
Urinary tract infection	40 (3.9)	21 (4.4)	8 (2.8)	69 (3.8)
Influenza	49 (4.7)	9 (1.9)	1 (0.3)	59 (3.3)
Bronchitis	35 (3.4)	14 (2.9)	4 (1.4)	53 (2.9)
Gastrointestinal Disorders	44 (4.3)	25 (5.2)	8 (2.8)	77 (4.3)
Nausea	33 (3.2)	15 (3.1)	3 (1.0)	51 (2.8)
Musculoskeletal and Connective Tissue Disorders	58 (5.6)	23 (4.8)	8 (2.8)	89 (4.9)
Back pain	36 (3.5)	14 (2.9)	6 (2.1)	56 (3.1)
Arthralgia	25 (2.4)	9 (1.9)	2 (0.7)	36 (2.0)
Nervous System Disorders	26 (2.5)	13 (2.7)	3 (1.0)	42 (2.3)
Dizziness	26 (2.5)	13 (2.7)	3 (1.0)	42 (2.3)

Abbreviations: AE = adverse event; CSR = clinical study report; EOD = every other day; PRN = as needed.
Source: BHV3000-201 CSR:[11] Table 14.2.1.6.3 (AEs ≥ 2%); Table 14.2.1.3.2 (total AEs)

Prophylactic treatment – On-treatment AEs – Study 305

The safety profile of rimegepant 75 mg administered EOD for up to 12 weeks was comparable to placebo in the DBT phase of BHV3000-305. The majority of AEs were mild, not related to study therapy, and resolved without treatment. There were no new safety signals, in either the double-blind or open-label phase, and the AEs reported were consistent with those reported in previous clinical studies of rimegepant. Overall, in the double-blind or open-label phase, the most commonly reported (⩾ 2%) on-treatment AEs were upper respiratory infection, nasopharyngitis, back pain, influenza, urinary tract infection, sinusitis, and nausea.

Table 53: Summary of On-treatment AEs Reported in at Least Two Percent of Subjects Overall: Treated Subjects in the Phase 2/3 Multiple-dose Studies Supporting Migraine Prophylaxis (BHV3000-305 and BHV3000-201: Scheduled EOD + PRN Group)

	n (%)			
	Pivotal Migraine Prophylaxis Study: BHV3000-305			Supportive Safety Study: BHV3000-201
	Double-blind Treatment (12 weeks)		≥ 1 dose Rimegepant in DB or OLE (up to 64 weeks)	Scheduled EOD + PRN (up to 12 weeks)
System Organ Class Preferred Term	Rimegepant (N = 370)	Placebo (N = 371)	(N = 671)[a]	(N = 286)
On-treatment AEs Overall	**133 (35.9)**	**133 (35.8)**	**361 (53.8)**	**109 (38.1)**
Reported in ≥ 2% subjects in any group				
Infections and Infestations				
Nasopharyngitis	13 (3.5)	9 (2.4)	47 (7.0)	9 (3.1)
Urinary tract infection	9 (2.4)	8 (2.2)	24 (3.6)	8 (2.8)
Upper respiratory tract infection	8 (2.2)	10 (2.7)	51 (7.6)	12 (4.2)
Sinusitis	4 (1.1)	11 (3.0)	21 (3.1)	7 (2.4)
Influenza	3 (0.8)	2 (0.5)	25 (3.7)	1 (0.3)
Gastrointestinal Disorders				
Nausea	10 (2.7)	3 (0.8)	16 (2.4)	3 (1.0)
Musculoskeletal and Connective Tissue Disorders				
Back pain	5 (1.4)	5 (1.3)	29 (4.3)	6 (2.1)
Reported Overall				
Severe AEs[b]	**7 (1.9)**	**4 (1.1)**	**18 (2.7)**	**3 (1.0)**
AEs related to study drug[b]	**40 (10.8)**	**32 (8.6)**	**109 (16.2)**	**46 (16.1)**
Severe AEs related to study drug[b]	**1 (0.3)**	**1 (0.3)**	**5 (0.7)**	**0**

Abbreviations: AE = adverse event; DB = double-blind; DBT = double-blind treatment; EOD = every other day; OLE = open-label extension; PRN = as needed; PT = preferred term.

Shaded columns for each study includes subjects whose data are also reported in the unshaded column(s) for that study.

[a] Number of subjects includes 370 subjects who were treated with rimegepant in the double-blind or open-label phase and 301 subjects who were treated with placebo in the double-blind treatment phase and rimegepant in the open-label phase.

[b] No PT was ≥ 2% for on-treatment severe AEs, on-treatment AEs related to study drug, and on-treatment severe AEs related to study drug. The numbers shown represent the overall incidence for all events.

Serious adverse events and deaths

In the Phase 3, single-dose, placebo-controlled rimegepant studies, a single on-treatment Serious AE (SAE) was reported in the rimegepant group (1/1,771 subjects, 0.1%; back pain). Two on-treatment SAEs were reported in the placebo group (2/1,782 subjects, 0.1%; chest pain and urinary tract infection).

On-treatment SAEs in long-term study 201 were reported in 47 (2.6%) subjects (PRN [2-8]: 28 [2.7%] subjects; PRN [9-14]: 16 [3.3%] subjects; Scheduled EOD + PRN: 3 [1.0%] subjects. The following SAEs were reported in more than 1 subject:

- Accidental overdose, appendicitis, osteoarthritis, and pulmonary embolism in 3 (0.2%) subjects each
- Constipation, pneumonia, and sepsis in 2 (0.1%) subjects each

No pattern of SAEs was observed that would suggest specific safety concerns for rimegepant.

One patient (60-70 years) with Crohn´s disease assigned to PRN9-14 group of study 201 experienced an imaged-confirmed SAE of ischaemic colitis and permanently discontinued the trial.

During the DBT phase of prevention study 305, SAEs were reported in 3 (0.8%) subjects in the rimegepant group and 4 (1.1%) subjects in the placebo group.

Table 54: On-treatment Serious AEs on Double-blind Treatment: Treated Subjects in the Pivotal Phase 2/3 Migraine Prophylaxis Study (BHV3000-305)

System Organ Class: n (%) Preferred Term: n (%)	Rimegepant (N = 370)	Placebo (N = 371)
Any Adverse Event	**3 (0.8)**	**4 (1.1)**
Infections and Infestations	1 (0.3)	3 (0.8)
Gastroenteritis	1 (0.3)	0
Appendicitis	0	1 (0.3)
Pneumonia	0	1 (0.3)
Pyelonephritis	0	1 (0.3)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.3)	0
Malignant melanoma	1 (0.3)	0
Psychiatric Disorders	1 (0.3)	0
Suicide attempt	1 (0.3)	0
Injury, Poisoning and Procedural Complications	0	1 (0.3)
Overdose	0	1 (0.3)

Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1.
Adverse events are listed in descending order of rimegepant frequency within system organ class and preferred term.

Deaths

There were no deaths in any of the studies supporting safety in the acute treatment of migraine.

There were 2 deaths in the pivotal Phase 2/3 migraine prophylaxis study BHV3000-305, both were deemed by the study investigators as not related to study drug and both occurred in the OLE phase of the study (septic shock likely related with diverticulitis and aortic aneurysm due to Marfan´s syndrome).

Laboratory findings

Analyses of serum chemistry, haematology, and urin were conducted and did not point to clinically relevant safety concerns.

Safety in special populations

Four categories of AEs of special interest were identified for the rimegepant clinical programme:

1) hepatic-related AEs;
2) suicidality AEs;
3) AEs categorised as potentially associated with drug abuse; and
4) CV AEs

Additionally, the applicant was requested to carefully collect AEs of special interest such as e.g. rebound, sleep disturbance, non-migraine headaches and gastrointestinal (GI) disturbances within the scope of EMA SA from May 2018.

Gastrointestinal Disorders Adverse Events

In long-term study 201, on-treatment AEs in the GI Disorders System Organ Class (SOC were reported overall in 232 (12.9%) subjects. The most frequent Preferred Terms (PTs were nausea (51 [2.8%] subjects) and diarrhoea (34 [1.9%] subjects). Constipation was reported in 29 (1.6%) subjects. In general, the overall frequency of AEs was somewhat higher in the PRN groups than the Scheduled EOD +PRN group, likely reflecting the longer treatment durations in the PRN groups.

Table 55: Summary of On-treatment AEs in the Gastrointestinal Disorders SOC: Treated Subjects in the Long-term, Open-label Safety Study 201

	n (%)			
	Enrollment Group			
Preferred Term	PRN (2-8) (N = 1,033)	PRN (9-14) (N = 481)	Scheduled EOD + PRN (N = 286)	Overall (N = 1,800)
AEs in Gastrointestinal Disorders System Organ Class	**131 (12.7)**	**77 (16.0)**	**24 (8.4)**	**232 (12.9)**
≥ 1% in any group				
Nausea	33 (3.2)	15 (3.1)	3 (1.0)	51 (2.8)
Diarrhoea	17 (1.6)	12 (2.5)	5 (1.7)	34 (1.9)
Constipation	17 (1.6)	7 (1.5)	5 (1.7)	29 (1.6)
Vomiting	16 (1.5)	4 (0.8)	3 (1.0)	23 (1.3)
Dyspepsia	8 (0.8)	8 (1.7)	2 (0.7)	18 (1.0)
Abdominal pain upper	8 (0.8)	6 (1.2)	3 (1.0)	17 (0.9)
Abdominal pain	7 (0.7)	6 (1.2)	3 (1.0)	16 (0.9)
Toothache	6 (0.6)	6 (1.2)	0	12 (0.7)

Abbreviations: AE = adverse event; CSR = clinical study report; EOD = every other day; PRN = as needed.

Irrespective of the single dose setting (studies 301/302/303), PRN dosing over up to 52 weeks, or EOD during the placebo-controlled 12-week DBT period of prevention study 305, nausea (1.5-2.8%) was reported most often, followed by diarrhoea (1.9-1.6%) and constipation (1.6-1.1%) after multiple dose administration.

Table 56: Summary of On-treatment AEs in the Gastrointestinal Disorders SOC: Treated Subjects in the Phase 2/3 Multiple-dose Studies Supporting Migraine Prophylaxis (305 and 201: Scheduled EOD + PRN Group)

	n (%)			
	Pivotal Migraine Prophylaxis Study: BHV3000-305			Supportive Safety Study: BHV3000-201
	Double-blind Treatment (12 weeks)		≥ 1 dose Rimegepant in DB or OLE (up to 64 weeks)	Scheduled EOD + PRN (up to 12 weeks)
Preferred Term	Rimegepant (N = 370)	Placebo (N = 371)	(N = 671)[a]	(N = 286)
AEs in Gastrointestinal Disorders SOC	**33 (8.9)**	**17 (4.6)**	**79 (11.8)**	**24 (8.4)**
≥ 1% in any group				
Nausea	10 (2.7)	3 (0.8)	16 (2.4)	3 (1.0)
Diarrhoea	6 (1.6)	4 (1.1)	11 (1.6)	5 (1.7)
Constipation	4 (1.1)	2 (0.5)	13 (1.9)	5 (1.7)
Vomiting	3 (0.8)	1 (0.3)	8 (1.2)	3 (1.0)
Abdominal pain upper	2 (0.5)	0	5 (0.7)	3 (1.0)
Abdominal pain	1 (0.3)	0	2 (0.3)	3 (1.0)

Abbreviations: AE = adverse event; DB = double-blind; DBT = double-blind treatment; EOD = every other day; OLE = open-label extension; PRN = as needed; PT = preferred term.

Shaded column for study BHV3000-305 includes subjects whose data are also reported in the unshaded column(s) for that study.

[a] Number of subjects includes 370 subjects who were treated with rimegepant in the double-blind or open-label phase and 301 subjects who were treated with placebo in the double-blind treatment phase and rimegepant in the open-label phase.

Sleep disturbance

On-treatment AEs of sleep disturbance were reported overall in 9 (0.5%) subjects of study 201 and were reported in a low frequency of subjects during DBT phase of study 305 in either treatment group (1 [0.3%] subject in the rimegepant group and 3 [0.8%] subjects in the placebo group).

Raynaud's phenomenon

Across the SD studies, 4 rimegepant-treated and 7 placebo-treated subjects had a reported medical history of Raynaud's phenomenon; no events of Raynaud's phenomenon were reported on treatment in these subjects.

In long-term study 201, a review of 14 subjects overall with a reported medical history of Raynaud's phenomenon, no events of Raynaud's phenomenon were reported on treatment in these subjects. One (0.1%) subject in the long-term, open-label safety study 201 reported an on-treatment AE of Raynaud's phenomenon (verbatim term: worsening of Raynaud's), moderate in intensity, on Study Day 246. Raynaud's phenomenon was not reported in the medical history for the subject.

One (0.3%) subject in the rimegepant group and 2 (0.5%) subjects in the placebo group of study 305 had a reported medical history of Raynaud's phenomenon. No events of Raynaud's phenomenon were reported on treatment in these subjects in the double-blind or open-label phases of study 305.

Liver Function Tests

Across the single-dose studies, there was a low frequency of on-treatment LFT elevations. The frequency of elevations was similar between the rimegepant group and the placebo group.

Table 57: On-treatment Liver Function Test Elevations: Treated Subjects in the Phase 2 and 3 SD Studies Supporting the Acute Treatment of Migraine (301, 302, 303, CN170003)

	Pivotal Placebo-controlled Single-dose Studies						Supportive Single-dose Study	
	Pooled Tablet Studies: BHV3000-301/ -302		ODT Study: BHV3000-303		Pooled Single-dose Phase 3 Studies		CN170003 (75-mg Group)	
	Rimegepant (N = 1,089)	Placebo (N = 1,089)	Rimegepant (N = 682)	Placebo (N = 693)	Rimegepant (N = 1,771)	Placebo (N = 1,782)	Rimegepant (N = 86)	Placebo (N = 209)
N with LFT data	**781**	**794**	**540**	**546**	**1,321**	**1,340**	**73**	**187**
ALT								
> ULN	11 (1.4)	16 (2.0)	16 (3.0)	11 (2.0)	27 (2.0)	27 (2.0)	3 (4.1)	10 (5.3)
> 3 x ULN	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)	0	0
> 5 x ULN	0	0	0	0	0	0	0	0
AST								
> ULN	7 (0.9)	11 (1.4)	5 (0.9)	10 (1.8)	12 (0.9)	21 (1.6)	1 (1.4)	7 (3.7)
> 3 x ULN	1 (0.1)	0	1 (0.2)	0	2 (0.2)	0	0	0
> 5 x ULN	0	0	1 (0.2)	0	1 (0.1)	0	0	0
ALT or AST								
> ULN	12 (1.5)	21 (2.6)	18 (3.3)	15 (2.7)	30 (2.3)	36 (2.7)	3 (4.1)	13 (7.0)
> 3 x ULN	1 (0.1)	1 (0.1)	1 (0.2)	0	2 (0.2)	1 (0.1)	0	0
> 5 x ULN	0	0	1 (0.2)	0	1 (0.1)	0	0	0
TBL								
> ULN	5 (0.6)	7 (0.9)	5 (0.9)	4 (0.7)	10 (0.8)	11 (0.8)	5 (6.8)	2 (1.1)
> 1.5 x ULN	3 (0.4)	1 (0.1)	0	0	3 (0.2)	1 (0.1)	1 (1.4)	1 (0.5)
> 2 x ULN	0	0	0	0	0	0	0	1 (0.5)
ALP								
> ULN	14 (1.8)	12 (1.5)	9 (1.7)	7 (1.3)	23 (1.7)	19 (1.4)	0	0
> 1.5 x ULN	1 (0.1)	0	0	0	1 (0.1)	0	0	0
> 2 x ULN	0	0	0	0	0	0	0	0

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; CSR = clinical study report; LFT = liver function test; ODT = orodispersible tablet; TBL = total bilirubin; ULN = upper limit of normal.

Categories are cumulative and not mutually exclusive.

Percentages are based on subjects with non-missing LFT data (i.e., ALT, AST, TBL, or ALP) at an on-treatment visit (n).

In the long-term, open-label safety study 201, on-treatment LFT elevations above the ULN were reported as follows: ALT: 9.0%; AST: 6.8%; ALT or AST: 11.1%; total bilirubin levels (TBL): 1.7%; and Alkaline phosphatase (ALP): 3.6%.

Table 58: On-treatment Liver Function Test Elevations: Treated Subjects in the Long-term, Open-label Safety Study Supporting the Acute Treatment of Migraine (BHV3000-201)

	n (%)			
	Enrollment Group			
	PRN (2-8) (N = 1,033)	PRN (9-14) (N = 481)	Scheduled EOD + PRN (N = 286)	Overall (N = 1,800)
N with LFT data	**1,017**	**466**	**279**	**1,762**
ALT				
> ULN	107 (10.5)	43 (9.2)	9 (3.2)	159 (9.0)
> 3 x ULN	7 (0.7)	5 (1.1)	0	12 (0.7)
> 5 x ULN	3 (0.3)	2 (0.4)	0	5 (0.3)
> 10 x ULN	1 (0.1)	1 (0.2)	0	2 (0.1)
> 20 x ULN	1 (0.1)	1 (0.2)	0	2 (0.1)
AST				
> ULN	82 (8.1)	32 (6.9)	5 (1.8)	119 (6.8)
> 3 x ULN	9 (0.9)	5 (1.1)	0	14 (0.8)
> 5 x ULN	4 (0.4)	2 (0.4)	0	6 (0.3)
> 10 x ULN	1 (0.1)	1 (0.2)	0	2 (0.1)
> 20 x ULN	1 (0.1)	1 (0.2)	0	2 (0.1)
ALT or AST				
> ULN	132 (13.0)	52 (11.2)	12 (4.3)	196 (11.1)
> 3 x ULN	12 (1.2)	6 (1.3)	0	18 (1.0)
> 5 x ULN	5 (0.5)	3 (0.6)	0	8 (0.5)
> 10 x ULN	1 (0.1)	1 (0.2)	0	2 (0.1)
> 20 x ULN	1 (0.1)	1 (0.2)	0	2 (0.1)
TBL				
> ULN	20 (2.0)	8 (1.7)	2 (0.7)	30 (1.7)
> 1.5 x ULN	2 (0.2)	2 (0.4)	2 (0.7)	6 (0.3)
> 2 x ULN	1 (0.1)	0	0	1 (0.1)
ALP				
> ULN	42 (4.1)	20 (4.3)	2 (0.7)	64 (3.6)
> 1.5 x ULN	5 (0.5)	4 (0.9)	0	9 (0.5)
> 2 x ULN	2 (0.2)	1 (0.2)	0	3 (0.2)
Composite Elevations				
ALT or AST > 3 x ULN concurrent with TBL > 2.0 x ULN[a]	1 (0.1)	0	0	1 (0.1)
ALT or AST > 3 x ULN concurrent with TBL > 2.0 x ULN and ALP ≤ 2 x ULN[a]	1 (0.1)	0	0	1 (0.1)

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; CSR = clinical study report; EOD = every other day; LFT = liver function test; PRN = as needed; TBL = total bilirubin; ULN = upper limit of normal.

Categories are cumulative and not mutually exclusive.

Percentages are based on subjects with non-missing LFT data (i.e., ALT, AST, TBL, ALP) at an on-treatment visit.

[a] Concurrent is on the same collection date.

Low frequencies of aminotransferase elevations were observed in prevention study 305. As reviewed by a panel of external clinical hepatic experts, there were no Hy's Law cases, and there was no signal of drug induced liver injury (DILI) due to rimegepant when administered at least EOD for up to 64 weeks of treatment.

During the DBT phase, there was a low frequency of on-treatment LFT elevations, which were comparable between the rimegepant group (n = 363 subjects with LFT data) and the placebo group (n = 358 subjects with LFT data). On-treatment ALT or AST elevations > ULN were reported in 31 (8.5%) subjects in the rimegepant group and 43 (12.0%) subjects in the placebo group.

Table 59: On-treatment Liver Function Test Elevations: Treated Subjects in the Phase 2/3 Multiple-dose Studies Supporting Migraine Prophylaxis (BHV3000-305 and BHV3000-201: Scheduled EOD + PRN Group)

	n (%)			
	Pivotal Migraine Prophylaxis Study: BHV3000-305			Supportive Safety Study: BHV3000-201
	Double-blind Treatment (12 weeks)		≥ 1 dose Rimegepant in DB or OLE (up to 64 weeks)	Scheduled EOD + PRN (up to 12 weeks)
	Rimegepant (N = 370)	Placebo (N = 371)	(N = 671)[a]	(N = 286)
n with LFT data	**363**	**358**	**660**	**279**
ALT				
> ULN	25 (6.9)	36 (10.1)	120 (18.2)	9 (3.2)
> 3 x ULN	3 (0.8)	2 (0.6)	14 (2.1)	0
> 5 x ULN	1 (0.3)	0	4 (0.6)	0
> 10 x ULN	1 (0.3)	0	1 (0.2)	0
> 20 x ULN	0	0	0	0
AST				
> ULN	16 (4.4)	19 (5.3)	85 (12.9)	5 (1.8)
> 3 x ULN	2 (0.6)	0	12 (1.8)	0
> 5 x ULN	1 (0.3)	0	4 (0.6)	0
> 10 x ULN	0	0	0	0
> 20 x ULN	0	0	0	0
ALT or AST				
> ULN	31 (8.5)	43 (12.0)	138 (20.9)	12 (4.3)
> 3 x ULN	4 (1.1)	2 (0.6)	20 (3.0)	0
> 5 x ULN	1 (0.3)	0	6 (0.9)	0
> 10 x ULN	1 (0.3)	0	1 (0.2)	0
> 20 x ULN	0	0	0	0
TBL				
> ULN	5 (1.4)	5 (1.4)	21 (3.2)	2 (0.7)
> 1.5 x ULN	1 (0.3)	0	1 (0.2)	2 (0.7)
> 2 x ULN	1 (0.3)	0	1 (0.2)	0
ALP				
> ULN	22 (6.1)	29 (8.1)	66 (10.0)	2 (0.7)
> 1.5 x ULN	3 (0.8)	0	5 (0.8)	0
> 2 x ULN	1 (0.3)	0	2 (0.3)	0
Composite Elevations				
ALT or AST > 3 x ULN concurrent with TBL > 2.0 x ULN[b]	0	0	0	0
ALT or AST > 3 x ULN concurrent with TBL > 2.0 x ULN and ALP ≤ 2 x ULN[b]	0	0	0	0

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; DB = double-blind; DBT = double-blind treatment; EOD = every other day; LFT = liver function test; OLE = open-label extension; PRN = as needed; TBL = total bilirubin; ULN = upper limit of normal.

Shaded column for each study includes subjects whose data are also reported in the unshaded column(s) for that study.

Categories are cumulative and not mutually exclusive.

Percentages for BHV3000-201 are based on subjects with non-missing LFT data (i.e., ALT, AST, TBL, or ALP) at an on-treatment visit (n).

[a] Number of subjects includes 370 subjects who were treated with rimegepant in the double-blind or open-label phase and 301 subjects who were treated with placebo in the double-blind treatment phase and rimegepant in the open-label phase.

[b] Concurrent is on the same collection date.

External Hepatic Expert Panel Assessment

A panel of external hepatic experts assessed LFT results from the clinical programme, as well as individual liver cases of special interest, for the likelihood of DILI due to rimegepant. Cases from the pivotal Phase 2/3 migraine prophylaxis study 305; long-term, open-label safety study 201; and the Phase 3, single-dose, placebo-controlled studies 301 and 303 were assessed by the panel. The criteria to identify cases of interest for the panel's review included the following: aminotransferase laboratory values > 3 x ULN, ALP > 2 x ULN, TBL > 2 x ULN, or AEs of cirrhosis, hepatitis, liver failure, or jaundice.

As of 02-Oct-2020, the external hepatic expert panel has assessed 55 cases from study 201 (29 cases), study 305 (24 cases), and the single-dose studies 301 and 303 (1 case each). The panel concluded that

the likelihood of DILI due to rimegepant was unlikely for 47 of the cases, and possible for 8 of the cases. All cases reviewed by the panel were assessed as unlikely related to study drug. There were no Hy's Law cases identified by the panel.

Vital Signs, Physical Findings, and Observations

In long-term study 201, approximately 20% of subjects had on-treatment SBP or DBP or heart rate (HR) abnormalities during the study. The on-treatment vital sign and physical abnormalities were generally more frequent in the PRN groups than the Scheduled EOD + PRN group, likely reflecting the longer duration of the LTT period in the PRN enrolment groups.

Table 60: On-treatment Vital Sign, Physical Measurement, and Electrocardiogram Abnormalities: Treated Subjects in the Phase 2/3 Long-term, Open-label Safety Study Supporting the Acute Treatment of Migraine (BHV3000-201)

	n (%)			
	Enrollment Group			
Vital sign/ Physical measurement/ QTc Interval	PRN (2-8) (N = 1,033)	PRN (9-14) (N = 481)	Scheduled EOD + PRN (N = 286)	Overall (N = 1,800)
Systolic blood pressure (mmHg)	**1,003**	**460**	**276**	**1,739**
< 90	44 (4.4)	27 (5.9)	2 (0.7)	73 (4.2)
> 140	178 (17.7)	75 (16.3)	14 (5.1)	267 (15.4)
> 160	12 (1.2)	11 (2.4)	0	23 (1.3)
Diastolic blood pressure (mmHg)	**1,003**	**460**	**276**	**1,739**
< 50	11 (1.1)	5 (1.1)	0	16 (0.9)
> 90	237 (23.6)	105 (22.8)	24 (8.7)	366 (21.0)
> 100	27 (2.7)	9 (2.0)	2 (0.7)	38 (2.2)
Heart rate (bpm)	**1,003**	**460**	**276**	**1,739**
< 60	216 (21.5)	78 (17.0)	29 (10.5)	323 (18.6)
> 100	64 (6.4)	34 (7.4)	7 (2.5)	105 (6.0)
Temperature (°C)	**1,004**	**460**	**276**	**1,740**
< 36	179 (17.8)	59 (12.8)	21 (7.6)	259 (14.9)
> 38	1 (0.1)	1 (0.2)	0	2 (0.1)
Respiratory rate (breaths/min)	**1,003**	**460**	**276**	**1,739**
< 12	39 (3.9)	8 (1.7)	0	47 (2.7)
> 20	21 (2.1)	8 (1.7)	3 (1.1)	32 (1.8)
Weight change from baseline	**1,003**	**460**	**276**	**1,739**
≤ -7%	117 (11.7)	51 (11.1)	6 (2.2)	174 (10.0)
≥ 7%	114 (11.4)	51 (11.1)	12 (4.3)	177 (10.2)
ECG: QTcF (msec)	**995**	**458**	**276**	**1,729**
> 450	3 (0.3)	4 (0.9)	1 (0.4)	8 (0.5)
> 480	1 (0.1)	0	0	1 (0.1)
> 500	0	0	0	0

Abbreviations: ECG = electrocardiogram; EOD = every other day; QTcF = QT interval corrected by Fridericia's formula; PRN = as needed.
Categories are not mutually exclusive. Subjects are counted in categories as long as they have at least 1 value during the safety analysis period that meets the criterion.
Percentages for all parameters except weight change are based on subjects with non-missing data at an on-treatment visit. Percentages for weight change are based on subjects with non-missing data at both baseline and an on-treatment visit.

Hypersensitivity

Anaphylactic reaction and rash were reported in 1 (0.1%) subject in the rimegepant group in 303 study.

In long-term safety study 201, hypersensitivity was reported as an AE in 4 (0.2%) subjects.

Overdose

In the long-term, open-label safety study 201, subjects were dispensed 30 open-label tablets that can be used PRN to treat migraine. In addition, a separate group received scheduled EOD dosing, as well as having the ability to dose PRN on non-scheduled dosing days. During long-term and frequent administration, no pattern of AEs suggestive of potential drug abuse was identified.

Overall, the pattern of usage during the treatment period was consistent with the subjects' historical frequency of migraine on entry to the study. At study entry, the mean subject-reported history of moderate to severe migraine was 5.0 per month in the PRN (2-8) group, 10.0 per month in the PRN (9-14) group, and 6.0 per month in the Scheduled EOD + PRN group. During the OP, the mean number of MDs per 4 weeks for moderate to severe migraine was 5.1 days in the PRN (2-8) group, 9.3 days in the PRN (9-14) group, and 6.5 days in the Scheduled EOD + PRN group. Overall, during the LTT, the mean number of MDs per 4 weeks for moderate to severe migraine was 5.2 days in the PRN (2-8) group, 8.4 days in the PRN (9-14) group, and 4.3 days in the Scheduled EOD + PRN group. In the PRN groups, subjects were instructed they could self-administer rimegepant PRN up to once per calendar day to treat migraine of any severity. Mean average rimegepant exposure (tablets per 4 weeks) during treatment with rimegepant PRN was consistent with the number of MDs reported (PRN [2-8]: 5.6 tablets; PRN [9-14]: 8.5 tablets). In this setting of subject access to 30 tablets of rimegepant per month for up to 52 weeks, there has been no signal suggestive of misuse, overuse, or abuse of rimegepant. No pattern of usage suggestive of euphoric effects or abuse was observed.

A total of 35 (1.9%) subjects in the long-term, open-label safety study (BHV3000-201) were reported as having taken > 1 tablet/day on any day with no pattern of associated AEs. Accidental overdose was reported as an AE in 4 (0.2%) subjects. In each instance, the subject took up to a total of 2 rimegepant tablets in 1 calendar day.

Drug Abuse

Potential drug abuse AEs were monitored in subjects with migraine treated with rimegepant 75 mg in the long-term, open-label safety study 201 and prevention study 305. The types and frequency of on-treatment AEs categorised as associated with potential drug abuse were generally consistent across enrolment groups of study 201. The most frequently reported on-treatment AEs categorised as associated with potential drug abuse ($\geqslant$ 1% of subjects overall) were fatigue (1.4%) and somnolence (1.3%). MoH (reported as verbatim term of rebound headaches; considered possibly related to study drug) was reported for 1 (0.1%) subject in study 201.

In the pivotal Phase 2/3 migraine prophylaxis study 305, no potential drug abuse AEs were reported in $\geqslant$ 1% of the subjects treated with rimegepant. The most frequently reported on-treatment potential drug abuse AEs were depression (0.9%), fatigue (0.7%), insomnia (0.6%), and somnolence (0.4%). There were no reports of medication overuse headache among subjects treated with rimegepant in this study. One subject had a follow-up potential drug abuse AE of fatigue.

Withdrawal and Rebound

The effect of rimegepant withdrawal and rebound was not directly studied. No evidence of rebound or withdrawal was identified during the follow-up periods of the Phase 3 single-dose studies (301, 302, and 303), in the long-term, open-label safety study (201), or pivotal Phase 2/3 migraine prophylaxis study (305). The only potential drug abuse AEs identified during follow-up in BHV3000-201 were depression, irritability, and syncope (each in 1 subject) and fatigue (1 subject) in BHV3000-305. No AEs for PTs in the MedDRA SMQ for drug withdrawal were identified across the clinical development programme for the acute treatment of migraine or migraine prophylaxis. Withdrawal or rebound effects are not anticipated for rimegepant.

Medication Overuse Headache

During the long-term, open-label 52-week safety study 201 subjects received a bottle with 30 tablets of rimegepant at each dispensing and could self-administer doses as often as necessary or desired, no suggestion of a potential for causing medication overuse headache was identified. An AE of medication overuse headache (considered possibly related to study drug) was reported for only 1 subject in the study. Of note, before taking any rimegepant, the subject had rebound headaches, which were reported as an AE (PT of MoH) that was mild in intensity. On the same day that the subject took the first dose of rimegepant, the subject had rebound headaches, which were reported as an AE (PT of medication overuse headache) that was moderate in intensity (an increase in intensity from the prior AE).

Effect on Ability of Drive or Operate Machinery

In the setting of acute treatment of migraine among the treated subjects in the Phase 3 SD studies 301/302/303 and the long-term, open-label safety study 201, or the setting of migraine prophylaxis among rimegepant-treated subjects in the migraine prophylaxis study 305, dizziness and somnolence were reported, often in subjects taking concomitant medications. These AEs were of low frequency, occurred at comparable frequencies in the rimegepant and placebo groups, were mostly mild in intensity, infrequently led to discontinuation of study drug, and were not reported in follow-up.

No dedicated driving impairment study was conducted. Based on available AE data, the applicant suggests that no special instructions for effect on ability to drive or operate machinery are required.

Immunological events

N/A

Discontinuation due to AES

A total of 20 (3.0%) subjects had AEs leading to DC of rimegepant in the double-blind or open-label rimegepant phase of study 305. These 20 subjects included 6 subjects in the rimegepant group who had AEs leading to DC of rimegepant during the DBT phase (excluding the event of blood creatinine increased), and 14 subjects treated with rimegepant in the open-label phase who had AEs leading to DC. Anxiety, depression, nausea, and ALT increased were the only PTs reported in more than 1 subject in the DBT and OLE phase (2 [0.3%] subjects each).

In long-term study 201, on-treatment AEs leading to DC of rimegepant were reported in 48 (2.7%) subjects. The frequencies of AEs leading to DC of rimegepant were consistent across enrolment groups.

The PTs of AEs leading to DC of rimegepant reported in more than 1 subject were:

- Dizziness in 5 (0.3%) subjects
- ALT increased and AST increased in 3 (0.2%) subjects each
- Anxiety, arthralgia, blood creatine phosphokinase increased, constipation, depression, hot flush, suicidal ideation, and vertigo in 2 (0.1%) subjects each.

Post marketing experience

Rimegepant was approved for the treatment of acute migraine attacks in the US on 27-Feb-2020. The post-authorisation exposure is based on the projected monthly prescription data and the daily affordability programme data. The product has been on the market only in the US, for the indication acute treatment of migraine. The recommended dose in the US is 75 mg taken orally, as needed. The maximum dose in a 24-hour period is one ODT.

As of 26-Aug-2020, approximately 70,900 patients have been treated. Post-marketing safety is available from the Periodic Benefit-Risk Evaluation Report (PBRER) Bi-annual Report covering the period from 27-Feb-2020 through 26-Aug-2020.

According to the tabulated overview of adverse drug reactions, *Drug ineffective* (115) in liaison with *Therapeutic effect incomplete* (26) were reported most often.

Gastrointestinal AEs known from pivotal trials were also observed post-marketing (*Nausea*: 30, *Vomiting*: 10). AEs potentially indicative of abuse potential were low (*Feeling of relaxation*: 1, *Hangover*: 2, *Accidental overdose*: 2, *Overdose*: 4, *Off-label use*: 6), however, there were 16 reports of *Somnolence*. Events of *Hypersensitivity* were reported for 6 subjects, 3 of these were categorised as serious. Cases of *Hypersensitivity* add to 16 reports of skin reactions encompassing *Angioedema* (1), *Pruritus* (3), *Rash* (4), *Urticaria* (2) and others.

2.8.1. Discussion on clinical safety

Safety data were analysed in pooled groups of Phase 2 and 3 single-dose (301, 302, 303) and multiple-dose (201, 305) studies in subjects with migraine who were treated with rimegepant 75 mg or placebo. Also, safety data were evaluated in healthy subjects receiving rimegepant doses ranging from single doses of 25 mg through 1,500 mg, multiple-dose regimens of up to 600 mg QD for 14 days, or 300 mg twice daily for up to 14 days.

Exposure

The safety database comprises a total of N=4,628 unique treated subjects receiving either single or multiple doses of rimegepant throughout the clinical development programme. These include a total of 527 subjects receiving rimegepant (EOD or EOD + PRN up to QD) for at least 6 months, and 311 subjects receiving rimegepant for at least 1 year. The OLE period of study 305 was ongoing at the time of dossier submission and has reached its final database lock on 23-April-2021. The minimum requirements for drug exposure as specified per ICH E1 Guidance are fulfilled.

Demographics

At screening, subjects were identified that present with a contraindication to triptan use. These were not per se excluded from single or multiple attack studies. Contraindications to triptans mainly concern CV safety. However, patients with uncontrolled, unstable or recently diagnosed CV disease, such as ischemic heart disease, coronary artery vasospasm, cerebral ischemia, MI, acute coronary syndrome etc. were excluded from 301/302/303/305. Hence, there is large overlap between the CV contraindications to triptans and the CV study exclusion criteria, which explains the low portion (0.4-1.2%) of subjects with apparent contraindications to triptans, but eligibility for studies 301/302/303. The applicant will conduct a PASS of Rimegepant in Patients with Migraine and a History of Cardiovascular Diseases to further characterise this population.

Subjects with general risk factors for CV disease that did not contraindicate triptan use (e.g. family history of coronary artery disease, treatment for hypertension, current smoker, treatment with a statin, or history of diabetes) were included in rimegepant trials. No upper limit of age was defined. The mean age of study participants was around 40 years. The subgroup of subjects $\geq$ 65 years of age was small, around 2-3% in SD studies and 5.8% in prevention study 305. MoH is common among severely affected patients requiring prophylactic migraine medication. The portion of subjects with existing MoH at the entry of long-term studies 201 and 305 is unclear. Subjects with MoH were initially excluded both from study 305 and 201. However, in study 201 this restriction was removed with revised Protocol V2.0. In study 305, 22.7% of subjects presented with a history of CM after implementation of Protocol

Amendment 4, which widened the entry criteria to also include CM. Given the high overlap between CM and MoH, there is a degree of uncertainty with regard to MoH among recruited subjects.

Adverse events – acute treatment

The applicant specifies on-treatment AEs as those occurring from the study drug first dose through the study drug last dose plus 7 days and differentiates on-treatment AEs from treatment-emergent AEs (defined as those occurring, worsening, or becoming serious during treatment relative to pre-treatment). This distinction was not expected and is not considered to contribute to easy overview of summarised safety data. Given the overlap between on-treatment AEs and TEAEs, similar findings were made. The overall rate of on-treatment AEs was low in pooled single dose phase 3 studies supporting the acute treatment of migraine attacks (rimegepant 10.8%, placebo 8.6%). The low frequency of on-treatment AEs in acute migraine treatment is to be seen in the context of the short intervention of single dose administration in studies 301/302/303. Nausea occurred most often (rimegepant 1.2%, placebo 0.8%), followed by urinary tract infections (rimegepant 0.8%, placebo 0.3%).

On-treatment AEs were reported considerably more often in the acute treatment setting of long-term study 201 (PRN 2-8 and PRN 9-14 enrolment groups, up to 52 weeks LTT) than in single dose studies 301/302/303. With regard to the nature of reported PTs, there was large overlap between the single dose and PRN (as needed) dosing scheme. In PRN groups of study 201, a mean number of 5.6 (PRN2-8), resp. 8.5 (PRN9-14) rimegepant doses were applied per 28-day dosing interval. In both clinical settings, urinary tract infections, and nausea were among most often reported PTs. On-treatment AEs related to study drug in long-term study 201 comprise mainly unspecific AEs like nausea (1.3%), constipation (1.1%), diarrhoea (0.4%), dizziness (1.5%). somnolence (1.1%).

The frequency of reported hepatic enzyme increases were low (0.3% in single attack studies both in the rimegepant and placebo group). The acute treatment safety database does not point to any increased suicidality related to rimegepant based on S-STS testing.

Rimegepant is not assumed to penetrate the blood brain barrier in humans in relevant quantities. Nonclinical data indicate rimegepant did not readily cross the blood-brain barrier in rats after daily oral doses of 30, 100, and 300 mg/kg for 14 days (brain-to-plasma ratio of 0.02 to 0.19) at 24 hours after the last dose. The list of nervous system-related on-treatment AEs in study 201 does not point to AEs particularly indicative of abuse liability, like e.g. feeling high, euphoria etc. Dizziness ranks highest with 2.5% (PRN2-8) resp. 2.7% (PRN9-14) subjects being affected. There were 4 cases of accidental overdose, all concerned exceeding the maximum daily dose of 1 rimegepant tablet per day by 1 further tablet. In 3 out of 4 cases this happened only once in the course of LTT. Safety analysis of acute migraine treatment with rimegepant does not point to abuse liability.

Adverse events – prophylactic treatment

Both in the 12-week EOD + PRN of study 201 and the prophylactic EOD dosing setting of study 305, the frequency of on-treatment AEs was low. During the 12-week DBT period of study 305, the overall frequency of any on-treatment AE was comparable between the rimegepant (35.9%) and placebo arm (35.8%). Also, the nature of on-treatment AEs was similar between acute as-needed and prophylactic EOD dosing. In both clinical settings, nausea and infections of the urinary tract were observed most often. Overall figures of on-treatment AEs were low (EOD rimegepant DBT study 305: nausea 2.7%, nasopharyngitis 3.5%, urinary tract infection 2.4%, upper respiratory tract infection 2.2%), pointing to a favourable safety profile of rimegepant.

A wide spectrum of PTs was screened to check for any signal pointing to potential abuse liability of rimegepant under EOD dosing conditions. CNS-related PTs were reported at low frequencies and point to a low degree of CNS depressant effects of rimegepant (e.g. depressed level of consciousness, memory impairment, lethargy, somnolence, confusional state etc. [0.1 – 0.4%]). No PTs were reported like

euphoria or feeling high. There is no signal of potential abuse liability of rimegepant under prophylactic EOD dosing conditions.

Safety data obtained from prevention study 305 did not point to an increased rate of CV AEs resulting from EOD rimegepant dosing. It is reminded, however, that the population of prevention study 305 was young (mean age 41.3 years) with only a small minority of subjects ≥ 65 years of age (5.8%). Patients with a current evidence of uncontrolled, unstable, or recently diagnosed CV disease were excluded from pivotal rimegepant studies.

One case of ischaemic colitis was reported as SAE in a RGP-treated subject in study 201.Given the theoretical plausibility of CGRP antagonism impacting ischaemic events, ischaemic colitis should be monitored post-marketing.

The overall rate of AEs leading to study discontinuation was low during the 12-week DBT period of study 305 (rimegepant: 1.9%, placebo 1.1%). No particular pattern of safety signal can be discerned. No PT was recorded by more than one single subject. Combined analysis of DBT and the subsequent 52-week OLE period reveals that AEs leading to discontinuation primarily occurred within the first 6 months of treatment.

Gastrointestinal disorders as AEs of special interest

On-treatment AEs related to GI disorders were summarised as requested during EMA SA. The overall frequency of GI AEs was not high. Irrespective of the single dose setting (studies 301/302/303), PRN dosing over up to 52 weeks in study 201, or EOD during the 12-week DBT period of prevention study 305, nausea (1.5-2.8%) was reported most often, followed by diarrhoea (1.9-1.6%) and constipation (1.6-1.1%) after multiple dose administration.

Raynaud's phenomenon

Subjects with a medical history of Raynaud's Syndrome were not a priori excluded from rimegepant clinical trials. Being a CGRP antagonist, there is the theoretical possibility that the inhibition of CGRP-mediated vasodilation could negatively affect existing or precipitate Raynaud symptoms associated with vasoconstriction. However, in the low number of subjects with a Raynaud history no worsening or precipitation of respective symptoms was observed.

Liver enzyme elevations - hepatotoxicity

A dedicated analysis of liver enzyme elevations and associated hepatotoxicity in patients receiving rimegepant was conducted to address concerns about potential hepatotoxic effects that were observed in other previously developed CGRP antagonist and lead to termination of their clinical study programme. With regard to drug exposure, most meaningful data are obtained from the12-week DBT period of prevention study 305 (rimegepant: N=370), its subsequent 52-week OLE phase, and the 12-week open-label EOD+PRN enrolment group (N=286) of long-term safety study 201. LFT results from the programme, as well as individual cases of aminotransferase elevations > 3 x ULN, ALP > 2 x ULN, or AEs of cirrhosis, hepatitis, liver failure, or jaundice were reviewed by a panel of external clinical hepatic experts. There were no reported elevations of ALT or AST > 3 x ULN with concurrent TBL > 2 x ULN among subjects treated with rimegepant in the double-blind or open-label phase. No cases of Hy's Law have been identified, and there was no signal of DILI due to rimegepant when administered at least EOD for up to 64 weeks of treatment or up to once daily PRN for up to 52 weeks of treatment. Given the low number of hepatic –related AEs, it is concluded that, based on available clinical data, there is no evidence of hepatotoxicity with the acute (PRN, as needed) or EOD preventive use of rimegepant 75 mg. However, relevant elevations of ALT or AST (study 305 DBT or OLE: > ULN: 20.9%), TBL (> ULN: 3.2%) and ALP (> ULN: 10.0%) were observed both in pivotal migraine studies and in PK/PD studies with healthy volunteers.

Vital signs

Recordings of vital sign abnormalities (categorical BP, HR recordings beyond pre-defined thresholds) were provided. However, these do not inform about the actual effect of rimegepant on vital signs, in particular when there is no placebo control and no temporal association between vital sign measurement (201/305: every 4 weeks) and as-needed administration of study medication (201). Meaningful data on the impact of rimegepant may be obtained from dedicated pharmacology studies systematically recording BP / HR changes after rimegepant dosing. Vital signs (BP, HR) were recorded in temporal relation to RPG administration in PK study CN170001 and QTc study 109. As part of pharmacology study BHV3000-109, changes in HR post-dose were measured at numerous time points. No clinically relevant changes in HR were observed as compared to placebo. Measurement of BP was less frequent. Recordings of BP pre-dose were compared at one time point 3h-4h post-dose only. Again, no clinically relevant changes in BP were found in healthy volunteers after 75 mg rimegepant administration in QTc study BHV3000-109.

Drug abuse

No signal suggestive of misuse, overuse, or abuse of rimegepant was reported with long-term administration in the long-term, open-label safety study 201 or prevention study 305 in subjects with migraine.

Withdrawal and rebound

Potential withdrawal of rimegepant resp. rebound of increased migraine attack frequency after abrupt cessation of longer term EOD preventive dosing of rimegepant was not monitored during follow-up of studies 201 and 305. However, PTs potentially indicative of withdrawal (e.g. irritability) were observed only very rarely (1/1693 of follow-up patients).

Medication overuse headache

The portion of subjects with existing MoH at the entry of studies 201/305 is unclear. Since MoH is commonly encountered among patients requiring migraine preventive medication, the IHS Guidance does not recommend to exclude MoH patients, but to stratify accordingly. MoH is widespread across a variety of headache medications with different modes of action. The liability of orally administered CGRP antagonist rimegepant as another type of drug contributing to the development of MoH cannot be evaluated on the present clinical database. It is also to be taken into account that the dosing interval of 48 hours proposed for migraine prevention is derived from acute migraine data of sustained efficacy from 2-48 hours post-dose. Since MoH is widespread across all types of specific and unspecific acute migraine medications, standard warnings on MoH need to be introduced in the label.

Post-marketing data

Rimegepant was approved for the treatment of acute migraine attacks in the US on 27-Feb-2020. Post-marketing safety data are available from the Periodic Benefit-Risk Evaluation Report (PBRER) Bi-annual Report covering the period from 27-Feb-2020 through 26-Aug-2020 covering about 70.000 subjects that have treated acute migraine attacks with rimegepant during the first 6 months of marketing in the US. According to the tabulated overview of adverse drug reactions, *Drug ineffective* (115) in liaison with *therapeutic effect incomplete* (26) were reported most often. GI AEs known from pivotal trials were also observed post-marketing (*nausea*: 30, *vomiting*: 10). AEs potentially indicative of abuse potential were low (*feeling of relaxation*: 1, *hangover*: 2, *accidental overdose*: 2, *overdose*: 4, *off-label use*: 6), however, there were 16 reports of *somnolence*. Events of *hypersensitivity* were reported for 6 subjects, 3 of these were categorised as serious. Cases of *hypersensitivity* add to 16 reports of skin reactions encompassing *angioedema* (1), *pruritus* (3), *rash* (4), *urticaria* (2) and others.

2.8.2. Conclusions on clinical safety

The clinical safety profile of rimegepant in the acute and prophylactic treatment of migraine is obtained from N=4,628 unique treated subjects receiving either single or multiple doses throughout the clinical development programme. By the entirety of available data, the safety profile of the orally administered CGRP antagonist rimegeapnt is considered rather favourable. On-treatment AEs related to study drug in long-term study 201 comprise mainly unspecific AEs like nausea (1.3%), constipation (1.1%), diarrhoea (0.4%), dizziness (1.5%). somnolence (1.1%). The first PBRER covering the first 6 months of marketing in the US (acute migraine indication) confirms findings based on the clinical trial data package. These include rather modest efficacy on the one side and overall good tolerability on the other side.

2.9. Risk Management Plan

2.9.1. Safety concerns

Summary of the safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant women Use in patients with cardiovascular diseases

2.9.2. Pharmacovigilance plan

Table 61: Table of on-going and planned additional pharmacovigilance studies/activities in the PV plan

Study ***Status***	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 – Required additional pharmacovigilance activities				
Rimegepant Pregnancy Registry study **BHV3000-402** *Ongoing*	Primary: • To compare the occurrence of major congenital malformations in the fetuses/infants of women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception) to 1) an internal cohort of women with migraine not exposed to rimegepant before or during pregnancy and 2) an external cohort of pregnant women without migraine. Secondary:	Use in pregnant women	Protocol Version 1.0 Submit Protocol Version 1.0 and Statistical Analysis Plan (SAP) for PRAC Review Annual interim reports Final report	Approved by FDA-16/08/2021 Within 1 month of Marketing Approval From 30/04/2022 30/04/2035

Study *Status*	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
	• To describe the occurrence of adverse fetal outcomes, maternal pregnancy complications, infant outcomes at birth, and infant events of interest up to 1 year post delivery in women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception), and to form comparisons to the same outcomes in 1) an internal cohort of women with migraine not exposed to rimegepant before or during pregnancy and 2) an external cohort of pregnant women without migraine: • Fetal outcomes • Maternal pregnancy complications • Infant outcomes • Other adverse events			
Rimegepant Pregnancy Outcomes study **BHV3000-403** *Ongoing*	Primary: • To evaluate the risk of pregnancy and infant outcomes among women with migraine exposed to rimegepant during pregnancy and in 2 rimegepant-unexposed comparator groups. Specific: • To describe patterns of use of rimegepant in pregnant women • To estimate the frequency of pregnancy outcomes and fetal/infant outcomes • To estimate the adjusted relative risks for the study outcomes among women exposed to rimegepant in pregnancy compared with each of the 2 unexposed comparator groups	Use in pregnant women	Protocol Version 1.0 Submit Protocol Version 1.0 and SAP for PRAC Review Annual interim reports Final report	Approved by FDA-14/12/2021 Within 1 month of Marketing Approval From 30/04/2022 30/04/2029
PASS of Rimegepant in Patients with Migraine and a	Primary: • To compare the incidence rate of major adverse cardiovascular	Use in patients with cardiovascular diseases	Submit Protocol and SAP for PRAC Review	Within 3 months of Marketing Approval

Study *Status*	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
History of Cardiovascular Diseases **[Protocol number to follow]** Planned	events (MACE) in new users of rimegepant with migraine and a history of cardiovascular diseases with the incidence rate of MACE in migraine patients with a history of cardiovascular diseases who are on other migraine treatments • To describe the characteristics and patterns of use of rimegepant among new users with migraine and a history of cardiovascular diseases		Annual interim reports Final report	From within one year of launch in each study country (3 annual interim reports) Within 4 years after launch

2.9.3. Risk minimisation measures

Table 62: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in pregnant women	Routine risk communication: SmPC section 4.6 PL section 2 Legal status: prescription only medication No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance: -Rimegepant Pregnancy Registry study (BHV3000-402) -Rimegepant Pregnancy Outcomes study (BHV3000-403)
Use in patients with cardiovascular diseases	Routine risk communication: Not applicable Legal status: prescription only medication No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance: - PASS of rimegepant in patients with migraine and a history of cardiovascular diseases

2.9.4. Conclusion

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

2.10. Pharmacovigilance

2.10.1. 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.

2.10.2. 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 27 February 2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.11. Product information

2.11.1. 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.*

2.11.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vydura (rimegepant) 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

3.1.1. Disease or condition

Migraine is a serious, chronic, disabling neurological disease characterised by attacks of moderate to severe headache 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.

3.1.2. Available therapies and unmet medical need

According to current treatment guidelines, unspecific analgesics like acetylic acid, ibuprofen, paracetamol etc. rank among first-line therapies, however, are typically used for less severe migraine attacks. Major progress in more specific treatment of acute migraine symptoms was achieved with the advent of the triptans in the nineties. Triptans target 5-HT1B and 5-HT1D receptors and their mechanism is thought to involve cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release (Rizatriptan SmPC). As the gold standard for acute treatment of migraine, they represent 28% to 36% of prescribed

acute migraine medications (Mafi et al. 2015; Molina et al. 2018). However, triptans are not efficacious for all patients: the main efficacy benchmark, i.e. the rates of pain freedom at 2 hours post-dose with triptans are in the range of 20% to 40% (Ferrari et al. 2002). Furthermore, efficacy and tolerability vary, both between agents (7 triptans approved so far), and from patient to patient.

Although forming the mainstay of current acute migraine therapy, it is concluded that around 30% of patients fail to respond to a particular triptan (Dodick DW 2005). The reasons therefore are not fully understood and may include inter- and intra-individual attack variability, on top of other factors modifying responsiveness, like e.g. concomitant use of preventive medication, MoH, inadequate dosing, the time point of medication intake relative to the onset of the attack, incomplete absorption due to concomitant gastric stasis or vomiting, presence resp. absence of aura symptoms etc. (Viana M 2013). Furthermore, the use of the triptans is limited with regard to their CV risk profile.

The inclusion criteria of rimegepant's RCTs specify that subjects with contraindications to triptans may be eligible, provided they meet all other study entry criteria. Contraindications to triptans mainly concern CV safety. However, patients with uncontrolled, unstable or recently diagnosed CV disease, such as ischemic heart disease, coronary artery vasospasm, cerebral ischemia, MI, acute coronary syndrome etc. were excluded from rimegepant trials. It remains therefore unclear which patients with existing contraindications to triptans would actually be eligible for treatment with rimegepant. There is no statement in the proposed rimegepant SmPC highlighting or claiming a potential advantage of RGP as compared to triptans in terms of the CV risk profile. Since rimegepant is not vasoconstrictive and the CV risk profile appears favourable, no CV contraindications were labelled for rimegepant.

As concerns migraine prophylaxis, the range of available oral treatment options (ß-blockers, topiramate, antidepressants etc.) most recently was complemented by ABs (so-called biologicals) targeting circulating CGRP or its receptor (erenumab, fremanezumab, galcanezumab). 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, the applicant claims potential advantages for RGP as a needle-free treatment option, that avoids polypharmacy (by offering acute and preventive treatment with one substance) and allows flexible treatment if immediate cessation of therapy is required, e.g. in case a serious AE or pregnancy.

Overall, in view of incomplete response to currently available acute migraine medications on the one side and limitations to their use due to CV safety concerns on the other side, there is a general need for new therapeutic approaches in acute migraine therapy. Based on its pharmacological profile as an orally administered CGRP antagonist and the assumed absence of any vasoconstrictive properties, RGP may potentially constitute a valuable contribution to currently available migraine therapeutics.

3.1.3. Main clinical studies

The clinical dossier of rimegepant includes efficacy data from two separate sets of clinical studies that were provided for the acute (single attack studies 301 [N=1.084] / 302 [N=1.072] / 303 [N=1.351]) and preventive treatment (study 305 [N=695]) of migraine under randomised, placebo-controlled conditions. In terms of baseline demographics of acute migraine studies, the mITT population is considered as typically representative of the migraine target population in terms of age (mean of 40-42 years, 96.8% < 65 years), gender (85-89% female), history of migraine with aura (30-37%), and the portion of subjects receiving preventive medication (13-17%). At screening, about one third of subjects was currently using triptans for the treatment of acute attacks. The mean duration of migraine history is about 20 years at study entry. The median number of moderate to severe migraine attacks per month is 4.0 across treatment arms. The majority of subjects is considered moderately to severely affected by the disease.

Supportive data include phase 2b dose-ranging study CN170003 ([N=811], with capsule) establishing rimegepant 75 mg as the minimum effective dose, and a phase 2/3, open-label, long-term safety study where subjects could receive rimegepant 75 mg doses for up to 52 weeks (201 [N=1.800]). All studies were conducted in the US.

The most relevant efficacy endpoints in single attack studies 301/302/303 are adequately chosen and are in line with guideline provisions. These include pain resp. MBS freedom at 2 hours post-dose (co-primary), sustained freedom from pain / MBS from 2-24 or 2-48 hours post-dose, and pain relief at early assessment time points.

An active control arm was not included in prevention study 305. 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 contextualize the clinical effect of the test medication, however, is not considered essential from the regulatory perspective. Throughout the 12-wk double blind treatment period, subjects had to treat acute attacks (if any occurred) using their usual standard medication, i.e. PRN rimegepant was not allowed. On the contrary, during the subsequent 1-year open-label extension (OLE) period (wk 13-64) PRN rimegepant could be used in case an acute migraine attack occurred. However, a MDD of 75 mg rimegepant had to be observed, i.e. PRN rimegepant could only be taken on days for which every-other-day (EOD) rimegepant for prevention was not scheduled.

The primary efficacy endpoint of study 305 was the change from the OP in the mean number of migraine days (MD) per month in the last month (Weeks 9 to 12) of the DBT phase. A migraine day was defined along the IHS guidance provisions for an EM population, i.e. as a day with headache lasting at least 30 minutes without intake of analgesics and meeting ICHD-3 criteria for migraine or probable migraine.

Subjects included in prevention study 305 were severely affected by the disease and experienced a median number of 8.0 migraine attacks per month with a portion of 12.9% subjects suffering $\geq$ 12 attacks per month.

3.2. Favourable effects

High rate of study completion

In terms of subject disposition, study completion was very high across the 3 single attack studies 301/302/303 and dose arms (around 99% for rimegepant 75 mg and placebo), which does not surprise, given the shortness of intervention. Equally, a high portion of subjects completed the 12-week double-blind treatment period of prevention study 305 (84.5%, equally distributed across arms: rimegepant 85.4%, placebo 83.6%). Only very few subjects discontinued due to AE on DBT or subsequent OLE period (n=13 [3.5%] rimegepant, n=5 [1.7%] placebo patients). About equal portions of subjects continued to the OLE phase after terminating the DBT period (rimegepant: 81.6%, placebo: 81.4%).

Co-primaries in acute studies: Effects significant, but modest

Across the 3 pivotal single attack studies, superiority over placebo could consistently be shown for both co-primary endpoints, i.e. portions of patients achieving pain freedom resp. MBS freedom at 2 hours post-dose.

Secondaries in acute studies: Modest effects, partly significant due to hierarchical testing

A multitude of secondary efficacy endpoints were tested hierarchically in studies 301, 302. In line with EMA Guideline provisions, demonstration of sustained freedom of pain from 2-24 hours and/or from 2-48 hours post-dose were included. Across all single attack studies, numerical differences in favour of RGP could be shown (risk difference (%) / p-values: pain freedom 2-24 hour: 301: 5.86 / 0.002, 302:

5.19 / 0.004, 303: 10.12 / <.0001*; pain freedom 2-48 hour: 301: 4.39 / 0.013, 302: 3.89 / 0.018, 303: 8.02 / <.0001*). Due to hierarchical testing, however, statistical superiority over placebo could only be shown for sustained pain freedom in study 303.

A multitude of secondary efficacy endpoints were tested hierarchically in studies 301 and 302. Freedom of associated symptoms (photophobia, phonophobia, nausea) was placed high in the hierarchy. After statistical significance could not be shown for freedom from nausea at 2 post-dose, all endpoints listed afterwards in the hierarchy were not considered statistically significant in either study. From the CHMP's perspective, there was no imminent necessity to arrange the hierarchical order of testing the secondary endpoints in the way it was conducted in studies 301/302. In study 303, the hierarchical order was modified. In line with EMA Guideline provisions, demonstration of sustained freedom of pain from 2-24 hours and/or from 2-48 hours post-dose are considered meaningful endpoints. In line with results obtained for the co-primary endpoints, net differences over placebo were modest for sustained effect-related endpoints. However, across all single attack studies, numerical differences in favour of rimegepant could be shown (risk difference (%) / p-values: pain freedom 2-24 hr: 301: 5.86 / 0.002, 302: 5.19 / 0.004, 303: 10.12 / <.0001*; pain freedom 2-48 hr: 301: 4.39 / 0.013, 302: 3.89 / 0.018, 303: 8.02 / <.0001*). Due to hierarchical testing, however, statistical superiority over placebo could only be shown for sustained pain freedom in study 303.

Reduction of MDs in prevention

In terms of migraine prevention, subjects receiving prophylactic EOD 75 mg rimegepant tablets reduced the mean number of MDs by -4.3, as opposed placebo subjects who achieved a reduction of MDs by -3.5 days throughout the last 4 weeks (week 9-12) of the DBT (primary GLMEM analysis; difference = -0.8 days; p=0.0099). In the analysis applying jump to reference targeting the treatment policy estimand, which was provided as sensitivity analysis, the net difference between RGP and placebo in evaluable mITT subjects in terms of MD reduction throughout the last 4 weeks (week 9-12) of the DBT is diminished to -0.7 MDs but still statistically significant (p=0.0400).

Although statistical superiority over placebo could be demonstrated (p=.0099) using the primary GLMEM analysis, the net difference of 0.8 MD per month is considered modest. Furthermore, the applied GLMEM analysis is not considered as the analysis that targets the effect of primary regulatory interest. The jump to referene analysis targeting the treatment policy estimand, which was provided as sensitivity analysis, is considered as the adequate analysis. If the sensitivity analysis Jump-to-Reference is applied, the net difference between rimegepant and placebo in evaluable mITT subjects in terms of MD reduction throughout the last 4 weeks (wk 9-12) of the DBT is further diminished to -0.7 MDs (p=0.0400).

Maintenance of effect

The mean number of MDs per month during the initial OP of study 305 was 9.9 MDs/month (10.1 MDs in previous rimegepant patients during DBT, 9.6 in placebo subjects). The major part of MD reduction was then achieved during the subsequent 12-week DBT. Nonetheless, the mean number of MDs per month continued to decline throughout the 52-week OLE period from a mean of 4.6 MDs at Month 1 (N=548) to 2.7 MDs at Month 13 (N=420). Thereby, maintenance of effect is shown over one year with OL regular EOD dosing plus PRN rimegepant on non-scheduled days. However, it has to be taken into account that in the course of the OLE the population progressively contains study completers, likely to be responders, while other subjects already discontinued.

3.3. Uncertainties and limitations about favourable effects

Despite significant effects that could be shown across pivotal trials in terms of primary endpoints, there are a number of uncertainties that mainly relate the magnitude of effect, lack of data (e.g. to proof

consistency of effect, no controlled data for acute attacks in EOD patients) and design-related shortcomings of the clinical programme.

Modest effect size and no proof of consistent effect in acute treatment

Despite statistical significance, the overall effect size of the 2-hour pain freedom coprimary endpoint is rather modest (net risk difference over placebo for 2-hr pain freedom: 301: 4.91%, 302: 7.59%, 303: 10.37%).

As concerns the co-primary rate of MBS freedom at 2-hours post-dose, both rimegepant and placebo response rates were higher as compared to response rates for pain freedom. The net risk difference over placebo, however, remains modest (net risk difference over placebo for 2-hr MBS freedom: 301: 8.90%, 302: 12.38%, 303: 8.29%). However modest with regard to the magnitude of the effect size, it is noted that placebo superiority could be reproduced in terms of the two co-primary endpoints across 3 independent single attack studies.

Freedom of associated symptoms (photophobia, phonophobia, nausea) was placed high in the hierarchy. After statistical significance could not be shown for freedom from nausea at 2 post-dose, all endpoints listed afterwards in the hierarchy were not considered statistically significant in either study. From the CHMP's perspective, there was no imminent necessity to arrange the hierarchical order of testing the secondary endpoints in the way it was conducted in studies 301/302. In study 303, the hierarchical order was modified. In line with results obtained for the co-primary endpoints, net differences over placebo were modest for sustained effect-related endpoints (see above).

The EMA Guideline recommends that single attack studies are supplemented with studies on consistency of effect with regard to general variability of migraine attacks. A consistency study 304 across 4 acute migraine attacks was originally planned (along EMA guideline provisions) and discussed within the scope of EMA SA from May 2018, however, no consistency data were submitted. The lacking proof of consistent effect is seen in the context of modest magnitude of effect in acute single attack trials 301/302/303, and poor outcome of long term study 201. In the largest PRN(2-8) [N=1023] enrolment group of study 201, the mean number of MDs increased by +0.1 MDs over the 52-week PRN open-label treatment period as compared to the OP. While concerns about long-term efficacy underline the importance of proving consistency of effect, a principal distinction is to be made between attrition of effect long term and the within-subject approach of demonstrating consistent efficacy according to guideline provisions.

In the absence of guideline-conforming prospective, placebo-controlled data on within-patient consistency in acute migraine, exploratory data obtained from acute migraine treatment during OLE of study 305 on unscheduled EOD dosing days were provided *post hoc*. These provide some insight into reproducibility of treatment success in consecutive acute attacks, however, have severe limitations. They reflect uncontrolled open-label conditions in patients with maintenance EOD preventive dosing that could only take rimegepant for acute migraine on non-scheduled dosing days. A focused analysis in subgroups of patients with > 3 moderate to severe MDs (N=350) and those with > 4 MDs (N=310) was provided on the first 3 resp. 4 attacks, detailing the number of patients achieving 2-hours pain freedom in 0, 1, 2, 3, (4) of the first attacks and calculating the portion of subjects achieving pain freedom in at least 2 out of first 3, resp. 3 out of first 4 attacks.

The profile obtained largely corresponds to the modest treatment effect already observed across the single attack studies 301/302/303. In both subgroups of patients with > 3, respectively > 4 moderate to severe migraine attacks, more than half of patients could not successfully treat a single attack of the first three resp. four attacks (0 out of 3: 58.4%; 0 out of 4: 52.4%). Only a very small minority of patients achieved pain freedom at 2 hours post-dose in every single of the first 3 resp. 4 attacks (3 out of 3: 5.3%; 4 out of 4: 3.4%).

As could be expected, the magnitude of requested within-patient consistency parameter (2 out of 3: 16.5%, resp. 3 out 4: 9.7%) is considerably smaller than the average absolute responder rates observed across the three single attack studies 301/302/303 of 19-21% (placebo 10.9 – 14.2%).

Lack of controlled data to show efficacy on acute attacks in EOD patients

It is inherent to claimed *comprehensive management* of migraine that rimegepant may be taken as needed for acute migraine attacks on top of regular preventive RGP administration. The lack of controlled data to demonstrate the efficacy and safety of combined acute and prophylactic use of rimegepant is considered a major limitation of the present clinical data package. The efficacy of RGP, taken for acute migraine attacks, was not demonstrated under placebo-controlled conditions in subjects already receiving regular preventive RGP.

The lacking proof of efficacy in case of acute attacks in EOD patients adds to concerns about the principal design of study 305. A maximum daily dose of 75 mg rimegepant was to be observed. Rescue medication (either rimegepant or NSAIDS) could be taken throughout the OLE of study 305 only on days which were not scheduled for EOD dosing of preventive rimegepant. It is unclear how restriction of rimegepant to be taken for acute treatment on non-scheduled days only, is compatible with clinical practice, which requires to treat acute attacks whenever they occur, irrespective of EOD dose schedules.

In order to more closely describe the implications of the proposed EOD+PRN dosing scheme in migraine prevention, the applicant was requested to show how remaining MDs and rescue medication use spread across scheduled and non-scheduled days during the OLE period of study 305. The results do not indicate any substantive difference between scheduled and non-scheduled days in the mean number of remaining MDs per month or in the mean number of rescue medication days per month. Remaining MDs were about equally distributed across scheduled and non-scheduled days with a mean of 1.7 days on scheduled days, and 1.9 on non-scheduled days across the 52-week OLE. The overall open-label mean number of rescue medication days per month was 1.3. This was also equally distributed between scheduled days (0.7 days) and non-scheduled days (0.7 days).

Clinical relevance of the effect in migraine prevention

While primary analysis and the sensitivity analysis of the primary endpoint in study 305 yielded statistically significant differences in the mean number of MDs between RGP and placebo in evaluable mITT subjects, the net difference (-0.8 MD in primary analysis and -0.7 in the sensitivity analysis) is considered modest.

In order to more accurately describe the clinical relevance of the net difference over placebo, the change of MDs from the OP over the 12-week DBT is to be taken into account. During the OP, subjects experienced 10.3 (rimegepant) resp. 9.9 (placebo) MDs. In both arms, the number of MDs per 28-day assessment period decreases constantly per month throughout the 12-week DBT period. In terms of percent reduction, the number of MDs was reduced by -50.3% in rimegepant subjects, while placebo subjects achieved to reduce the mean number of MDs from week 9-12 by -41.7%. The overall net difference of -0.7 MDs per month between rimegepant and placebo corresponds to less than 10% of the number of MDs experienced at baseline.

Subjects recruited for study 305 were stratified according to concomitant prophylactic migraine medication. In the subgroup of subjects receiving concomitant non-study migraine prophylactic medication rimegepant numerically hardly separated from placebo. Subjects without concomitant preventive treatment reduced MDs to the same degree as observed in the total mITT population of study 305. The impact of month-to-month variability in a relatively small group of subjects is taken into account. However, it is noted that reduction in MDs in prophylactic medication users continues to decline from an initial reduction of -1.6 MDs during the first four weeks of DBT, to -0.8 MDs during month 2, and finally an increase in mean MDs by 0.1 from week 9-12.

Throughout the 12-week DBT period of study 305, subjects could use their individual rescue medication in case an acute migraine attack occurred despite preventive study medication. Across arms and the three 28-day treatment intervals of the DBT, subjects used rescue on a mean of about 4-5 days per month. Rimegepant did not significantly separate from placebo in any of the three 28-day intervals of the DBT in terms of rescue medication use.

The MIDAS Migraine Disability Assessment score retrospectively reflects on how many days a patient was negatively affected by migraine throughout the preceding 3 months period. Baseline mean MIDAS scores were 36.9 in the rimegepant group and 35.3 in placebo patients, reflecting that subjects were severely affected by the disease. Rimegepant numerically hardly separated from placebo in reducing migraine-related disability (MIDAS: rimepgepant: -11.8, placebo -11.7, p=0.9616) during the 12-week DBT period. However, the course of MIDAS score changes over the 52-week OLE period of study 305 provides further reassurance. Meaningful reductions in MIDAS scores were achieved over time (week 24, week 64) over the 1-year OLE period of study 305.

Design of study 305

Apart from lacking controlled data for efficacy in acute attacks and restriction to administer rimegepant on non-scheduled EOD days only, there are further design-related uncertainties about prevention study 305.

Handling of EM vs CM sub-populations

To be eligible for participation in prevention study 305, subjects had to present with 4-18 migraine attacks per month, respectively at least 6 MD and not more than 18 headache days. With the 4th of 8 amendments implemented to the Protocol of study 305, eligibility criteria were expanded to also include subjects with CM, which were previously excluded. The number of allowed days per month with headache was increased to 18. Hence, the inclusion criteria of study 305 may include both EM and CM patients. The applicant did not provide respective IHS codes 1.1, 1.2.1, or 1.3 of included patients.

Subjects reported at study entry whether there was a history of CM (yes 22.7%) after implementation of Protocol Amendment 4. Reported history does not inform about current state. A stratified analysis of migraine prevention results in EM vs CM was not pre-specified. Only *ad hoc* exploratory results are presented, not yielding robust effects for the subgroup of "historical CM" in terms of the primary efficacy endpoint (Total MD reduction from OP to week 9-12 of DBT). The applicant claimed a broad indication of migraine prevention irrespective of EM / CM classification. However, the CM subgroup was too small to be able to show any effect independently. Furthermore, data does not allow a precise estimation on the treatment effect in this subgroup.

Evaluable mITT as primary population

Primary and secondary efficacy endpoints were analysed using *evaluable mITT subjects,* i.e. enrolled subjects who were randomised only once, received at least 1 dose of double-blind study medication (rimegepant or placebo), and had $\geqslant$ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and at least 1 month (i.e., 4-week interval) in the DBT phase of study 305. The portion of subjects not considered mITT evaluable due to less than 14 days of eDiary efficacy data in any of the 3 treatment months (28 day intervals) was low (rimegepant 5.9%, placebo 6.5%) and equally distributed across arms. Based on the EMA-SA (Dec 2018), there were initial concerns about exclusion of subjects from the primary efficacy analysis for incomplete eDiary data entry, since the reason for missing post-baseline measurements may be related to treatment and/or to the outcome. However, sensitivity analyses in *treated* subjects were provided showing that calculation of the primary endpoint in the evaluable mITT population does not create a bias in favour of rimegepant.

Definition of MD

The primary efficacy endpoint of study 305 was the change from the OP in the mean number of migraine days (MD) per month in the last month (Weeks 9 to 12) of the DBT phase. In the context of recruiting a mixed of EM/CM population in study 305, implications result as concerns definition of a MD. The IHS issued two guidance documents for preventive treatment of migraine attacks with different definitions (i.e. required duration of the headache is at least 30 minutes for EM while at least 4 hours are required for CM). Since reduction from baseline in the mean number of MDs per month in the last 4 weeks of the 12-week DBT period is defined as primary efficacy endpoint, the definition of a MD is of critical importance. In the present study 305, the sponsor defined a MD along the provisions for an EM population. Given the mixed EM/CM population of study 305, the impact of the EM-concordant MD definition on the outcome is unknown.

Acute studies: No effect against nausea and implications for other secondary endpoints in studies 301/302

Contrary to freedom from photophobia and phonophobia at 2 hours post-dose, for which consistent superiority over placebo could be shown, rimegepant did not significantly separate from placebo for the freedom from nausea as associated symptom. The differential effect of rimegepant, on the associated symptoms, photophobia/phonophobia on the one side, and nausea/vomiting on the other side, could be explained by different pathophysiological mechanisms causing the symptoms, with the ones being affected by rimegepant's CGRP antagonism, while the others aren't. Additionally, due to the placement of effect against nausea on the #3rd order in the hierarchical strategy of secondary endpoints for study 301 and 302, a statistically significant effect on other secondary endpoints (including regulatory relevant endpoints such as sustained pain freedom from 2 to 24 / from 2 to 48 hours post-dose) could not be claimed.

Long-term efficacy in study 201

Exploratory efficacy analysis of study 201 demonstrates that the long-term overall effect in acute migraine treatment is modest in the PRN (9-14) group (-0.9 MDs) [N=468]. Virtually no beneficial effect was observed in the course of the 52-week open-label treatment period in terms of reduced mean MDs per month as compared to OP in the largest enrolment group PRN (2-8) [N=1023] of subjects historically experiencing 2-8 attacks per month (+0.1 MDs, by moderate to severe severity).

3.4. Unfavourable effects

The overall safety profile of rimegepant appeared favourable.

Safety database

The safety database comprises a total of N=4,628 unique treated subjects receiving either single or multiple doses of rimegepant throughout the clinical development programme. These include a total of 527 subjects receiving rimegepant (EOD or EOD + PRN up to QD) for at least 6 months, and 311 subjects receiving rimegepant for at least 1 year. The open-label extension period of study 305 was ongoing at the time of dossier submission and has reached its final database lock on 23-April-2021. The minimum requirements for drug exposure as specified per ICH E1 Guidance are fulfilled.

At screening, subjects were identified that present with a contraindication to triptan use. These were not per se excluded from single or multiple attack studies. Contraindications to triptans mainly concern cardiovascular safety. However, patients with uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, cerebral ischemia, myocardial Infarction (MI), acute coronary syndrome etc. were excluded from 301/302/303/305. Hence, there is large overlap between the CV contraindications to triptans and the CV study exclusion criteria,

which explains the low portion (0.4-1.2%) of subjects with apparent contraindications to triptans, but eligibility for studies 301/302/303.

Subjects with general risk factors for CV disease, that did not contraindicate triptan use (e.g. family history of coronary artery disease, treatment for hypertension, current smoker, treatment with a statin, or history of diabetes) were included in rimegepant trials. No upper limit of age was defined. The mean age of study participants was around 40 years.

Adverse events – acute treatment

The overall rate of on-treatment AEs was low in pooled single dose phase 3 studies supporting the acute treatment of migraine attacks (rimegepant 10.8%, placebo 8.6%). The low frequency of on-treatment AEs in acute migraine treatment is to be seen in the context of the short intervention of single dose administration in studies 301/302/303. Nausea occurred most often (rimegepant 1.2%, placebo 0.8%), followed by urinary tract infections (rimegepant 0.8%, placebo 0.3%).

With regard to the nature of reported PTs, there was large overlap between the single dose and PRN (as needed) dosing scheme. In PRN groups of study 201, a mean number of 5.6 (PRN2-8), resp. 8.5 (PRN9-14) rimegepant doses were applied per 28-day dosing interval. In both clinical settings, urinary tract infections, and nausea were among most often reported PTs. On-treatment AEs related to study drug in long-term study 201 comprise mainly unspecific AEs like nausea (1.3%), constipation (1.1%), diarrhoea (0.4%), dizziness (1.5%). somnolence (1.1%).

The list of nervous system-related on-treatment AEs in study 201 does not point to AEs particularly indicative of abuse liability, like e.g. feeling high, euphoria etc. Dizziness ranks highest with 2.5% (PRN2-8) resp. 2.7% (PRN9-14) subjects being affected.

One case of ischaemic colitis was reported as SAE in a RGP-treated subject in study 201. Given the theoretical plausibility of CGRP antagonism impacting ischaemic events, ischaemic colitis should be monitored post-marketing.

Adverse events – prophylactic treatment

Both in the 12-week EOD + PRN of study 201 and the prophylactic EOD dosing setting of study 305, the frequency of on-treatment AEs was low. During the 12-week DBT period of study 305, the overall frequency of any on-treatment AE was comparable between the rimegepant (35.9%) and placebo arm (35.8%). Also, the nature of on-treatment AEs was similar between acute as-needed and prophylactic EOD dosing. In both clinical settings, nausea and infections of the urinary tract were observed most often. Overall figures of on-treatment AEs were low (EOD rimegepant DBT study 305: nausea 2.7%, nasopharyngitis 3.5%, urinary tract infection 2.4%, upper respiratory tract infection 2.2%), pointing to a favourable safety profile of rimegepant.

No signal suggestive of misuse, overuse, or abuse of rimegepant was reported with long-term administration in the long-term, open-label safety study 201 or prevention study 305 in subjects with migraine.

Through inhibition of vasodilatory activity of CGRP, rimegepant may theoretically attenuate compensatory vasodilation in ischaemia-related conditions. Subjects with a medical history of Raynaud's Syndrome were not a priori excluded from rimegepant clinical trials. There is the theoretical possibility that the inhibition of CGRP-mediated vasodilation could negatively affect existing or precipitate Raynaud symptoms associated with vasoconstriction. However, in the low number of subjects with a Raynaud history no worsening or precipitation of respective symptoms was observed. There were no CV AEs reported in the DBT period of study 305. There was 1 case (0.1%) of MI during the OLE in a 60-70 years patient with a medical history of CV risks factors.

Post-marketing data

Rimegepant was approved for the treatment of acute migraine attacks in the US on 27-Feb-2020. Post-marketing safety data are available from the PBRER Bi-annual Report covering the period from 27-Feb-2020 through 26-Aug-2020 including about 70.000 subjects that have treated acute migraine attacks with rimegepant during the first 6 months of marketing in the US. According to the tabulated overview of adverse drug reactions, *Drug ineffective* (115) in liaison with *therapeutic effect incomplete* (26) were reported most often. AEs known from pivotal trials were also observed post-marketing (*nausea*: 30, *vomiting* : 10). AEs potentially indicative of abuse potential were low. Events of *hypersensitivity* were reported for 6 subjects, 3 of these were categorised as serious. Cases of *hypersensitivity* add to 16 reports of skin reactions encompassing *angioedema* (1), *pruritus* (3), *rash* (4), *urticaria* (2) and others.

3.5. Uncertainties and limitations about unfavourable effects

Liver enzyme elevations - hepatotoxicity

A dedicated analysis of liver enzyme elevations and associated hepatotoxicity in patients receiving rimegepant was conducted to address concerns about potential hepatotoxic effects that were observed in other previously developed CGRP antagonist and lead to termination of their clinical study programme. There were no reported elevations of ALT or AST > 3 x ULN with concurrent TBL > 2 x ULN among subjects treated with rimegepant in the double-blind or open-label phase. No cases of Hy's Law have been identified, and there was no signal of DILI due to rimegepant when administered at least EOD for up to 64 weeks of treatment or up to once daily PRN for up to 52 weeks of treatment. Given the low number of hepatic–related AEs, it is concluded that, based on available clinical data, there is no evidence of hepatotoxicity with the acute (PRN, as needed) or EOD preventive use of rimegepant 75 mg. However, relevant elevations of ALT or AST (study 305 DBT or OLE: > ULN: 20.9%), TBL (> ULN: 3.2%) and ALP (> ULN: 10.0%) were observed both in pivotal migraine studies and in PK/PD studies with healthy volunteers.

Vital signs

Recordings of vital sign abnormalities were provided. However, these do not inform about the actual effect of rimegepant on vital signs, in particular when there is no placebo control and no temporal association between vital sign measurement (201/305: every 4 weeks) and as-needed administration of study medication (201). However, vital signs (BP, HR) were recorded in temporal relation to RPG administration in PK study CN170001 and QTc study 109. As part of pharmacology study 109, changes in HR post-dose were measured at numerous time points. No clinically relevant changes in HR were observed as compared to placebo. Measurement of BP was less frequent. Recordings of BP pre-dose were compared at one time point 3h-4h post-dose only. Again, no clinically relevant changes in BP were found in healthy volunteers after 75 mg rimegepant administration in QTc study 109.

Withdrawal and rebound

Potential withdrawal of rimegepant resp. rebound of increased migraine attack frequency after abrupt cessation of longer term EOD preventive dosing of rimegepant was not monitored during follow-up of studies 201 and 305. However, PTs potentially indicative of withdrawal (e.g. irritability) were observed only very rarely (1/1693 of follow-up patients).

Medication overuse headache (MoH)

Since MoH is commonly encountered among patients requiring migraine preventive medication, the IHS Guidance does not recommend to exclude MoH patients, but to stratify accordingly. MoH is widespread across a variety of headache medications with different modes of action. The liability of orally administered CGRP antagonist rimegepant as another type of drug contributing to the development of

MoH cannot be evaluated on the present clinical database. Subjects with MoH were initially excluded both from study 305 and 201. However, in study 201 this restriction was removed with revised Protocol V2.0. In study 305, 22.7% of subjects presented with a history of CM after implementation of Protocol Amendment 4, which widened the entry criteria to also include CM. Given the high overlap between CM and MoH, there is a degree of uncertainty with regard to MoH among recruited subjects. It is also to be taken into account that the dosing interval of 48 hours proposed for migraine prevention is derived from acute migraine data of sustained efficacy from 2-48 hours post-dose. Since the liability of rimegepant to contribute to the development of MoH is unclear, respective standard warnings are labelled.

Use in pregnant women

In order to characterize the missing information regarding rimegepant use in pregnant women, the applicant propose to collect data via two FDA approved studies (402 and 403) conducted in the US to obtain information on rimegepant use in pregnant women in an EU-based population.

Use in patients with CV diseases

The applicant has proposed a PASS to further characterize the risk in "patients with CV diseases." The proposed PASS is an observational cohort study to compare the incidence rate of MACE in new users of with migraine and a history of CV disease with similar patients but on other migraine treatments by using secondary data from multiple healthcare databases in Europe. The feasibility assessment and the study design are adequate to further characterise the risk in "patients with CV diseases."

Use in older patients

The subgroup of subjects $\geq$ 65 years of age was small, around 2-3% in SD studies and 5.8% in prevention study 305.

3.6. Effects Table

Table 63: Effects Table of Rimegepant for the Comprehensive Management of Migraine with or without Aura in Adults

Effect	Short Description	PBO Single dose	RGP 75 mg Single dose	RGP 75 mg - placebo	PBO EOD	RGP 75 mg EOD	RGP 75 mg – PBO (%)	Strengths / Uncertainties / Limitations
	Favourable Effects[a] Acute migraine							
Pain freedom at 2 hours, Co-primary	Patients pain free at 2h, Risk[a], n (%) (95% CI), resp. Risk difference[a,b] (95% CI) vs PBO, p-value	301: 77 (14.2) (11.3, 17.2)	104 (19.2) (15.8, 22.5)	4.91 (0.5, 9.3) **0.0298***				•Study population representative for clinical practice in acute therapy •Co-Primary endpoints (2 hour pain free / MBS free) met across all SD studies •Magnitude of effect in acute attacks lower than triptans •Within patient consistency of effect in 2/3 attacks not shown •No controlled data to show efficacy in case of acute attacks in EOD patients •Uncertain efficacy against nausea as associated symptom •Unclear clinical relevance of MD reduction by -0.7
		302: 64 (12.0) (9.2, 14.7)	105 (19.6) (16.2, (22.9)	7.59 (3.3, 11.9) **0.0006***				
		303: 74 (10.9) (8.5, 13.2)	142 (21.2) (18.1, 24.3)	10.37 (6.5, 14.2) **<0.0001***				
MBS freedom at 2 hours, Co-primary	Patients MBS free at 2h, Risk[a], n (%) (95% CI), resp. Risk difference[a,b] (95% CI) vs PBO, p-value	301: 150 (27.7) (24.0, 31.5)	199 (36.6) (32.6, 40.7)	8.90 (3.4, 14.4) **0.0016***				
		302: 135 (25.2) (21.6, 28.9)	202 (37.6) (33.5, 41.7)	12.38 (6.9, 17.9) **<0.0001***				
		303: 183 (26.8) (23.5, 30.2)	235 (35.1) (31.5, 38.7)	8.29 (3.4, 13.2) **0.0009***				
Consistency of effect		No data provided						
	Migraine prevention							

Effect	Short Description	PBO Single dose	RGP 75 mg Single dose	RGP 75 mg - placebo	PBO EOD	RGP 75 mg EOD	RGP 75 mg – PBO (%)	Strengths / Uncertainties / Limitations
Primary: Change in Migraine Days	Change from OP in mean number of MDs during wk9-12 of DBT, Least square mean (95% CI) Difference vs PBO (95% CI) p-value				-3.5 (-4.00, -3.04)	-4.3 (-4.83, -3.87)		per 28-days interval in prevention trial 305 •No option to treat an acute attack with rimegepant on days scheduled for EOD dosing due to limiting the MDD to 75 mg rimegepant/day •Unclear demographic composition of subjects with regard to EM/CM subtype in study 305 and no stratified analysis •Secondary endpoints (rescue use, MIDAS) not supporting clinical relevance of the primary treatment effect (-0.7 MDs) in study 305 •No difference between RGP and placebo in reduction of MDs in patients stratified for concomitant
							-0.8 (-1.46. -0.20)	
							0.0099*	
Primary: Sensitivity analysis: Change in Migraine Days	Change from OP in mean number of MDs during wk9-12 of DBT, GLMEM, J2R Difference vs PBO (95% CI) p-value				-4.0 (-5.27, -2.73)	-4.7 (-5.94, -3.39)		
							-0.7 (-1.29, -0.03)	
							0.0400	
Secondary endpoint	Mean number of rescue Mx days from wk9-12, Least square mean (95% CI), Difference vs PBO (95% CI) p-value				4.0 (3.53, 4.39)	3.7 (3.29, 4.15)		
							-0.2 (-0.80, 0.31)	
							0.3868[†]	

Effect	Short Description	PBO Single dose	RGP 75 mg Single dose	RGP 75 mg - placebo	PBO EOD	RGP 75 mg EOD	RGP 75 mg – PBO (%)	Strengths / Uncertainties / Limitations
Secondary endpoint	Change from baseline in MIDAS Total score at wk12 of the DBT, Least square mean (95% CI), Difference vs PBO (95% CI), P-value				-11.7 (-15.3, -8.1)	-11.8 (-15.4, -8.2)		prophylactic Mx in study 305 •No reduction of MDs over the 52-week treatment course in the largest PRN(2-8) enrolment group of study 201
							-0.1 (-4.7, 4.5)	
							0.9616†	
Efficacy in acute attacks in patients receiving preventive EOD rimegepant		No controlled data provided						

Table 64: Unfavourable Effects Table of Rimegepant for the Comprehensive Management of Migraine with or without Aura in Adults

Effect	Short Description	PBO	LTN 50 mg	LTN 100 mg	LTN 200 mg	L50–PBO(%)	L100–PBO(%)	L200–PBO(%)	ALPZ	Strengths / Uncertainties / Limitations
	Unfavourable Effects									
	Safety profile appears favourable, however, further elucidation of rimegepant's liability to induce liver enzyme elevations is requested									

*Asterisk = statistically significant
[a] Risks (percentages) are calculated using Cochran-Mantel-Haenszel weights, stratified by use of prophylactic migraine medication
[b] Risk difference is the difference in the percentage of subjects with a positive result for the rimegepant minus the placebo treatment groups.
† Nominal p-value in hierarchical testing

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Rimegepant is introduced as the first orally administered CGRP antagonist with claimed benefit for both the acute treatment and prophylaxis of migraine. Accordingly, Vydura™ was proposed to be indicated for the *comprehensive management* of migraine in adults, including prophylaxis and acute treatment of migraine with or without aura.

The clinical dossier of includes pivotal efficacy data from two sets of clinical studies that were provided for the acute (single attack studies 301/302/303) and preventive treatment (study 305) of migraine under randomised, placebo-controlled conditions. Supportive data include phase 2b dose ranging study CN170003 (with free base RGP capsules, establishing rimgepant 75 mg as the minimum effective dose) , and phase 2/3 open-label, long-term safety study 201, during which subjects could receive 75 mg RGP doses as needed for up to 52 weeks.

The overall safety profile of rimegepant appears favourable. On-treatment AEs related to the study drug comprise mainly unspecific AEs like nausea (1.3%), constipation (1.1%), diarrhoea (0.4%), dizziness (1.5%), somnolence (1.1%) and were reported at low frequency. There were no signs for potential abuse or hepatotoxicity. No relevant effects on vital signs like HR or BP were observed.

The effect size of rimegepant, however, was shown to be modest both in the acute and prophylactic clinical trial programme.

Single attack studies 301/302/303 followed standard guidance and were almost identical in design. Significant superiority over placebo could be shown in terms of the co-primary endpoints, freedom from pain and most-bothersome associated symptoms at 2 hours post-dose. The magnitude of effect, however, was modest. The modest treatment effect, shown in single attack studies, contributes to concerns that arise from the lacking proof of consistency of effect across multiple attacks. Although a consistency of effect study was planned and discussed within the scope of CHMP-SA (May 2018), no such data were actually provided. Concerns over consistency of effect are further underlined by the poor outcome of long-term study 201. In the largest PRN(2-8) enrolment group (N=1023), representing the majority of patients in clinical practice, i.e. subjects with a history of 2-8 attacks experienced per month, mean MD were not reduced over the 52-week treatment period, as compared to the 28-day OP.

Concerns over lacking proof of within-patient consistency were addressed by exploratory analysis of efficacy data obtained from PRN use of rimegepant on unscheduled days during the OLE period of study 305. A focused analysis in subgroups of patients with > 3 moderate to severe MDs and those with > 4 MDs was provided on the first 3 resp. 4 attacks. The profile obtained largely corresponds to the modest treatment effect already observed across the single attack studies 301/302/303. As could be expected, the magnitude of requested within-patient consistency parameter is considerably smaller than the average absolute responder rates observed across the three single attack studies 301/302/303 of 19-21%.

The limitations of the requested *post hoc* data on the efficacy of rimegepant for acute migraine attacks experienced during the OLE period of study 305 are evident: they were generated *post hoc* under uncontrolled, open-label conditions in patients receiving maintenance RGP on scheduled EOD days and reflect only those attacks that were experienced on days not scheduled for regular EOD preventive dosing. In the absence of guideline-conforming data prospectively demonstrating within-patient consistency, however, they provide some exploratory insight into within-patient consistency of effect of rimegepant in a series of 3-4 consecutive migraine attacks.

Similarly, there remain concerns about the clinical relevance of the effect in prophylactic migraine treatment with rimegepant. During the 12-week DBT of study 305 migraine days were reduced by only -0.7 MDs (net effect over placebo, p=0.040), corresponding to far less than 10% of the number of MDs experienced during the observation period (rimegepant: 10.3, placebo 9.9 MDs).

The clinical relevance of the -0.7 MDs net difference over placebo is not supported by results for important secondary endpoints, like rescue medication use. In the relevant subgroup of patients with concomitant non-study prophylactic medication (rimegepant arm 75/348, 21.6%), rimegepant did not separate from placebo. Equally, the modest treatment effect for the primary endpoint goes along with non-significant treatment effects in the subgroups of patients with CM history, subjects with less than 8 attacks per month, and subjects $\geq$ 65 years of age. It is acknowledged that study 305 was not powered to demonstrate significant effects in subgroups. On the other side, however, it is considered that the findings in subgroups round up the profile of rimegepant as a moderately effective agent.

In the case of prevention study 305, subjects with a reported history of CM were initially excluded, however, were admitted with Protocol Amendment vs. 04 (07-March-2019). A stratified analysis according to migraine subtypes was not pre-specified. Robust efficacy in the "CM history" subgroup could not be shown. This contrasts with the general label claim of comprehensive management of migraine in adults, irrespective of the underlying EM/CM subtype. The available clinical database does not provide sufficient evidence for a positive B/R balance in the CM population. Therefore, the wording of indication has been revised in section 4.1 of the SmPC to restrict the indication of preventive migraine to those with EM in adults who have at least 4 migraine attacks per month.

With regard to timelines in the course of clinical development, it could be that the concept of also testing rimegepant for migraine prophylactic treatment was prompted after receipt of preceding single attack study results. The observation that rimegepent achieved sustained pain relief over 48 hours post-dose in a subgroup of patients in acute attacks, contributed to the concept of administering rimegepant in migraine prevention EOD. In so far, it is different from migraine prevention with other orally administered agents like ß-blockers, topiramate etc., for which no effect in acute attacks could be shown.

There are no controlled data to prove efficacy against acute attacks occurring in subjects receiving EOD rimegepant for migraine prevention. Separate RCTs were undertaken for efficacy in single attacks (301/302/303) and prevention (305, 12-week DBT). The efficacy of rimegepant in acute attacks in EOD patients was not shown under placebo-controlled conditions.

On the other side, it could be shown in the 1-yr OLE period of study 305 that the reduction in MMDs was maintained following the EOD+PRN dosing scheme. The mean number of MDs per month during the initial observation period of study 305 was 9.9 MDs/month (10.1 MDs in previous rimegepant patients during DBT, 9.6 in placebo subjects). The major part of MD reduction was then achieved during the subsequent 12-week DBT. Nonetheless, the mean number of MDs per month continued to decline throughout the 52-week OLE period from a mean of 4.6 MDs at Month 1 (N=548) to 2.7 MDs at Month 13 (N=420).

A maximum daily dose of 75 mg rimegepant was specified, i.e. in case an acute attack occurs, rimegepant may only be taken on days not scheduled for regular EOD dosing. It is unclear how restriction of rimegepant to be taken for acute treatment on non-scheduled days only, is compatible with clinical practice, which requires to treat acute attacks whenever they occur, irrespective of EOD dose schedules.

The applicant argued that it would be common practice to have recourse to other types of rescue medication once the MDD maximum daily dose of the "standard therapy" is achieved. This is self-evident, however, contrasts with the claimed "comprehensive management of migraine" with a single agent, i.e. rimegepant. Indeed, the use of rimegepant in case of an acute migraine attack occurring on a scheduled EOD dosing day is ruled out.

Further insight was obtained from an analysis how the remaining MDs and rescue medication use spread across scheduled and unscheduled days across the 1-year OLE period. The results do not indicate any substantive difference between scheduled and non-scheduled days in the mean number of remaining MDs per month or in the mean number of rescue medication days per month. Remaining MDs were about equally distributed across scheduled and non-scheduled days across the 52-week OLE. The overall open-label mean number of rescue medication days of 1.3 per month was also equally distributed between scheduled days and non-scheduled days.

3.7.2. Balance of benefits and risks

The overall safety profile of rimegepant appears favourable. Statistically significant superiority over placebo could be shown across primary endpoints, i.e. freedom of pain and MBS at 2-hours post-dose in acute treatment and for the reduction of MMDs in migraine prevention. However, the magnitude of effect achieved in both treatment settings is considered modest. The clinical relevance of the net treatment effect over placebo may still be acknowledged in view of the favourable safety profile of rimegepant. The clinical database did not point to CV or hepatic safety risks associated with the use of rimegepant in acute and preventive migraine treatment.

3.7.3. Additional considerations on the benefit-risk balance

NA

3.8. Conclusions

The overall benefit/risk balance of Vydura is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vydura is favourable in the following indication(s):

- Acute treatment of migraine with or without aura in adults
- Preventive treatment of episodic migraine in adults who have at least 4 migraine attacks 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 subject to medical prescription.

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.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that rimegepant 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.