CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

Office of Clinical Pharmacology

Integrated Clinical Pharmacology Review

NDA Numbers	(b) (4) (Tablet) 212728 (Orally Disintegrating Tablet)
Link to EDR	\\CDSESUB1\evsprod\NDA (b) (4) \\CDSESUB1\evsprod\NDA212728\
Submission Date	27-Jun-2019 (Orally Disintegrating Tablet) 28-Jun-2019 (Tablet)
Submission Type	505(b)(1) Application (Priority Review for NDA 212728) (Standard Review for NDA (b) (4)
Brand Name	To be determined
Generic Name	Rimegepant Sulfate (BHV-3000, BMS-927711)
Dosage Form (Strength)	Tablet (75 mg), Orally Disintegrating Tablet (75 mg)
Proposed Indication	Acute Treatment of Migraine with or without aura in Adults
Applicant	Biohaven Pharmaceuticals, Inc.
Associated IND	IND- (b) (4)
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List of Abbreviations

AE	Adverse event
AUC	Area under the concentration-time curve
AUClast	AUC from time 0 to last measurable concentration
BCRP	Breast cancer resistance protein
CGRP	Calcitonin gene-related peptide receptor
Cmax	Maximum (peak) drug concentration
EC50	Serum concentration associated with the half maximal effect
ESRD	End-stage renal disease
LLOQ	Lower limit of quantification
MBS	Most bothersome symptoms
NDA	New Drug Application
ODT	Orally disintegrating tablet
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
SAE	Serious adverse event
SD	Standard deviation
Tmax	Time of maximum (peak) drug concentration

1 Executive Summary

In these original New Drug Applications (NDA), Biohaven Pharmaceuticals Inc. is seeking approval of rimegepant tablet (NDA-(b) (4) and orally disintegrating tablet (NDA-212728) for the acute treatment of migraine in adults. Rimegepant is a new molecular entity (NME) and is not marketed in the US for any indication. It is a calcitonin gene-related peptide (CGRP) receptor antagonist developed for oral administration. CGRP, an endogenous 37 amino acid peptide within pain signaling nociceptive afferents, is believed to play a causal role in migraine. Recently, multiple CGRP inhibitors such as Erenumab (Aimovig; BLA-761077, 05/17/2018), Fremanezumab (Ajovy; BLA-761089, 09/14/2018), and Galcanezumab (Emgality; BLA-761083, 09/27/2018) have been approved by the FDA for migraine prevention in adults. The proposed dose of rimegepant is 75 mg (free base equivalent) as needed to be administered orally using (b) (4) tablet (tablet) formulation or orally disintegrating tablet (ODT) formulation. The maximum dose in a 24-hour period is 75 mg.

To demonstrate efficacy, the applicant is relying on 3 randomized, double-blind, placebo-controlled safety and efficacy studies in patients with acute migraine. The tablet formulation was utilized in 2 studies (# BHV3000-302, and BHV3000-301) and ODT was utilized in one study (# BHV3000-303). The patients with acute migraine were defined as those who had at least 1-year history of migraine (with or without aura) and not more than 8 attacks of moderate or severe pain intensity per month within last 3 months (International Classification of Headache Disorders criteria; 3rd Ed. beta, 2013).

All three studies demonstrated that 75 mg dose is superior to placebo for the acute treatment of migraine based on the co-primary efficacy endpoints (pain freedom and absence of the most bothersome migraine-associated symptom at 2 hours; MBS). The applicant is seeking approval for 75 mg of both tablet and ODT. These single attack studies did not assess an option of redosing following the initial dose. Thus, the maximum daily dose should not exceed 75 mg. The long-term safety study was also conducted at 75 mg dose level (Study # BHV3000-201). In addition to the pivotal efficacy and safety studies, the applicant included 18 phase-1 studies, and one phase-2 study in migraine patients.

The primary focus of this review is to evaluate the need for dose adjustments based on intrinsic and extrinsic factors.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted under (b) (4) NDA-212728 (ODT) and we recommend approval of 75 mg dose of rimegepant (as needed; with the maximum dose of 75 mg in a 24-hour period) for the acute treatment of migraine with or without aura in adults.

Key review issues with specific recommendations and comments are summarized below in Table 1-1:

Table 1-1 Summary of Review Issues and OCP Recommendations

Review Issues	Recommendations and Comments
Evidence of effectiveness:	The evidence of effectiveness of rimegepant for the acute treatment of migraine in adults is from – three, multi-center, double-blind, placebo-controlled, single-dose, phase-3, studies: # BHV3000-303 using 75 mg ODT, and BHV3000-302 and BHV3000-301 using 75 mg tablet.
General dosing instructions:	The recommended dose is 75 mg taken orally as needed. The maximum dose in a 24-hour period is 75 mg.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• **Severe hepatic impairment (Child-Pugh C):** Increased plasma concentrations of rimegepant were observed in subjects with severe hepatic impairment (Child-Pugh C). Avoid use of rimegepant in patients with severe hepatic impairment. • No dosage adjustment of rimegepant is required in patients with mild (Child-Pugh A) or moderate hepatic impairment (Child-Pugh A). • **Subjects with ESRD (eGFR: < 15 mL/min/1.73 m^2):** Rimegepant has not been studied in patients with ESRD and in patients on dialysis. It is recommended to avoid use of rimegepant in patients with ESRD. • No dosage adjustment of rimegepant is required in patients with mild (eGFR: 60 to 89 mL/min/1.73 m^2), moderate (eGFR: 30 to 59 mL/min/1.73 m^2), and severe (eGFR: 15 to 30 mL/min/1.73 m^2) renal impairment. <u>Modified dose/regimen is needed for the following extrinsic factors:</u> • **Strong inhibitors of CYP3A4:** Concomitant administration of rimegepant with a strong inhibitor of CYP3A4 results in significant increase in plasma concentrations of rimegepant. Avoid concomitant administration of rimegepant with a strong inhibitor of CYP3A4. • **Moderate inhibitors of CYP3A4:** No dose adjustment is needed. However, avoid another dose of rimegepant within 48 hours when concomitantly administered with a moderate inhibitor of CYP3A4. • **Strong inducers of CYP3A4:** Concomitant administration of rimegepant with a strong inducer of CYP3A results in reduced plasma concentrations of rimegepant which may lead to loss-of-efficacy. Avoid concomitant administration of rimegepant with a strong inducer of CYP3A. • **Moderate inducers of CYP3A4:** Concomitant administration of rimegepant with a moderate inducer of CYP3A may result in reduced plasma concentrations of rimegepant potentially leading to loss-of-efficacy. Avoid concomitant administration of rimegepant with a moderate inducer of CYP3A.

Review Issues	Recommendations and Comments
	• No dose/regimen change is necessary for weak inducers of CYP3A4. • **Inhibitors of P-gp or BCRP transporters:** Rimegepant is a substrate of P-gp and BCRP transporters. Concomitant administration of rimegepant with inhibitors of P-gp or BCRP may result in increased plasma concentrations of rimegepant. Avoid concomitant administration of rimegepant with an inhibitor of P-gp or BCRP.
Labeling	The product label requires changes to reflect the recommended dose/regimen optimizations based on intrinsic and extrinsic factors described above.
Bridge between the "to-be-marketed" and clinical trial formulations	Pivotal studies utilized both tablet and ODT (Table 3-2). The clinical trial formulations were the same as the to-be marketed formulations. Therefore, no PK bridging studies are required. The applicant also demonstrated bioequivalence between the to-be marketed tablet and ODT (see Section 3.3.5).

1.2 Post-marketing Requirements

In vitro studies demonstrated that rimegepant is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. The applicant did not conduct clinical studies assessing the impact of concomitant administration inhibitors of P-gp or BCRP on the pharmacokinetics of rimegepant. Since the safety information for rimegepant is limited to 75 mg dose level, there are concerns regarding potential increase in exposure of rimegepant upon concomitant administration with inhibitors of P-gp or BCRP. Therefore, a clinical drug-drug interaction study should be conducted to verify the drug interaction potential for inhibitors of P-gp/BCRP with rimegepant.

2 Summary of Clinical Pharmacology Assessment

2.1 The Pharmacology and Clinical Pharmacokinetics

Mechanism of Action:

Rimegepant (BHV-3000, BMS-927711, MW: 534.56 free base) is a CGRP receptor antagonist developed for oral administration. CGRP is an endogenous 37 amino acid peptide contained within pain signaling nociceptive afferents. It is believed that rimegepant binds to the human CGRP receptor and antagonizes CGRP receptor function, thus inhibiting CGRP-induced enhancement of pain signaling, blocking CGRP-induced vasodilation, and halting CGRP-induced neurogenic inflammation.

Absorption:

The mean absolute bioavailability of rimegepant following oral administration is 64% (90% CI: 53%, 77%). The results of relative bioavailability study in healthy subjects demonstrated that the bioavailability of rimegepant from ODT is comparable to that with the tablet formulation. The median Tmax of rimegepant with ODT and tablet were 1.5 h and 1.9 h, respectively.

Food effect:

Following administration of tablet or ODT under fed condition with high fat meal, the rate and extent of absorption of rimegepant was reduced compared to that observed under fasting condition. For ODT administered sublingually, the time to maximum plasma concentration was delayed by 1-hour, peak concentration was reduced by 42% and total exposure was reduced by 32%. For ODT administered supra-lingually (on top of the tongue), the time to maximum plasma concentration was delayed by 1-hour, peak concentration was reduced by 53% and total exposure was reduced by 38%. For tablet, the time to maximum rimegepant plasma concentration was delayed by 1-hour, peak concentration was reduced by 33% and total exposure was reduced by 30%. However, the pivotal efficacy and safety studies were performed without regard to food. No information on fasted/fed state during efficacy assessments were collected in these studies and the impact of food effect on the efficacy of rimegepant could not be assessed.

Distribution:

The mean apparent volume of distribution of rimegepant is approximately 120 L at steady-state. Rimegepant is approximately 96% bound to human plasma proteins.

Metabolism:

Metabolism of rimegepant is primarily mediated by CYP3A4 and to a lesser extent by CYP2C9, resulting in the formation of several minor, inactive metabolites. Rimegepant is primarily eliminated in the unchanged form (~77% of the dose) with no major metabolites (i.e., metabolites that represented >10% of drug-related material) detected in plasma. Hydroxylation, forming mono- and bis-hydroxylated metabolites, was the most significant biotransformation pathway of rimegepant. Other metabolites excreted were glucuronides, a desaturation product and an N-dealkylation product.

Excretion:

The average elimination half-life in healthy subjects is approximately 11 hours. The mean plasma clearance of rimegepant is approximately 9.3 L/h. Following single oral dose administration of [^{14}C]-rimegepant to healthy male subjects, primary route of elimination is through the biliary/fecal pathway (~78% radioactivity) and the urinary pathway is a minor route of elimination (~24% radioactivity).

Special Populations:

Renal Impairment

In a clinical study comparing pharmacokinetics of rimegepant in subjects with mild (eGFR: 60 to 89 mL/min/1.73 m^2), moderate (eGFR: 30 to 59 mL/min/1.73 m^2), and severe (eGFR: 15 to 30 mL/min/1.73 m^2) renal impairment, no clinically meaningful differences in the pharmacokinetics of rimegepant were observed compared to subjects with normal renal function (eGFR: >90 mL/min/1.73 m^2). Subjects were assigned to groups based on eGFR calculated at screening (based on serum creatinine using MDRD equation). No dose or dosing frequency adjustment is required in patients with renal impairment. Rimegepant has not been studied in patients with ESRD (eGFR: < 15 mL/min/1.73 m^2) and in patients on dialysis. It is recommended to avoid use of rimegepant in patients with ESRD (see Section 3.3.3.1).

Hepatic Impairment

In a clinical study comparing pharmacokinetics of rimegepant in subjects with mild or moderate hepatic impairment (Child-Pugh class A and B), no clinically meaningful differences in the pharmacokinetics were observed compared to subjects with normal hepatic function. Higher exposures of rimegepant (AUC and Cmax increased by 2-fold) were observed in subjects with severe hepatic impairment (Child-Pugh C). The applicant has neither developed a lower strength for marketing nor the developed formulations (tablet or ODT) are functionally scored to deliver lower doses. Due to unavailability of lower strength required to support dosing in patients with severe hepatic impairment, it is recommended to avoid use of rimegepant in patients with severe hepatic impairment (see Section 3.3.3.2).

Effects of Body Weight, Gender, Race, Age, and migraine state

Body weight, gender, race, age, and migraine state did not have a clinically relevant effect on the exposure (AUC and Cmax) of rimegepant (see Section 3.3.3.3).

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

For the acute treatment of migraine, the recommended dose is 75 mg to be administered orally as needed. The maximum dose in a 24-hour period is 75 mg.

2.2.2 Therapeutic individualization

Therapeutic individualization is necessary for following extrinsic/intrinsic factors.

Drug Interactions

Inhibitors of CYP3A4:

In a dedicated drug interaction study, concomitant administration of 75 mg rimegepant (single dose) with itraconazole (200 mg once daily; at steady state) resulted in increased exposures of rimegepant (AUC by 4-fold & Cmax by ~1.5-fold). It is recommended to avoid concomitant administration of rimegepant with a strong inhibitor of CYP3A4 (see Section 3.3.4.1.1).

No dedicated drug interaction study was conducted to assess the effect of concomitant administration of moderate or weak inhibitors of CYP3A4 on the pharmacokinetics of rimegepant. Based on the drug interaction studies with CYP3A4 modulators, rimegepant is considered as a moderately sensitive CYP3A4 substrate[1]. Thus, concomitant administration of rimegepant with a moderate inhibitor of CYP3A4 could increase rimegepant exposures (AUC) up to 2-fold. Drug interaction study with fluconazole, a combined moderate CYP3A4 and CYP2C9 inhibitor demonstrated about 1.8-fold increase in rimegepant AUC but no major changes to its Cmax. Therefore, no dose adjustment is needed for rimegepant with moderate CYP3A4 inhibitors. However, it is recommended to avoid another dose of rimegepant within 48 hours when it is concomitantly administered with a moderate inhibitor of CYP3A4 (see Section 3.3.4.1.1).

Since the impact on the rimegepant exposures with a weak inhibitor of CYP3A4 will be lower than that with moderate inhibitors, no dose/regimen adjustment is recommended during concomitant administration of rimegepant with a weak inhibitor of CYP3A4.

Inducers of CYP3A:

Concomitant administration of 75 mg rimegepant (single dose) with rifampin (600 mg once daily; at steady state), a strong inducer of CYP3A4, resulted in reduced exposures of rimegepant (AUC decreased by 80% & Cmax by 64%), which may lead to loss-of-efficacy. It is recommended to avoid concomitant administration of rimegepant with a strong inducer of CYP3A4 (see Section 3.3.4.1.2).

No dedicated drug interaction study was conducted to assess effect of concomitant administration of moderate or weak inducers of CYP3A4 on the pharmacokinetics of rimegepant. Concomitant administration of rimegepant with moderate inducers of CYP3A4 may result in decreased rimegepant exposures and may reduce efficacy. The dose finding study results indicate that lower doses studied such as 25 and 10 mg were not effective (see Section 3.1). Assuming a linear dose-response relationship between doses 25 mg and 75 mg, the efficacy may be reduced upon administration of rimegepant with moderate inducers of CYP3A4. It is recommended to avoid concomitant administration of rimegepant with a moderate inducer of CYP3A4. No change in dose or dosing regimen of rimegepant is necessary for concomitant administration with a weak inducer of CYP3A4 (see Section 3.3.4.1.2).

[1] *https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers*

Inhibitors of CYP2C9:

In a dedicated drug interaction study, concomitant administration of 75 mg rimegepant (single dose) with fluconazole (400 mg once daily; at steady state) resulted in increased exposures of rimegepant (AUC by 1.8-fold) with no relevant effect on Cmax. Rimegepant is primarily metabolized by CYP3A4 and to a lesser extent CYP2C9. Fluconazole is a moderate inhibitor of CYP2C9 and a moderate inhibitor of CYP3A4. Considering that concomitant administration of rimegepant with a strong inhibitor of CYP3A4 results in ~4-fold increase in AUC of rimegepant, it can be classified as a moderately sensitive substrate for CYP3A4 (with ≥2 to <5-fold increase in AUC expected with strong CYP3A4 inhibitors). Thus, increase in the exposure of rimegepant with fluconazole can be attributed mainly to CYP3A4 inhibition, with a lower contribution from CYP2C9. No dose adjustment is recommended during concomitant administration of rimegepant with an inhibitor of CYP2C9 (see Section 3.3.4.1.3).

Transporters:

Rimegepant is a substrate of P-gp and BCRP based on the in vitro studies. Concomitant administration of inhibitors of P-gp or BCRP may increase the exposure of rimegepant. No dedicated drug interaction study was conducted to assess their effects on the pharmacokinetics of rimegepant. Since the safety information for rimegepant is limited only to the 75 mg dose level, there are concerns regarding potential increase in exposure of rimegepant upon concomitant administration with inhibitors of P-gp or BCRP. It is recommended to avoid concomitant administration of rimegepant with an inhibitor of P-gp or BCRP (see Section 3.3.4.2).

Specific Populations

Renal Impairment:

In a dedicated clinical study comparing the pharmacokinetics rimegepant in subjects with mild (eGFR: 60 to 89 mL/min/1.73 m^2), moderate (eGFR: 30 to 59 mL/min/1.73 m^2), and severe (eGFR: 15 to 30 mL/min/1.73 m^2) renal impairment to that with healthy matched control (eGFR: > 90 mL/min/1.73 m^2), the exposure of rimegepant following single 75 mg dose was approximately 40% higher in subjects with moderate renal impairment. However, there was no clinically meaningful difference in the exposure of rimegepant in subjects with severe renal impairment compared to subjects with normal renal function. There was no trend observed with increase in plasma concentrations of rimegepant with decrease in renal function. No dosage adjustment of rimegepant is required in patients with mild or moderate or severe renal impairment.

Rimegepant has not been studied in patients with ESRD (eGFR: < 15 mL/min/1.73 m^2) and in patients on dialysis. It is recommended to avoid use of rimegepant in patients with ESRD (see Section 3.3.3.1).

Hepatic Impairment:

In a dedicated study comparing the pharmacokinetics of rimegepant in subjects with mild, moderate, and severe hepatic impairment to that with healthy matched control subjects, the exposure of rimegepant (both Cmax and AUC) following single 75 mg dose was approximately 2-fold higher in subjects with severe impairment (Child-Pugh class C). There were no clinically

meaningful differences in the exposure in subjects with mild (Child-Pugh class A) and moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. No dosage adjustment is required in patients with mild (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). However, it is recommended to avoid use of rimegepant in patients with severe hepatic impairment (Child-Pugh class C) (see Section 3.3.3.2).

Other Specific Populations:

No clinically significant differences in the pharmacokinetics of rimegepant were observed based on age, sex, race/ethnicity, body weight, migraine state and CYP2C9 genotype (see Section 3.3.3.3 & 4.4).

2.2.3 Outstanding Issues

None.

2.2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following labeling concepts to be included in the final package insert.

- The recommended dose of rimegepant is 75 mg tablet or ODT. The maximum dose in a 24-hour period is 75 mg.
- The exposure of rimegepant is reduced when administered under fed conditions compared to that under fasting conditions. For ODT, the time to maximum rimegepant plasma concentration was delayed by 1-hour, peak concentration was reduced by 42% and total exposure was reduced by 32%. For tablet, the time to maximum rimegepant plasma concentration was delayed by 1-hour, peak concentration was reduced by 33% and total exposure was reduced by 30%. However, the pivotal efficacy and safety studies were conducted without food restrictions and no information on fasted/fed state during efficacy assessments were collected. The impact of food effect on the efficacy of rimegepant is unclear (see Section 3.3.4.3.1).
- The bioavailability of rimegepant from ODT administered sublingually is similar to that from ODT administered on the top of the tongue. Thus, ODT can be placed on top of tongue or sublingually during the administration (see Section 3.3.5).
- Dose adjustment is not required for mild, moderate, or severe renal impairment. Rimegepant has not been studied in patients with ESRD and in patients on dialysis. It is recommended to avoid use of rimegepant in patients with ESRD (eGFR: < 15 mL/min/1.73 m^2) (see Section 3.3.3.1).
- No dose adjustment is required in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Higher exposures of rimegepant (AUC and Cmax by 2-fold) were observed in subject with severe hepatic impairment (Child-Pugh C). It is recommended to avoid use of rimegepant in patients with severe hepatic impairment (see Section 3.3.3.2).
- Dose adjustment is not required based on demographic factors such as age, sex, race, and body weight (see Section 3.3.3.3).

- Concomitant administration of rimegepant with a strong inhibitor of CYP3A4 results in significant increase in plasma concentrations of rimegepant. It is recommended to avoid concomitant administration of rimegepant with a strong inhibitor of CYP3A4 (see Section 3.3.4.1.1).
- No dose adjustment is needed for rimegepant when concomitantly administered with a moderate inhibitor of CYP3A4. However, avoid another dose of rimegepant within 48 hours when concomitantly administered with a moderate inhibitor of CYP3A4 (see Section 3.3.4.1.1).
- Concomitant administration of rimegepant with a strong inducer of CYP3A results in significant reduction in plasma concentrations which may lead to loss-of-efficacy. It is recommended to avoid concomitant administration of rimegepant with a strong inducer of CYP3A (see Section 3.3.4.1.2).
- No dedicated drug interaction study was conducted to assess effect of concomitant administration of moderate or weak inducers of CYP3A4 on the pharmacokinetics of rimegepant. Concomitant administration of rimegepant with a moderate inducer of CYP3A4 may result in decreased rimegepant exposures and loss of efficacy. It is recommended to avoid concomitant administration of rimegepant with a moderate inducer of CYP3A (see Section 3.3.4.1.2).
- No dose/regimen change is necessary when concomitantly administered with weak inducers of CYP3A4 (see Section 3.3.4.1.2).
- No clinically significant pharmacokinetic interactions were observed at therapeutic dose (75 mg) when rimegepant was concomitantly administered with oral contraceptives containing norgestimate and ethinyl estradiol (see Section 3.3.4.1.5).
- Concomitant administration of rimegepant (at steady-state; 75 mg once daily for 4 days) with sumatriptan (12 mg subcutaneous, given as two 6 mg doses separated by one hour) had no effect on resting blood pressure compared with sumatriptan alone. There was no pharmacokinetic interaction between sumatriptan and rimegepant (see Section 3.3.4.1.6).

3 Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

Rimegepant is a human CGRP receptor antagonist and is formulated as – 1) (b) (4) tablet (b) (4) and 2) ODT (developed using Catalent's Zydis technology). Both formulations are intended for oral administration and contains 75 mg (equivalent to free base) of rimegepant sulfate.

The clinical development program to demonstrate the safety and efficacy for rimegepant consisted of three phase-3 registration studies (Studies # BHV3000-303, BHV3000-302, and BHV3000-301) and one phase-2 study (Study # CN170003). The pivotal studies were conducted with single 75 mg strength in patients with acute migraine. The application also included 18 phase-1 clinical studies.

3.2 General Pharmacological and Pharmacokinetic Characteristics

The pharmacokinetic properties of rimegepant have been characterized in the phase-1 and 2 studies.

Table 3-1 Summary of Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Rimegepant is a human calcitonin gene-related peptide receptor antagonist.
Active Moieties	Rimegepant
QT Prolongation	No significant QTc prolongation of rimegepant was detected in a thorough QT study # BHV3000-109 (Refer to the QT-IRT review dated 11/12/2019).
General Information	
Bioanalysis	The concentrations of rimegepant human plasma were determined using a validated LC-MS/MS method (see Section 4.1).
Healthy Subjects vs. Patients	No significant difference in exposure.
Dose Proportionality	Rimegepant exhibits linear pharmacokinetics following single oral administration over the dose range of 25 to 150 mg (Study # CN170001). However, a greater than dose proportional increase was observed from 300 to 600 mg, with less than proportional increase at 1,500 mg.
Accumulation	The product is intended for intermittent use with a maximum single dose of 75 mg in a 24-h period. No significant accumulation was observed following repeated once daily dosing (see Section 4.5).

Pharmacokinetic Variability	coefficient of variation of ~30% and 35% for AUCinf and Cmax, respectively (see Table 4-4 & Section 4.5).
Absorption	
Bioavailability	The mean absolute bioavailability of rimegepant following oral administration is 64% (90% CI: 53% to 77%; Study # CN170006) (evaluated using 2×150 mg capsules under fasting condition vs. 15 minute-infusion of 100 µg ^{14}C rimegepant)
Tmax	Approximately, 1.5 h for ODT Approximately, 1.9 h for tablet
Food Effect	Rimegepant exhibits food effect with decreased exposures under fed condition (with high-fat meal) compared to fasting condition. • ODT sublingual: AUCinf decreased by ~32%, Cmax by ~42% • ODT top of tongue: AUCinf decreased by ~38%, Cmax by ~53% • Tablet: AUCinf decreased by ~30%, Cmax by ~33% Tmax was delayed by ~1 hour for both the formulations.
Distribution	
Apparent Volume of Distribution	120 L
Protein Binding	~96% (Study # 930045988)
Transports	In vitro human transporter studies indicated that rimegepant is a substrate of P-gp and BCRP (see Section 3.3.4.2). It was not found to be a substrate of OATP1B1 and OATP1B3. Rimegepant was not evaluated as a substrate of the OAT1, OAT3, OCT2, MATE1, and MATE2-K transporters since its renal clearance was <25% (Studies # 930045988, XT188055). Rimegepant was not found to be a potent inhibitor of P-gp (IC50 ≥ 100 µM), BCRP (IC50 ≥ 10 µM), OAT1 (IC50 ≥ 10 µM), MATE2-K (IC50 ≥ 10 µM). It is a weak inhibitor of OATP1B1 (11% at 5 µM), and OAT3 (24% at 5 µM). Rimegepant inhibited OATP1B3 (IC50 = 6.04 µM), OCT2 (IC50 = 1.08 µM) and MATE1 (IC50 = 1.18 µM). However, clinically relevant drug interactions are less-likely at therapeutic concentrations (see Section 3.3.4.2).
Elimination	
Mean Terminal Elimination Half-life	Approximately 11 hours

Metabolism	
Metabolic Pathway	Rimegepant is not metabolized extensively. Oxidation to form a variety of mono-hydroxylated metabolites was the most significant biotransformation pathway. CYP3A4 is the primary CYP enzyme involved in the metabolism of rimegepant. There were no major metabolites (i.e., metabolites that represented >10% of drug-related material) identified in human plasma. The metabolites are not reported to be pharmacologically active.
Inhibitor / Inducer	In-vitro studies using human liver microsomes indicated that rimegepant is not an inhibitor of CYP1A2 (> 40 µM), 2B6 (> 40 µM), 2C9 (> 40 µM), 2C19 (> 40 µM), 2D6 (> 40 µM), or UGT1A1 (> 50 µM). However, it was found to be a weak inhibitor of CYP3A4 with time-dependent inhibition (IC50, T0 = 33 µM, IC50, T30 min = 5 µM). Clinical drug interaction study with midazolam, a sensitive CYP3A4 substrate, indicates that rimegepant is a weak inhibitor of CYP3A4. In-vitro studies using primary human hepatocyte culture indicated that rimegepant is not an inducer of CYP1A2 or 2B6 and it did not induce CYP3A4 at clinically relevant concentrations.
Metabolism	
Excretion Pathway	The primary route of elimination of rimegepant is through the feces (~78% of total radioactivity) with urinary excretion as a minor elimination pathway (~24% of total radioactivity). Approximately, 42% and 51% of the dose was recovered as unchanged rimegepant in feces and urine, respectively. In plasma during first 4 hours, unchanged parent was the most prominent drug-related circulating component (88 to 92% of total radioactivity; Study # CN170006; administered as oral suspension of 300 mg of ^{14}C rimegepant under the fasting condition).

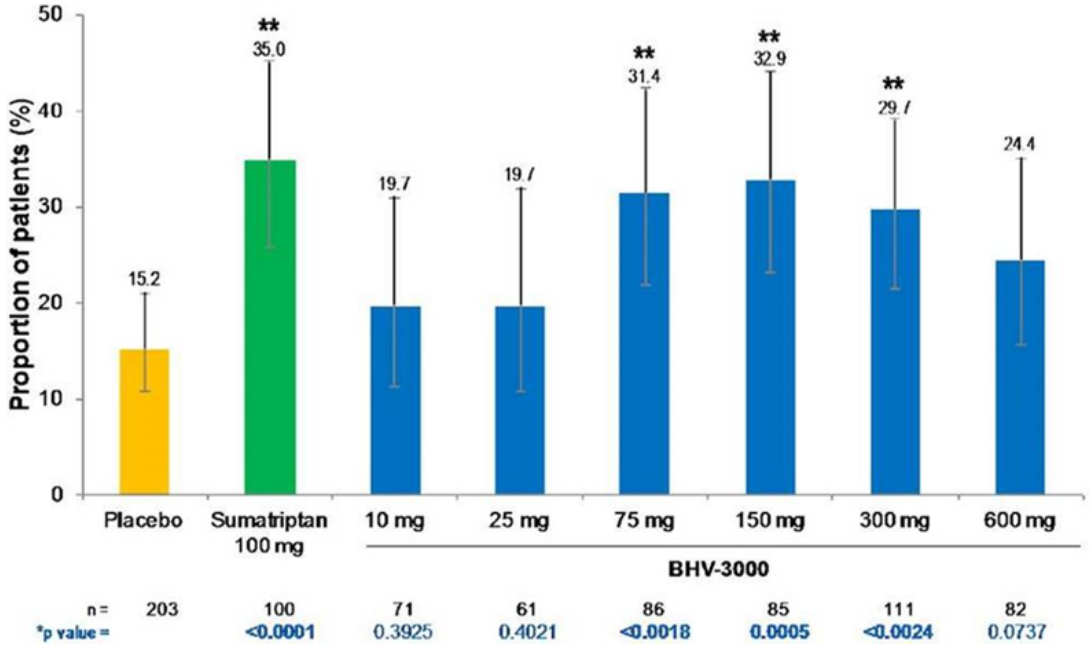
3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The evidence of effectiveness of rimegepant for the treatment of acute migraine is from three pivotal clinical studies (# BHV3000-301, # BHV3000-302, and # BHV3000-303).

To inform the dosing in pivotal studies, the applicant conducted a randomized, double-blind, placebo-controlled, dose-ranging study for the acute treatment of migraine (Study # CN170003). The primary efficacy endpoint was pain freedom (headache pain intensity level reported as "no pain") at 2 hours post-dose using a four-point rating scale (no pain, mild pain, moderate pain, severe pain). This was a response-adaptive, outpatient evaluation of the safety, efficacy, and dose-response of rimegepant as compared to placebo, in the treatment of moderate to severe migraine headache. Subjects were randomized to receive placebo, sumatriptan 100 mg, or 1 of 6 doses of rimegepant: 10, 25, 75, 150, 300, or 600 mg.

Figure 3-1 Proportions of Patients with Pain Freedom* [Study # CN170003]



*at 2 hours post-dose (primary endpoint). *Source: Applicant's Analysis*

Three doses of rimegepant (75 mg, 150 mg, and 300 mg) were considered effective in the acute treatment of migraine pain compared with placebo. The efficacy with 75, 150 and 300 mg doses of rimegepant were similar, with response rates of 31.4%, 32.9% and 29.7%, 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 and consistent with previous reports. The lowest doses of 25 mg and 10 mg did not demonstrate efficacy as compared with placebo (Figure 3-1). The 75-mg dose was considered to be the optimal dose to achieve required efficacy with minimum exposure. There were no consistently meaningful improvements in efficacy at doses above 75 mg. Thus, 75 mg dose was selected as the only dose level for pivotal safety/efficacy studies.

Pivotal safety and efficacy studies included three identically designed, multicenter, randomized, double-blind, placebo-controlled studies assessing (outpatient) single 75 mg dose of rimegepant using tablet (Studies # BHV3000-301 and BHV3000-302) or ODT (# Study BHV3000-303) formulations for the acute treatment of migraine with moderate or severe pain intensity (Table 3-2). Studies 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 visit within 7 days after the administration of the study medication. Subjects were randomized (in a 1:1 ratio) and dispensed 1 dose of study medication consisting of rimegepant 75-mg (n=1771) or matching placebo (n=1782). Patients (age ≥ 18 years) who had at least 1-year history of migraine (with or without aura) and not more than 8 attacks of moderate or severe pain intensity per month within last 3 months were enrolled in these studies (International Classification of Headache Disorders criteria; 3rd Ed. beta, 2013).

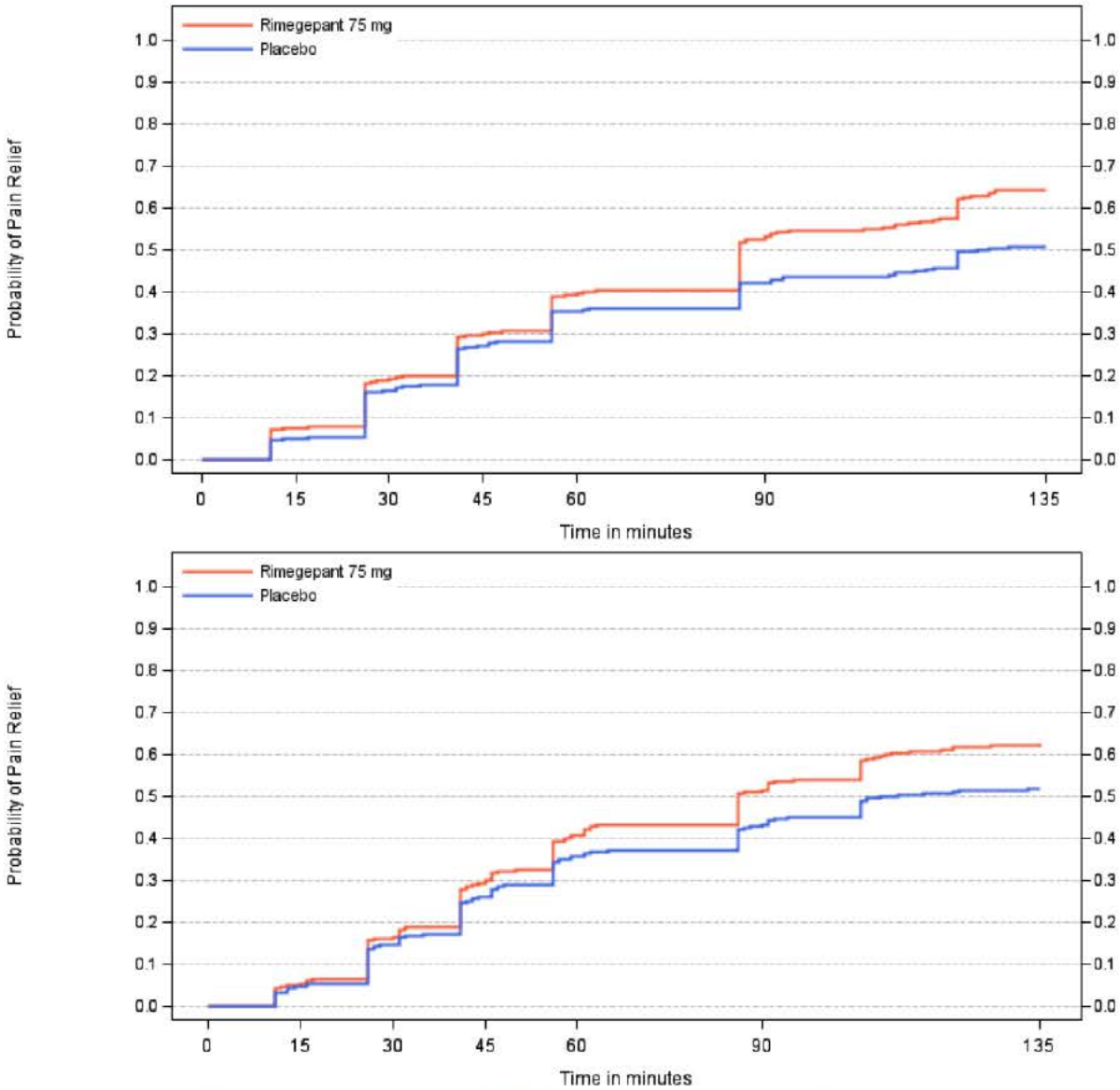
Table 3-2 Summary of Clinical Safety and Efficacy Studies

Clinical Studies	**Study # BHV3000-303**	**Study # BHV3000-302**	**Study # BHV3000-301**
Primary endpoints	1. Freedom from Pain* 2. Freedom from MBS*		
Objective	Superiority to placebo		
Design	multicenter, randomized, double-blind, placebo-controlled		
Treatment	75 mg single dose		
Formulation	ODT	Tablet	Tablet
Sample Size	(rimegepant 669 + placebo 682)	(rimegepant 537 + placebo 535)	(rimegepant 543 + placebo 541)

** at 2 hours post-dose.*

In each study, the co-primary efficacy endpoints of pain freedom and absence of the most bothersome migraine-associated symptom at 2 hours after the single dose of rimegepant demonstrated statistically significant treatment differences compared to placebo (Figure 3-2). For the pain freedom at 2 hours post-dose, the differences from placebo were 5%, 7.6%, and 10.3% for studies # BHV3000-301, BHV3000-302, and BHV3000-303, respectively.

Figure 3-2 Kaplan-Meier Plots of Time to Pain Relief in the Phase-3 Studies with Rimegepant 75 mg and Placebo (top: Studies # BHV3000-301 and BHV3000-302 combinedly for tablet; bottom: Study # BHV3000-303 for ODT).



Source: Applicant's Analysis; appendixes 2.5.1 & 2.5.2; Pain relief is defined as patients who have either mild pain or no pain during the specified interval. Estimates computed using the mITT population. Subjects using rescue medications at or before the assessment, and subjects not providing data, are classified as failures.

Similarly, the differences from placebo for freedom from most bothersome symptoms at 2 hours post-dose were 8.9%, 12.4%, and 8.3% for studies # BHV3000-301, BHV3000-302, and BHV3000-303, respectively (Refer to the clinical review by Dr. Laura Jawidzik). Results from all

three safety and efficacy studies confirmed a statistically significant freedom from pain at 2 h post-dose and freedom from MBS at 2 h post-dose with 75-mg rimegepant doses in comparison with placebo (Refer to the statistical review by Dr. Jinnan Liu).

3.3.2 Is the proposed dosing regimen appropriate for the general population for which the indication is being sought?

Yes, three pivotal studies (Studies # BHV3000-303, # BHV3000-302, and # BHV3000-301) demonstrated that rimegepant 75 mg single dose administered as (b) (4) ODT is superior to placebo for the acute treatment of migraine for both pain freedom and absence of the most bothersome migraine-associated symptom at 2 hours after the single dose (See Section 3.3.1).

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Population pharmacokinetic analysis did not reveal a significant impact of disease state, age, gender, bodyweight on the exposures of rimegepant. Dose adjustment is not necessary based on intrinsic factors such as age, gender, or bodyweight. The applicant conducted dedicated clinical studies assessing the impact of renal function and hepatic function on the exposures of rimegepant (see below).

3.3.3.1 Renal Impairment

The applicant conducted a dedicated renal impairment study (Study # BHV3000-106) to assess the effect of renal function on the pharmacokinetics of rimegepant. This was an open-label, parallel group study evaluating the pharmacokinetics of rimegepant in subjects with renal impairment compared to that in subjects with normal renal function (healthy matched controls). Subjects were assigned to groups based according to their estimated glomerular filtration rate (eGFR) obtained from the Modification of Diet in Renal Disease-4 (MDRD-4) study equation using serum creatinine at screening. Subjects with normal (eGFR: > 90 mL/min/1.73 m^2; n=18), mild (eGFR: 60 to 89 mL/min/1.73 m^2, n=6), moderate (eGFR: 30 to 59 mL/min/1.73 m^2, n=6), or severe (eGFR: 15 to 30 mL/min/1.73 m^2, n=6) renal function groups received a single 75 mg dose of rimegepant (using tablet under fasting condition). Subjects with ESRD were not included in this study. Blood samples were collected up to 120 h post-dose for the determination of total rimegepant and unbound rimegepant concentrations.

Rimegepant plasma concentration (Mean ± SD) versus time profiles following single oral administration of 75 mg tablet in healthy adult subjects compared to subjects with renal impairment are presented in Figure 3-3. The summary of pharmacokinetic parameters is presented in Table 3-3.

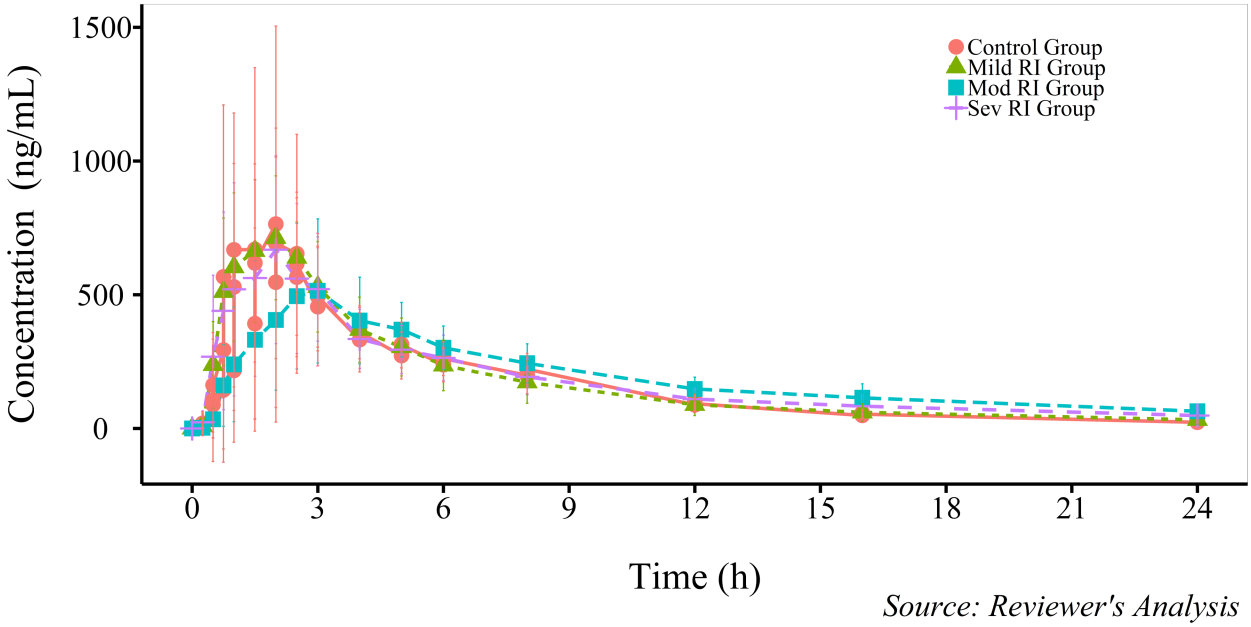
Table 3-3 Summary of pharmacokinetics Parameters [Study # BHV3000-106]

Renal Impairment Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUC (ng·h/mL)
Mild	779 ±242, n=6; 854 (414, 1010)	4720 ±1690, n=6; 4960 (2030, 7250)	1.20 (0.75 to 1.92)	1.06 (0.74 to 1.51)
Moderate	591 ±245, n=6; 575 (273, 881)	5770 ±1680, n=6; 6360 (3470, 7410)	0.76 (42.5 to 137)	1.40 (0.96 to 2.01)
Severe	705 ±356, n=6; 659 (333, 1220)	5050 ±1900, n=6; 5240 (2260, 7200)	0.90 (0.50 to 1.62)	1.04 (0.69 to 1.56)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation, number of subjects followed by median and range.*

The peak concentrations of 794 ± 524 ng/mL (AUCinf: 4410 ± 1450 ng·h/mL, pooled n=18) were observed in the subjects with normal renal function. Although the exposure of rimegepant was found to be increased in subjects with moderate renal impairment (5770 vs 4410 ng·h/mL), there was no trend observed indicating the increase in exposures of rimegepant with decrease in renal function (measured as creatinine clearance).

Figure 3-3 Rimegepant Plasma Concentration (Mean ± SD) versus Time Profiles following Single Oral Administration of 75 mg Tablet in Healthy Adult Subjects compared to Subjects with Renal impairment [Study # BHV3000-106].



Source: Reviewer's Analysis

Data presented as mean ± SD on a linear scale (up to 24 h post-dose).

The renal elimination is not a major excretion pathway for rimegepant. Thus, no clinically meaningful differences in the pharmacokinetics of rimegepant were observed in subjects with reduced renal function compared to subjects with normal renal function. Based on these observations, the applicant proposed no adjustment of dose or dosing frequency in patients with renal impairment. We agree with the applicant's proposal that no dose or dosing frequency adjustment is required in subjects with mild, moderate, and severe renal impairment.

Rimegepant has not been studied in subjects with ESRD (eGFR: < 15 mL/min/1.73 m^2) and in patients on dialysis. It is recommended to avoid use of rimegepant in patients with ESRD.

3.3.3.2 Hepatic Impairment

The applicant conducted a dedicated hepatic impairment study (Study # BHV3000-107) to assess the effect of hepatic function on the pharmacokinetics of rimegepant. This was an open-label, parallel group study evaluating the pharmacokinetics of rimegepant in subjects with hepatic impairment compared to that in subjects with normal hepatic function (healthy matched controls). Subjects with normal (n=18), mild (Child-Pugh Group A: 5 to 6 points; n=6), moderate (Child-Pugh Group B: 7 to 9 points; n=6), or severe (Child-Pugh Group C: 10 to 15 points; n=6) groups of hepatic impairment received a single 75 mg dose of rimegepant (using tablet under fasting condition). Blood samples were collected up to 120 h post-dose for the determination of total rimegepant and unbound rimegepant concentrations.

Rimegepant plasma concentration (Mean ± SD) versus time profiles following single oral administration of tablet in healthy adult subjects compared to subjects with hepatic impairment are presented in Figure 3-4. The summary of pharmacokinetic parameters is presented in Table 3-4.

Table 3-4 Summary of PK Parameters [Study # BHV3000-107]

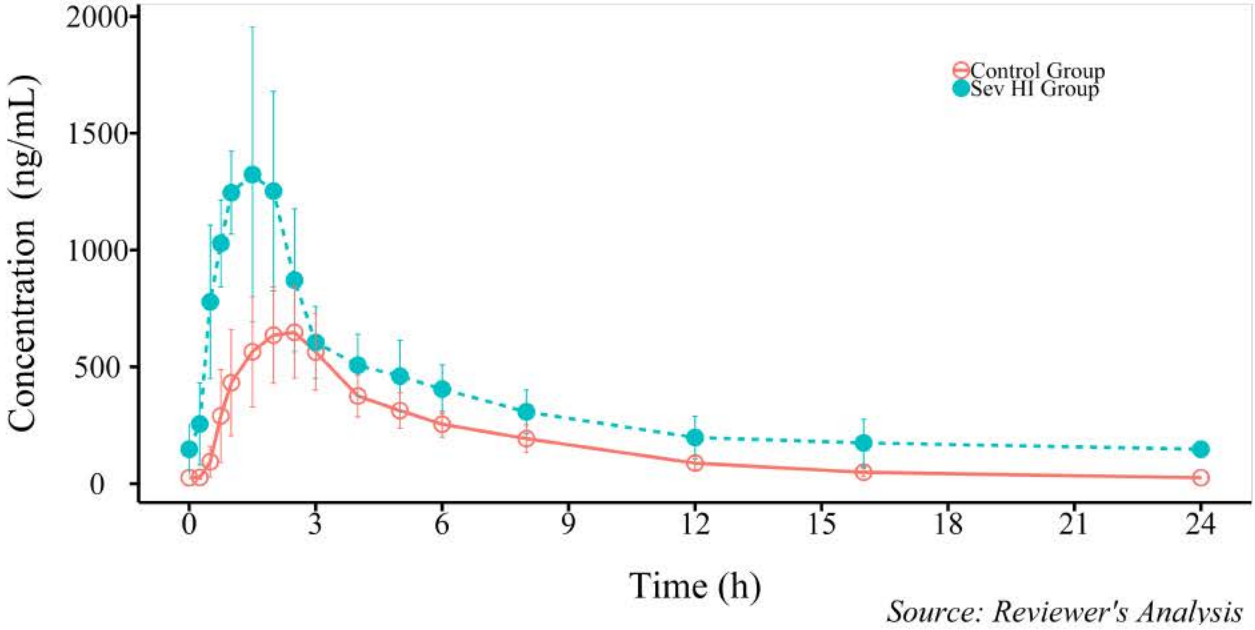
Hepatic Impairment Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUC (ng·h/mL)
Mild	591 ±219, n=6; 576 (270, 864)	4570 ±2550, n=6; 3340 (2520, 8570)	0.92 (0.64 to 1.33)	0.84 (0.59 to 1.20)
Moderate	597 ±407, n=6; 495 (112, 1300)	4360 ±1900, n=6; 4070 (2000, 6550)	0.86 (0.45 to 1.64)	1.07 (0.69 to 1.66)
Severe	1370 ±488, n=6; 1240 (790, 2180)	8290 ±2610, n=6; 7510 (5350, 12600)	1.89 (1.32 to 2.71)	2.02 (1.54 to 2.65)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation, number of subjects followed by median and range.*

The peak concentrations of 632 ±173 ng/mL (AUCinf: 4200 ±864 ng·h/mL, pooled n=18) were observed in the subjects with normal hepatic function. No clinically meaningful differences in the pharmacokinetics of rimegepant were observed in subjects with mild (Child-Pugh class A) and

moderate (Child-Pugh class B) hepatic impairment compared to subjects with normal hepatic function (healthy matched control).

Figure 3-4 Simulated Rimegepant Plasma Concentration (Mean ± SD) versus Time Profiles following Single Oral Administration of 75 mg Tablet in Healthy Adult Subjects compared to Subjects with Hepatic impairment [Study # BHV3000-107; by Superposition].



Source: Reviewer's Analysis

Data presented as mean ± SD on a linear scale (24 h post-dose at steady-state).

However, the exposure of rimegepant was increased in subjects with severe hepatic impairment compared to that with subject with normal hepatic function (~2-fold for Cmax and AUCinf). Similarly, half-life of rimegepant was increased in subjects with severe hepatic impairment to 15.7 h (from 11 h). (b) (4)

The pivotal safety and efficacy studies included only one dose level (75 mg) for treating single migraine attach. The available safety data is limited to long-term extension study evaluating only the 75 mg dose (Refer to the clinical review by Dr. Laura Jawidzik). The long-term safety data associated with higher exposures of rimegepant as observed with severe hepatic impairment (2-fold Cmax and AUC) is not available from the development program of rimegepant.

Moreover, the applicant has neither developed a lower strength for marketing nor the developed formulations (tablet or ODT) are functionally scored to deliver lower dose. Due to unavailability of lower strength required to support dosing in patients with severe hepatic impairment, it is recommended to avoid use of rimegepant in patients with severe hepatic impairment.

3.3.3.3 Sex and Age

The applicant conducted a clinical study (Study # BHV3000-108) to assess the effect of sex and age on the pharmacokinetics of rimegepant. This was an open-label, parallel group study evaluating the pharmacokinetics of rimegepant in elderly (male/female) subjects compared to that in adult non-elderly control (male/female) subjects. Healthy subjects (age: ≥ 18 to ≤ 45; n=14) and elderly subjects (age: ≥ 65; n=14) received a single 75 mg dose of rimegepant (using tablet under fasting condition). Blood samples were collected up to 96 h post-dose for the determination of rimegepant concentrations. The summary of pharmacokinetic parameters is presented in Table 3-5.

Table 3-5 Summary of PK Parameters [Study # BHV3000-108]

Age Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Adult	1050 ±317, n=14; 1060 (440, 1710)	4720 ±1610, n=14; 4220 (2150, 8710)	-	-
Elderly	1090 ±491, n=14; 979 (174, 1990)	5010 ±1510, n=14; 4790 (1210, 7250)	0.97 (0.71 to 1.32)	1.05 (0.82 to 1.34)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation, number of subjects followed by median and range.*

The exposure of rimegepant was found to be similar between 2 groups indicating no significant impact of age on the pharmacokinetic of rimegepant. (b) (4) Moreover, the exposure of rimegepant was found to be slightly higher in females possibly due to lower body weight compared to male. Thus, there was no significant impact of sex on the pharmacokinetic of rimegepant (see Section 4.5).

Additional evaluation of the effect of intrinsic factors was conducted as part of the population pharmacokinetics analysis. Population pharmacokinetics analysis concluded that age, body weight, and sex are not expected to significantly affect the exposure of rimegepant (see Section 4.5). The reported differences in exposure across these intrinsic factors are minimal and are not expected to be significant considering the safety and efficacy data for the 75 mg dose from clinical studies.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

The applicant conducted in vitro studies suggesting that rimegepant metabolism is primarily mediated by CYP3A4 and to lesser extent by CYP2C9. (Section 2.1.3). Concomitant administration of rimegepant with CYP3A4 enzyme modulators is expected to impact rimegepant exposures. The applicant conducted clinical drug interaction studies to assess the interaction potential with - 1) Inhibitors of CYP3A4 (Study # BHV3000-103) and 2) Inducer of CYP3A4 (Study # BHV3000-104), and 3) Inhibitors of CYP2C9 (Study # BHV3000-105).

3.3.4.1 Drug Interactions - CYP3A4 Modulators

3.3.4.1.1 Drug Interaction with Inhibitors of CYP3A4

The applicant conducted a clinical drug interaction study (Study # BHV3000-103) to assess the effect of a strong inhibitor of CYP3A4 on the pharmacokinetics of rimegepant. This was an open-label, one-arm, fixed-sequence study evaluating the effect of concomitant administration of itraconazole (multiple dose) on the pharmacokinetics of rimegepant (single dose) in healthy subjects.

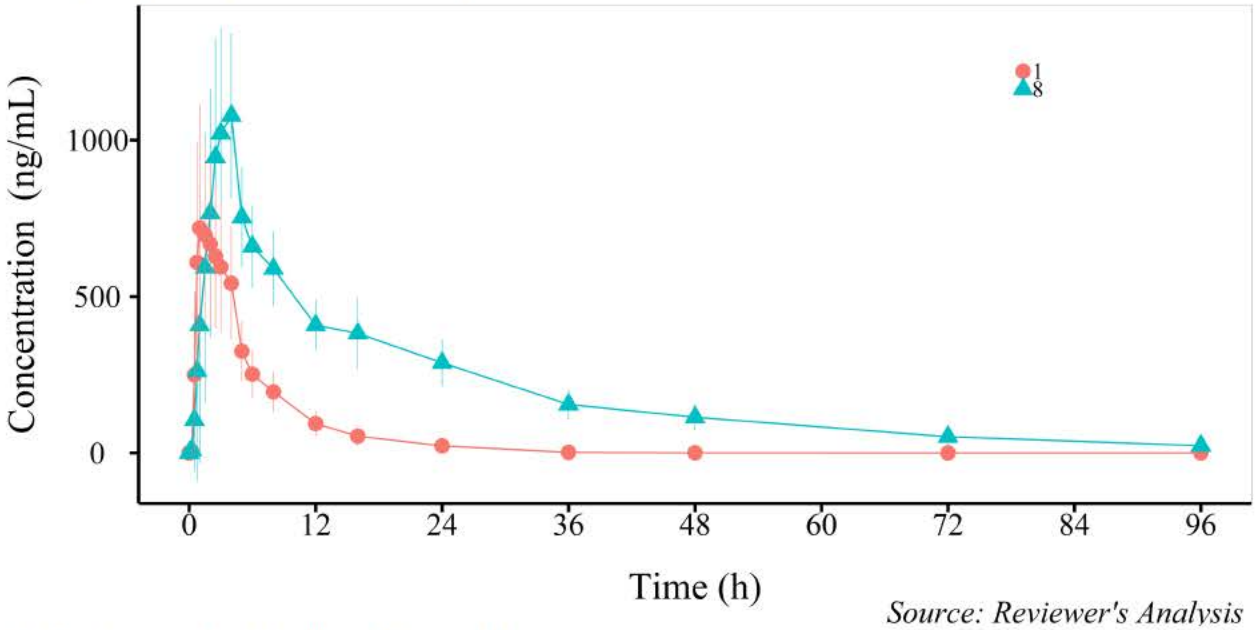
Subjects (n=24) received a single 75 mg dose of rimegepant (using tablet) under the fasting condition on Day 1 which was followed by itraconazole administration (200 mg once daily; 20 mL oral solution 10 mg/mL) under the fasting condition for 7 days (Day 5 through Day 11). On Day 8, all subjects received a single 75 mg dose of rimegepant (using tablet) with itraconazole under the fasting condition. Blood samples were collected for the determination of total rimegepant concentrations. Rimegepant plasma concentration (Mean ± SD) versus time profiles following single oral administration of tablet compared to that administered with itraconazole administration under fasting condition are presented in Figure 3-5. The summary of pharmacokinetic parameters is presented in Table 3-6.

Table 3-6 Summary of PK Parameters [Study # BHV3000-103]

Treatment Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Day 1	846 ±303, n=24; 844 (344, 1450)	4740 ±1480, n=24; 4580 (2210, 8170)	-	-
Day 8	1180 ±285, n=22; 1130 (826, 1710)	19100 ±4550, n=22; 18200 (12400, 29100)	1.43 (1.26 to 1.63)	4.03 (3.77 to 4.31)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation, number of subjects followed by median and range*

Figure 3-5 Rimegepant Plasma Concentration (Mean ± SD) versus Time Profiles following Single Oral Administration of 75 mg Tablet (Day 1; red color circles) in Healthy Adult Subjects compared to that Administered with Itraconazole (Day 8; green color triangles) [Study # BHV3000-103]



Source: Reviewer's Analysis

Data presented as mean ± SD on a linear scale.

Concomitant administration of rimegepant with itraconazole (at steady state; 20 mL oral solution 10 mg/mL) resulted in increased exposures of rimegepant (AUC: ~4-fold & Cmax: ~1.5-fold). (b) (4)

The applicant's population pharmacokinetics modeling showed that concentrations of rimegepant 75 mg achieved with once daily dosing are not meaningfully different than those of a single rimegepant 75 mg dose (see Section 4.5). However, the applicants' s population pharmacokinetics model under predicted exposures of rimegepant during interaction with inhibitors of CYP3A4. The FDA reviewer performed steady-state simulations using superposition principle and pharmacokinetics parameters with concomitant administration of strong inhibitor of CYP3A4 at steady-state is described in Table 3-7.

These simulations indicate that there is a significant increase in exposures of rimegepant on Day 1 with altered dosing regimens (every 48 h or every 72 h; Figure 3-6). The long-term safety experience associated with these high exposures is not available from the development program of rimegepant. Safety data is limited to the long-term extension study with only the 75 mg dose (Refer to the clinical review by Dr. Laura Jawidzik). For this reason, we recommend that the

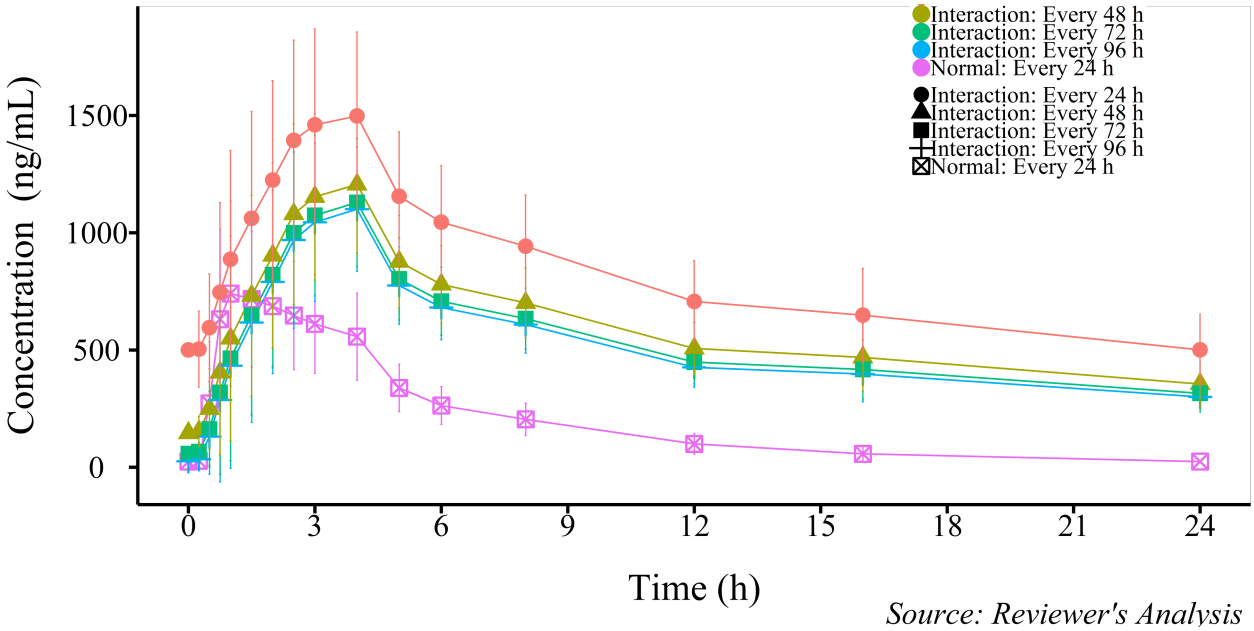
concomitant administration of rimegepant with a strong inhibitor of CYP3A4 (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, ritonavir, saquinavir, nelfinavir, indinavir, telithromycin and conivaptan) should be avoided.

Table 3-7 Summary of Simulated PK Parameters with Different Dosing Frequencies

Concomitant Administration	Dosing Frequency	PK Parameters*		
		Cmax (ng/mL)	AUC0-24h (ng·h/mL)	AUClast (ng·h/mL)
Without Inhibitor	Every 24 h	741	4740	4740
With Inhibitor	Every 24 h	1500	19600	19600
	Every 48 h	1210	9850	19700
	Every 72 h	1130	6600+	19800

*Source: Reviewer's analysis. *Data presented as mean using steady-state simulations by superposition, +presented as an average AUC*

Figure 3-6 Simulated Plasma Concentration (Mean ± SD) versus Time Profiles following Multiple Dosing 75 mg Tablet in Healthy Adult Subjects compared to that Administered with Itraconazole at different Dosing Frequencies [Study # BHV3000-103; by Super-position]



Source: Reviewer's Analysis

Data presented as mean ± SD on a linear scale (24 h at steady-state).

No dedicated drug interaction study was conducted to evaluate the drug interaction potential of rimegepant with moderate and weak inhibitors of CYP3A4. The applicant proposed no adjustment of dose or dosing frequency for moderate to weak inhibitors of CYP3A4.

The above described drug interaction study with itraconazole indicated that the concomitant administration of rimegepant with a strong inhibitor of CYP3A4 results in ~4-fold increase in AUC of rimegepant. Thus, rimegepant can be classified as a moderately sensitive substrate for CYP3A4 (with ≥2 to <5-fold increase in AUC expected with a strong inhibitor of CYP3A4). In general, the concomitant administration of any moderately sensitive substrate for CYP3A4 with a moderate inhibitor of CYP3A4 is expected to result in increased exposures (AUC) up to 2-fold. Thus, similar increase in exposure (i.e., up to 2-fold increase in AUC) is also expected with concomitant administration of rimegepant with a moderate inhibitor of CYP3A4.

In order to evaluate the impact of moderate inhibitors of CYP3A4 on the rimegepant exposures, the results from drug interaction study with fluconazole were also used. Concomitant administration of rimegepant with fluconazole (at steady state) resulted in increased exposures of rimegepant (AUC: ~1.8-fold) without significant impact on its peak concentrations. Since rimegepant is a substrate of both CYP3A4 and CYP2C9 enzymes, this increased exposure of rimegepant can be attributed to the combined inhibition of CYP2C9 and CYP3A4 with fluconazole. Although studies indicate that rimegepant metabolism is primarily mediated by CYP3A4 with lesser contribution from CYP2C9, the concomitant administration of moderate inhibitors of CYP3A4 with rimegepant is not expected to increase its exposures by 2-fold (~1.8-fold) and no significant change in its Cmax.

The review team recommended to avoid administration of rimegepant in patients with hepatic impairment with 2-fold increase in exposures in both Cmax and AUC of rimegepant. However, the concomitant administration of rimegepant with a moderate inhibitor of CYP3A4 may increase AUC of rimegepant up to 2-fold without meaningful change in Cmax. Since there is no meaningful change in the Cmax of rimegepant, alternate dosing regimen is considered as a viable option. For this purpose, it is recommended that no dose adjustment is needed when rimegepant is administered with a moderate inhibitor of CYP3A4. However, it is recommended to avoid another dose of rimegepant for next 48 hours.

As the expected increase in exposures (Cmax and AUC) of rimegepant with a weak inhibitor of CYP3A4 is not considered clinically meaningful, no dose adjustment is recommended during concomitant administration of rimegepant with a weak inhibitor of CYP3A4.

3.3.4.1.2 Drug Interaction with Inducers of CYP3A4

The applicant conducted a clinical drug interaction study (Study # BHV3000-104) to assess the effect of a strong inducer of CYP3A4 and P-gp on the pharmacokinetics of rimegepant. This was an open-label, one-arm, fixed-sequence study evaluating the effect of concomitant administration of rifampin (multiple dose) on the pharmacokinetics of rimegepant (single dose) in healthy subjects.

Healthy subjects (n=24) received a single 75 mg dose of rimegepant (using tablet) under the fasting condition on Day 1 which was followed by rifampin administration (600 mg once daily) under the fasting condition for 11 days (Day 5 through Day 15). On Day 12, all subjects received a single

75 mg dose of rimegepant with rifampin under the fasting condition. Blood samples were collected on Day 1 and Day 12 for the determination of rimegepant concentrations.

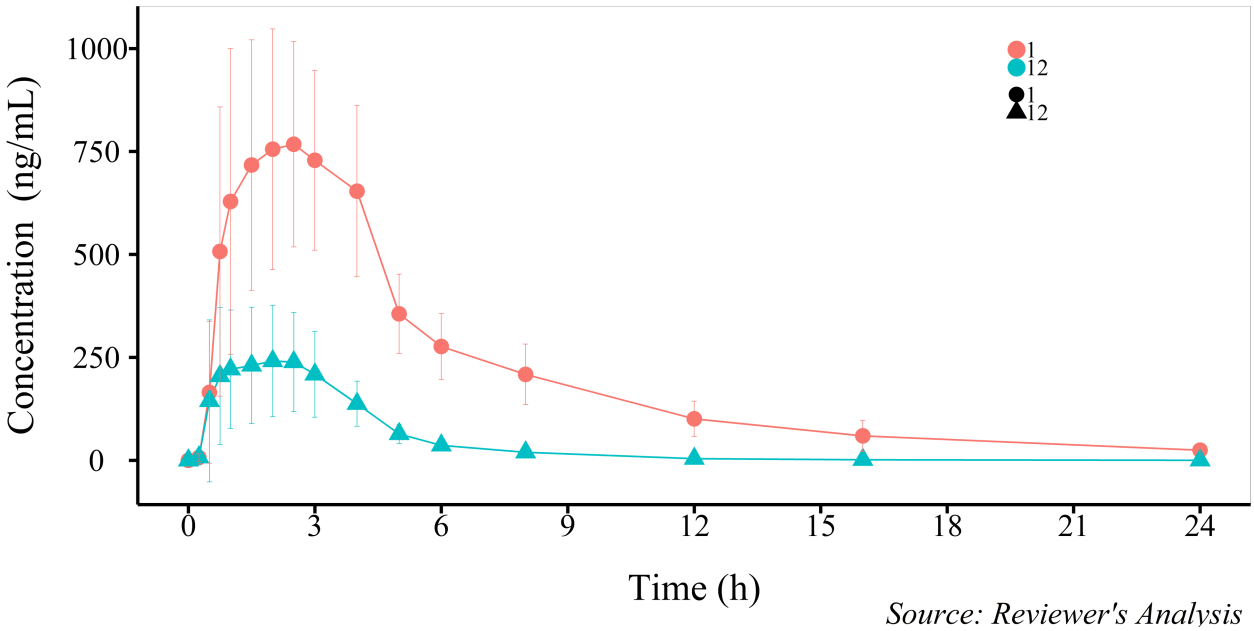
Rimegepant plasma concentration (Mean ± SD) versus time profiles following single oral administration of tablet compared to that administered with rifampin under fasting condition are presented in Figure 3-7. The summary of pharmacokinetic parameters is presented in Table 3-8.

Table 3-8 Summary of PK Parameters [Study # BHV3000-104]

Treatment Group	PK Parameters		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Day 1	921 ±269, n=24; 891 (439, 1430)	5280 ±1690, n=24; 4860 (2610, 8450)	-	-
Day 12	349 ±162, n=21; 342 (173, 663)	1030 ±412, n=21; 979 (412, 1920)	0.36 (0.31 to 0.42)	0.19 (0.16 to 0.21)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation, number of subjects followed by median and range*

Figure 3-7 Rimegepant Plasma Concentration (Mean ± SD) versus Time Profiles following Single Oral Administration of 75 mg Tablet (Day 1; red color circles) in Healthy Adult Subjects compared to that Administered with Rifampin (Day 12; green color triangles) [Study # BHV3000-104]



Source: Reviewer's Analysis

Data presented as mean ± SD on a linear scale (up to 24 h post-dose).

Studies indicate that rimegepant metabolism is primarily mediated by CYP3A4. Concomitant administration of rimegepant with rifampin (at steady state) resulted in decreased exposures of rimegepant due to induction of CYP3A4 (AUC: ~80% & Cmax: ~64%) compared to administration of rimegepant alone. Thus, concomitant administration of a strong inducer of CYP3A4 with rimegepant is expected to result in loss of efficacy. Therefore, concomitant administration of rimegepant with a strong inducer of CYP3A4 is not recommended.

No dedicated drug interaction study was conducted to assess effect of concomitant administration of moderate or weak inducers of CYP3A4 on the pharmacokinetics of rimegepant. The concomitant administration of a moderate inducer of CYP3A4 may result reduced exposures of a sensitive substrate of CY3A4 by ≥ 50% to < 80%[2]. However, based on itraconazole drug interaction study results, rimegepant is can be classified as moderately sensitive substrate of CYP3A4 (~4-fold increase in AUC with itraconazole). Thus, concomitant administration of any moderate inducer of CYP3A4 may result decreased exposures of rimegepant by ~50%. The impact of decreased exposure of rimegepant on its efficacy was not well studied. The dose finding study results indicate that lower doses studied such as 25 and 10 mg were not effective (see Section 3.1). Assuming a linear dose-response relationship between doses 25 mg and 75 mg, the efficacy may be reduced upon administration of rimegepant with moderate inducers of CYP3A4 compared to 75 mg single dose. Thus, it is recommended to avoid concomitant administration of rimegepant with a moderate inducer of CYP3A.

Although a dedicated drug interaction study was not conducted to evaluate the effect of concomitant administration of rimegepant with weak inducers, the applicant analyzed the data from subjects on concomitant medication with topiramate (a weak inducer) across the pivotal phase-3 clinical studies (~7% population) suggesting no clear impact on the efficacy because of weak induction of CYP3A4. However, the applicant did not collect dosing data on the topiramate administrations for these analyses.

In general, the concomitant administration of any weak inducer of CYP3A4 may result decreased exposures of a sensitive substrate of CY3A4 by ≥ 20% to < 50%[2]. Since, rimegepant is can be classified as moderately sensitive substrate of CYP3A4, concomitant administration of any weak inducer of CYP3A4 may result decreased exposures of rimegepant by ~20%. Thus, it is recommended that no change in dose/regimen is necessary upon concomitant administration of rimegepant with a weak inducer of CYP3A4.

3.3.4.1.3 Drug Interaction with Inhibitors of CYP2C9

The applicant conducted a clinical drug interaction study (Study # BHV3000-105) to assess the effect of moderate inhibitor of CYP2C9 (and moderate inhibitor of CYP3A4) on the pharmacokinetics of rimegepant. This was an open-label, one-arm, fixed-sequence study

[2] *https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers*

evaluating the effect of concomitant administration of fluconazole (multiple dose) on the pharmacokinetics of rimegepant (single dose) in healthy subjects.

Healthy subjects (n=24) received a single 75 mg dose of rimegepant (using tablet) under the fasting condition on Day 1 which was followed by fluconazole administration (400 mg once daily) under the fasting condition for 8 days (Day 5 through Day 12). On Day 9, all subjects received a single 75 mg dose of rimegepant with fluconazole under the fasting condition. Blood samples were collected on Day 1 and Day 9 for the determination of rimegepant concentrations.

Rimegepant plasma concentration (Mean ± SD) versus time profiles following single oral administration of tablet compared to that administered with fluconazole under fasting condition are presented in Table 3-8. The summary of pharmacokinetic parameters is presented in Table 3-9.

Table 3-9 Summary of PK Parameters [Study # BHV3000-105]

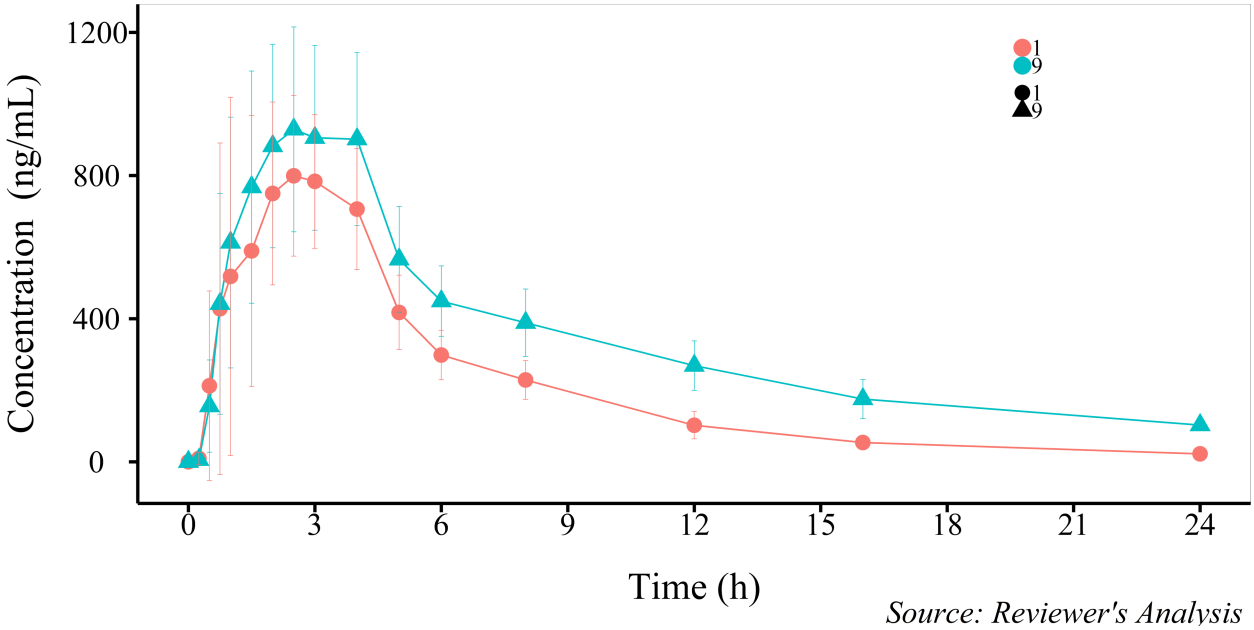
Treatment Group	PK Parameters		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Day 1	971 ±271, n=24; 896 (575, 1590)	5280 ±1210, n=24; 5210 (3610, 7770)	-	-
Day 9	993 ±300, n=23; 956 (459, 1720)	9570 ±2550, n=23; 9290 (4680, 16900)	1.02 (0.93 to 1.14)	1.80 (1.68 to 1.93)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation, number of subjects followed by median and range*

Concomitant administration of rimegepant with fluconazole (at steady state) resulted in increased exposures of rimegepant (AUC: ~1.8-fold) without significant impact on its peak concentrations. Considering a less than 2-fold increase in AUC of rimegepant, it can be expected that the fluconazole moderately inhibits metabolism of rimegepant. Although fluconazole is a moderate index inhibitor of CYP2C9, it is also a moderate inhibitor of CYP3A4. Moreover, rimegepant is a substrate of both CYP2C9 and CYP3A4 enzymes. Thus, this ~2-fold increase in AUC can be attributed to combined inhibition of CYP2C9 and CYP3A4 with fluconazole administration (steady-state).

In order to assess the relative contribution of CYP2C9 and CYP3A4 inhibition in this study, the results from drug interaction study with a strong inhibitor of CYP3A4 were used. The drug interaction study with itraconazole indicated that the concomitant administration of rimegepant with a strong inhibitor of CYP3A4 results in ~4-fold increase in AUC of rimegepant. Thus, rimegepant can be classified as a moderately sensitive substrate for CYP3A4 (with ≥2 to <5-fold increase in AUC) based on its 4-fold increase with a strong inhibition of CYP3A4.

Figure 3-8 Rimegepant Plasma Concentration (Mean ± SD) versus Time Profiles following Single Oral Administration of 75 mg Tablet (Day 1; red color circles) in Healthy Adult Subjects compared to that Administered with Fluconazole (Day 9; green color triangles) [Study # BHV3000-105]



Source: Reviewer's Analysis

Data presented as mean ± SD on a linear scale (up to 24 h post-dose).

The concomitant administration of any moderately sensitive substrate of CYP3A4 with a moderate inhibitor of CYP3A4 may increase its exposures by up to 2-fold. Similar increase in exposure is also expected with concomitant administration of rimegepant with fluconazole due to its moderate CYP3A4 inhibition activity. Also, it important to highlight that human mass balance study results indicates that rimegepant is primarily eliminated in unchanged form (~77% of the dose; with the mean absolute bioavailability ~64%) with no major metabolite (i.e., metabolites that represented >10% of drug-related material) detected in plasma. Thus, it is less likely that the concomitant administration of rimegepant with inhibitors of CYP2C9 would result in considerable increase in exposure of rimegepant. Studies also indicate that rimegepant metabolism is primarily mediated by CYP3A4 with lesser contribution from CYP2C9. Thus, no dose adjustment is recommended during concomitant administration of rimegepant with inhibitors of CYP2C9.

3.3.4.1.4 Drug Interaction with a CYP3A4 Substrate (rimegepant as a perpetrator)

In vitro studies indicated that rimegepant is a weak to moderate time-dependent inhibitor of human CYP3A4 (IC50s at T0 min: 33 µM, and at 30 min: 5 µM). The applicant conducted a clinical drug interaction studies (Studies # CN170007) to assess the effect of rimegepant administration on the pharmacokinetics of the sensitive CYP3A4 substrate. This was an open-label, single-sequence,

cross-over study evaluating the effect of concomitant administration of rimegepant (single 600 mg dose and 150 mg multiple doses) on the pharmacokinetics of midazolam (single dose) in healthy subjects. Considering the 5-fold increase in non-clinical studies, dose of midazolam was reduced to 2 mg to avoid potential adverse events.

Healthy subjects (n=14) received - A) a single 2 mg midazolam dose on Day 1, B) 300 mg rimegepant administered with 2 mg midazolam on Day 3, C) 150 mg rimegepant once daily on Days 4 to 7, D) 150 mg rimegepant administered with 2 mg midazolam on Day 8, and E) a single 2 mg midazolam dose on Day 11 (recovery). Blood samples were collected for the determination of plasma rimegepant, 4-β-OH-cholesterol, 4-α-OH-cholesterol, and urine 6-β-OH-cortisol/cortisol ratio and total cholesterol (on Day 1, 3, 8, and 11).

Table 3-10 Summary of Parameters [Studies # CN170007]

Analytes	Rimegepant 300 mg Single Dose Geometric Mean Ratio (90% CI)		Rimegepant 150 mg Multiple Doses Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUC0-t (ng·h/mL)	Cmax (ng/mL)	AUC0-t (ng·h/mL)
Midazolam	1.38 (1.13 to 1.67)	1.83 (1.56 to 2.16)	1.53 (1.32 to 1.78)	1.91 (1.61 to 2.27)
1'-OH Midazolam	1.47 (1.20 to 1.81)	1.34 (1.24 to 1.45)	1.20 (1.03 to 1.40)	1.16 (1.08 to 1.25)

*Source: Reviewer's analysis. *Comparisons of analytes in the absence and presence of rimegepant doses (single and multiple dosing).*

Concomitant administration of rimegepant with midazolam resulted in increased midazolam exposures. Single-dose rimegepant 300 mg with midazolam on Day 3 (Treatment B) resulted in increased midazolam exposures (GMR AUC: 1.83). Similarly, rimegepant 150 mg with midazolam on Day 8 (Treatment D), following once daily administration of rimegepant (Day 4 to 7) resulted in increased midazolam exposures (GMR AUC: 1.91). However, the increase in exposure of midazolam at steady-state was below 2-fold indicating that rimegepant can be classified as a weak inhibitor of CYP3A (Table 3-10). Study results also indicated that the inhibition of CYP3A4 enzyme activity by rimegepant was reversible within 3 days after discontinuation of rimegepant 150 mg once daily dosing. Note that this drug interaction study used rimegepant doses that are higher than the recommended therapeutic dose of 75 mg.

3.3.4.1.5 Drug Interaction with Oral Contraceptives

In vitro studies indicated that rimegepant is a weak to moderate time-dependent inhibitor of human CYP3A4 (IC50s at T0 min: 33 μM, and at 30 min: 5 μM). CYP3A4-mediated metabolism is the major pathway of oxidative metabolism of oral contraceptives (i.e. norelgestromin and ethinyl estradiol). Concomitant administration of rimegepant with oral contraceptives may inhibit metabolism of contraceptives leading to increased concentrations affecting safety. The applicant

conducted two clinical drug interaction studies (Studies # CN170002 & BHV3000-101) to assess the effect of rimegepant pharmacokinetics on the exposures of oral contraceptives. Both studies were an open-label, single-sequence (2-cycle), multiple dose studies evaluating the drug interaction between oral contraceptive (250 ng norgestimate, 35 ng ethinyl estradiol) and rimegepant in normal healthy adult female subjects. In both studies, following a run-in period (lead-in cycle) consisting of administration of once daily oral contraceptive for 21 days followed by 7 days of inactive agent, a second 28-day cycle (Cycle 1) followed in which the same oral contraceptive was administered once daily with or without rimegepant.

- First study utilized higher dose of rimegepant - a single dose of rimegepant 600 mg (Day 14 of cycle) and 450 mg rimegepant once daily (Days 15 to 21 of cycle) with no rimegepant on Days 1 to 13 of cycle.
- Second study utilized therapeutic doses of rimegepant - 75 mg rimegepant once daily (Days 12 to 19 of cycle) with no rimegepant on Days 1 to 11 of cycle.

Ethinyl estradiol, norgestrel (only in # CN170002), and norelgestromin pharmacokinetics were determined after the first rimegepant 75 mg dose and after all 8 rimegepant doses had been administered. Rimegepant concentrations were only determined in Study # BHV3000-101. The summary of pharmacokinetic parameters is presented in Table 3-11.

Table 3-11 Summary of Parameters [Studies # CN170002 & BHV3000-101]

Analytes	Rimegepant 450 mg Geometric Mean Ratio (90% CI)		Rimegepant 75 mg Geometric Mean Ratio (90% CI)	
	Cmax,ss (pg/mL)	AUC0-t,ss (pg·h/mL)	Cmax,ss (pg/mL)	AUC0-t,ss (pg·h/mL)
Ethinyl Estradiol	1.70 (1.41 to 2.05)	1.78 (1.56 to 2.02)	1.12 (1.06 to 1.18)	1.03 (1.01 to 1.06)
Norgestrel	2.91 (2.15 to 3.93)	3.47 (2.63 to 4.59)	-	-
Norelgestromin	1.87 (1.58 to 2.22)	2.33 (2.04 to 2.66)	1.13 (1.06 to 1.21)	1.16 (1.13 to 1.20)

*Source: Reviewer's analysis. *Comparisons of analytes in the absence and presence of multiple once daily rimegepant doses*

Although the administration of a single 75 mg rimegepant dose did not affect Ortho Cyclen component pharmacokinetic considerably, multiple dosing (75 mg once daily) resulted in increased ethinyl estradiol and norelgestromin exposures (~1.5-fold). Similarly, concomitant administration of rimegepant at higher doses (450 mg 7 days) increased the exposure of Ortho Cyclen component considerably (2.5 to 4-fold), which was higher than that observed with single 600 mg dose of rimegepant (<2-fold). Although there was a slight increase in rimegepant exposure (GMR for Cmax: 1.14 and GMR for AUC: 1.21) in presence of oral contraceptives at

steady-state, it is not considered to be clinically relevant (Cmax: 1350 ± 40 ng/mL; AUC: 5810 ± 30 ng·h/mL).

3.3.4.1.6 Drug Interaction with Sumatriptan

Considering the potential of concomitant administration of rimegepant with triptans, the applicant conducted a clinical drug interaction studies (Study # BHV3000-114) to assess the effect of rimegepant administration on the pharmacokinetics and pharmacodynamics (resting BP) of sumatriptan.

This was a single center, randomized, partially-blinded, placebo-controlled, one-arm study. On days 1 and 5, subjects received 12 mg single dose of sumatriptan open-label (administered as 2 subcutaneous injection - 6 mg/0.5 ml separated by 1 h; n=42). On Day 5, sumatriptan injections were administered ~2 and 3 hours following rimegepant or placebo tablet administration. Subjects were randomly assigned to receive either rimegepant (single 75 mg once daily for 4 days; Day 2 to 5; n=33) or matching placebo in a 6 to 1 ratio (n=36 on rimegepant, n=6 on placebo). Blood samples were collected for the determination of plasma rimegepant and sumatriptan concentrations (on Day 1, 4, and 5). Ambulatory blood pressure monitoring (~15 h) was performed at pre-dose and following sumatriptan injection on Day 1 and rimegepant administration on Days 4 and 5.

Table 3-12 Summary of PK Parameters [Studies # BHV3000-114]

Analytes	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (pg/mL)	AUCinf (pg·h/mL)	Cmax (pg/mL)	AUCinf (pg·h/mL)
Sumatriptan	100400 ± 24500 n=32	185400 ± 26200 n=32	-	-
Sumatriptan and Rimegepant	105960 ± 23500 n=30	194400 ± 28900 n=30	1.05 (1.03 to 1.07)	1.09 (1.01 to 1.17)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation followed by number of subjects; Comparisons of analytes in the absence and presence of rimegepant doses (Day 1 and Day 5).*

The results of the study indicated that the concomitant administration of sumatriptan (single dose) with rimegepant (at steady-state) did not affect the pharmacokinetics of each other. In addition, no considerable differences were observed in the time-weighted average of mean arterial pressure between 2 treatments (sumatriptan alone on Day 1 vs. sumatriptan give with rimegepant on Day 5).

3.3.4.2 Drug Interactions – Transporters

3.3.4.2.1 Substrate

Applicant conducted in vitro studies to assess if rimegepant is a substrate of following transporters.

<u>P-glycoprotein and BCRP:</u>

In vitro studies demonstrated that rimegepant is a P-gp substrate with the rate of secretory transport exceeding its rate of absorptive transport in the bi-directional transport assays. These assays were conducted using Caco-2 cells expressing P-gp (1.9 μM, 5.1 μM, 17.5 μM, and 67.9 μM). The bi-directional (B-A/A-B) transport ratios were > 10.3, > 12.3, ≥ 11.8, and 5.4, respectively. The secretory transport of rimegepant was inhibited by co-incubation with the inhibitors of P-gp (ketoconazole and cyclosporin A) indicating that concomitant administration of rimegepant with inhibitors of P-gp may increase the exposure of rimegepant.

The applicant did not conduct a dedicated clinical study assessing the impact of concomitant administration with inhibitors of P-gp on the pharmacokinetics of rimegepant. The applicant suggested that rimegepant exhibits high passive permeability. Its permeability coefficient at a nominal concentration of 100 μM in the non-cell-based parallel artificial membrane permeability (PAMPA) assay was 193 to 316 nm/sec (pH 5.5 = 193 nm/s; pH 7.4 = 316 nm/s). Further the applicant indicated that rimegepant is rapidly absorbed (Tmax ~2 h) with a high oral bioavailability (F~0.65) and assumed that concomitant administration of rimegepant with P-gp inhibitor can possibly increase its systemic availability of rimegepant by ~36% only.

However, the bioavailability (human mass balance) study conducted at 300 mg dose with the expectation that rimegepant exhibits dose proportional pharmacokinetics. Dose proportionality assessment from single / multiple- ascending dose study indicates more than dose proportional increase in exposure of rimegepant. Moreover, the drug interaction with itraconazole (a combined P-gp inhibitor and strong inhibitor of CYP3A4) resulted in increased exposure of rimegepant (AUC by ~4-fold). Based on these considerations, it is difficult to rule out that the concomitant administration of rimegepant with P-gp inhibitors (e.g. quinidine) would not result in significantly increased rimegepant exposures. Thus, the review team recommends that the applicant conduct a dedicated clinical study to evaluate the impact of concomitant administration with inhibitors of P-gp on rimegepant pharmacokinetics.

Rimegepant (0.1, 1, 10, and 100 μM) was found to be a BCRP substrate in the bi-directional transport assays conducted using MDCKII cells expressing the human BCRP. The efflux ratio was > 2.0 and was reduced > 50% in the presence of BCRP transport inhibitors. Similar to P-gp, BCRP is an efflux transporter localized on the luminal membrane. Accordingly, the same rationale discussed above, it is difficult to rule out that the concomitant administration of rimegepant with BCRP inhibitor (e.g. eltrombopag, curcumin) would not result in significantly increased rimegepant exposures. Thus, the review team recommends that the applicant conduct a dedicated clinical study to evaluate the impact of concomitant administration with inhibitors of BCRP on rimegepant pharmacokinetics.

<u>OATP1B1 and OATP1B3:</u>

Rimegepant was not found to be a substrate of OATP1B1 and OATP1B3.

<u>OAT, OCT, and MATE:</u>

Applicant did not conduct studies to assess whether rimegepant is a substrate of renal transporters as rimegepant does not appear to undergo active renal secretion (NMT ≥ 25% of total clearance).

3.3.4.2.2 Inhibition

Applicant evaluated potential inhibitory effects of rimegepant on following transporters.

P-gp and BCRP:

Rimegepant did not inhibit P-gp (IC50 > 100 μM) and BCRP (IC50 > 10 μM) suggesting that it is less likely to alter the absorption and distribution of drugs that are substrates these transporters.

OATP1B1 and OATP1B3:

Rimegepant was not found to be a potent inhibitor of OATP1B1 (11% at 5 μM). However, rimegepant inhibited OATP1B3 (IC50 = 6.04 μM).

OAT, OCT, and MATE:

Rimegepant was not found to be a potent inhibitor of OAT1 (IC50 > 10 μM), OAT3 (24% at 5 μM), and MATE2-K (IC50 > 10 μM). However, rimegepant inhibited MATE1 (IC50 = 1.18 μM) and OCT2 (IC50 = 1.08 μM).

Considering the peak concentrations at steady-state with therapeutic doses (Cmax ~1.5 μM) and protein binding (~96%), a clinically relevant drug interactions are less likely (Imax,u/IC50; ≤ 0.06). As an additional evidence, clinical studies conducted by the applicant did not indicate elevated serum creatinine levels over time in subjects receiving therapeutic doses of rimegepant suggesting interaction with OCT2, OAT2, and MATEs.

3.3.4.3 Food effect & Gastric pH Modifying Agents

3.3.4.3.1 Food Effect

The applicant conducted 2 clinical studies (Study # BHV3000-112 and Study # BHV3000-113) to assess the effect of food on the pharmacokinetics of rimegepant from tablet and ODT.

Study # BHV3000-112 evaluated effect of food on the pharmacokinetics of rimegepant from ODT and tablet. This was an open-label, randomized, single-dose, parallel-group (group by formulations), cross-over (2-period, 2-sequence; within group) study in healthy subjects (n=32; 16/group).

In this 2-groups study, the first group evaluated food effect of ODT with a crossover (2-period, 2-sequence) design. Healthy subjects (n=16) received a single 75 mg doses of rimegepant using ODT (administered sublingually) under fed (Test, a high fat meal; TRT-A) and fasting (Reference; TRT-B) conditions. While, the second group evaluated food effect of tablet with a crossover (2-period, 2-sequence) design. Healthy subjects (n=16) received a single 75 mg doses of rimegepant using tablet under fed (Test, a high fat meal; TRT-C) and fasting (Reference; TRT-D) conditions. In each period, a total of 21 blood samples were collected up to 72 h post-dose for the determination of rimegepant concentrations.

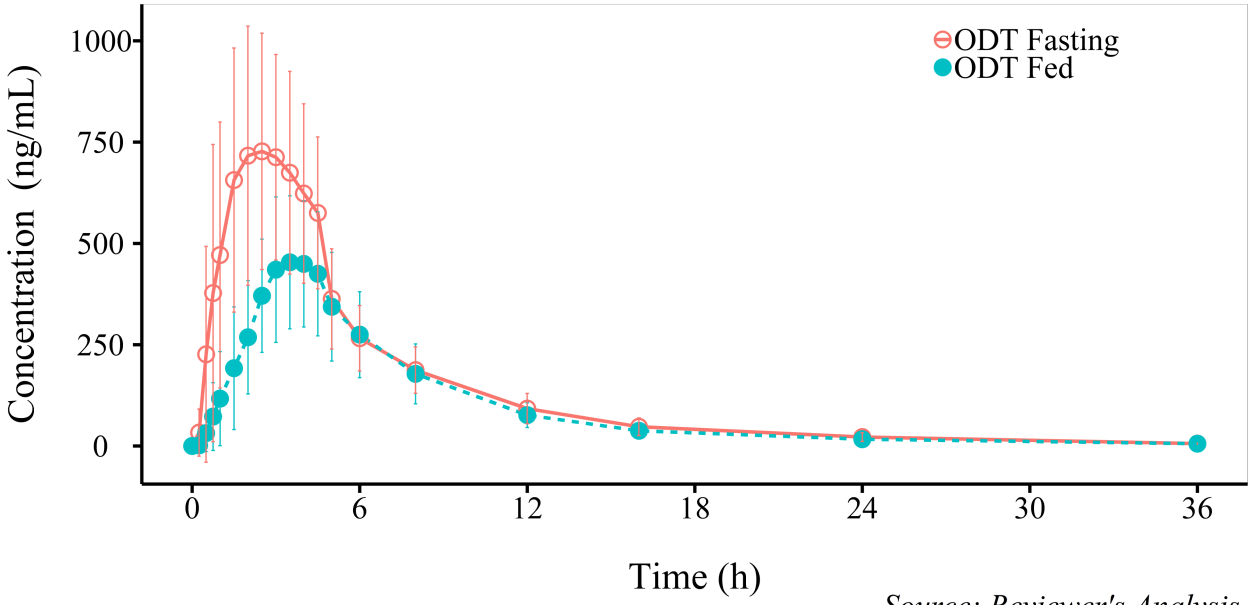
Rimegepant plasma concentration (Mean ± SD) versus time profiles following single oral administration of tablet fed condition compared to that administered under fasting condition are presented in Figure 3-9. The summary of pharmacokinetic parameters is presented in Table 3-13.

Table 3-13 Summary of PK Parameters [Study # BHV3000-112; Group-1: ODT]

Treatment Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Fasting Condition	859 ±337, n=16; 736 (444, 1530)	4910 ±1590, n=16; 4340 (2720, 8040)	-	-
Fed Condition	482 ±164, n=15; 464 (314, 990)	3380 ±1180, n=15; 3170 (1690, 5990)	0.58 (0.52 to 0.67)	0.68 (0.62 to 0.76)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation, number of subjects followed by median and range.*

Figure 3-9 Rimegepant Plasma Concentration (Mean ± SD) versus Time Profiles following Single Oral Administration of 75 mg ODT 75 mg under Fed (High Fat Breakfast) Condition Compared to that Fasting condition in Healthy Adult Subjects [Study # BHV3000-112; Group 1].



Source: Reviewer's Analysis

Data presented as mean ± SD on a linear scale.

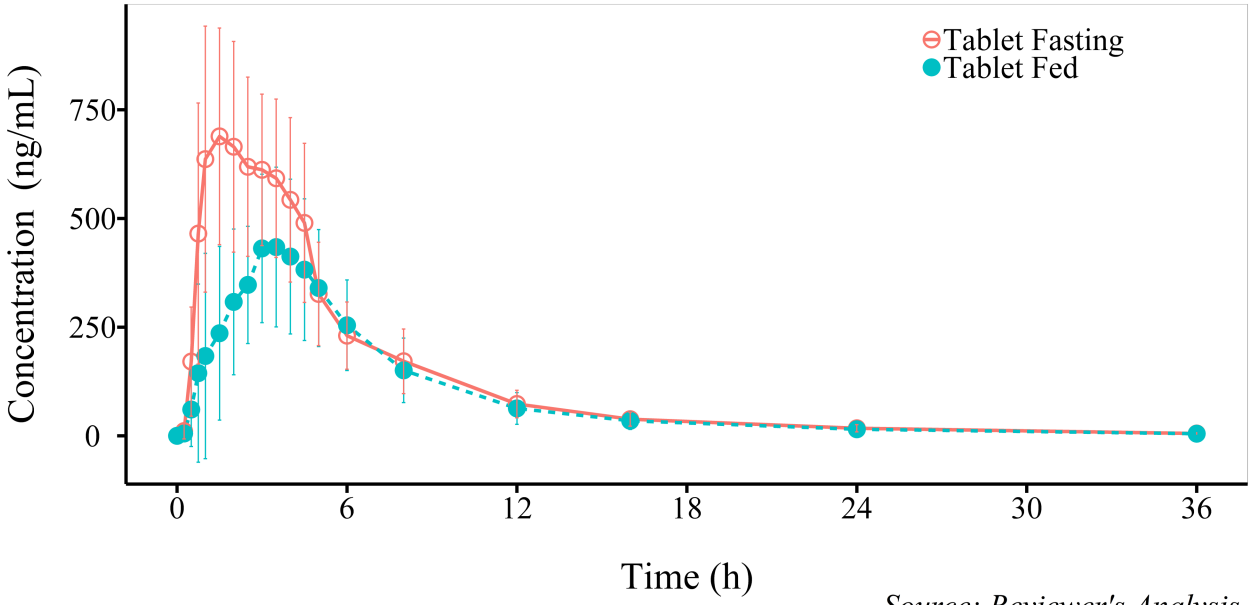
Similarly, rimegepant plasma concentration (Mean ± SD) versus time profiles following single oral administration of ODT fed condition compared to that administered under fasting condition are presented in Figure 3-10. The summary of pharmacokinetic parameters is presented in Table 3-14.

Table 3-14 Summary of PK Parameters [Study # BHV3000-112; Group-2: Tablet]

Treatment Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Fasting Condition	788 ±222, n=15; 742 (373, 1150)	4420 ±1270, n=15; 4050 (2700, 6450)	-	-
Fed Condition	525 ±165, n=16; 516 (264, 858)	3200 ±1040, n=16; 3220 (1790, 4910)	0.67 (0.54 to 0.82)	0.70 (0.62 to 0.79)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation, number of subjects followed by median and range.*

Figure 3-10 Rimegepant Plasma Concentration (Mean ± SD) versus Time Profiles following Single Oral Administration of 75 mg Tablet under Fed (High Fat Breakfast) Condition Compared to that Fasting condition in Healthy Adult Subjects [Study # BHV3000-112; Group 2]



Source: Reviewer's Analysis

Data presented as mean ± SD on a linear scale.

Study # BHV3000-113 evaluated effect of food on the pharmacokinetics of rimegepant from ODT. This was an open-label, randomized, crossover, single-dose study evaluating the bioequivalence between tablet (75 mg) formulation and ODT (75 mg, administered on top of the tongue) in healthy subjects. In this 2-parts study, the second part evaluated food effect with a crossover (2-period, 2-sequence; CD or DC) design. Healthy subjects (n=16) received a single 75 mg doses of rimegepant using ODT (top of the tongue until fully dissolved then swallowed without water) under fed (Test, a high fat meal; TRT-C) and fasting (Reference; TRT-D) conditions. In each period, a total of 21

blood samples were collected up to 72 h post-dose for the determination of rimegepant concentrations.

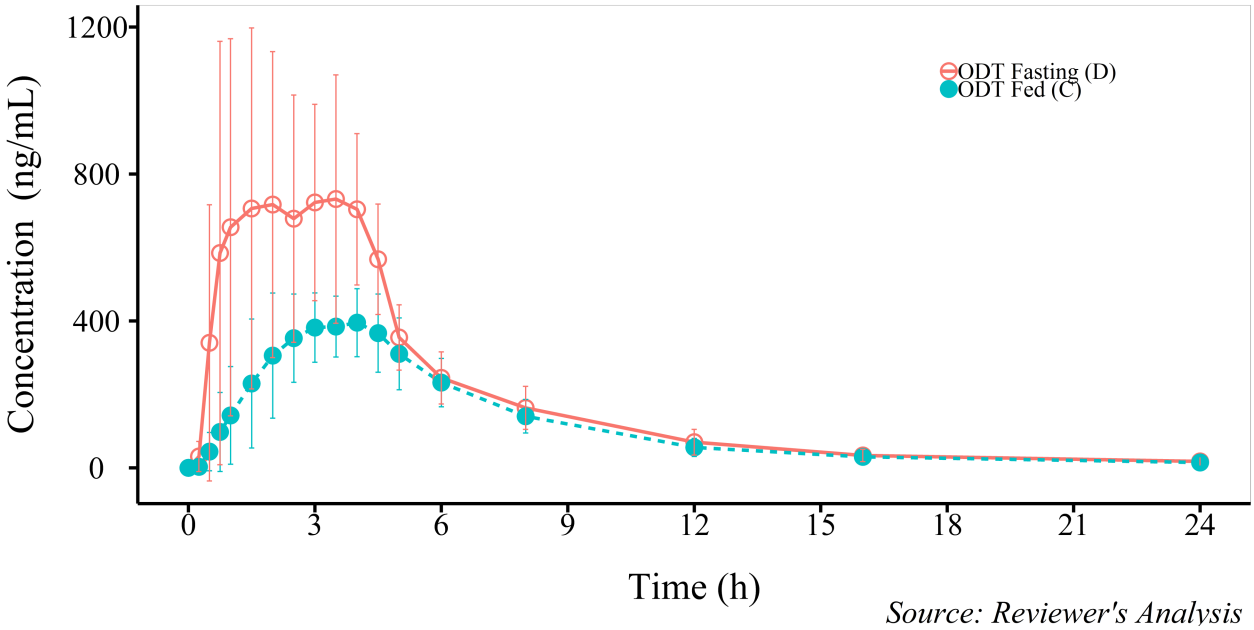
Rimegepant plasma concentration (Mean ± SD) versus time profiles following single oral administration of 75 mg ODT under fed condition (top of the tongue) compared to that administered under fasting condition are presented in Figure 3-11. The summary of pharmacokinetic parameters is presented in Table 3-15.

Table 3-15 Summary of PK Parameters [Study # BHV3000-113; Part-2: ODT]

Treatment Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Fasting Condition	1010 ±458, n=16; 847 (493, 2110)	4800 ±1590, n=15; 4750 (3030, 9320)	-	-
Fed Condition	441 ±109, n=15; 420 (286, 610)	2960 ±929, n=15; 2830 (1860, 5730)	0.47 (0.41 to 0.53)	0.62 (0.56 to 0.70)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation, number of subjects followed by median and range. Pooled both replicates for each sequence.*

Figure 3-11 Rimegepant Plasma Concentration (Mean ± SD) versus Time Profiles following Single Oral Administration of 75 mg ODT under Fed (High Fat Breakfast; top of the tongue) Condition Compared to that Fasting condition in Healthy Adult Subjects [Study # BHV3000-113; Part-2: ODT]



Source: Reviewer's Analysis

Data presented as mean ± SD on a linear scale (up to 24 h post-dose).

For ODT, the time to maximum rimegepant plasma concentration was delayed by 1-hour, peak concentration was reduced by 42% and total exposure was reduced by 32%. For tablet, the time to maximum rimegepant plasma concentration was delayed by 1-hour, peak concentration was reduced by 33% and total exposure was reduced by 30%.

Table 3-16 Summary Across Studies

Treatment Group	PK Parameters*		Study Number
	Cmax (% reduction)	AUCinf (% reduction)	
ODT Sublingual	42%	32%	BHV3000-112; Part-1
ODT Supra-lingual	53%	38%	BHV3000-113; Part-2
Tablet	33%	30%	BHV3000-112; Part-2

*Source: Reviewer's analysis. *Percent reduction under fed conditions.*

In summary, both formulations exhibited food effect with decrease in the rate of rimegepant absorption (Cmax) and its extent of absorption (AUCinf) with high-fat breakfast (Table 3-16). The exposure of rimegepant is reduced when administered under fed conditions compared to that under fasting conditions. However, the pivotal efficacy and safety studies (BHV3000-301, BHV3000-302, BHV3000-303) were conducted without food restrictions. No information on fasted/fed state were collected during efficacy assessments in these studies. The impact of food effect on the efficacy of rimegepant is unclear.

3.3.4.3.2 Gastric pH Modifying Agents

The applicant evaluated effect of acid-reducing agents on the pharmacokinetics of rimegepant in their first-in-human study (Study # CN170001). The applicant utilized famotidine (H2-receptor antagonist) to assess the effect on the pharmacokinetics of rimegepant following its single 150 mg dose (given as capsule formulation of free base) under the fasting condition. In period-2 (Panel-3) of the study, following washout (≥ 7-days from Day 1) form dosing in period-1, subjects who previously received a single oral dose of 150 mg rimegepant or placebo, received 40 mg famotidine 2 h prior to receiving a single oral dose of 150 mg rimegepant or placebo.

The results indicated an overall reduction of rimegepant exposures (AUC to 43% and Cmax to 26%) when rimegepant is administered with famotidine. Subsequently, to alleviate this effect through the reformulations process, the applicant optimized tablet (hemisulfate sesquihydrate salt vs. free base) using in-vitro dissolution and non-clinical bioavailability study (# BHV-3000-NCPK102). The oral administration of rimegepant as free base resulted in decreased exposures (decreased Cmax by 33-fold and AUC by 22-fold; Tmax reduced to 1 h) in dogs treated with famotidine. However, the oral administration of rimegepant sulfate resulted in increased exposures (Cmax by 10-fold and AUC by 8-fold; Tmax reduced to 1 h) compared to that administered as free

base in dogs treated with famotidine. Therefore, the hemisulfate sesquihydrate salt form (BMS-927711-11) showing lower sensitivity to pH was developed.

Although a dedicated drug interaction study was not conducted to evaluate the effect of acid-modifying agents on the pharmacokinetics of rimegepant from tablet, the applicant analyzed the data from subjects on concomitant medication with proton pump inhibitors across the 3 pivotal phase-3 clinical studies (n=158/1749; ~9% population).

- Pain freedom: The overall rate of pain freedom at 2 hours post-dose was 20.27% for subjects treated with rimegepant alone versus 18.34% for subjects treated concomitantly with proton pump inhibitors.
- MBS: The overall rate of freedom from MBS at 2 hours post-dose was 36.43% for subjects treated with rimegepant alone versus 34.17% for subjects treated concomitantly with proton pump inhibitors.

Since the applicant did not collect dosing data on the proton pump inhibitors administrations, it is unclear whether the subjects received proton pump inhibitors continuously or not and also, if the subjects received it on the day of rimegepant administration. It is also important to note that rimegepant exhibits pH dependent solubility profile (with pKa 2.1, 6.5 and 9.8; log P: 0.8) and its pH solubility profile indicates that rimegepant is relatively less-soluble under neutral to alkaline pH conditions compared to that acidic conditions (pH 2: 3.7 mg/mL vs pH 6.8: 0.1 mg/mL). Although lower systemic exposures (Cmax or AUC) of rimegepant are possible due to its poor solubility with increased pH when administered with acid-reducing agents, the magnitude of effect would not be greater than what was studied previously with capsule formulation containing free base. Moreover, the expected changes in the exposure of rimegepant may be similar to those observed in food effect studies. Thus, the review team is not recommending any dose optimization for rimegepant with pH modifying agents.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support approval of the to-be-marketed formulation?

Yes. The applicant developed two distinct formulations of rimegepant for commercialization – 1) 75 mg tablet and 2) 75 mg ODT. Both formulations were used in independent pivotal safety and efficacy studies (Table 3-2 & Table 4-3) and the clinical trial formulations were the same as the to-be marketed formulations. Thus, no PK bridging studies are required.

The applicant conducted a relative bioavailability study (BHV3000-110), to assess bioequivalence between the tablet and ODT (at 75 mg single-dose; sublingual administration).

It was an open-label, randomized, crossover study conducted in 2 parts in healthy subjects (n=60). Part I was 4-period, 2-sequence, fully-replicated crossover bioequivalence study (n=26) and Part II was 2-period, 2-sequence, crossover relative bioavailability study (n=24). The results from this study support bridging of data between two to-be-marketed 75 mg formulations (tablet vs ODT).

A consult request for biopharmaceutic inspections of the analytical site for Study BHV3000-110 was issued on 14-Aug-2019 to the Office of Study Integrity and Surveillance (OSIS). The Division

of New Drug Bioequivalence Evaluation within the OSIS recommended accepting data on 20-Aug-2019 without on-site inspection because recent inspections of the analytical sites (b) (4) were completed, and sites were classified as 'No Action Indicated'.

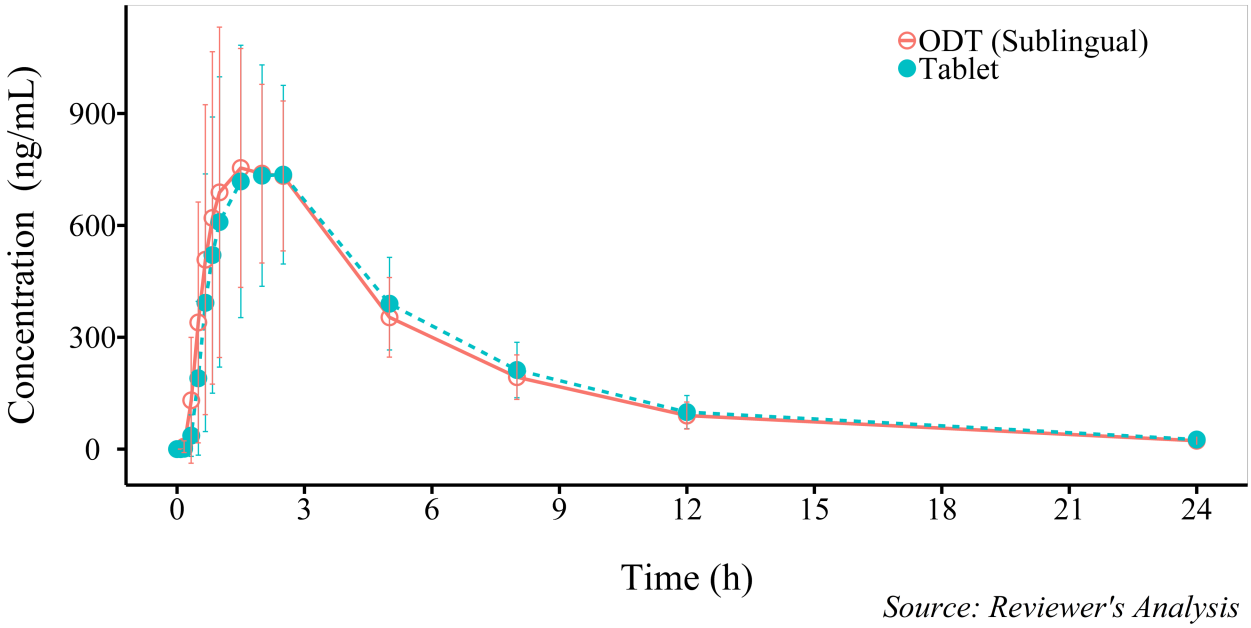
Rimegepant plasma concentration (Mean ± SD) versus time profiles following single oral administration of tablet compared ODT administered sublingually under fasting condition are presented in Figure 3-12. The summary of pharmacokinetic parameters is presented in Table 3-17.

Table 3-17 Summary of PK Parameters [Study # BHV3000-110; Part-1]

Treatment Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
ODT+	920 ±310, n=33; 920 (380, 1530)	5360 ±1520, n=33; 5420 (2360, 8870)	-	-
Tablet	834 ±290, n=33; 800 (390, 1670)	5510 ±1680, n=33; 5300 (2940, 9850)	1.05 (0.97.0 to 1.13)	0.97 (0.93 to 1.01)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation, number of subjects followed by median and range. +Sublingual administration (test product); *Pooled both replicates for each sequence.*

Figure 3-12 Rimegepant Plasma Concentration (Mean ± SD) versus Time Profiles following Single Oral Administration of 75 mg Tablet Compared to ODT Administered Sublingually Under Fasting Condition in Healthy Adult Subjects [Study # BHV3000-110; Part-1; only 24 h].

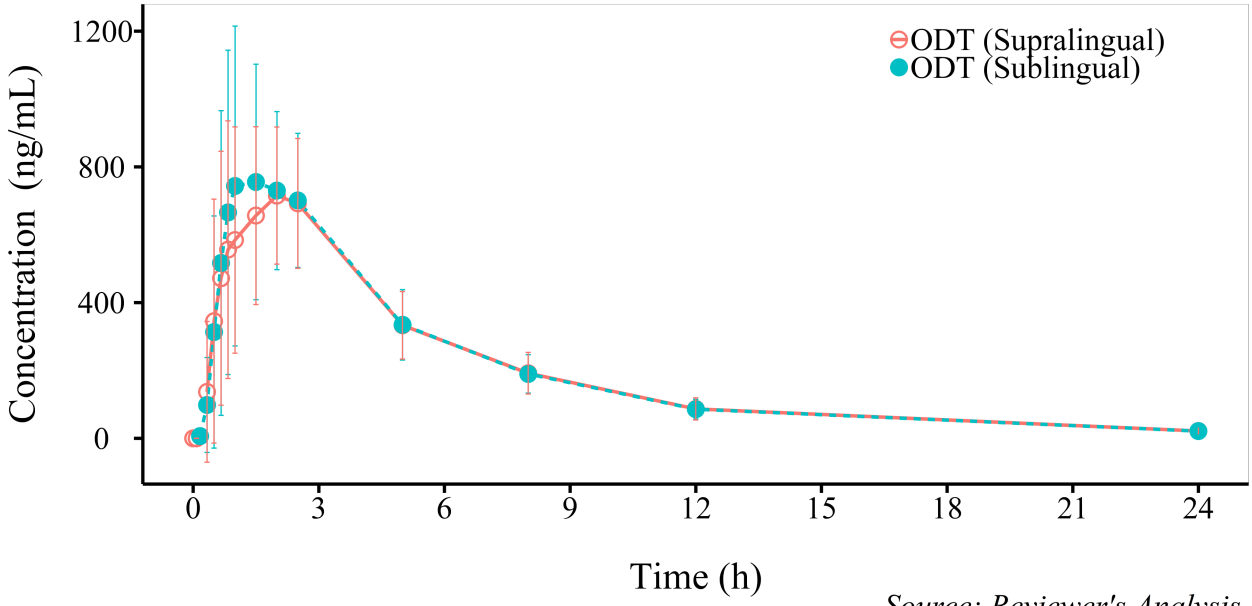


Source: Reviewer's Analysis

Data presented as mean ± SD on a linear scale.

Part II of the study indicates that the placement of ODT (sublingual vs supra-lingual) does not impact the pharmacokinetics of rimegepant. Rimegepant plasma concentration (Mean ± SD) versus time profiles following single oral administration of ODT administered sublingually compared to that administered supra-lingually are presented in Figure 3-13. The summary of pharmacokinetic parameters is presented in Table 3-18.

Figure 3-13 Rimegepant Plasma Concentration (Mean ± SD) versus Time Profiles following Single Oral Administration of 75 mg ODT Administered Sublingually compared to that administered Supra-lingually Under Fasting Condition in Healthy Adult Subjects [Study # BHV3000-110; Part-1; only 24 h].



Source: Reviewer's Analysis

Data presented as mean ± SD on a linear scale.

Table 3-18 Summary of PK Parameters [Study # BHV3000-110; Part-2]

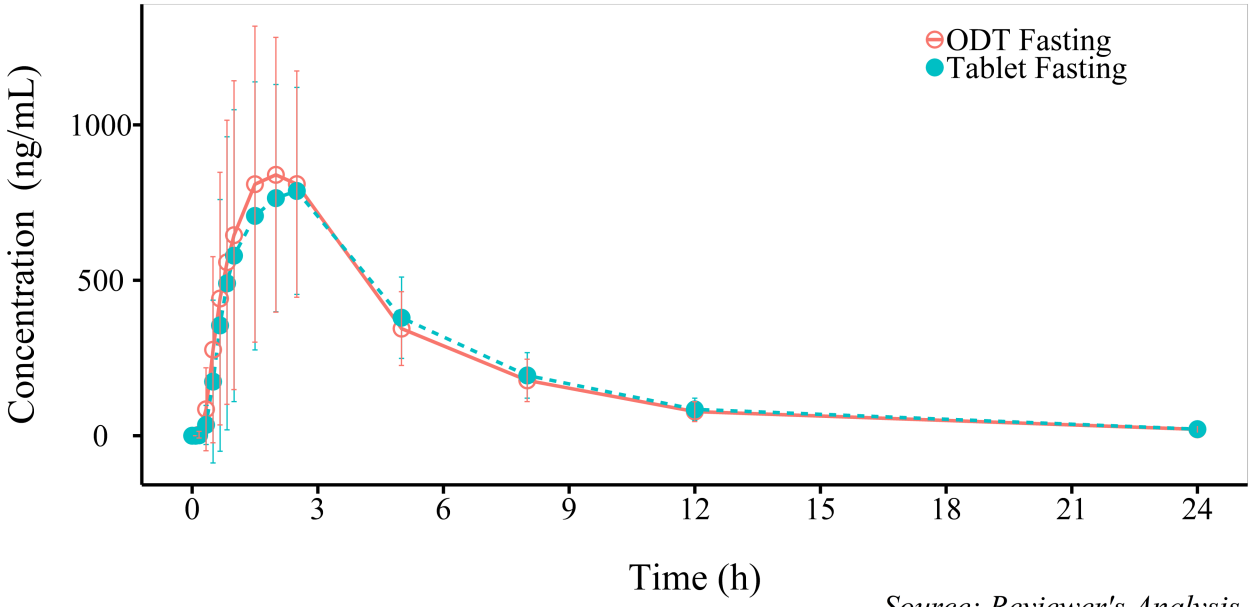
Formulation (ODT)	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Supra-lingual	861 ±269, n=24; 768 (394, 1580)	4920 ±1240, n=24; 4820 (2160, 7440)	-	-
Sub-lingual	959 ±352, n=24; 876 (333, 1860)	5040 ±1180, n=24; 4930 (2860, 6920)	1.10 (0.94 to 1.27)	1.03 (0.96 to 1.11)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation, number of subjects followed by median and range.*

The applicant also conducted a single-dose study evaluating the bioequivalence between tablet (reference: TRT-B) and ODT (test: TRT-A) in healthy subjects with a fully-replicated crossover (4-period, 2-sequence; ABAB or BABA) design (Study # BHV3000-113). In this 2-parts study, the first part evaluated the rate and extent of rimegepant absorption from ODT (top of the tongue until fully dissolved then swallowed without water) compared to that from tablet (swallowed with water) administered under fasting condition. Healthy subjects (n=36) received two treatments twice - a single 75 mg doses of rimegepant as ODT and tablet. In each period, pharmacokinetics samples were collected up to 72 h post-dose for the determination of rimegepant concentrations.

Rimegepant plasma concentration (Mean ± SD) versus time profiles following single oral administration of ODT fasting condition compared to tablet administered under fasting condition are presented in Figure 3-14. The summary of pharmacokinetic parameters is presented in Table 3-19.

Figure 3-14 Pharmacokinetic Profiles [Study # BHV3000-113; Part-1]



Source: Reviewer's Analysis

Data presented as mean ± SD on a linear scale.

Table 3-19 Summary of PK Parameters [Study # BHV3000-113; Part-1]

Treatment Group (under fasting condition)	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
ODT	982 ±502, n=34; 874 (181, 2450)	5100 ±2010, n=34; 4690 (1760, 10300)	-	-
Tablet	934 ±423, n=36; 846 (256, 2290)	5130 ±1780, n=36; 4840 (2050, 10200)	1.03 NA	0.98 (0.93 to 1.03)

*Source: Reviewer's analysis. *Data presented as mean ± standard deviation, number of subjects followed by median and range. Pooled both replicates for each sequence.*

Thus, relative bioavailability assessment between ODT and tablet (as reference) indicated that 90% CIs of the point estimate for Cmax, AUCinf, and AUClast are within 80 to 125% for ODT (administered sublingually) with reference to tablet. Since the bioavailability of rimegepant from ODT administered sublingually is not substantially different than that of rimegepant from ODT administered on the top of the tongue, it can be placed on top of tongue or sublingually during the administration.

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation

For the determination of rimegepant concentrations in human plasma, the applicant used validated high- or ultra- performance liquid chromatographic (HPLC/UPLC) methods with tandem mass spectrometry detection methods (LC-MS/MS; (b) (4) Bristol-Myers Squibb). In addition, the Applicant used high performance liquid chromatography-accelerator mass spectrometry (LC-AMS; (b) (4)) method for the determination of [^{14}C]-rimegepant concentrations in human plasma from the mass balance study.

Plasma samples containing EDTA as an anticoagulant (b) (4) were processed using automated protein precipitation prior to LC-MS/MS analysis. Summary of bioanalytical methods used in the clinical development program is provided in Table 4-1.

Table 4-1 Summary of Analytical Methods Utilized in Clinical Development

Study Numbers	Validation Summary	Clinical Studies
10, 101, BAS RPT-359, BAS RPT-379, BAS RPT-447	Range: 0.5 to 500 Accuracy: ±13.1 (max) Precision: ≤ 9.9 (max)	CN170001, CN170002, CN170004, CN170006, CN170007
AMS	Range: 0.1919 – 101.4 Accuracy: -4.80 to -6.82 Precision: 7.39 to 0.00	CN170006
167126APJT	Range: 10 - 5000 Accuracy: -2.49 to 3.39* Precision: 3.28 to 6.96	BHV3000-101, BHV3000-102, BHV3000-103, BHV3000-105, BHV3000-109
177202ASFC	Range: 0.5 - 1000 Accuracy: -4.26 to 1.48* Precision: 2.21 to 5.42	BHV3000-104, BHV3000-106, BHV3000-107, BHV3000-108, BHV3000-110, BHV3000-112, BHV3000-113, BHV3000-114

** Between run accuracy bias*

Summary of bioanalytical method used in the clinical bioequivalence study is provided in Table 4-2. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Incurred samples reanalysis was carried out on approx. 10% of randomly selected samples from above studies. More than 2/3rd of the incurred sample reanalysis were within 20% deviation. Results of incurred sample reanalysis were within acceptable limits.

Table 4-2 Summary of Bioanalytical Method [Study # BHV3000-110]

Report Details	Matrix and Analyte	Range and QCs	Accuracy and Precision	Study Number	Method Reports
Report Number 170337ARRI (b) (4) Dates: 2017/12/15 to 2018/02/06	Matrix: Plasma (K_2 EDTA) Analyte: Rimegepant IS: BMS-927711-04 Method: UPLC-MS/MS	LLOQ: 0.5 ng/mL ULOQ: 1000 ng/mL QCs: (0.5, 1.5, 500, and 750 ng/mL)	9 CSs (0.5-1000 ng/mL): Accuracy: -2.49 to 5.20% Precision: 2.66 to 16.6% (Between run) Accuracy: -4.26 to 1.48% Precision: 2.21 to 5.42% Recovery of Analyte: 83.5 - 94.4%	Study No. BHV3000-110 (total samples 3156 from 58/59 subjects) Storage: 61 days	Validation Report 177202ASFC Method ANI 11444.01 & ANI-157 ISR 214/3156 (99.53% met criteria ≤ 20%)

CSs: Calibration Standards, QCs: Quality Control Samples, LLOQ: Lower Limit of Quantification, ULOQ: Upper Limit of Quantification

Reviewer's Comments:

The bioanalytical method used in analysis of pharmacokinetic samples fulfill the required criterion for 'method validation' and 'application to routine analysis' provided in the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

4.2 Summary of Formulations Utilized in Clinical Studies

During the development, three oral formulation viz. an immediate release capsule (free-base), an (b) (4) tablet (b) (4) and ODT (developed using Catalent's Zydis technology) were utilized. Both tablet and ODT were developed for pivotal studies using hemisulfate sesquihydrate salt (75 mg; equivalent to free base) of rimegepant.

Table 4-3 Summary of Formulations Utilized in Clinical Studies

Formulations	Clinical Studies
Capsule (10, 25, 150 mg)	CN170001, CN170002, CN170003, CN170004, CN170006, CN170007, BHV3000-101, and BHV3000-102*
Tablet# (75 mg)	BHV3000-102*, BHV3000-103, BHV3000-104, BHV3000-105, BHV3000-106, BHV3000-107, BHV3000-108, BHV3000-109, BHV3000-110*, BHV3000-112, BHV3000-113*, BHV3000-114, BHV3000-201, BHV3000-301, and BHV3000-302
ODT# (75 mg)	BHV3000-110*, BHV3000-112*, BHV3000-113*, and BHV3000-303

**Relative bioavailability / Food effect studies using multiple formulations; #To-be marketed formulations*

The capsule formulation was utilized in 8 clinical studies (# CN170001, CN170002, CN170003, CN170004, CN170006, CN170007, BHV3000-101 and BHV3000-102).

The applicant conducted a relative bioavailability study (BHV3000-102) to assess bioavailability between the capsule formulation and the tablet at 75 mg strength (single-dose). The study results indicated that the exposure of rimegepant (AUC: 0.94 and Cmax: 0.91; tablet/capsule) from both formulations were comparable.

Pharmacokinetics variability associated with administration of various formulations (capsule, tablet, and ODT) across clinical studies conducted during development are comparable (Table 4-4).

Table 4-4 Comparison of PK Variability Across Clinical Studies

Study and Formulation	Intra- and Inter- subject Variability			
	Cmax (ng/mL)		AUCinf (ng·h/mL)	
	Intra-subject CV (%)	Inter-subject CV (%)	Intra-subject CV (%)	Inter-subject CV (%)
BHV3000-102 Capsule Vs tablet	60.0	36.8	36.9	23.1
BHV3000-112 Tablet (food effect)	31.2	13.3	18.6	27.0
BHV3000-112 ODT (food effect)	20.6	29.2	15.9	30.6
BHV3000-113 ODT (food effect)	20.1	30.5	17.6	22.6

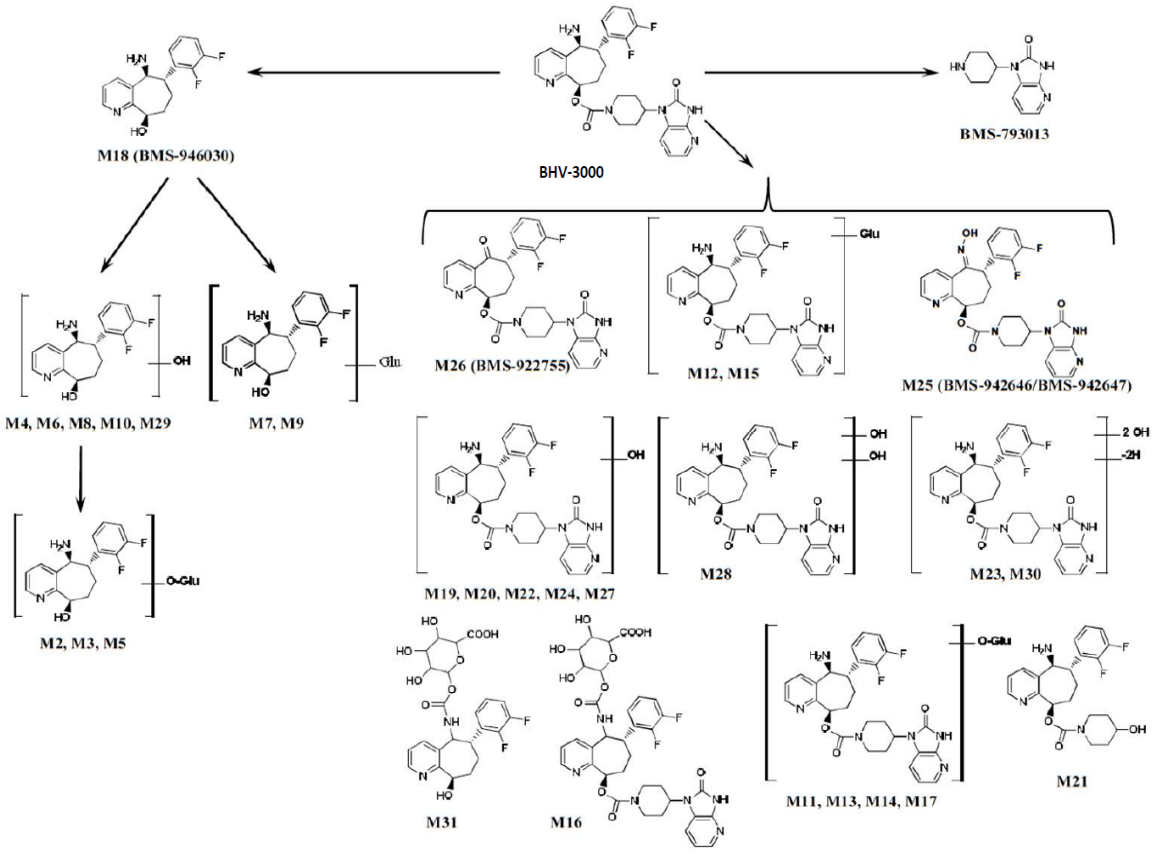
Relative bioavailability studies.

4.3 Human Mass Balance Study

The applicant conducted a dedicated human mass-balance study (Study # CN170006) to characterize absorption, metabolism, and elimination of rimegepant following its oral administration. Study also evaluated the absolute bioavailability of rimegepant from the immediate release capsule in healthy male subjects (n=8). This was an open-label, non-randomized, 2-period, 3-treatment, sequential cross-over study in healthy male subjects. In period-1, subjects received reference oral formulation (150 mg capsule × 2) under the fasting condition, and a 15-minute infusion of [^{14}C]-rimegepant (100 µg; ≤ 10 kBq) ending at 1 hour after the oral dose was administered. In period-2, subjects received oral suspension (300 mg, ≤ 3.29 MBq) under the fasting condition.

The study results indicate that the mean absolute bioavailability is 64% (90% CI: 53%, 77%). The mean apparent terminal half-life estimates following oral and intravenous administration were 10.5 and 5.8 hours, respectively. The mean plasma clearance and steady-state volume of distribution following intravenous administration were 9.3 L/h and 58.0 L, respectively.

Figure 4-1 Proposed in Vivo Metabolic Profile of Rimegepant [Study # CN170006]



Following oral administration, the total recovery of radioactivity was approximately 100% (~144 h pot-dose). The mean plasma concentration-time profiles for rimegepant and total radioactivity were comparable over the first 24 hours after study drug administration. None of the subjects were found to be poor metabolizers of CYP2C9 in the genotype analysis. Rimegepant appears to be primarily eliminated in unchanged form (~77% of the dose; as determined by the ratio of rimegepant AUC0-inf and radioactivity AUC0inf) with no major metabolite (i.e., metabolites that represented >10% of drug-related material) detected in plasma. The primary route of elimination is through the biliary/fecal pathway (~78% radioactivity, 70.72 to 84.87%; 216 h post-dose) and the urinary pathway is a minor route of elimination (~24% radioactivity, 11.97 to 30.77%; 216 h post-dose). Also, the unchanged rimegepant is the major single component in feces (~42%) and urine (~51%). Rimegepant is expected to be metabolized to a wide variety of minor metabolites with an overall low rate of metabolic clearance. Hydroxylation forming mono- and bis-hydroxylated metabolites is the most significant biotransformation pathway of rimegepant. The applicant described additional metabolites such as the combination of M16 and M18 (up to 11.8% of human dose), M23 (up to 4.6 % of human dose) and the combination of M25 and M27 (up to 12% of human dose). Other metabolites excreted are direct glucuronides (M12 & M15), a desaturation product (M23) and an N-dealkylation (M21) product. The applicant's results indicate that these metabolites (>500-fold lower activity that parent against human CGRP receptor) are not expected to contribute to the pharmacological activity of rimegepant.

4.4 Pharmacogenomic Analysis

In vitro studies indicated that rimegepant is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C9. As shown in section 3.3.4.1.3, in a drug interaction study (Study # BHV3000-103) with a CYP3A4 strong inhibitor (itraconazole) the exposure (i.e., AUCinf) of rimegepant was increased approximately 4-fold. About 1.8-fold increase in exposure (i.e., AUCinf) of rimegepant was observed in a drug interaction study with fluconazole, a CYP2C9 moderate inhibitor and moderate inhibitor of CYP3A4. To evaluate the effect of CYP2C9 genotype on rimegepant exposure, the applicant conducted an analysis combining subjects from five clinical pharmacology studies.

The five studies included a total of 117 subjects receiving doses of rimegepant ranging from 75 mg to 300 mg (studies CN170006, n=24; BHV3000-104, n=33; BHV3000-109, n=36; BHV3000-110, n=20; and BHV3000-112, n=21). For study CN170006, CYP2C9 alleles *2, *3, *8, *11, *12 were assayed using a DNA sequencing approach and *2 was analyzed using TaqMan® approach. For studies BHV3000-104, BHV3000-109, BHV3000-110, and BHV3000-112, CYP2C9 *2, *3, *5, * 6, *8 and *11 were assayed using a DNA sequencing approach and CYP2C9*13 was analyzed using the TaqMan approach.

The applicant assigned the "extensive metabolizer" phenotype (i.e., "normal metabolizer" phenotype) for subjects with the presence of two wild-type (WT) alleles. Subsequently, in this review, extensive metabolizers will be referred to as "normal metabolizers (NM)". The presence of one alternative, reduced function allele, was assigned "intermediate metabolizer" phenotype and the presence of two reduced function alleles was assigned "poor metabolizer" phenotype. Based on the assignment criteria, CYP2C9*1/*1 genotype was assigned as normal metabolizer (NMs), *1/*3, *1/*5, *1/*6, *1/*8, *1/*11, *1/*13, and *1 /*2 genotypes were designated as intermediate metabolizers (IMs) and *2/*3, *2/*5, *2/*6, *2/*8, *2/*11, *2/*13 genotypes were assigned as poor metabolizers (PMs). (b) (4)

(b) (4)

The CYP2C9*2/*2 genotype should be assigned as an intermediate metabolizer. (References: University of Washington School of Pharmacy Drug Interaction Database: CYP2C9 Gene Polymorphisms (https://didb.druginteractioninfo.org). FDA re-analyzed the provided CYP2C9 pharmacogenomic data after re-assigning CYP2C9*2/*2 genotype as intermediate metabolizers. In the revised analyses conducted by FDA, 72 subjects with genotype of *1/*1 were assigned as normal metabolizers, 43 subjects with genotypes *2/*1, *3/*1or *2/*2 were assigned as intermediate metabolizers, and 2 subjects with genotype *2/*3 were assigned as poor metabolizers. No subjects carried *3/*3 genotypes in this dataset of 117 subjects.

Based on the revised analyses, the dose normalized geometric mean of rimegepant Cmax increased 49% (90 % CI: 24-76%) for poor metabolizers as compared to normal metabolizers. The dose normalized geometric mean of rimegepant AUCinf increased 38% (90% CI: 13-65%) for poor metabolizers as compared to normal metabolizers. The pharmacokinetics parameters (Cmax and

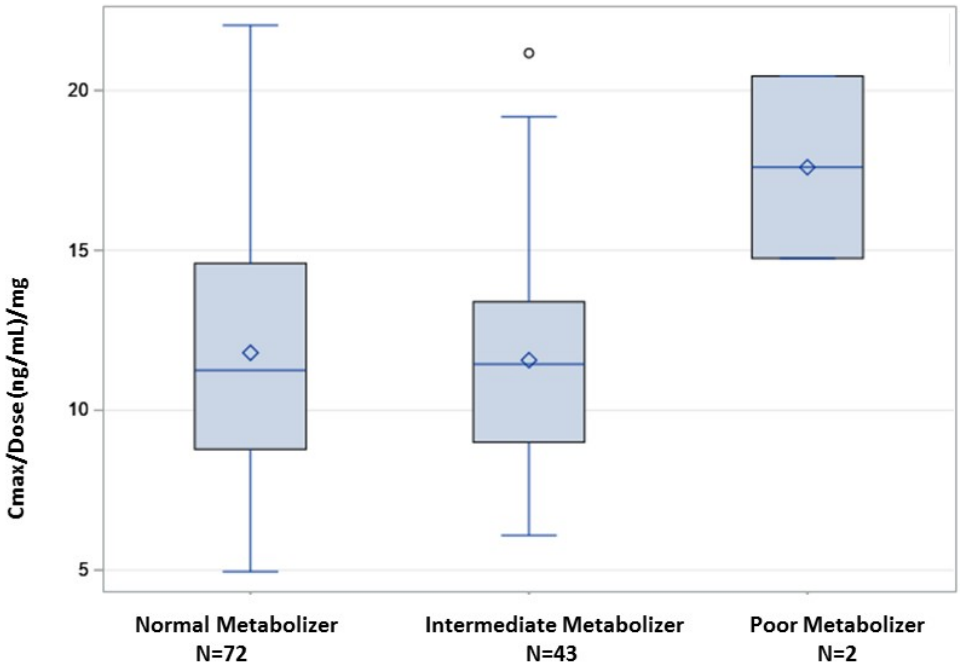
AUCinf) were similar for intermediate metabolizers, compared with normal metabolizers (Figure 4-2 and Figure 4-3).

Table 4-5 Association Between CYP2C9 Phenotypes and Rimegepant PK Parameters

Parameters	Number of Subjects	Dose Normalized Geometric LS Means	Geometric LS Mean Ratio (%)	90% Geometric CI (%)
Cmax	72	Normal Metabolizer	NA	NA
	43	Intermediate Metabolizer	98.03	95.9 to 99.9
	2	Poor Metabolizer	149.2	123.6 to 176.3
AUCinf	72	Normal Metabolizer	NA	NA
	43	Intermediate Metabolizer	97.8	95.7 to 99.6
	2	Poor Metabolizer	138.2	113.3 to 165.2

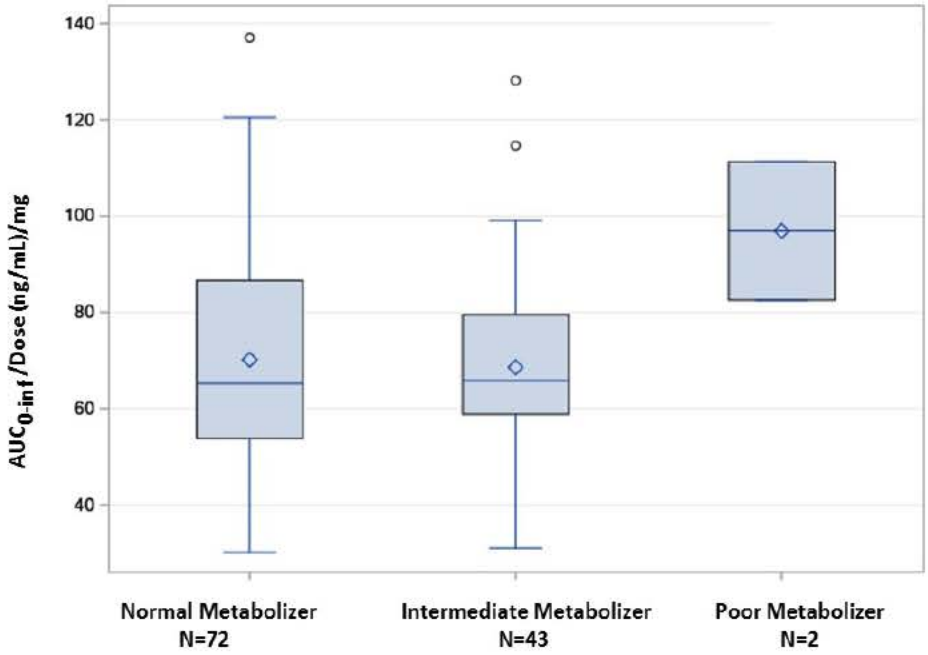
Source: Reviewer's table

Figure 4-2 Box Plots of Rimegepant Cmax in Normal, Intermediate, and Poor CYP2C9 Metabolizer Subjects



Source: Reviewer's figure, N=117. In the box plots, the solid line inside box represents the median; the diamond symbol represents the mean. The lower and upper edge of the box is the 25th and 75th percentile, respectively. The endpoint of lower whisker shows the lowest data value still within the 1.5 interquartile range of the lower quartile, and the endpoint of higher whisker shows the highest data value still within 1.5 interquartile range of the upper quartile, where the interquartile range is the difference between the third and first quartiles.

Figure 4-3 Box Plots of Rimegepant AUCinf in Normal, Intermediate, and Poor CYP2C9 Metabolizer Subjects



Source: Reviewer's figure, N=117. In the box plots, the solid line inside box represents the median; the diamond symbol represents the mean. The lower and upper edge of the box is the 25th and 75th percentile, respectively. The endpoint of lower whisker shows the lowest data value still within the 1.5 interquartile range of the lower quartile, and the endpoint of higher whisker shows the highest data value still within 1.5 interquartile range of the upper quartile, where the interquartile range is the difference between the third and first quartiles.

Reviewer comment: *The genotyping approaches for assessing CYP2C9 alleles are acceptable.* (b) (4) *those individuals were re-assigned to intermediate metabolizers. Based on the revised analyses, the dose normalized geometric mean of rimegepant Cmax and AUC_{0-inf} increased 49% and 38% for poor metabolizers (N=2) as compared to normal metabolizers, respectively.*

4.5 Pharmacometric Analysis

This section describes the review of the sponsor's population pharmacokinetic (PK) analysis which supports labeling statements. Few changes are suggested to Section 12.3 of the proposed label. Supportive information is also provided for these proposed changes in the document.

4.5.1 Sponsor's Analysis

Objectives

- To develop a population pharmacokinetics model of rimegepant following oral administration of 75 mg rimegepant
- To evaluate the impact of age, weight, sex, DDI, renal impairment, hepatic impairment, formulation, and ethnicity on the pharmacokinetics of rimegepant
- To utilize population pharmacokinetics model of rimegepant to simulate dosing scenarios of interest

4.5.1.1 Data

The pharmacokinetics data of 75 mg rimegepant from 8 clinical studies (BHV3000-102, BHV3000-103, BHV3000-105, BHV3000-106, BHV3000-107, BHV3000-108, BHV3000-110, and BHV3000-112) were used to develop the population pharmacokinetics model for rimegepant. The developed pharmacokinetics model was then validated with the pharmacokinetics data from a clinical study BHV3000-109.

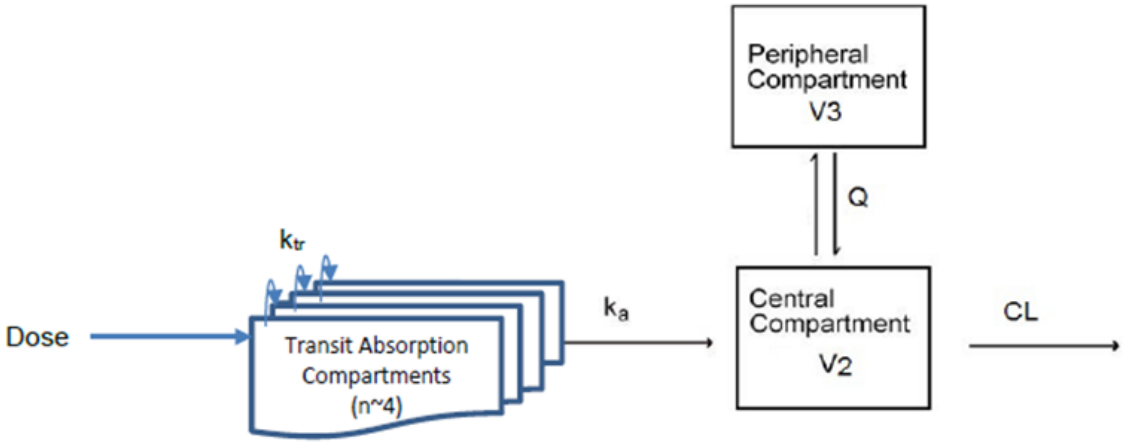
4.5.1.2 Method

Nonlinear mixed effect modeling was used for pharmacokinetics model development. A base model was first developed to describe rimegepant pharmacokinetics profile. Covariate modeling was done using forward addition and backward deletion process. The relationship of continuous covariates and pharmacokinetics parameter was described with power models; and categorical covariate-pharmacokinetics parameter relationship was described with linear models. The reduced, validated population pharmacokinetics model was finally used to simulate scenarios of interest including different formulations, inhibitor use, hepatic impairment, and different potential dosing regimens.

4.5.1.3 Results

The pharmacokinetics of rimegepant was described by 2-compartment model with 4-transit absorption compartments and a linear elimination (Figure 4-4). Covariates such as weight, fluconazole, hepatic impairment, itraconazole were added on clearance. Covariates such as food, formulation and itraconazole were added on the transit rate. Weight was added on volume, and food effect was added on bioavailability. The parameter estimates of the final population pharmacokinetics model was given in Table 4-6.

Figure 4-4: Schematic of Sponsor's Final Population Pharmacokinetics Model



CL=elimination clearance; ktr= transit compartment rate constant; ka=absorption rate constant; n=sample size; PK=pharmacokinetic; Q=inter-compartment clearance; V2=central volume of distribution; V3=peripheral volume of distribution.

Source: BHV-PPK-RIMEGEPANT-722; Page-29; Figure-3

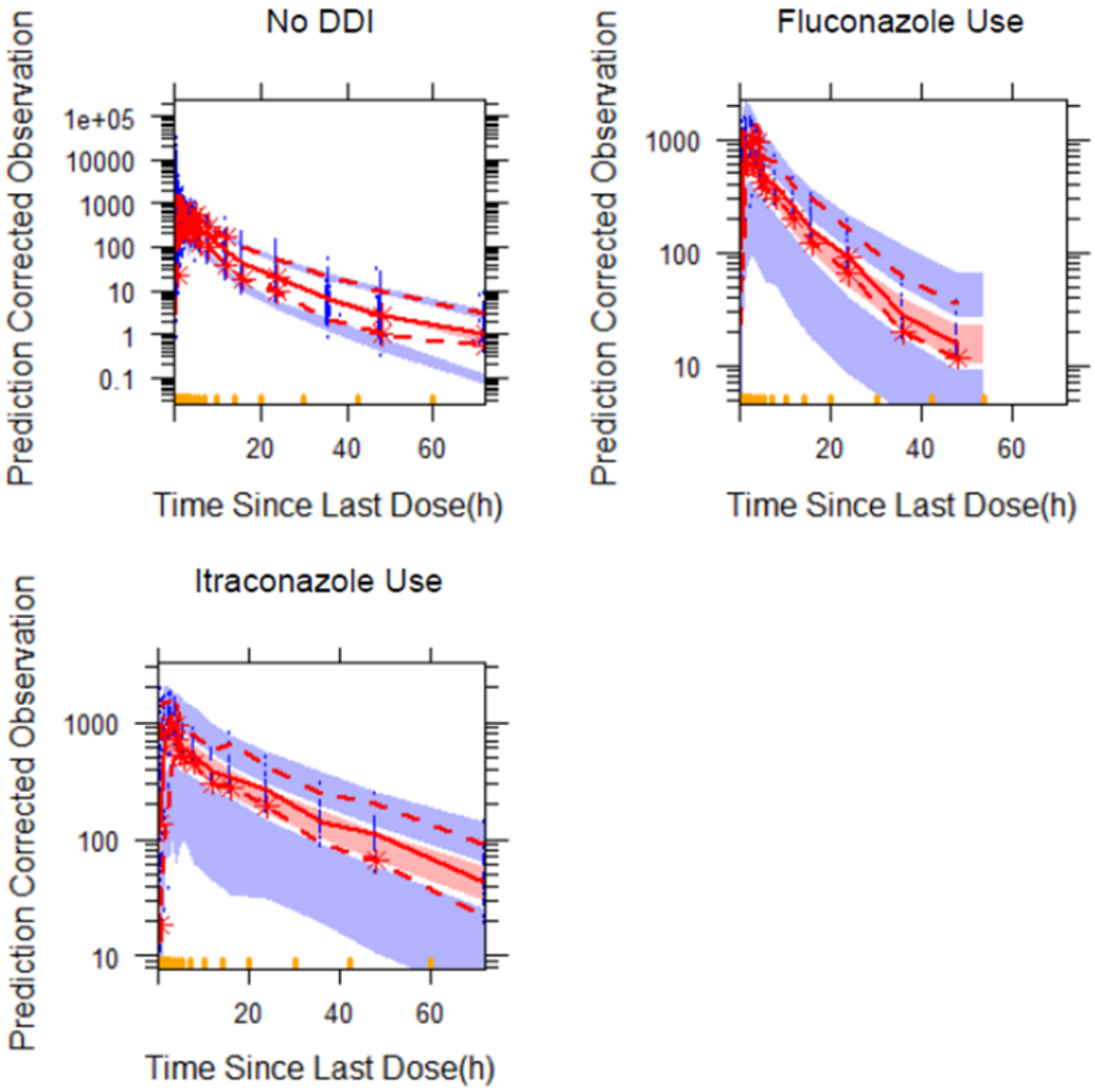
Table 4-6: Parameter estimates of sponsor's final population PK model of rimegepant

Parameter (Unit)	Estimate	%RSE	IIV% (%RSE)
NONMEM model estimates			
θ_1: CL/F (L/h)	17.2	2.0%	29.3% (5.8%)
θ_2: V2/F (L)	85.9	2.7%	38.8% (6.8%)
θ_3: ka (1/h)	9.6	37.6%	-
θ_4: V3/F (L)	32.6	3.1%	29.5% (9.2%)
θ_5: Q/F (L/h)	2.51	5.1%	-
θ_6: Transit absorption rate constant, ktr (1/h)	7.23	7.6%	49.2% (6.4%)
θ_8: Fluconazole use on CL	-0.427	2.9%	-
θ_{11}: Severe Hepatic Impairment on CL	-0.421	24.1%	-
θ_{12}: Itraconazole use on CL	-0.742	1.3%	-
θ_{13}: Fed on F1	-0.318	9.6'%	-
θ_{16}: Fed on ktr	-0.678	3.7%	-
θ_{17}: Oral Disintegrating Tablet on ktr	0.347	28.3%	-
θ_{18}: Capsule Formulation on ktr	1.66	28.2%	-
θ_{19}: Itraconazole use on ktr	-0.323	32.4%	-
θ_{24}: Moderate Hepatic Impairment on CL	-0.208	33.6%	-
CL/F – V2/F Correlation	0.72	8.1%	
CL/F – V3/F Correlation	0.45	12.6%	
V2/F – V3/F Correlation	0.65	9.7%	
Additive error (ng/L)	0.37	2.3%	-
Proportional error (%)	32.5%	13.0%	-

Source: BHV-PPK-RIMEGEPANT-722; Page-32; Table-9

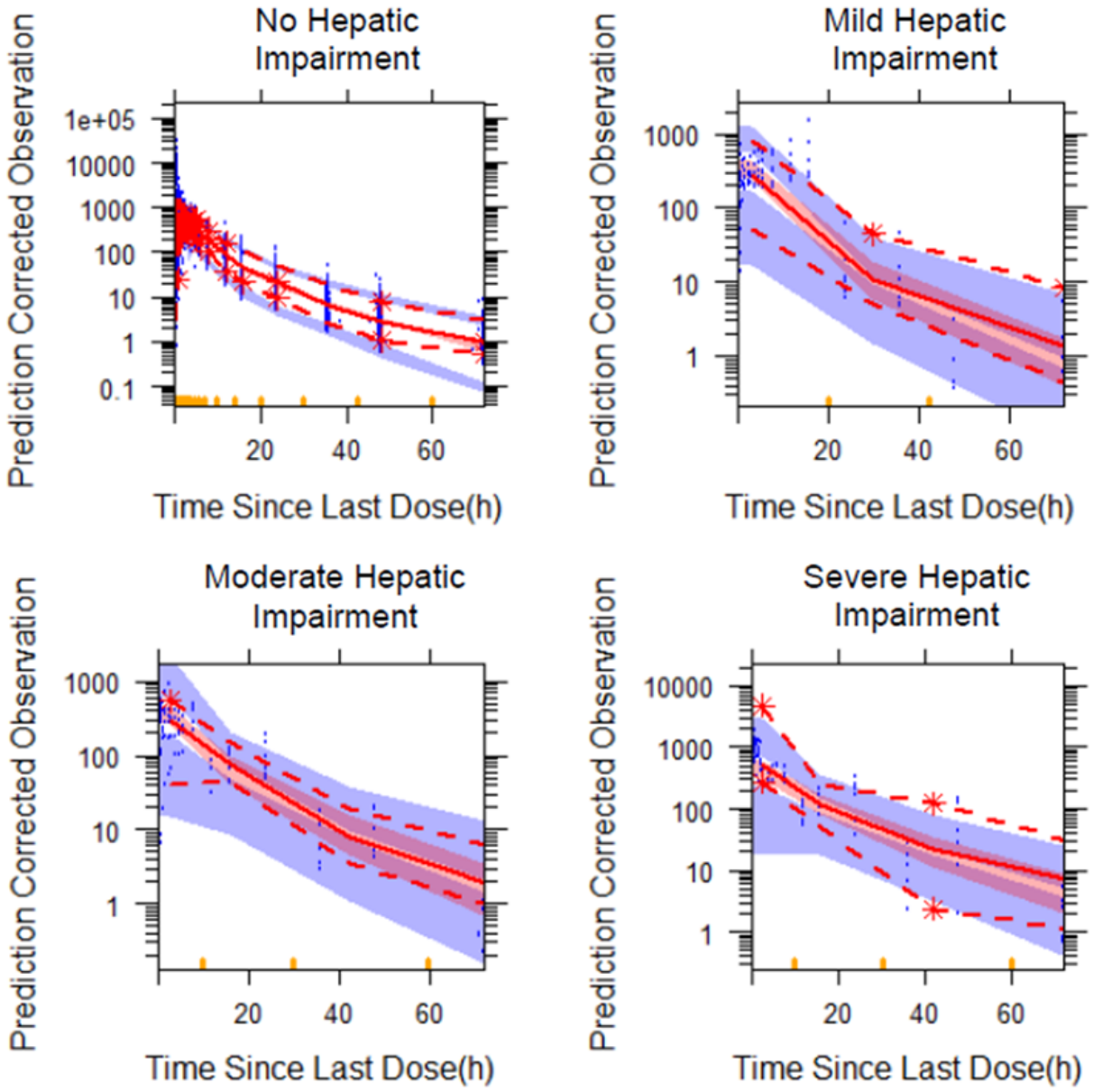
The population pharmacokinetics model was assessed with diagnostics plots including goodness-of-fit (Figure 4-11), visual predictive checks (VPC) (Figure 4-5, Figure 4-6, Figure 4-7, and Figure 4-8), and individual plots of observed and overlaid predicted plasma concentration-time courses. Overall, goodness-of-fit plots along with VPC plots (large predictions bands when compared with observed data) suggest the presence of variability not explained by the model.

Figure 4-5: Prediction-correction VPCs for the final population PK model by DDI



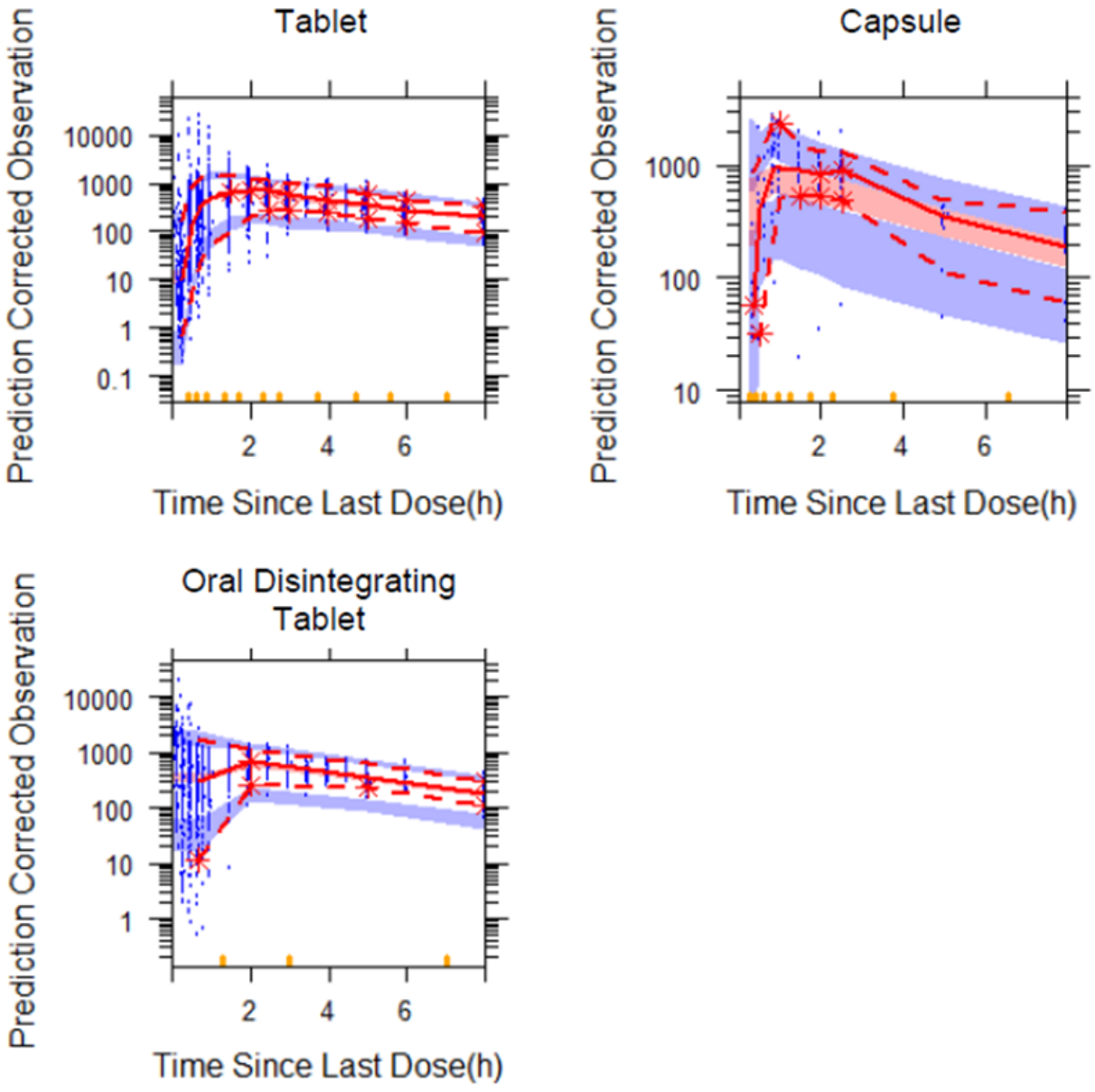
Source: BHV-PPK-RIMEGEPANT-722; Page-36; Figure-6

Figure 4-6: Prediction-correction VPCs for the final population PK model by hepatic impairment



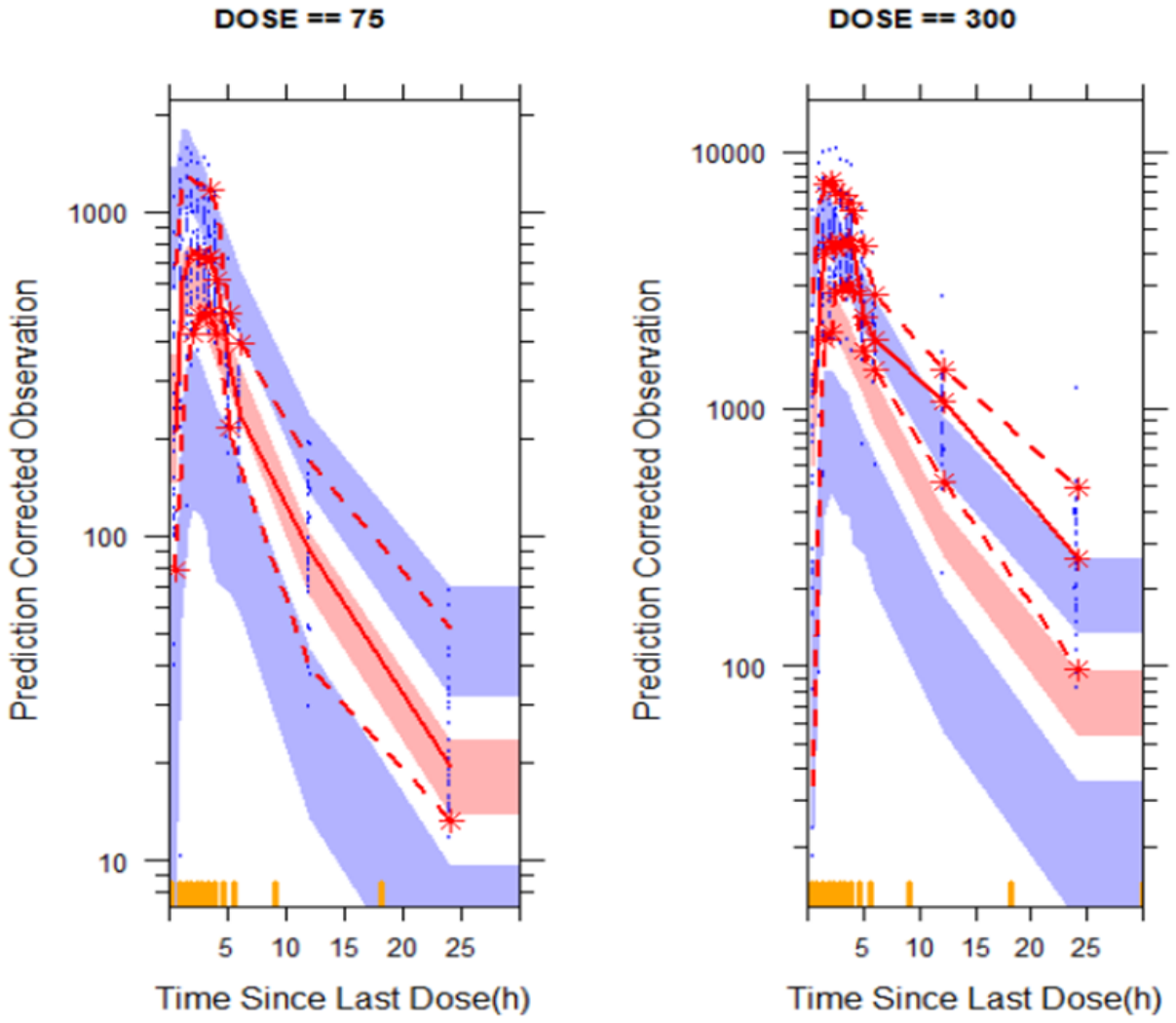
Source: BHV-PPK-RIMEGEPANT-722; Page-37; Figure-7

Figure 4-7: Prediction-correction VPCs for the final population PK model by formulation



Source: BHV-PPK-RIMEGEPANT-722; Page-38; Figure-8

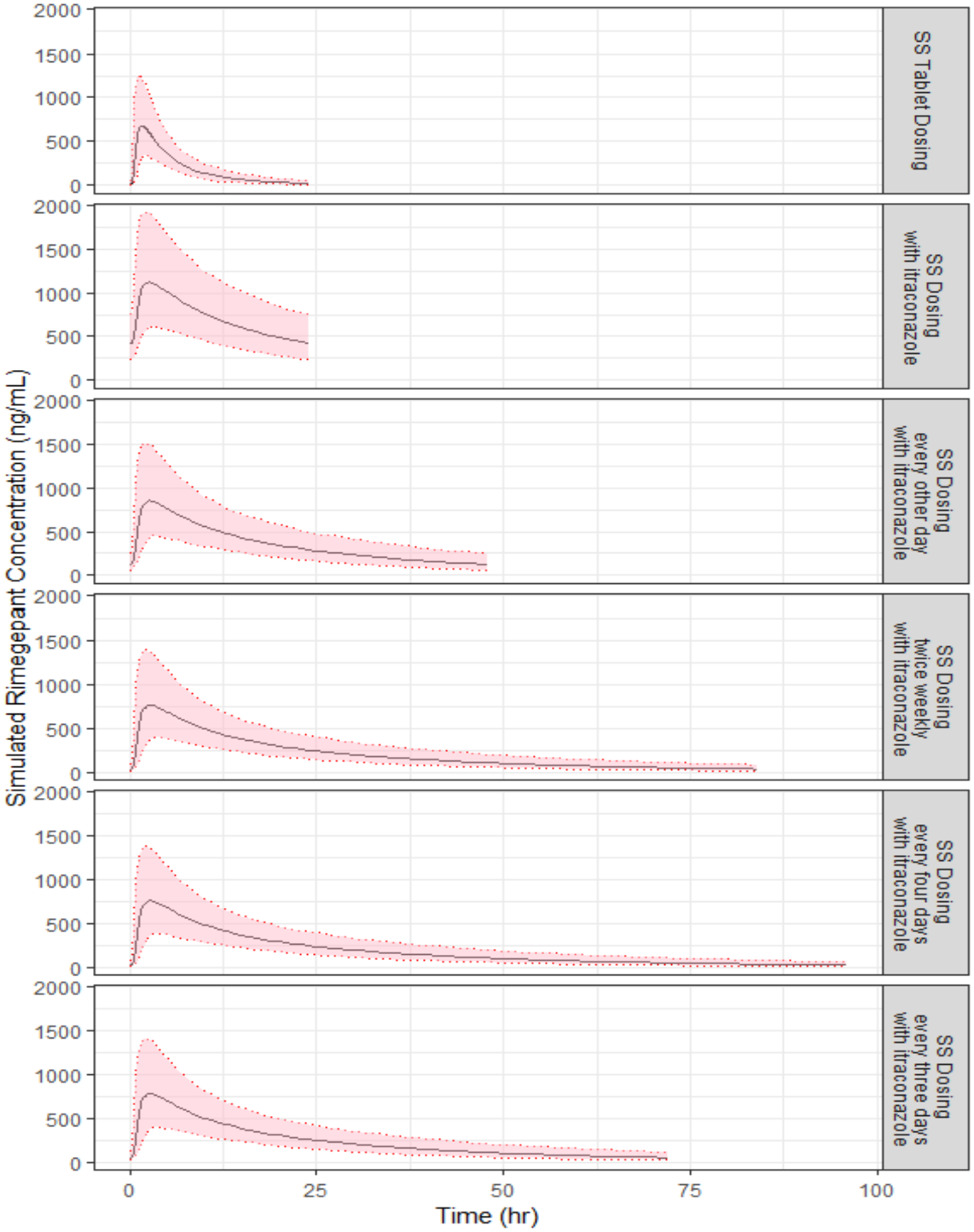
Figure 4-8: Prediction-correction VPCs for the final population PK model in the validation study BHV3000-109 dataset by typical and supratherapeutic dose



Source: BHV-PPK-RIMEGEPANT-722; Page-39; Figure-9

The final pharmacokinetics model was then used to simulate (n=1000 subjects) the impact of fed status, hepatic impairment (moderate and severe), DDI with CYP3A4 (moderate-fluconazole and severe-itraconazole) and ODT on pharmacokinetics of 75 mg rimegepant. Significant impact on rimegepant pharmacokinetics was observed in the case of itraconazole DDI and thus alternative dosing intervals i.e. 2 days, 3 days, 3.5 and 4 days were explored (Figure 4-9). Per sponsor, the dosing intervals of 3-days was optimal for this scenario based on exposure-matching (Table 4-7).

Figure 4-9: Simulated rimegepant PK profiles to evaluate different dosing regimens in the scenario of itraconazole-rimegepant interaction



Source: BHV-PPK-RIMEGEPANT-722; Page-173

Table 4-7: PK metrics of rimegepant in subjects in which rimegepant 75mg QD is co-administered with itraconazole at steady state

Subject and Regimen*	C_{max} (ng/mL)	$AUC_{0\text{-}24\ hr}$ (ng•hr/mL)	C_{trough} (ng/mL)
Normal healthy subject + rimegepant 75 mg QD ss[2]	681 (339, 1258)	4348 (2148, 8048)	24 (9, 56) ($C_{24\ hr}$)
Subject dosed itraconazoless[1] + rimegepant 75 mg Q3 days ss[2]	783 (402, 1416)	5658 (3044, 9947)	51 (20, 114) ($C_{72\ hr}$)

* Based on population PK methods: simulated rimegepant median (5th, 95th Percentile) of PK parameters

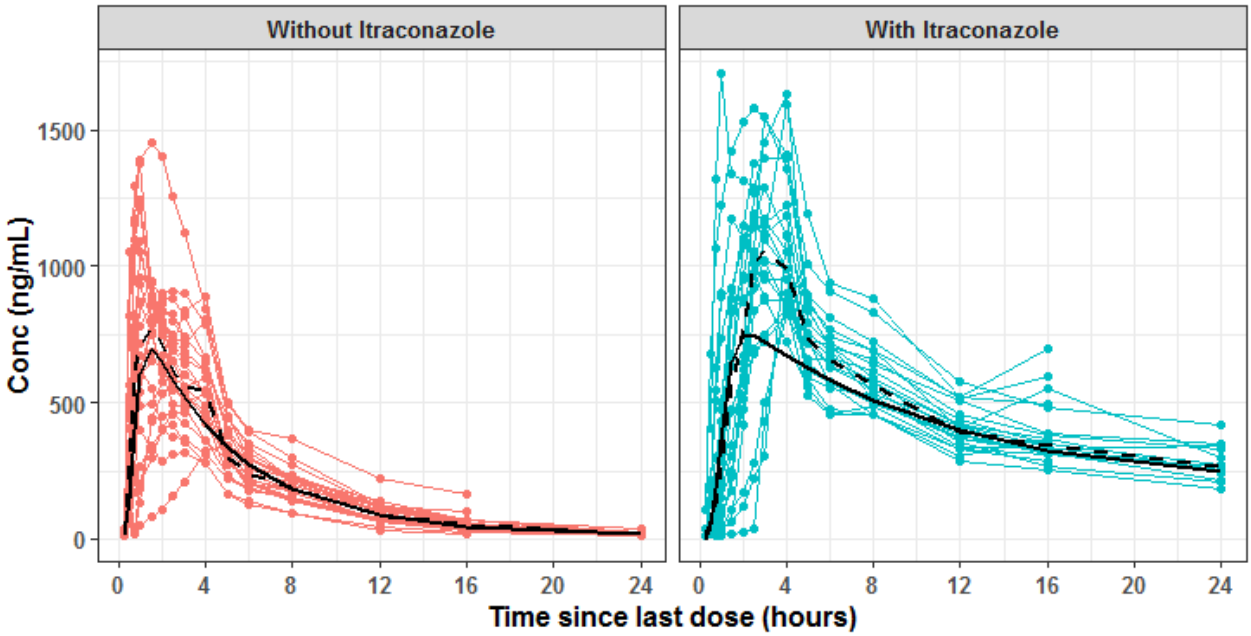
[1] Itraconazole at steady state

[2] Subjects are dosed their regimens to steady state

Source: BHV-PPK-RIMEGEPANT-722; Page-174

However, due to underprediction of Cmax by population pharmacokinetics model as shown in Figure 4-10, subsequent simulations were done using superposition principles (Figure 3-6 and Table 3-7) .

Figure 4-10: Individual PK profiles of rimegepant in DDI-itraconazole study. Solid black line represents population predicted PK profile; Dashed black line represents median of observed PK profiles; Red color indicates subjects without itraconazole, and strong cyan color indicates subjects with itraconazole



4.5.2 Reviewer's Analysis

Evaluation of sponsor's final population PK model

The reviewer was able to run the sponsor's final pharmacokinetics model and obtained similar results as reported by the sponsor. Model diagnostics are shown in Figure 4-11 and Figure 4-12.

Figure 4-11: General goodness-of-fit plots for rimegepant from the sponsor's final population PK model

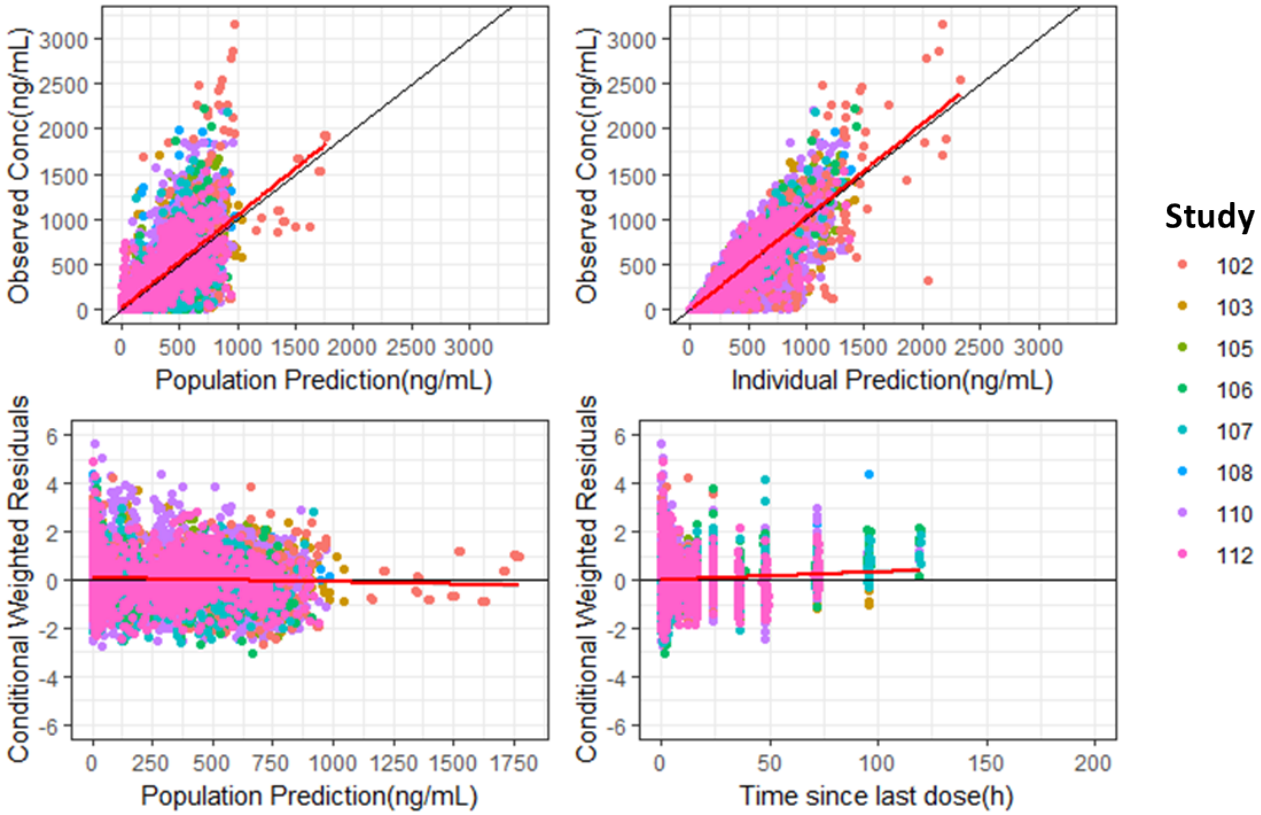
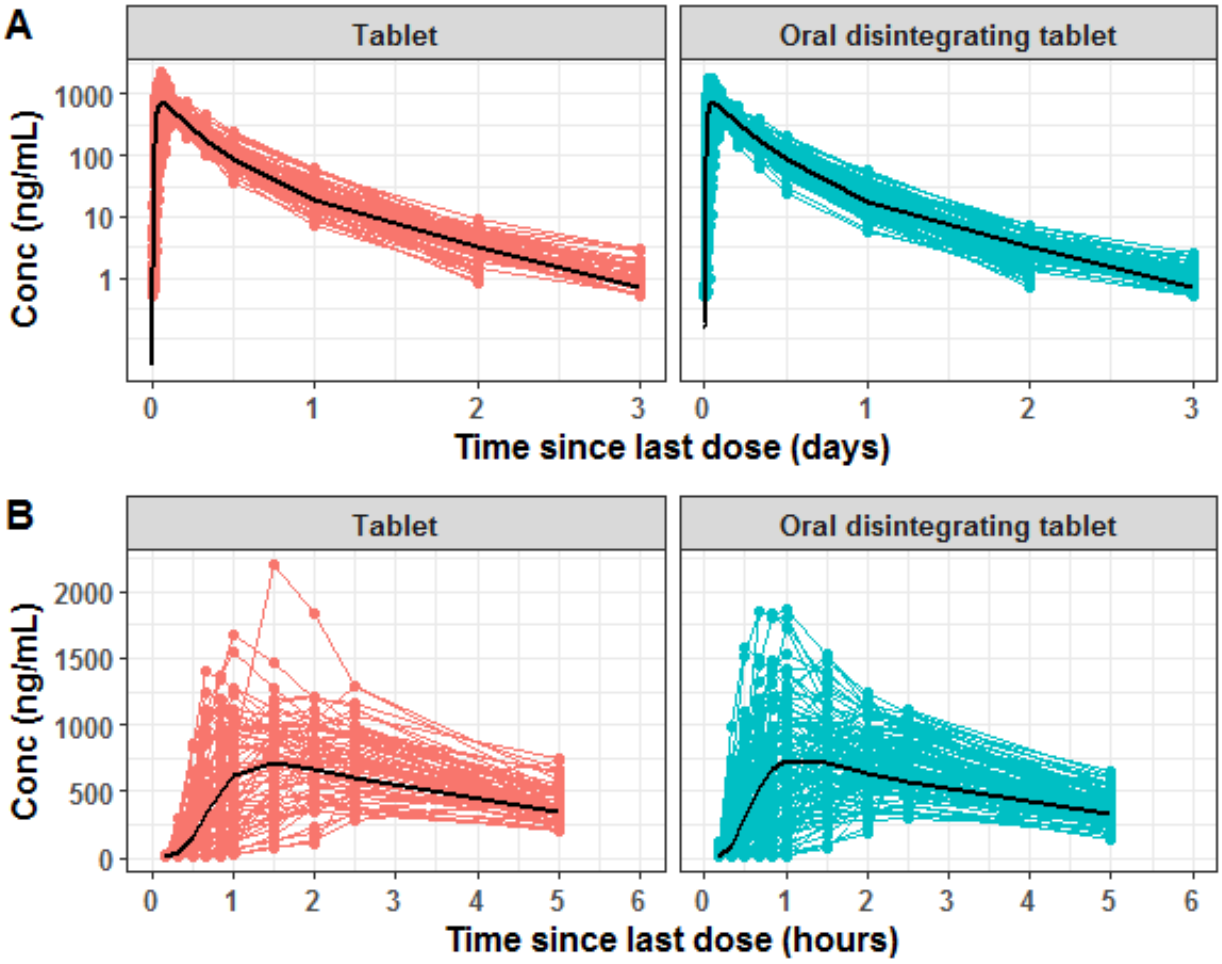


Figure 4-12: Population PK predictions for rimegepant from sponsor's final PK model for Study 110 (as a representative study) by-formulation overlaid with individual PK profiles

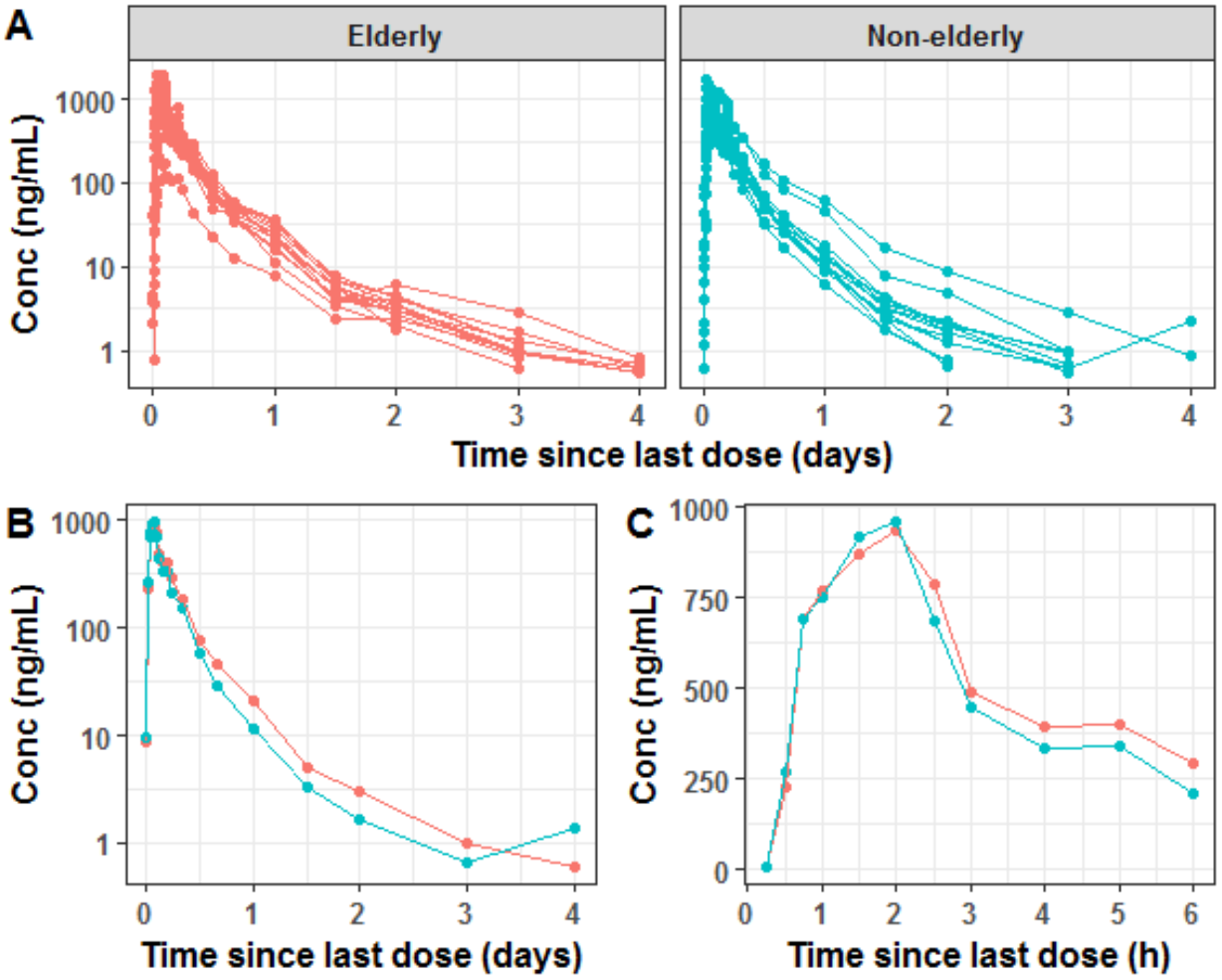


The sponsor's pharmacokinetics dataset was a compilation of 8 dedicated clinical studies which were evaluating the impact of formulation (study 102 and study 110), drug-drug interaction (study 103 and study 105), renal impairment (study 106), hepatic impairment (study 107), age (study 108) and food effect (study 112). Reviewer has used pharmacokinetics data from the dedicated study, if available, to evaluate the impact of covariates. Otherwise, pharmacokinetics data was pooled from all 8 studies to evaluate the covariate impact. Subjects from cross-over studies have contributed more than one pharmacokinetics profile in the analysis.

4.5.2.1 Age

Data from clinical study BHV3000-108 (study-108) suggested no differences in pharmacokinetics between non-elderly (N=14; 18-45 years) and elderly (N=14; ≥65 years) subjects (Figure 4-13).

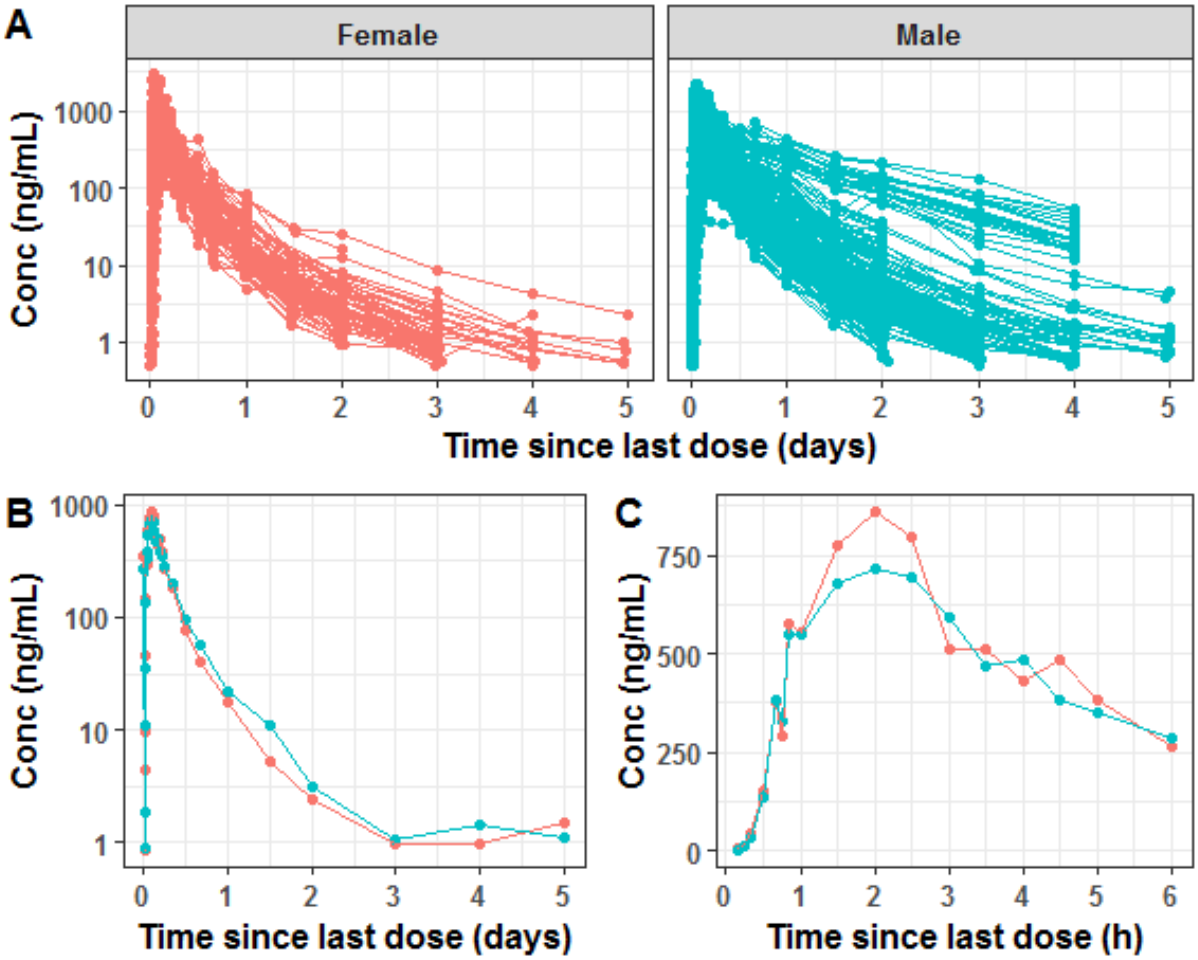
Figure 4-13: A) Individual PK profiles of rimegepant by age category; B) Median PK profile of rimegepant by age category; C) Median PK profile of rimegepant up to 6 hours by age category. Red color indicates elderly and strong cyan color indicates non-elderly subjects



4.5.2.2 Sex

Data was pooled from 8 clinical studies to compare the pharmacokinetic profiles of 106 female and 404 male subjects (Figure 4-14). The pharmacokinetic profiles from males have higher variability, but these wide range is due to data pooling from wide range of clinical studies including subjects of different formulations, DDI, hepatic and renal impairment. However, on adjusting other factors in the population pharmacokinetics model, there was no significant effect of sex on the pharmacokinetics of rimegepant.

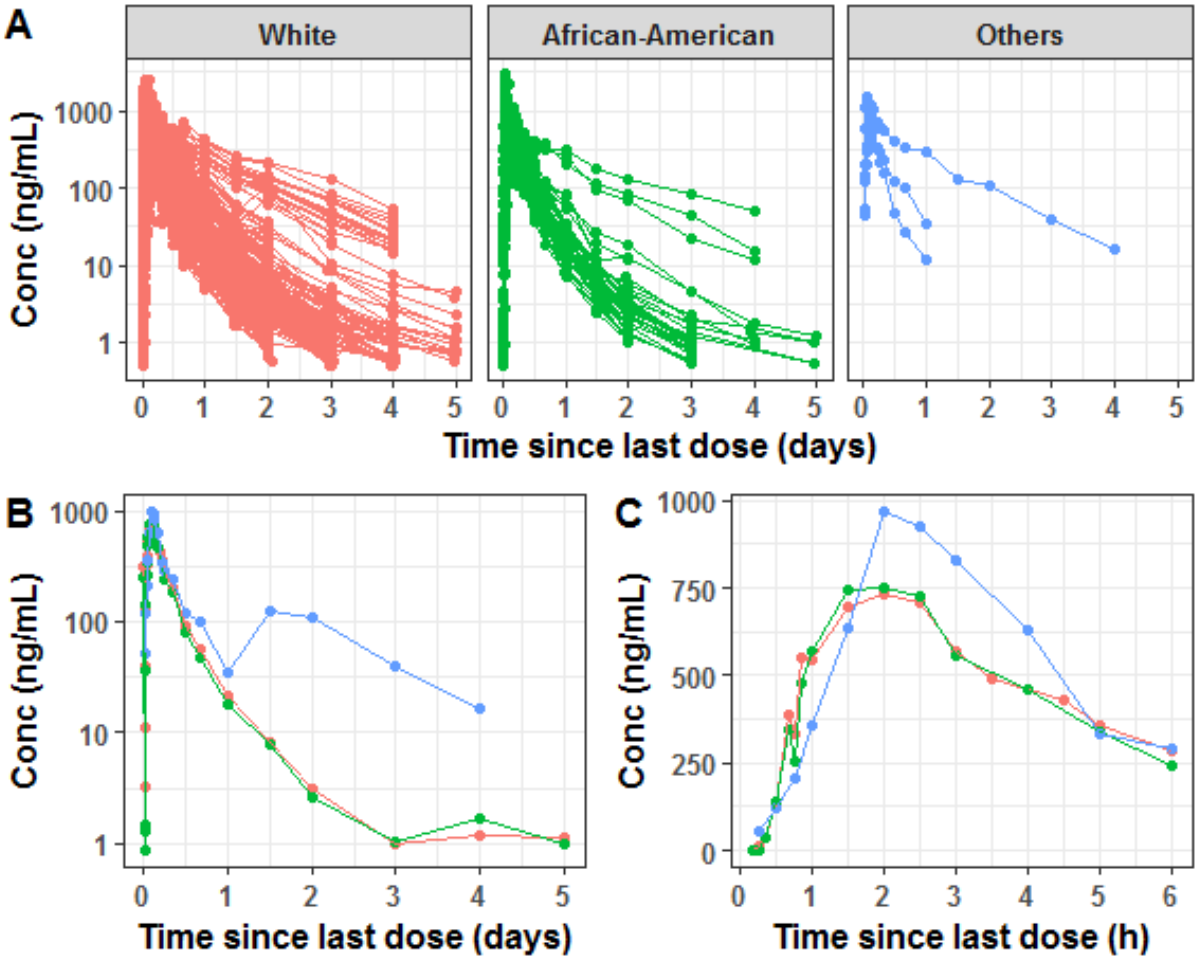
Figure 4-14: A) Individual PK profiles of rimegepant by gender; B) Median PK profile of rimegepant by sex; C) Median PK profile of rimegepant up to 6 hours by sex. Red color indicates female and strong cyan color indicates male subjects



4.5.2.3 Race

The pharmacokinetics data was pooled from 8 clinical studies to compare the pharmacokinetics profile of 443 White, 64 African-American and 3 other subjects. The pharmacokinetic profiles of Whites and African-Americans were only compared considering limited data (3 pharmacokinetic profiles) for "others" category. The 3 pharmacokinetic profiles of "others" were coming from DDI studies in which a subject (showing 4-days of pharmacokinetic profiles) was on itraconazole. This resulted in higher concentrations of rimegepant in "other" subject category (Figure 4-15). However, on adjusting other factors in the population pharmacokinetics model, there was no significant effect of race on the pharmacokinetics of rimegepant.

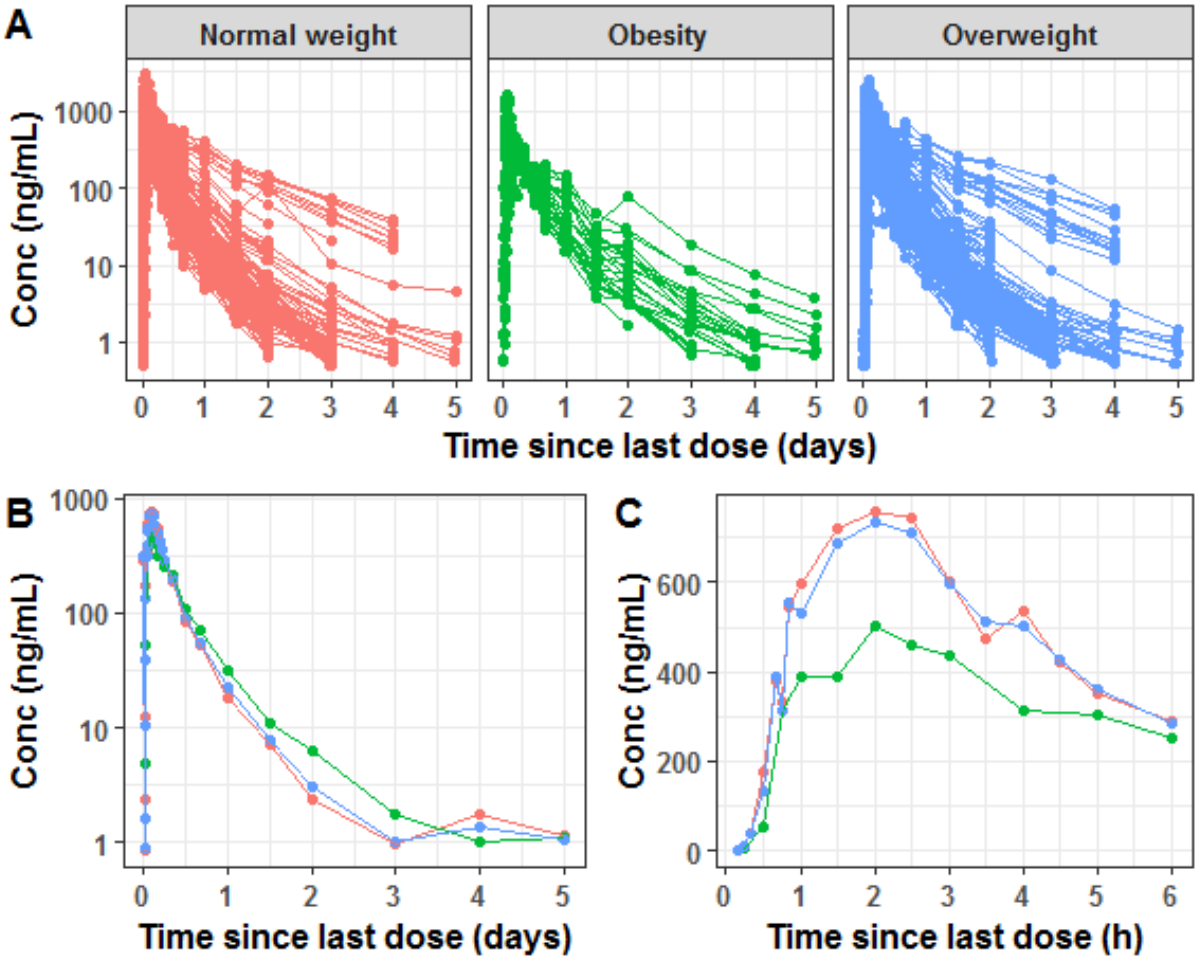
Figure 4-15: A) Individual PK profiles of rimegepant by race; B) Median PK profile of rimegepant by race; C) Median PK profile of rimegepant up to 6 hours by race. Red color indicates White, green color indicate African-American, and blue color indicates other subjects



4.5.2.4 Body Weight

The pharmacokinetics data was pooled from 8 clinical studies to compare the pharmacokinetic profiles of 173 normal weight, 311 overweight and 26 obese subjects. All the subjects were categorized into different weight categories based on the BMI classification [1]. The pharmacokinetic profiles of rimegepant for normal weight and overweight subjects were similar (Figure 4-16). The pharmacokinetic profiles of rimegepant in obese subjects have shown lower elimination and absorption. However, on adjusting other factors in the population pharmacokinetics model, there was no significant effect of weight on the pharmacokinetics of rimegepant.

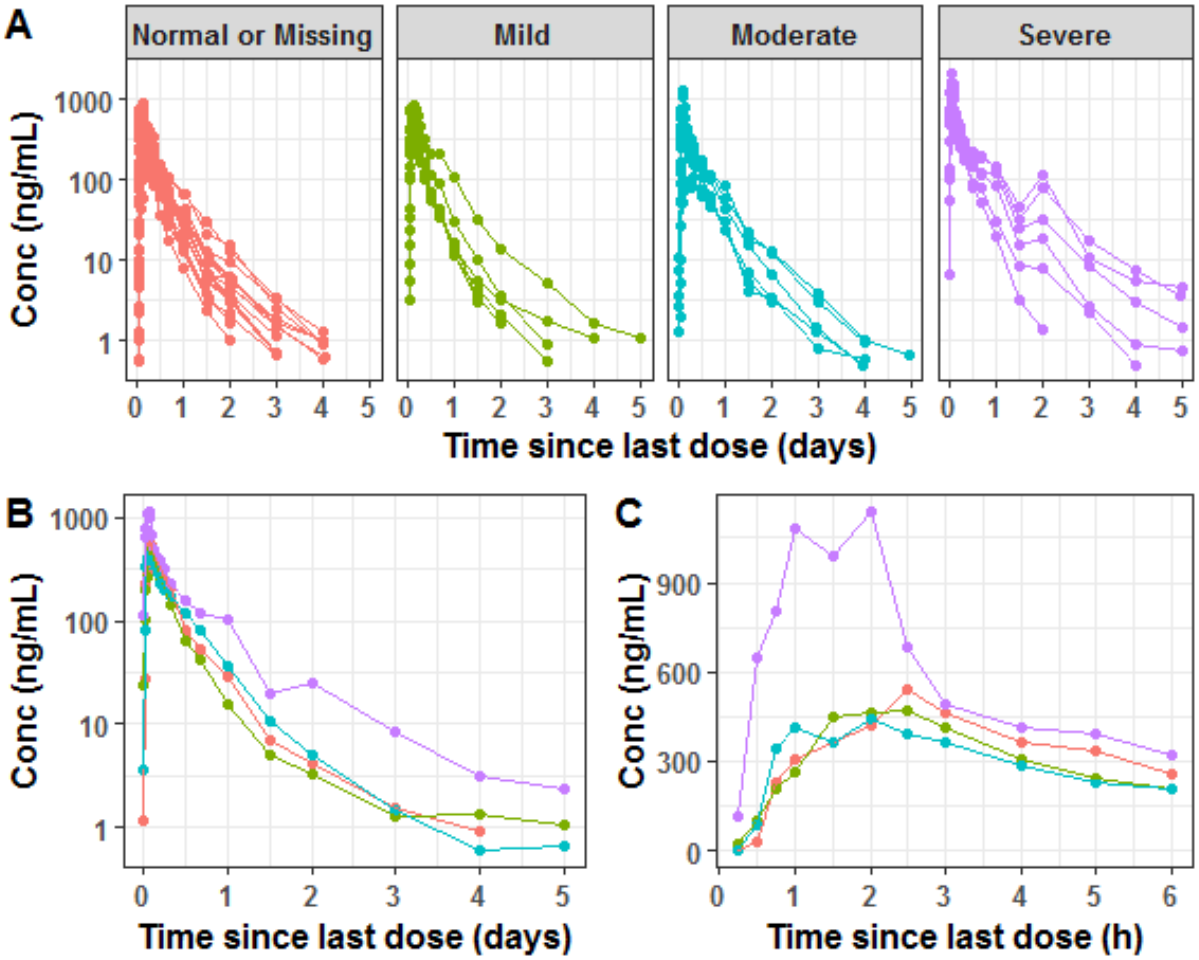
Figure 4-16: A) Individual PK profiles of rimegepant by weight category; B) Median PK profile of rimegepant by weight category; C) Median PK profile of rimegepant up to 6 hours by weight category. Red color indicates normal, green color indicate obesity, and blue color indicates overweight subjects



4.5.2.5 Hepatic impairment

The pharmacokinetics data from clinical study BHV3000-107 (study-107) was used to compare the pharmacokinetics profile of 18 normal, 6 mild, 6 moderate and 6 severe renal impaired subjects. The pharmacokinetic profiles of rimegepant in normal, mild and moderately hepatic impaired subjects were similar (Figure 4-17). However, severely hepatic impaired subjects have shown higher concentration-time profiles and ~2-fold increase in exposure. The sponsor's population pharmacokinetics model has predicted ~42% reduction in clearance which is similar to the observed pharmacokinetics data.

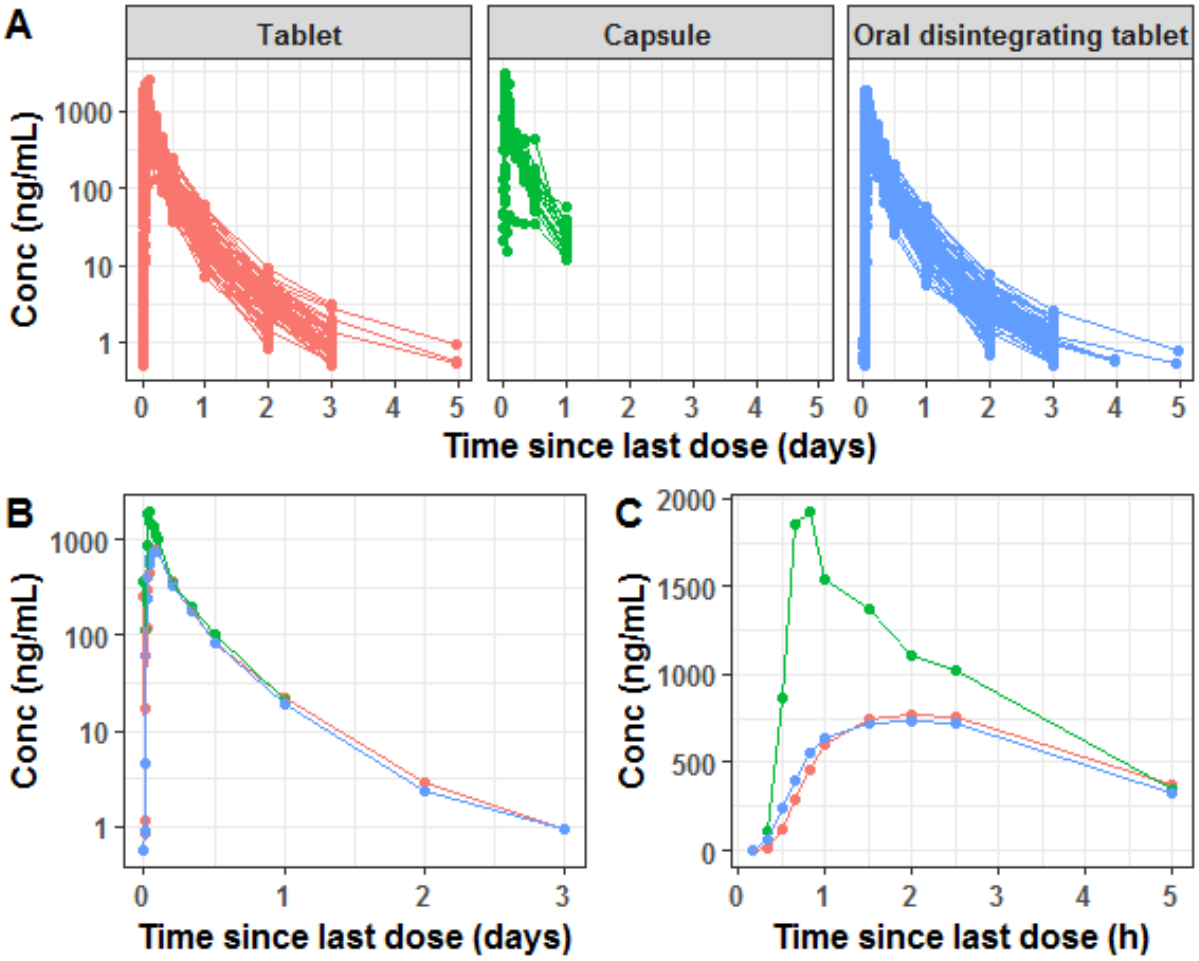
Figure 4-17: A) Individual PK profiles of rimegepant by hepatic impairment; B) Median PK profile of rimegepant by hepatic impairment; C) Median PK profile of rimegepant up to 6 hours by hepatic impairment. Red color indicates normal/missing, green color indicates mild, strong cyan color indicates moderate, and purple color indicates severe renal impaired subjects



4.5.2.6 Formulation

The pharmacokinetics data from clinical studies BHV3000-102 (study-102) and BHV3000-110 (study 110) was used to compare the pharmacokinetic profiles of 102 subjects taking tablet, 18 subjects taking capsules and 135 subjects taking oral disintegrating tablet. Subjects taking tablet or ODT have shown similar pharmacokinetic profiles of rimegepant (Figure 4-18). Subjects taking capsules have shown ~2.5-fold increase in Cmax, but the sponsor is not seeking approval of capsule formulation (b) (4)

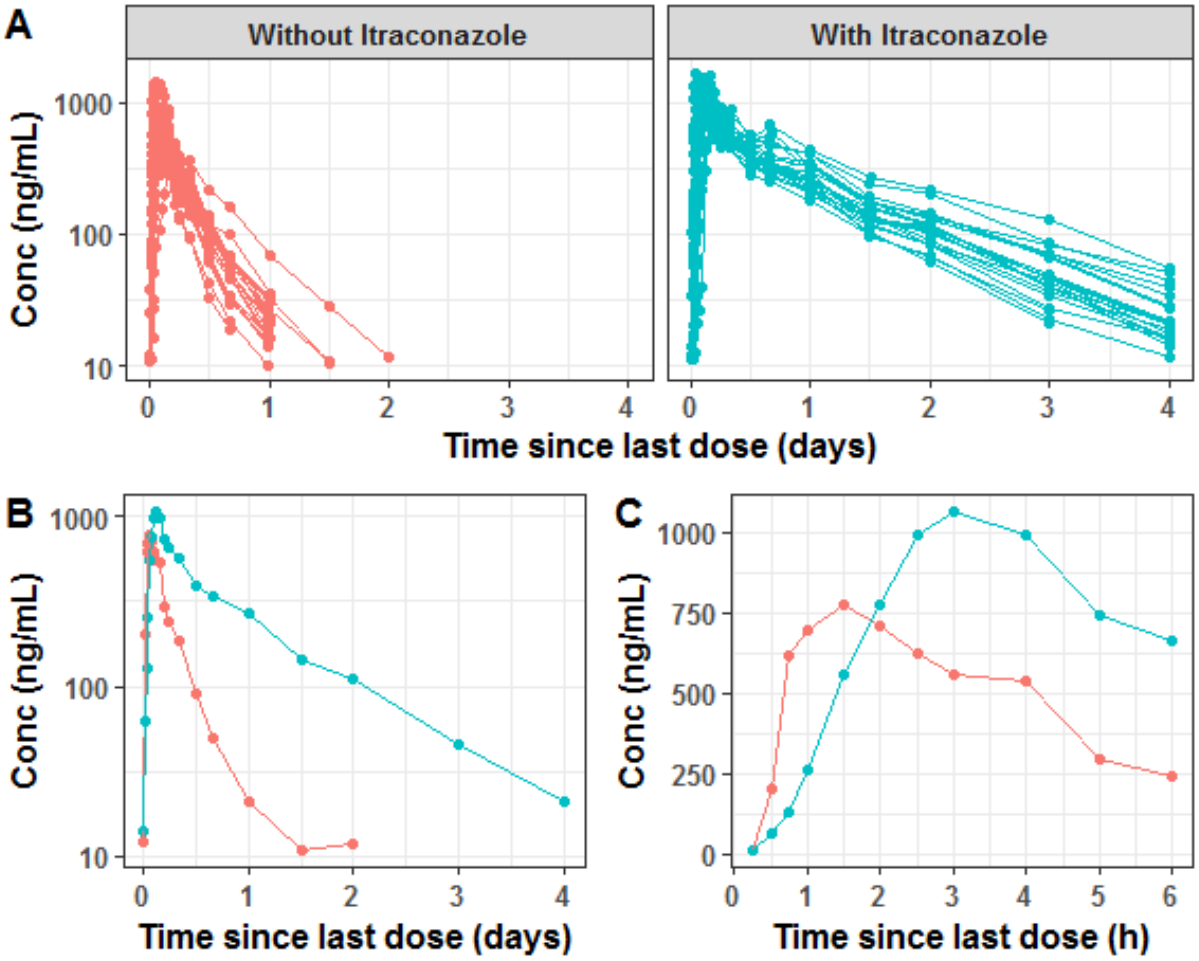
Figure 4-18: A) Individual PK profiles of rimegepant by formulation; B) Median PK profile of rimegepant by formulation; C) Median PK profile of rimegepant up to 6 hours by formulations. Red color indicates tablet, green color indicates capsule, and blue color indicates ODT administered subjects



4.5.2.7 Drug Interaction - Itraconazole

The pharmacokinetics data from clinical study BHV3000-103 (study-103) was used to compare the pharmacokinetics profile of 24 subjects without itraconazole and 22 subjects with itraconazole. Itraconazole reduced the clearance of rimegepant which resulted in increase of Cmax by ~1.5-fold, Tmax by 1.4 hours and AUC by ~4-fold (Figure 4-19). The sponsor's population pharmacokinetics model shows a ~74% reduction in clearance, which is similar to the observed data.

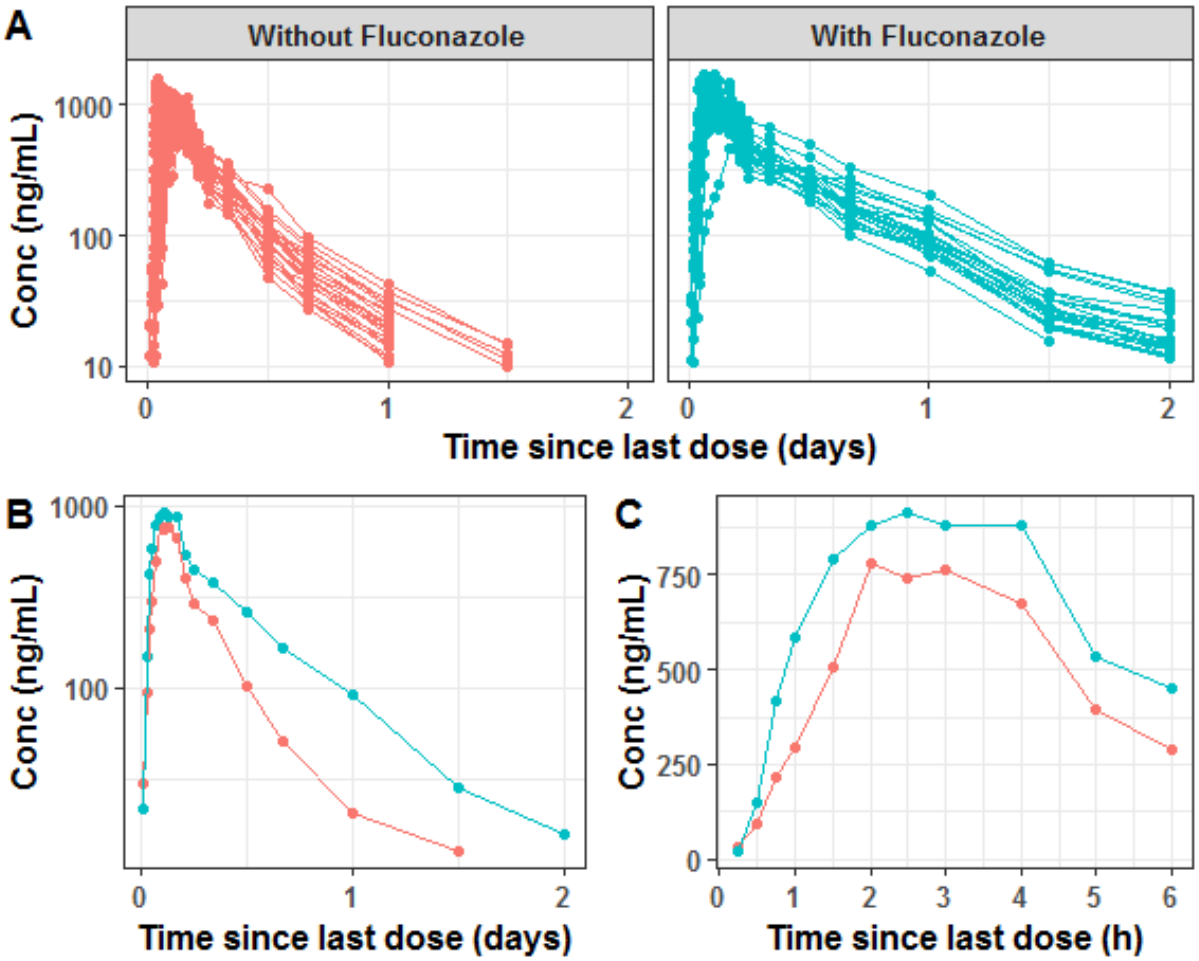
Figure 4-19: A) Individual PK profiles of rimegepant by DDI-itraconazole; B) Median PK profile of rimegepant by DDI-itraconazole; C) Median PK profile of rimegepant up to 6 hours by DDI-itraconazole. Red color indicates subjects without itraconazole, and strong cyan color indicates subjects with itraconazole



4.5.2.8 Drug Interaction - fluconazole

The pharmacokinetics data from clinical study BHV3000-105 (study-105) was used to compare the pharmacokinetics profile of 24 subjects without fluconazole and 23 subjects with fluconazole. Fluconazole reduced the clearance of rimegepant which resulted in increase of AUC by ~1.8-fold with Cmax and Tmax remains in the similar range (Figure 4-20). The sponsor's population pharmacokinetics model shows a ~43% reduction in clearance, which is similar to the observed data.

Figure 4-20: A) Individual PK profiles of rimegepant by DDI-fluconazole; B) Median PK profile of rimegepant by DDI-fluconazole; C) Median PK profile of rimegepant up to 6 hours by DDI-itraconazole. Red color indicates subjects without fluconazole, and strong cyan color indicates subjects with fluconazole



4.5.3 Listing of Analysis Codes and Output Files

File Name	Description	Location
pk_analysis.R	Exploratory PK analysis	\\Reviews\Rimegepant_NDA(b) (4)_VS\Reviewer\Rscripts

4.5.4 References

1. BMI classification". World Health Organization. Retrieved 15 February 2014.

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