Report on the Deliberation Results

September 4, 2015
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Viekirax Combination Tablets
[Non-proprietary name]	Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir (JAN*)
[Applicant]	AbbVie GK
[Date of application]	February 12, 2015

[Results of deliberation]
In a meeting held on August 31, 2015, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a powerful product. The re-examination period is 8 years. Ombitasvir hydrate and paritaprevir hydrate, the drug substances, are not classified as a poisonous drug, a powerful drug, a biological product, or a specified biological product.

[Conditions for approval]
The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

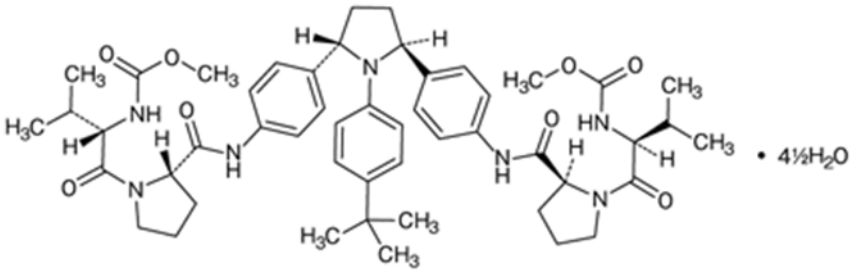
August 20, 2015
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Viekirax Combination Tablets
[Non-proprietary name]	Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir
[Applicant]	AbbVie GK
[Date of application]	February 12, 2015
[Dosage form/Strength]	Each tablet contains 13.6 mg of ombitasvir hydrate (equivalent to 12.5 mg of ombitasvir), 78.5 mg of paritaprevir hydrate (equivalent to 75 mg of paritaprevir), and 50 mg of ritonavir.
[Application classification]	Prescription drug, (1) Drug with new active ingredients; (2) New prescription combination drug

[Chemical structure]

Ombitasvir hydrate

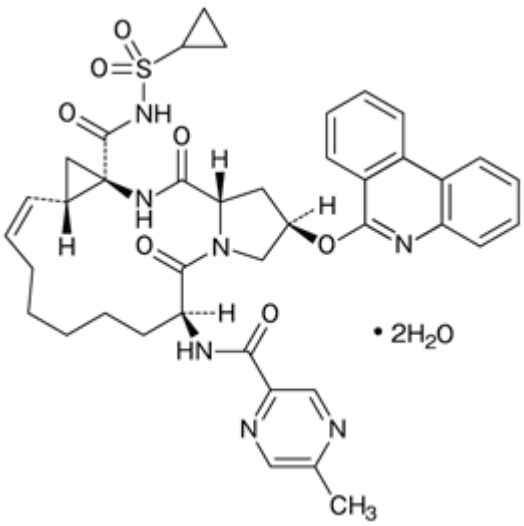


Molecular formula: $C_{50}H_{67}N_7O_8 \cdot 4^1/_2H_2O$

Molecular weight: 975.18

Chemical name: Dimethyl *N*,*N*'-{(2S,5S)-1-[4-(1,1-dimethylethyl)phenyl]pyrrolidine-2,5-diyl} bis{[(4,1-phenyleneazanediyl)carbonyl][(2*S*)-pyrrolidine-2,1-diyl][(2*S*)-3-methyl-1-oxobutane-1,2-diyl]}biscarbamate heminonahydrate

Paritaprevir hydrate



Molecular formula: $C_{40}H_{43}N_7O_7S \cdot 2H_2O$

Molecular weight: 801.91

Chemical name: (2*R*,6*S*,12*Z*,13a*S*,14a*R*,16a*S*)-*N*-(Cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5*H*)-carboxamide dihydrate

[Items warranting special mention] Priority review (Notification No. 0403-6 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated April 3, 2015);
A product subject to prior assessment consultation for drugs

[Reviewing office] Office of New Drug IV

Review Results

August 20, 2015

[Brand name]	Viekirax Combination Tablets
[Non-proprietary name]	Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir
[Applicant]	AbbVie GK
[Date of application]	February 12, 2015

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis has been demonstrated and its safety is acceptable in view of its observed benefits.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

[Indication]	Suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis
[Dosage and administration]	The usual adult dosage is 25 mg of ombitasvir, 150 mg of paritaprevir, and 100 mg of ritonavir (2 tablets) once daily, administered orally after a meal for 12 weeks.
[Conditions for approval]	The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

July 21, 2015

I. Product Submitted for Registration

[Brand name]	Viekirax Combination Tablets
[Non-proprietary name]	Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir
[Applicant]	AbbVie GK
[Date of application]	February 12, 2015
[Dosage form/Strength]	Each tablet contains 13.6 mg of ombitasvir hydrate (equivalent to 12.5 mg of ombitasvir), 78.5 mg of paritaprevir hydrate (equivalent to 75 mg of paritaprevir), and 50 mg of ritonavir.
[Proposed indication]	Suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients, including those with compensated cirrhosis, who have high or low HCV RNA levels and who fall under either of the following categories: 1) Treatment-naïve patients who are eligible or ineligible for interferon therapy 2) Patients who have been intolerant to, have failed to respond to, or have relapsed after prior treatment including interferon
[Proposed dosage and administration]	The usual adult dosage is 150 mg of paritaprevir, 100 mg of ritonavir, and 25 mg of ombitasvir (2 tablets) once daily, administered orally during or immediately after meal for 12 weeks.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

The proposed product “Viekirax Combination Tablets” is a fixed-dose combination of 3 active substances: ombitasvir hydrate (OBV), paritaprevir hydrate (PTV), and ritonavir (RTV) (the fixed-dose combination product is hereafter referred to as the “PTV/RTV/OBV combination product”). OBV, PTV, and RTV were discovered by Abbott Laboratories (currently AbbVie Inc.) in the United States. OBV and PTV suppress the proliferation of the hepatitis C virus (HCV) by inhibiting HCV NS5A and NS3/4A proteases, respectively, which are involved in HCV replication. RTV is a human immunodeficiency

virus (HIV) protease inhibitor, and in Japan, it is approved not only as a single agent[1)] but also as a component of a combination drug[2)] for the treatment of HIV infection. RTV also inhibits a human cytochrome P450 (CYP) isozyme, CYP3A, and is therefore sometimes used in an attempt to increase the blood concentration of other anti-HIV drugs that are metabolized by CYP3A. Accordingly, despite its weak anti-HCV activity, RTV is included in the PTV/RTV/OBV combination product in order to increase the blood concentration of PTV.

The number of HCV-infected patients are estimated to be approximately 170 million worldwide and 1.5 to 2 million (those with genotype 1 HCV infection accounting for approximately 70%[3)]) in Japan. The following products are currently approved in Japan for patients with chronic hepatitis C (genotype 1): single-agent drugs including interferons, ribavirin, NS3/4A protease inhibitors (telaprevir, simeprevir sodium, asunaprevir, and vaniprevir), daclatasvir hydrochloride (NS5A inhibitor), and sofosbuvir (NS5B polymerase inhibitor); and a combination drug containing sofosbuvir and ledipasvir acetone (NS5A inhibitor).

The applicant has filed a new drug application based on the results obtained from Japanese clinical studies in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1b).

Outside Japan, PTV/RTV/OBV combination product was developed by AbbVie Inc. in the United States, and as of June 2015, is approved as a component of combination regimens with dasabuvir (NS5B inhibitor) or ribavirin in 49 countries including the United States and Europe. The treatment with the PTV/RTV/OBV combination product alone is also approved in 36 countries.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance (ombitasvir hydrate)

2.A.(1).1) Characterization

Drug substance ombitasvir hydrate (OBV) is a white to pale yellowish white or pale red powder, and its solubility, hygroscopicity, melting point, thermal analysis, dissociation constant, distribution coefficient, crystalline polymorphism, and optical rotation have been determined. Four crystal forms (Forms [redacted] to [redacted]) of OBV have been identified during manufacture. However, the proposed manufacturing process controls the crystal form of drug substance OBV as Form [redacted] (4.5-hydrate forming a crystal lattice with 2 ombitasvir molecules binding to 9 water molecules).

1) Norvir Tablets 100 mg and Norvir Oral Solution 8% are approved.
2) Kaletra Tablets and Kaletra Oral Solution are approved as a combination drug with lopinavir (HIV protease inhibitor).
3) Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. *JSH Guidelines for the Management of Hepatitis C Virus Infection.* 3.4th ed.; 2015

The chemical structure of drug substance OBV has been elucidated by mass spectrometry, ultraviolet spectroscopy, infrared spectrophotometry (IR), hydrogen nuclear magnetic resonance spectrometry and carbon nuclear magnetic resonance spectrometry (^{1}H-NMR and ^{13}C-NMR), and X ray crystallography.

2.A.(1).2) Manufacturing process

[redacted]

The quality by design (QbD) approach has been used for specifying the critical quality attributes (CQAs) of drug substance OBV, evaluating the effect of the CQAs of drug substance OBV on the CQAs of the drug product, establishing control strategies, and other relevant activities.[4)]

[redacted]

2.A.(1).3) Control of drug substance

[redacted] During the review, the crystal form (X-ray powder diffraction) was included in the specifications for drug substance OBV.

2.A.(1).4) Stability of drug substance

The stability studies of drug substance OBV are shown in Table 1. Photostability testing demonstrated that drug substance OBV is photostable.

Table 1. Stability studies of OBV

Study	Primary batch	Temperature	Humidity	Storage period	Storage container
Long term	3 batches manufactured at approximately [redacted]% of production scale	25˚C	65%RH	24 months	Double-layered polyethylene bag in a plastic drum
Accelerated	3 batches manufactured at approximately [redacted]% of production scale	40˚C	75%RH	6 months	

Based on the results of the above studies, a shelf life of [redacted] months has been proposed for drug substance OBV when stored at ≤25˚C in a double-layered polyethylene bag placed in a plastic drum, in accordance with the “Guideline on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June

4) Use of QbD was not for QbD application. The final process parameters were determined using conventional methods.

3, 2003, hereinafter referred to as “ICH Q1E Guidelines”). The long-term testing will be continued for up to [redacted] months.

2.A.(2) Drug substance (paritaprevir hydrate)

2.A.(2).1) Characterization

Drug substance paritaprevir hydrate (PTV) is a white to pale yellow powder, and its solubility, hygroscopicity, melting point, thermal analysis, dissociation constant, distribution coefficient, crystalline polymorphism, and optical rotation have been determined. Three crystal forms (Forms [redacted] to [redacted]) of PTV have been identified at the development stage. However, the proposed manufacturing process controls the crystal form of drug substance PTV as Form [redacted] (dihydrate) [see “2.B.(1) Control of crystal form of drug substance PTV”].

The chemical structure of drug substance PTV has been elucidated by mass spectrometry, ultraviolet spectroscopy, IR, nuclear magnetic resonance spectrometry (^{1}H-NMR and ^{13}C-NMR), and X ray crystallography.

2.A.(2).2) Manufacturing process

[redacted]

The QbD approach has been used for specifying the CQAs of drug substance PTV, evaluating the effect of the CQAs of drug substance PTV on the CQAs of the drug product, establishing control strategies, and other relevant activities.[4)]

[redacted]

2.A.(2).3) Control of drug substance

[redacted] During the review, the crystal form (X-ray powder diffraction) was included in the specifications for drug substance PTV.

2.A.(2).4) Stability of drug substance

The stability studies of drug substance PTV are shown in Table 2. Photostability testing demonstrated that drug substance PTV is photolabile.

Table 2. Stability studies of PTV

Study	Primary batch	Temperature	Humidity	Storage period	Storage container
Long term	2 pilot batches	25˚C	65%RH	24 months	Double-layered polyethylene bag in a plastic drum
	2 production batches				
Accelerated	2 pilot batches	40˚C	75%RH	6 months	
	2 production batches				

Based on the results of the above studies, a shelf life of [redacted] months has been proposed for drug substance PTV when stored at ≤25˚C in a double-layered polyethylene bag placed in a plastic drum protected from light in accordance with the ICH Q1E Guidelines. The long-term testing will be continued for up to [redacted] months.

2.A.(3) Drug substance (ritonavir)

Drug substance ritonavir (RTV) is identical with RTV contained in the approved products, Norvir Oral Solution 8% and Norvir Tablets 100 mg.

2.A.(4) Drug product

2.A.(4).1) Description and composition of the drug product

The drug product is a film-coated tablet containing 13.6 mg of OBV, 78.5 mg of PTV, and 50.0 mg of RTV. [redacted]

2.A.(4).2) Manufacturing process

[redacted]

The QbD approach has been used for specifying the CQAs of the drug product, performing risk assessment of the drug product components and the manufacturing process for the CQAs of the drug product, establishing control strategies, and other relevant activities.[4)]

2.A.(4).3) Control of drug product

[redacted][5)]

2.A.(4).4) Stability of drug product

The stability studies of the drug product are shown in Table 3. Photostability testing demonstrated that the drug product is photostable.

5) [redacted]

Table 3. Stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage period	Storage container
Long term	3 pilot batches	30˚C	75%RH	24 months	PTP
Accelerated	3 pilot batches	40˚C	75%RH	6 months	

Based on the results of the above studies, a shelf life of 36 months has been proposed for the drug product when stored at room temperature in a push-through pack (PTP; a multi-layer film consisting of polyvinyl chloride, polyethylene, and polychlorotrifluoroethylene covered with aluminum foil) in accordance with the ICH Q1E Guidelines. The long-term testing will be continued for up to [redacted] months.

2.B Outline of the review by PMDA

PMDA's view:

On the basis of the submitted data and the following discussion, the quality of the drug substances and the drug product is appropriately controlled.

2.B.(1) Control of crystal form of drug substance PTV

The applicant's explanation on the generation of Form [redacted] (dihydrate) of the drug substance PTV and its control:

Three crystal forms (Forms [redacted] to [redacted]) of PTV were discovered at the development stage. However, drug substance PTV is consistently manufactured as thermodynamically stable Form [redacted] (dihydrate).

[redacted][6)][redacted] X-ray powder diffraction is performed in the release testing and is compared with the diffraction pattern of the reference substance to ensure that the manufactured drug substance PTV is of Form [redacted] (dihydrate). Therefore, the crystal form is to be included in the specifications for drug substance PTV.

PMDA concluded that there should be no particular problems with the control of the crystal form of drug substance PTV.

6) [redacted]

2.B.(2) Acceptance criterion for dissolution of drug product

The acceptance criterion for dissolution of the drug product for all 3 drug substances is as follows: the Q-value at [redacted] minutes is [redacted]%.

In the dissolution test, the mean dissolution rate of the individual drug substances after the start of the test was approximately [redacted]% and [redacted]% at [redacted] minutes and [redacted] minutes, respectively, suggesting that it reached a plateau between [redacted] and [redacted] minutes. PMDA asked the applicant to explain the rationale for the acceptance criterion.

The applicant's explanation:

Assuming that the Q-value at [redacted] minutes was [redacted]% based on the Acceptance Table 6.10-1[7)] in the Japanese Pharmacopoeia (JP), all samples[8)] required the S2 test and met the acceptance criterion for S2. When a Monte Carlo simulation analysis was performed using the acceptance criterion, "the Q-value at [redacted] minutes is [redacted]%," samples were estimated to require the S2 test at a frequency of up to 72% but not the S3 test. Therefore, an analysis was performed on the assumption that the dissolution rate at [redacted] minutes was [redacted]% based on the Acceptance Table 6.10-2[9)] of JP. As a result, samples were estimated to require the L2 test at a frequency of up to 21% and the L3 test at a frequency of up to 0.2%. [redacted][10)] [redacted][11)] [redacted]

On the basis of the above, the acceptance criterion for dissolution will be changed as follows: the dissolution for [redacted] minutes is ≥[redacted]%. [redacted]

PMDA asked the applicant whether the acceptance criterion for dissolution after the change is sufficient to exclude formulations with unacceptable dissolution profiles that may affect the consistency of the drug product's quality.

The applicant's explanation:

[redacted][12)] [redacted]

7) Table of acceptance criteria for immediate-release preparations
8) Data from 4 batches tested for stability of the drug product were used.
9) Table of acceptance criteria for extended-release preparations
10) It was formulated in the course of development and used in clinical studies.
11) Drug product formulations that dissolve at ≥[redacted]% within [redacted] to [redacted] minutes in *in vitro* dissolution test
12) [redacted]

[redacted]

On the basis of the above, formulations with unacceptable dissolution profiles are considered identifiable by referring to the changed acceptance criterion for dissolution.

PMDA considered that the applicant's explanation is acceptable and that there is no particular problems in defining the acceptance criterion for dissolution as "the dissolution for [redacted] minutes is ≥[redacted]%."

2.B.(3) Novel excipient

The drug product contains copolyvidone, a novel excipient, in an amount greater than previously used in oral preparations. PMDA concluded that the use of copolyvidone is of no particular concern for the reasons stated below.

2.B.(3).1) Specifications and stability

Copolyvidone has satisfied the quality standards for excipients, indicating that there is no problem with its specifications and stability.

2.B.(3).2) Safety

On the basis of the submitted data, PMDA concluded that there are no particular safety problems with copolyvidone when used in accordance with the specified clinical dose of the drug product.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

In primary pharmacodynamic studies of paritaprevir hydrate (PTV) and ombitasvir hydrate (OBV), antiviral activity against hepatitis C virus (HCV) and other activities were investigated. In addition, secondary pharmacodynamic and safety pharmacology studies were conducted.

3.(i).A.(1) Primary pharmacodynamics (PTV)

3.(i).A.(1).1) *In vitro* studies

(a) Inhibitory activity against HCV NS3/4A protease (4.2.1.1.1, 4.2.1.1.2)

The inhibitory activity of PTV against HCV NS3/4A protease and human proteases was determined. The inhibitory activity (50% inhibitory concentration [IC_{50}]) against each protease is shown in Table 4.

Table 4. Inhibitory activity of PTV against NS3/4A protease derived from various HCV genotypes and against human proteases

	IC_{50} (nmol/L)
HCV NS3/4A protease	
Genotype 1a	0.18
Genotype 1b	0.43
Genotype 2a	2.4
Genotype 2b	6.3
Genotype 3a	14.5
Genotype 4a	0.16
Human protease	
Chymase	> 200,000
Elastase	> 200,000
Cathepsin B	> 200,000
Chymotrypsin Type II	> 200,000
Chymotrypsin Type VII	> 200,000
Kallikrein	> 200,000
Urokinase	> 200,000

Mean

(b) Antiviral activity in HCV replicon assay (4.2.1.1.1, 4.2.1.1.2, 4.2.1.1.3)

An HCV replicon assay was conducted to investigate the antiviral activity (50% effective concentration [EC_{50}]) of PTV against HCV replicon cells and the effect of the addition of human plasma on this activity. The results of the assay are shown in Table 5.

Table 5. Antiviral activity of PTV observed in HCV replicon assay

HCV genotype (virus strain)	EC_{50} (nmol/L)
Genotype 1a (H77)[a)]	1.0
Genotype 1a (H77) + 40% human plasma[a)]	23
Genotype 1b (Con-1)[a)]	0.21
Genotype 1b (Con-1) + 40% human plasma[a)]	8.7
Genotype 2a (JFH-1)[b)]	5.3
Genotype 3a[a,c)]	19
Genotype 4a[a,c)]	0.09
Genotype 6a[a,c)]	0.68

Mean

a) EC_{50} was calculated based on the number of HCV replicon copies using a luciferase reporter gene assay.
b) EC_{50} was calculated based on the amount of HCV RNA using the RT-PCR method.
c) HCV genotype 1b chimeric replicon cells containing amino-acid sequences in the NS3 domain from samples of various genotypes were used.

The antiviral activity of PTV was examined using HCV genotype 1a (H77) and genotype 1b (Con-1) replicon cells containing the NS3 domain derived from treatment-naïve patients with HCV genotype 1a and genotype 1b infection. The EC_{50} values against these HCV genotype 1a and genotype 1b replicon cells were 0.86 and 0.06 nmol/L, respectively. In a 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay in which the cytotoxicity of PTV against replicon cells was evaluated, the median toxic dose (TD_{50}) was 37 μmol/L.

(c) Antiviral activity against HIV-1 and HBV (4.2.1.1.4)

The antiviral activity of PTV against human immunodeficiency virus type 1 (HIV-1) and hepatitis B virus (HBV) was determined. The EC_{50} values against HIV-1 and HBV were 21.6 and 29.6 μmol/L, respectively.

(d) Resistance profiles (4.2.1.1.1, 4.2.1.1.2, 4.2.1.1.5, 4.2.1.1.6)

The resistance profile of PTV was studied in HCV replicon cells cultured in the presence of PTV. At concentrations 10- to 100-fold over the EC_{50}, the following amino acid mutations[13)] were observed: Q41R, R155K, D168E/N and I170T/V[14)] in the NS3 domain of the HCV genotype 1a (H77) replicon; and R155Q, A156T/V and D168H/V in the NS3 domain of the HCV genotype 1b (Con-1) replicon. The antiviral activity of PTV was evaluated in HCV genotype 1a (H77) and 1b (Con-1) replicon-harboring cell lines with one of the mutations found in HCV genotypes 1a and 1b or mutations reported for other NS3/4A protease inhibitors[15),16),17),18),19)] at amino acid positions 54, 55, 155, 156, 168, and 170. The results are shown in Table 6.

In HCV genotype 2a (JFH-1) replicon-harboring cells cultured in the presence of PTV at a concentration 10-fold over the EC_{50}, the mutation most commonly observed in the NS3 domain was D168A/V/Y, and the antiviral activity of PTV was also evaluated in HCV genotype 2a (JFH-1) replicon-harboring cell lines with this and other NS3 mutations. The results are also shown in Table 6.

13) Mutations observed in at least 2 of 10 to 12 samples for each genotype and concentration, in which amino-acid sequences were analyzed
14) When Q41R and I170T/V were detected, they were always detected with D168E.
15) TELAVIC Tablets 250 mg [package insert] 12th ed; September, 2014
16) SOVRIAD Capsules 100 mg [package insert] 4th ed; October, 2014
17) SUNVEPRA Capsules 100 mg [package insert] 2nd ed; September, 2014
18) VANIHEP Capsules 150 mg [package insert]; September, 2014
19) Jiang M et al., *Antimicrob Agents Chemother*. 2013;57:6236-6245

Table 6. Antiviral activity of PTV against wild-type and mutant replicon cells

HCV genotype (Viral strain)	Mutation	EC_{50} (nmol/L)	EC_{90} (nmol/L)	Resistance[a)]	Replication (%)
Genotype 1a (H77)	Wild-type	1.4	3.0	–	100
	T54S	0.54	1.2	0.4	6.2
	Y56H	4.1	11	3	3.5
	R155K	51	96	37	31
	A156T	24	43	17	5.2
	D168A	70	365	50	35
	D168E	20	25	14	34
	D168N	19	42	13	28
	D168V	135	274	96	1.5
	D168Y	307	658	219	3.5
	Y56H + D168V	785	1487	561	15
Genotype 1b (Con-1)	Wild-type	0.11	0.26	–	100
	T54A	0.09	0.41	0.8	59
	T54S	nd [b)]	nd [b)]	nd [b)]	< 0.5
	V55A	0.07	0.31	0.6	14
	R155K	4.4	17	40	73
	R155Q	nd [b)]	nd [b)]	nd [b)]	< 0.5
	A156S	0.06	0.30	0.5	61
	A156T	0.81	3.4	7	19
	D168A	3.0	11	27	69
	D168E	0.48	1.1	4	80
	D168H	8.3	16	76	108
	D168V	17	40	159	157
	D168Y	37	57	337	70
	V170A	0.09	0.29	1	64
	Y56H + D168V	272	519	2472	22
Genotype 2a (JFH-1)	Wild-type	26	–	–	–
	D168A	522	–	20	–
	D168V	468	–	18	–
	D168Y	427	–	17	–

Mean
–, Not detectable
a) EC_{50} value against mutant replicon/EC_{50} value against wild-type replicon; b) Not detectable due to a low replication level

(e) Effect of combination with ritonavir (4.2.1.1.7)

The antiviral activity of PTV in combination with ritonavir (RTV) was determined in HCV genotype 1b (Con-1) replicon cells. The EC_{50} value of RTV as a single agent against HCV genotype 1b (Con-1) replicon cells was 15 μmol/L. Use of RTV (concentration range, 0.012-3 μmol/L) in combination with PTV had no impact on the PTV EC_{50} value. Because PTV is mainly metabolized by human cytochrome P450 (CYP) 3A4, PTV/RTV/OBV combination product contains RTV that inhibits CYP3A in order to increase PTV exposure in humans. However, RTV used in combination with PTV is unlikely to increase the concentration of PTV in HCV replicon cells *in vitro*, and therefore the applicant explained that RTV had no impact on the PTV EC_{50} value.

(f) Effect of combination with OBV (4.2.1.1.8)

The antiviral activity of PTV in combination with OBV, an HCV NS5A inhibitor, was determined in HCV genotype 1b (Con-1) replicon cells. Either additive or synergistic increase in antiviral activity[20] was observed at most of the concentrations[21] investigated when PTV (concentration range, 0.023-0.75 nmol/L) was used in combination with OBV (concentration range, 0.0002-0.0063 nmol/L).

(g) Effect of combination with anti-HIV preparations (4.2.1.4.1)

The effect of PTV in combination with HIV protease inhibitors (lopinavir [LPV] and darunavir [DRV]) on the anti-HIV activities of LPV and DRV was evaluated in MT-4 cells infected with HIV-1 (NL4-3). The EC_{50} value of LPV and DRV as a single agent was 25 and 11 nmol/L, respectively, and that in combination with PTV (1.8 nmol/L) was 26 and 12 nmol/L, respectively.

The effect of PTV in combination with LPV or DRV on the anti-HIV activity of PTV was evaluated in HCV genotype 1b (Con-1) replicon cells. The EC_{50} value of PTV as a single agent was 0.14 to 0.15 nmol/L, and that in combination with LPV (0.1 μmol/L) and DRV (0.1 μmol/L) was 0.14 and 0.13 nmol/L, respectively.

3.(i).A.(2) Secondary pharmacodynamics (PTV)

3.(i).A.(2).1) Effects on receptors and ion channels (4.2.1.2.1)

The inhibitory activity of PTV against ligand binding to 75 different G-protein-coupled receptors and ion channels was evaluated. PTV (10 μmol/L) exhibited no particular inhibitory effects on the ligand binding to any of these receptors or ion channels.

3.(i).A.(3) Safety pharmacology (PTV) (Reference data 4.2.1.3.1, 4.2.1.3.2, reference data 4.2.1.3.3, reference data 4.2.1.3.4, reference data 4.2.1.3.5, 4.2.1.3.6, 4.2.1.3.7, reference data 4.2.1.3.8)

In safety pharmacology studies, the effects of PTV on the central nervous system, cardiovascular system, respiratory system, gastrointestinal system, and other organs were investigated (Table 7).

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20) The Prichard and Shipman method (Prichard MN and Shipman C. *Antiviral Res*. 1990;14:181-206) was used to find 95% confidence intervals of the mean differences between measured values and theoretical values, calculated by percent inhibition at concentrations of each drug combination. When the lower limit of the 95% confidence interval calculated was >0 and the higher limit of that was <0, the combination was assessed as having a synergetic effect and an antagonistic effect, respectively. When the interval calculated was not applicable to either of the cases above, the combination was assessed as having an additive effect. Theoretical values were calculated by the following equation:
$Z = X + Y (1 – X)$
X = percent inhibition (%) of Drug X as a single agent
Y = percent inhibition (%) of Drug Y as a single agent

21) The applicant explained that antagonistic action was observed in 4 different combinations of OBV (1.6 and 3.2 pmol/L) and low-dose PTV (23 and 47 pmol/L, exhibiting no antiviral activity), out of 36 combinations of concentrations, though its mechanism remains unknown.

Table 7. Summary of safety pharmacology studies of PTV

Organ evaluated	Study sample	Route of administration	Dose or concentration	Sex (n/group)	Noteworthy findings
Central nervous system	Wistar rats (Irwin method)	Oral	3,10, 30, 100, or 300 mg/kg (in combination with 15 mg/kg of RTV)	Male (4)	Mild excitatory effect at 100 mg/kg (increased response to auditory stimuli) Signs of excitation at 300 mg/kg (e.g., twitch of the head, increased chewing movements, mild mydriasis)
	Wistar rats (pentylenetetrazole-induced seizures)	Oral	10, 30, 100, or 300 mg/kg (in combination with 15 mg/kg of RTV)	Male (20)	None
	Wistar rats (motor activity)	Oral	10, 30, 100, or 300 mg/kg (combined with 15 mg/kg of RTV)	Male (10)	None
	Wistar rats (ethanol-induced hypnosis)	Oral	10, 30, 100, or 300 mg/kg (in combination with 15 mg/kg of RTV)	Male (10)	None
	SD rats (FOB method)	Oral	50, 150, or 500 mg/kg (in combination with 15 mg/kg of RTV)	Female (8)	None
Cardio-vascular system	HEK-293 cells (hERG channel current)	*In vitro*	6.86 or 19.15 μg/mL	–	hERG current:7.5% inhibition at 6.86μg/mL and 17.7% inhibition at 19.15 μg/mL
			8.24 μg/mL	–	hERG current: 5.3% inhibition
	Beagle dogs (anesthetized)	Intravenous	7.2 mg/kg[a)]	Male (6)	Dose-independent QTcV prolongation (4-7 ms) at plasma concentration of ≥1.53 μg/mL
	Beagle dogs (telemetry)	Oral	10, 30, or 100 mg/kg	Male (6)	No effects up to 100 mg/kg (plasma concentration, 96.9 ± 22.5 μg/mL)
Respiratory system	SD rats (conscious)	Oral	50, 150, or 500 mg/kg (in combination with 15 mg/kg of RTV)	Male (8)	No effects up to 500 mg/kg (plasma concentration, 0.7 ± 0.08 μg/mL)
Gastro-intestinal system	SD rats (gastrointestinal propulsion)	Oral	30, 100, or 300 mg/kg	Male (8)	None
Other	Ferrets (emetic effect)	Oral	7.5, 25, or 75 mg/kg	Male (5-6)	Vomiting occurred in 1 of 6 animals at 75 mg/kg (plasma concentration, 8.15 ± 4.47 μg/mL)

a) Cumulative dose in this study only. PTV was administered at 0.017 mg/kg/min for the first 30 minutes, at 0.056 mg/kg/min from 30 to 60 minutes, and at 0.167 mg/kg/min from 60 to 90 minutes after the start of administration.

In rats, the maximum plasma concentration (C_{max}) after administration of PTV 100 mg/kg (in combination with 15 mg/kg of RTV), the dose at which a mild excitatory effect was observed, was 1.72 μg/mL,[22)] which was approximately 0.45-fold human exposure (C_{max} of PTV, 3.84 μg/mL).[23)] However, the applicant considers that these results are unlikely to be of clinical significance because similar

22) Because the Irwin study evaluating the effect on the central nervous system lacked a study population for toxicokinetics, the C_{max} was estimated based on the exposure obtained in the FOB study of the effect on the central nervous system.

23) Phase I study (M[redacted]-247) in which PTV/RTV/OBV was administered once daily to Japanese healthy adults to evaluate the steady-state pharmacokinetics of PTV and OBV

findings were also detected in vehicle-treated rats, the negative control group, and because no excitatory effects were observed in rats examined by the FOB method or in a series of toxicity and clinical studies. The PTV concentrations (6.86 and 19.15 μg/mL) at which hERG channel current was inhibited by 7.5% and 17.7% were approximately 1.8- and 5-fold human exposure,[23)] and that at which a slight prolongation was observed in QTcV intervals in anesthetized beagle dogs (1.53-65.72 μg/mL) was approximately 0.4- to 17.1-fold human exposure.[23)] Meanwhile, no effects were observed on electrocardiograms (ECG) or on cardiovascular organs in conscious dogs up to 96.9 μg/mL (approximately 25.2-fold human exposure[23)]).

3.(i).A.(4) Primary pharmacodynamics (OBV)

3.(i).A.(4).1) *In vitro* studies

(a) Antiviral activity in HCV replicon assay (4.2.1.1.9, 4.2.1.1.10)

Although the inhibitory activity of OBV against HCV NS5A was not evaluated, resistance mutations detected in HCV replicon cells cultured in the presence of OBV were observed at amino acid positions 24, 28, 30, 31, 58, or 93 only in NS5A domain 1 from any HCV genotype [see "3.(i).A.(4).1).(c) Resistant profiles"]. Taking the above results into account, the applicant explained that OBV inhibits the function of HCV NS5A by binding to NS5A domain 1.

The antiviral activity (EC_{50}) of OBV against HCV replicon cells and the effect of adding human plasma on the antiviral activity of OBV against the HCV replicon were evaluated in an HCV replicon assay (luciferase reporter gene assay) based on the HCV RNA replication in HCV replicon cells. The results are shown in Table 8.

Table 8. Antiviral activity of OBV in HCV replicon assay

HCV genotype (virus strain)	EC_{50} (pmol/L)
Genotype 1a (H77)	14
Genotype 1a (H77) + 40% human plasma	186
Genotype 1b (Con-1)	5.0
Genotype 1b (Con-1) + 40% human plasma	56
Genotype 2a (JFH-1)	0.8
Genotype 2a[a)]	12
Genotype 2b[a)]	4.3
Genotype 3a[a)]	19
Genotype 4a[a)]	1.7
Genotype 5a[a)]	3.2
Genotype 6a[a)]	366

Mean

a) Used HCV genotype 1b chimeric replicon cells containing amino-acid sequences in the NS5A domain substituted from samples of various genotypes.

The antiviral activity of OBV was studied using HCV genotype 1a (H77) and HCV genotype 1b (Con-1) replicon cell lines containing the NS5A domain derived from treatment-naïve patients with HCV genotype 1a and genotype 1b infection. The EC_{50} value against these HCV genotype 1a and genotype 1b replicon cells was 0.66 and 1.0 pmol/L, respectively. Cytotoxicity of OBV against replicon cell lines was evaluated in an MTT assay, and the median toxic dose (TD_{50}) was >32 μmol/L.

(b) Antiviral activity against HIV-1 and HBV (4.2.1.1.4)

The antiviral activity of OBV against HIV-1 and HBV was determined. The EC_{50} value against both viruses was >31.6 μmol/L.

(c) Resistance profiles (4.2.1.1.5, 4.2.1.1.9, 4.2.1.1.10)

Resistance mutations in the NS5A domain were studied in HCV replicon cell lines cultured in the presence of OBV. The results are shown in Table 9. The antiviral activity of OBV against replicon cell lines containing amino acid mutations observed in respective genotypes was also investigated. The results are shown in Table 10.

Table 9. Summary of OBV-resistant colony selection

HCV genotype	OBV concentration (Ratio to EC_{50})	Amino acid mutation[a)] (colony count)
Genotype 1a (H77)	10	M28V (10/23), Q30R (4/23), Y93C (4/23), Y93H (4/23)
	100	M28T (4/21), Q30R (4/21), Y93C (5/21), Y93H (5/21)
	1000	M28T (4/24), Q30R (8/24), Y93C (3/24), Y93H (9/24)
Genotype 1b (Con-1)	10	L31F (4/23), L31V (2/23), Y93H (12/23), L28M + Y93H (2/23)
	100	Y93H (9/23), R30Q + Y93H (7/23), P58A + Y93H (2/23)
	1000	L28T (2/8), Y93H (1/8), L28M + L31F (1/8), L28V + L31F (1/8), L31F + Y93H (2/8), L31V + Y93H (1/8)
Genotype 2a [b)]	50	T24A (8/15), F28S (4/15)
Genotype 2b [b)]	50	L28F (1/24), L31V (8/24), Y93H (13/24)

a) For HCV genotype 1a and 1b, the table shows mutations observed in at least 2 samples out of 20 to 25 samples for each genotype and concentration, in which amino sequences were analyzed. However, for HCV genotype 1b, all mutations observed in 8 samples obtained at a concentration 1,000-fold over the EC_{50} are presented. For HCV genotype 2a and 2b, all mutations observed are presented.

b) Used were HCV genotype 1b chimeric replicon cell lines containing amino-acid sequences in the NS5A domain from samples of HCV genotype 2a or 2b.

Table 10. Antiviral activity of OBV against wild-type and mutant replicon cells

HCV genotype	Mutation	EC_{50} (nmol/L)	EC_{90} (nmol/L)	Resistance [a)]	Replication (%)
Genotype 1a (H 77)	Wild-type	0.003	0.008	–	100
	M28T	24.4	71.7	8965	100
	M28V	0.2	0.6	58	87
	Q30R	2.2	22.6	800	60
	Y93C	4.6	31.7	1675	24
	Y93H	113	> 200	41,383	18
Genotype 1b (Con-1)	Wild-type	0.0008	0.002	–	100
	L28T	0.5	34.2	661	17
	R30Q	0.0003	0.0009	0.4	nd [b)]
	L31F	0.008	0.02	10	127
	L31M	0.0007	0.001	0.9	119
	L31V	0.007	0.03	8	86
	P58S	0.66	1.5	0.8	80
	Y93H	0.06	0.3	77	73
	L28M + Y93H	0.3	1.2	415	104
	R30Q + Y93H	0.2	0.7	284	60
	L31F + Y93H	8.1	63.7	10,272	35
	L31M + Y93H	0.1	0.6	142	11
	L31V + Y93H	9.7	46.8	12,328	24
	P58A + Y93H	0.97	–	810	11
	P58S + Y93H	1.1	5.5	1401	34
Genotype 2a [c, d)]	Wild-type	0.001	–	–	–
	T24A	0.05	–	38	–
	T24A (L31) [f)]	0.02	–	15	–
	F28S	–	–	4710 [i)]	–
Genotype 2b [c, e)]	Wild-type	0.0007	–	–	–
	L28F	0.003	–	47	–
	L28F (M31) [g)]	0.2	–	247	–
	L31V	0.4	–	511	–
	Y93H	nd [h)]	–	–	–

Mean; –, not evaluated

a) EC_{50} value against the mutant/EC_{50} value against the wild-type

b) Replication was not calculated because the sample was clinical isolates

c) Used HCV genotype 1b chimeric replicon cells containing amino-acid sequences in the NS5A domain from samples of HCV genotype 2a or 2b.

d) Replicon cells containing Met at position 31

e) Replicon cells containing Leu at position 31

f) Because polymorphism of Met and Leu was reported at position 31 in the HCV genotype 2a NS5A domain (Combet C et al., *Nucleic Acids Res.* 2007;35:D363-D366), replicon cells containing Leu at position 31 were used.

g) Because polymorphism of Met and Leu was reported at position 31 in the HCV genotype 2b NS5A domain (Combet C et al., *Nucleic Acids Res.* 2007;35:D363-D366), replicon cells containing Met at position 31 were used.

h) Not evaluated because of a low replication level

i) Resistance was evaluated using stable chimeric replicon cells because of a low replication level.

(d) Antiviral activities of OBV metabolites (4.2.1.1.11, 4.2.1.1.12)

The antiviral activities of OBV metabolites (m23, m29, m36, and m37) against replicon cell lines of each genotype were determined. The results are shown in Table 11.

Table 11. Antiviral activities of OBV metabolites in HCV replicon assay

	EC_{50} (nmol/L)	
	Genotype 1a (H77)	Genotype 1b (Con-1)
OBV	0.0023	0.0015
m23[a)]	201	119
m29[a)]	23,630	13,590
m36[a)]	22,790	12,720
m37[a)]	54,160	47,920

Mean
a) Measured once

3.(i).A.(5) Secondary pharmacodynamics (OBV)

3.(i).A.(5).1) Effects on receptors and ion channels (4.2.1.2.2, 4.2.1.2.3, 4.2.1.2.4, 4.2.1.2.5, 4.2.1.2.6, 4.2.1.2.7)

The inhibitory activities of OBV and its metabolites (m23, m29, and m36) against ligand binding to 80 different G-protein-coupled receptors and ion channels were determined. Addition of OBV, m23, m29, or m36 (≤10 μmol/L) exhibited no particular inhibitory effects on the ligand binding to any of these receptors or ion channels except that m23 inhibited the ligand binding to the chloride channel by 96% (IC_{50} value, 1.5 μmol/L).

3.(i).A.(6) Safety pharmacology (OBV) (Reference data 4.2.1.3.9, 4.2.1.3.10, reference data 4.2.1.3.11, 4.2.1.3.12, reference data 4.2.1.3.13, 4.2.1.3.14, 4.2.1.3.15, reference data 4.2.1.3.16)

In safety pharmacology studies, the effects of OBV on the central nervous system, cardiovascular system, respiratory system, gastrointestinal system, and other organs were investigated (Table 12).

Table 12. Outline of safety pharmacology studies of OBV

Organ evaluated	Study sample	Route of administration	Dose or concentration	Sex (n/group)	Noteworthy findings
Central nervous system	Wistar rats (motor activity)	Oral	0.3, 1, 3, 10, or 30 mg/kg	Male (10)	None
	ICR mice (FOB)	Oral	10, 40, or 120 mg/kg	Female (8)	None
Cardiovascular system	HEK-293 cells (hERG channel current)	*In vitro*	0.043 μg/mL	–	None
			4.56 μg/mL	–	Inhibition of hERG current, 14.3%
	Beagle dogs (anesthetized)	Intravenous	0.25 mg/kg[a)]	Male (6)	None
	Beagle dogs (telemetry)	Oral	2, 10, or 60 mg/kg	Male (6)	None
Respiratory system	ICR mice (conscious)	Oral	5, 20, or 60 mg/kg	Male (8)	None
Gastrointestinal system	SD rats (gastrointestinal propulsion)	Oral	1.5, 5, or 15 mg/kg	Male (6)	None
Other	Ferrets (emetic effect)	Oral	0.5, 1.5, 5, or 15 mg/kg	Male (6)	None

a) Cumulative dose in this study only. OBV was administered at 0.001 mg/kg/min for the first 30 minutes, at 0.002 mg/kg/min from 30 to 60 minutes, and at 0.006 mg/kg/min from 60 to 90 minutes after the start of administration.

The concentration of OBV 4.56 μg/mL, at which hERG current was inhibited by 14.3%, was approximately 30.4-fold the clinical exposure (C_{max} of OBV, 0.15 μg/mL).[23)]

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Antiviral activity of PTV and OBV against HCV

PMDA's view:

On the basis of the submitted data, PTV and OBV have promising antiviral activity against HCV. As suggested in the evaluation of the antiviral activity of PTV in combination with OBV against HCV replicon cells, the combined use of PTV and OBV is expected to exhibit additive or synergistic anti-HCV activity.

3.(i).B.(2) Resistance to PTV and OBV

The applicant's explanation on the resistance profiles of PTV and OBV on HCV genotypes 1a and 1b:
In vitro studies revealed that, in HCV genotypes 1a and 1b, mutations related to resistance to PTV occurred at amino acid positions 155, 156, or 168 in the HCV NS3 domain. These mutations are similar to those reported in other approved NS3/4A protease inhibitors: telaprevir, simeprevir sodium, asunaprevir, and vaniprevir.[15,16,17,18)] However, other mutations related to resistance to these drugs at amino acid positions 54, 55, and 170 did not reduce the antiviral activity of PTV [see "3.(i).A.(1).(d) Resistance profiles"].

In vitro studies also revealed that, in HCV genotypes 1a and 1b, mutations related to resistance to OBV occurred at amino acid positions 28, 30, 31, or 93 in the HCV NS5A domain. A single Y93H mutation and a compound L31V/Y93H mutation,[24)] which are related to resistance to daclatasvir hydrochloride, an HCV NS5A inhibitor approved in Japan, reduced the antiviral activity of OBV [see "3.(i).A.(4).(c) Resistance profiles"].

PMDA's view:

As shown by *in vitro* studies [see "3.(i).A.(1).(d) Resistance profiles" and "3.(i).A.(4).(c) Resistance profiles"], the antiviral activity of PTV, like those of drugs of the same class, is reduced by mutations at amino acid positions 155, 156, or 168. It was also shown that the antiviral activity of OBV is reduced by mutations at amino acid positions 28, 30, 31, or 93, and that a single Y93H mutation and a compound L31V/Y93H mutation confer cross-resistance to drugs in the same class. Furthermore, the resistance to PTV and OBV conferred by mutations at positions 56 and 168 and at positions 58 and 93, respectively, was found to be greater when these mutations were compounded than when they occurred as single mutations. The relationship between the occurrence of resistance mutations and the efficacy of PTV, RTV, and OBV used in combination, as shown by clinical studies, will be described in "4.(iii).B.(2) Efficacy." However, given the limited information available from clinical studies before filing of the application, and because the occurrence of any resistance mutations is considered to be potentially important information in terms of the efficacy of PTV, RTV, and OBV, it is desirable that post-marketing information from sources including the published literature on the resistance to these agents should also

24) DAKLINZA Tablets 60 mg [package insert] 2nd ed.; September, 2014

be sought, and any new findings should be promptly distributed to healthcare professionals in the clinical settings.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

Pharmacokinetics of PTV (radiolabeled or non-radiolabeled PTV) and OBV (radiolabeled or non-radiolabeled OBV) as a single agent or in combination with RTV was investigated in mice, rats, monkeys, and dogs. Concentrations of PTV, RTV, OBV, and their metabolites in biological samples were determined by liquid chromatography/tandem mass spectrometry.[25)] Radioactivity levels in biological samples were determined by liquid scintillation counter and those in tissues by whole-body autoradiography.[26)] For oral administration of PTV, a lipid-based vehicle (Cremophor EL/PEG-400/oleic acid [weight ratio, 10:10:80]) was used. For oral administration of OBV, a lipid- and surfactant-based vehicle (a solution of PEG-400, Tween 80, poloxamer 124, and d-alpha-tocopherol polyethylene glycol succinate [weight ratio, 50:20:10:20] or a solution of PEG-400, Tween 20, and poloxamer 124 [volume ratio, 70:20:10]) was used.

3.(ii).A.(1) Absorption (PTV; 4.2.2.2-2, 4.2.2.2-3, 4.2.2.6-8, 4.2.3.2-9, 4.2.3.2-14, 4.2.3.5.2-5)

The apparent membrane permeability (P_{app}) of PTV was determined using Caco-2 cell membranes. The results showed that the P_{app} of PTV at concentrations ranging from 0.1 to 10 μmol/L was 6.7×10^{-6} to 9.8×10^{-6} cm/sec.

Table 13 shows the pharmacokinetic parameters in rats, monkeys, and dogs after a single intravenous dose of PTV, and Table 14 shows those after a single oral dose of PTV as a single agent or in combination with RTV. Coadministration of RTV increased the PTV exposure in plasma.

25) Lower limit of quantitation was as follows:
- PTV: approximately 10 or 20.1 ng/mL for mice; approximately 10, 19.3, 19.5, or 19.7 ng/mL for rats; approximately 10 or 19.3 ng/mL for dogs; and approximately 10 ng/mL for rabbits and monkeys
- RTV: 2.04 ng/mL for mice; 2.02, 2.06, or 2.12 ng/mL for rats; and 2.04 or 2.06 ng/mL for dogs
- OBV: approximately 1 or 4.49 ng/mL for mice; approximately 1 or 4.73 ng/mL for rats and rabbits; and approximately 1 or 27.6 ng/mL for dogs
- m29 (a metabolite of OBV): 5.08 ng/mL for mice
- m36 (a metabolite of OBV): 5.02 ng/mL for mice

26) Lower limit of quantitation was as follows:
- PTV-derived radioactivity, 278 or 311 ng·eq./g
- OBV-derived radioactivity, 49.2 ng·eq./g

Table 13. Pharmacokinetic parameters after a single intravenous dose of PTV

Animal species	Dose (mg/kg)	Sex (n)	$t_{1/2}$ (h)[a)]	V_{ss} (L/kg)	CL_p (L/h·kg)	$AUC_{0-\infty}$ (μg·h/mL)
Rat	5	Male (3)	0.4	0.98 ± 0.50	3.0 ± 1.1	1.88 ± 0.83
Monkey	2.5	Female (3)	0.4	0.52 ± 0.25	1.93 ± 0.50	1.36 ± 0.40
Dog	2.5	Male and female (3 in total)	1.2	0.15 ± 0.02	0.11 ± 0.01	22.8 ± 1.71

Mean ± standard deviation
$t_{1/2}$, half-life; V_{ss}, volume of distribution; CLp, plasma clearance; $AUC_{0-\infty}$, area under the plasma concentration-time curve from zero to infinity
a) Harmonic mean

Table 14. Pharmacokinetic parameters after a single oral dose of PTV as a single agent or in combination with RTV

Animal species	Dose (mg/kg)		Sex (n)	Target agent	$t_{1/2}$ (h)[a)]	C_{max} (μg/mL)	T_{max} (h)	$AUC_{0-\infty}$ (μg·h/mL)	F (%)[b)]
	PTV	RTV							
Rat	5	0	Male (3)	PTV	–	0	–	0	0
	5	5	Male (3)	PTV	–	0.03 ± 0.04	1.3 ± 2.3	0.14 ± 0.24	NA
				RTV	1.6	0.04 ± 0.01	7.3 ± 2.9	0.32 ± 0.06	NA
Monkey	10	0	Female (3)	PTV	–	0	–	0	0
	10	10	Female (3)	PTV	1.8	0.05 ± 0.05	3.0 ± 1.4	0.27 ± 0.23	NA
				RTV	1.8	0.02 ± 0.02	3.5 ± 0.7	0.11 ± 0.11	NA
Dog	5	0	Male and female (3 in total)	PTV	0.9	6.32 ± 1.81	3.3 ± 0.6	18.7 ± 1.6	40.9 ± 3.4
	5	5	Male and female (3 in total)	PTV	1.8	22.7 ± 1.36	3.7 ± 0.6	84.8 ± 14.1	NA
				RTV	0.7	3.7 ± 0.6	3.7 ± 0.6	9.1 ± 2.6	NA

Mean ± standard deviation; –, not measurable; C_{max}, maximum concentration; T_{max}, time to maximum concentration; F, bioavailability; NA, not available;
a) Harmonic mean
b) Calculated using $AUC_{0-\infty}$ after an oral or intravenous dose ($AUC_{0-\infty}$ in monkeys and dogs after an oral dose was obtained based on that after administration at 2.5 mg/kg).

Table 15 shows the pharmacokinetic parameters of PTV and RTV administered orally to mice, rats, rabbits, and dogs once-daily in the repeated-dose toxicity studies. In mice and rats, there were no clear gender-related differences in exposure to PTV or RTV. In dogs, gender-related differences were observed in exposure to PTV, though with no consistency among dose groups. While PTV or RTV exposure in mice increased after repeated doses compared with Day 1, no accumulation of PTV or RTV occurred in any other animal species examined and the exposure tended to decrease with repeated doses.

Table 15. Pharmacokinetics of PTV and RTV during repeated oral administration of PTV or RTV

Animal species	Dose (mg/kg/day)		Sex (n)	Day of administration	C_{max} (μg/mL)		AUC_{0-24h} (μg·h/mL)	
	PTV	RTV			PTV	RTV	PTV	RTV
Mouse	30	30	M and F (3/sex)	Day 1	3.74 ± 2.67	5.18 ± 2.39	14.6	20.5
				Day 90	6.36 ± 5.64	5.88 ± 4.89	21.8	24.4
	100	30	M and F (3/sex)	Day 1	27.5 ± 19.7	3.12 ± 1.82	173	21.7
				Day 90	36.2 ± 17.0	4.11 ± 1.41	231	23.4
	300	30	M and F (3/sex)	Day 1	46.3 ± 17.0	1.86 ± 1.07	374	12.4
				Day 90	65.2 ± 36.4	3.49 ± 1.75	417	22.5
Rat	100	15	M and F (10/sex)	Day 1	9.43 ± 5.37	0.573 ± 0.297	62.9 ± 36.8	5.82 ± 3.61
				Day 87	12.2 ± 8.11	1.83 ± 0.553	73.9 ± 53.0	15.0 ± 4.53
	300	30	M and F (10/sex)	Day 1	11.8 ± 8.43	1.09 ± 0.35	93.0 ± 70.2	14.7 ± 6.20
				Day 87	17.9 ± 10.3	3.67 ± 0.862	104 ± 45.3	43.8 ± 10.2
	450	45	M and F (10/sex)	Day 1	12.3 ± 6.90	1.09 ± 0.413	91.5 ± 42.3	15.9 ± 6.15
				Day 87	17.8 ± 13.3	4.53 ± 0.827	91.1 ± 52.7	57.9 ± 12.9
Rabbit	100	100	F (4)	Day 7	0.248 ± 0.116	0.288 ± 0.218	1.6 ± 0.53	1.85 ± 1.42
				Day 19	0.140 ± 0.0751	2.05 ± 2.52	0.56 ± 0.25	11.7 ± 14.3
	200	200	F (4)	Day 7	2.54 ± 3.84	2.00 ± 1.58	13.6 ± 19.7	24.9 ± 19.8
				Day 19	0.166 ± 0.128	2.57 ± 1.49	0.98 ± 0.24	25.3 ± 19.9
	400	400	F (4)	Day 7	3.73 ± 4.05	3.99 ± 2.15	39.1 ± 48.5	57.2 ± 37.2
				Day 19	0.333 ± 0.325	2.16 ± 1.05	2.39 ± 2.25	21.3 ± 7.76
Dog	5	5	M and F (3/sex)	Day 1	17.8 ± 10.8	2.64 ± 2.34	70.6 ± 38.6	7.69 ± 6.58
				Day 91	10.1 ± 6.14	2.23 ± 2.54	44.0 ± 25.9	6.81 ± 7.13
	10	5	M and F (3/sex)	Day 1	49.0 ± 16.0	3.51 ± 1.78	252 ± 92.4	10.3 ± 5.56
				Day 91	42.2 ± 22.3	3.96 ± 1.97	206 ± 114	12.7 ± 7.28
	20	10	M and F (3/sex)	Day 1	92.8 ± 16.6	9.66 ± 3.91	632 ± 186	34.6 ± 16.4
				Day 91	89.3 ± 24.1	10.9 ± 4.85	650 ± 314	43.3 ± 21.0
	40[a)]	20[a)]	M and F (3/sex)	Day 1	80.6 ± 10.9	7.44 ± 3.48	467 ± 93.1[b)]	24.2 ± 10.2[b)]
				Day 91	75.1 ± 40.9	5.51 ± 4.31	466 ± 292[b)]	20.4 ± 16.8[b)]

Mean ± standard deviation, or mean; M, male; F, female
a) PTV 20 mg/kg or RTV 10 mg/kg was administered twice daily with an interval of 12 hours.
b) AUC_{0-12h}

3.(ii).A.(2) Distribution (PTV)

3.(ii).A.(2).1) Plasma protein binding and distribution in red blood cells (4.2.2.3-1, 4.2.2.3-4)

The plasma protein unbound fraction of PTV (1 μmol/L) in the plasma of mice, rats, dogs, monkeys, and humans was 0.54%, 0.75%, 0.097%, 1.0%, and 1.7%, respectively, showing no dose-dependent changes within a range from 0.1 to 10 μmol/L.

The blood-to-plasma concentration ratio of PTV (1 μmol/L) in dogs, humans, monkeys, and rats was 0.58, 0.68, 0.85, and 1.0, respectively.

3.(ii).A.(2).2) Tissue distribution (4.2.2.3-5)

The radioactivity levels in tissues of rats (pigmented, male, n = 1/time point) were determined after a single oral dose of ^{14}C-PTV 30 mg/kg in combination with RTV 15 mg/kg. C_{max} was observed at 4 hours post-dose in most tissues. The radioactivity level was highest in the liver among all tissues at 0.5 to 48 hours post-dose.[27)] The radioactivity level fell below the lower limit of quantitation (LLOQ) (278 ng·eq./g) by 24 hours post-dose in all tissues other than the cecum, liver, small intestine, and bladder,

27) 154,000 ng·eq./g at 4 hours post-dose

and by 96 hours post-dose in those tissues. Distribution was similar between the melanin-containing and melanin-free cells in the same tissue.

3.(ii).A.(2).3) Placental transfer (4.2.2.3-6)

The radioactivity levels in tissues in maternal animals and fetuses were determined after a single oral dose of ^{14}C-PTV 30 mg/kg in combination with RTV 15 mg/kg to pregnant rats on gestation day 18 (n = 1/time point). In fetuses, a negligible level of radioactivity was detected in the liver at 8 and 12 hours post-dose (626 and 827 ng·eq./g, respectively) but not in any other tissues or in the amniotic fluid. Radioactivity in maternal animals reached C_{max} at 2 hours post-dose and was detected until 8 hours post-dose in the uterus and mammary gland, and until 24 hours post-dose in the amniotic sac and placenta. The radioactivity level in any tissue decreased to below the LLOQ (311 ng·eq./g) by 72 hours post-dose.

3.(ii).A.(3) Metabolism (PTV)[28)]

3.(ii).A.(3).1) *In vivo* metabolism (4.2.2.2-7, 4.2.2.2-8, 4.2.2.4-3 to 9)

After repeated oral administration of PTV 300 mg/kg to mice (male, n = 18), unchanged PTV, M1, M2, M3, M5, and M6 were identified in plasma. Following repeated oral administration of PTV 300 mg/kg in combination with RTV 30 mg/kg to mice (male, n = 42), unchanged PTV, M1, M2, M3, M8, and M12 were identified in plasma.

After a single oral dose of ^{3}H-PTV 20 mg/kg to rats (male, n = 3), unchanged PTV and M1 were identified in plasma. After a single oral dose of ^{14}C-PTV 30 mg/kg in combination with RTV 15 mg/kg to rats with biliary cannulation (male, n = 2), the following were identified: unchanged PTV, M1, M2, M3, M13, and M29 in bile; M13 in urine; and unchanged PTV, M29, and M13 in feces.

After a single oral dose of ^{14}C-PTV 1 mg/kg in combination with RTV 5 mg/kg to dogs (male; n = 3), the following were identified: unchanged PTV and M13 in plasma; M13 in urine; and unchanged PTV, M1, M2, M13, and M29 in feces.

After a single oral dose of ^{14}C-PTV 200 mg in combination with RTV 100 mg to healthy men (n = 4), the following were identified: unchanged PTV, M2, M3, M6, M13, and M29 in plasma; unchanged PTV, M2, and M13 in urine; and unchanged PTV, M2, M3, M6, M13, M14, M17, M22, M24, and M29 in feces.

Based on the above results, the metabolic pathways of PTV were deduced from metabolites identified in the plasma of mice, rats, dogs, and humans as shown in Figure 1.

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28) The metabolites presented in this section are as follows:
M1, M2, M6, and M8, monohydroxides; M3 and M12, dihydroxides; M4, glutathione conjugate of an oxide; M5, M9, M10, and M17, dioxides; M11, hydrated oxide; M13, methylpyrazine-2- carboxylic acid; M14, monoxide of M29 (acetylcyclopropane-sulfonamide hydrolysate); M22, unknown metabolite; M29, acetylcyclopropane-sulfonamide hydrolysate

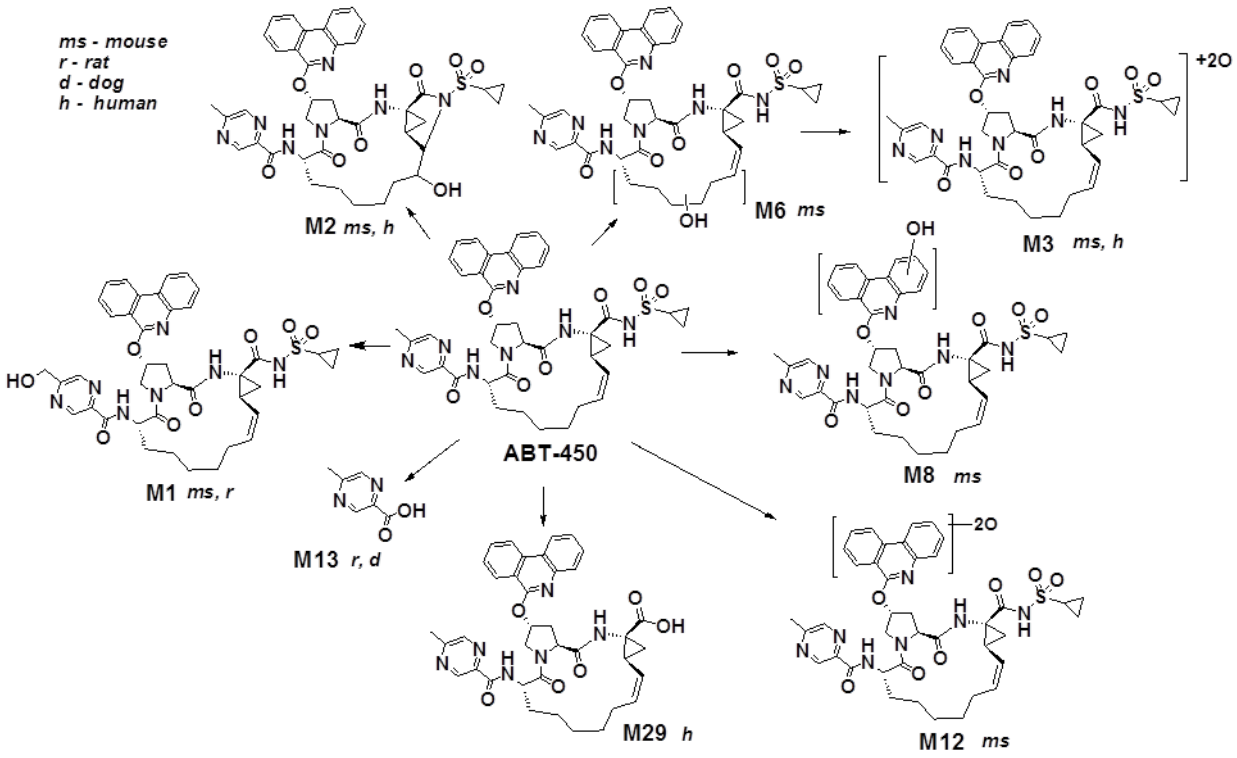

Figure 1. Possible metabolic pathways of PTV (ABT-450) in the plasma of various animal species and humans

3.(ii).A.(3).2) *In vitro* metabolism (4.2.2.4-1, 4.2.2.4-2)

The intrinsic clearance of PTV was determined using liver microsomes and hepatocytes in rats, dogs, monkeys, and humans. The intrinsic clearance in liver microsomes in rats, dogs, monkeys, and humans was 50, 31, 94, and 88 μL/min/mg tissue, respectively, and that in hepatocytes was 8.2×10^{-6}, 3.2×10^{-6}, 22.1×10^{-6}, and 19.3×10^{-6} μL/min/cells, respectively, which were all higher in monkeys and humans than in rats and dogs. The following metabolites were identified in hepatocytes: M1 to M7 and M10 in rats; M1 to M4 and M6 in dogs; M1 to M7 and M9 to M11 in monkeys; and M1 to M4, M6, and M9 in humans.

Evaluation of the metabolism of PTV in the human cytochrome P450 (CYP) expression system[29)] suggested that CYP3A4/5 is mainly involved in the metabolism of PTV. When the enzymatic reaction rates were examined using the expression systems of human CYP3A4 and CYP3A5, the Michaelis constant (K_m) was 6.1 and 23.3 μmol/L, respectively, and the maximum velocity (V_{max}) was 15.7 and 13.2 mol/min per 1 mol of CYP, indicating that CYP3A4 is the main metabolic enzyme of PTV.

3.(ii).A.(4) Excretion (PTV)

3.(ii).A.(4).1) Excretion in bile, urine, and feces (4.2.2.2-7, 4.2.2.2-8, 4.2.2.4-5)

After a single oral dose of ^{3}H-PTV 20 mg/kg to rats with biliary cannulation (male; n = 2), the cumulative excretion of radioactivity in bile, feces, and urine up to 48 hours post-dose was 15.3%, 100%, and 0.1%,

29) CYP1A1, CYP 1A2, CYP 2A6, CYP 2B6, CYP 2C8, CYP 2C9*1, CYP 2C18, CYP 2C19, CYP 2D6*1, CYP 3A4, and CYP 3A5

respectively, of the administered radioactivity. Similarly, after a single oral dose of ^{14}C-PTV 30 mg/kg in combination with RTV 15 mg/kg, the cumulative excretion of radioactivity in bile, feces, and urine up to 72 hours post-dose was 50.6%, 39.9%, and 0.6%, respectively.

After a single oral dose of ^{14}C-PTV 1 mg/kg in combination with RTV 5 mg/kg to dogs (male, n = 3), the cumulative excretion of radioactivity in feces and urine up to 72 hours post-dose was 87.7% and 5.7%, respectively, of the administered radioactivity.

3.(ii).A.(4).2) Excretion in milk (4.2.2.3-6, 4.2.2.4-4)

After a single oral dose of ^{14}C-PTV 30 mg/kg in combination with RTV 15 mg/kg to rats on postpartum Day 10 to Day 12 (n = 3/time point), radioactivity was detected in milk up to 24 hours post-dose, and the C_{max}, $AUC_{0-\infty}$, and $t_{1/2}$ were 693 ng·eq./g, 5200 ng·eq·h/g, and 11.9 hours, respectively. The mean milk-to-plasma radioactivity ratio in individual animals was 0.173 (at 0.5 hour post-dose) to 1.86 (at 24 hours post-dose), showing an increase over time. The radioactivity excreted in milk consisted of M13 (84.1% of radioactivity in milk) and unchanged PTV (15.9%).

3.(ii).A.(5) Pharmacokinetic drug interactions (PTV)

3.(ii).A.(5).1) Enzyme inhibition and induction (4.2.2.4-1, 4.2.2.6-1 to 4)

Human liver microsomes were used to evaluate the inhibitory effects of PTV on CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) and UDP-glucuronosyltransferase (UGT) 1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7. The results suggested that PTV inhibits the activities of CYP2C8, UGT1A1, UGT1A4, and UGT1A6 with the 50% inhibitory concentration (IC_{50}) values of 13, 3.6, 6.81, and 46.7 μmol/L, respectively. PTV showed no inhibitory effects on CYP isoforms other than CYP2C8 (IC_{50} >30 μmol/L).

Human hepatocytes were used to evaluate the induction effects of PTV (0.5-10 μmol/L) on CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) were evaluated. The results suggested that PTV has a slight induction effect on CYP3A4.[30)]

3.(ii).A.(5).2) Substrate of drug transporters and inhibitory effects (4.2.2.7.1, 4.2.2.6-5 to 7, 4.2.2.6-9 to 15)

Human embryonic kidney (HEK) cells expressing organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3 were used to examine the uptake of PTV mediated by these transporters. The results suggested that PTV is a substrate of OATP1B1 and OATP1B3 with K_m values of 0.18 and 0.089 μmol/L, respectively.

30) In the presence of 10 μmol/L of PTV, the mRNA level of CYP3A4 was increased by 15%. This mRNA induction rate of PTV (10 μmol/L) was 31% of that of the positive control (rifampicin 10 μmol/L).

The efflux ratio[31)] of ^{14}C-PTV in Madin-Darby canine kidney strains II (MDCK-II) expressing multidrug resistance protein (MDR) 1 and breast cancer resistance protein (BCRP) was 13.1 and 5.0, respectively. The AUC[32)] of PTV in the plasma and liver after an intravenous dose of PTV 0.1 mg/kg to Mdrl/Bcrp knockout mice increased to 3- and 2.1-fold, respectively, those of wild-type mice. These results suggested that PTV is a substrate of P-glycoprotein (P-gp) (MDR1) and BCRP.[33)]

Cells expressing OATP1B1, OATP1B3, OATP2B1, organic cation transporter (OCT) 1, OCT2, organic anion transporter (OAT) 1, OAT3, organic cation/H^+ exchange transporter (MATE) 1, MATE2K, P-gp (MDR1), BCRP, multidrug resistance-associated protein (MRP) 2, and bile salt export pump (BSEP) were used to evaluate the inhibitory effects of PTV on human drug transporters. Taking into account the IC_{50} values against the transporters and plasma PTV concentrations (C_{max}, 3840 ng/mL[34)]) obtained in a clinical study, the applicant explained that PTV may have an inhibitory effect on OATP1B1, OATP1B3, OATP2B1, P-gp (MDR1), BCRP, MRP2, and BSEP.[35,36)]

3.(ii).A.(6) Absorption (OBV; 4.2.2.2-16, 4.2.2.2-17, 4.2.2.6-35)

The P_{app} of OBV was determined by using MDCK cell membranes. The results showed that the P_{app} of OBV at 1 μmol/L was 0.9×10^{-6} and 3.3×10^{-6} cm/sec.[37)]

Table 16 shows the pharmacokinetic parameters in mice, rats, monkeys, and dogs after a single intravenous dose of OBV, and Table 17 shows those after a single oral dose of OBV.

31) Defined as the ratio of the permeation coefficient in the basolateral membrane–apical membrane direction to the permeation coefficient in the apical membrane– basolateral membrane direction

32) PTV in plasma, $AUC_{0-\infty}$; PTV in the liver, AUC_{0-24h}

33) The AUCs of PTV in the plasma and liver in Mdrl- or Bcrp-knockout mice were similar to those in wild-type mice. The applicant interpreted this result as suggesting the involvement of compensatory transporters for P-gp and BCRP.

34) The C_{max} value was obtained in the phase I study (M[redacted]-247), i.e., PTV/RTV/OBV 150, 100, and 25 mg administered once daily to healthy Japanese adult subjects, conducted to evaluate the steady-state pharmacokinetics of PTV and OBV.

35) Discussed based on Food and Drug Administration *Guidance for Industry: Drug Interaction Studies–Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Draft Guidance*, 2012. US Dept of Health and Human Services

36) When 30 μmol/L of PTV was added, OCT1, OCT2, and MATE1 were inhibited by <20%, <10%, and <20%, respectively. On the basis of these results, it was assumed in a discussion that the IC_{50} value of PTV against any of them was >30 μmol/L.

37) Values obtained from 2 measurements

Table 16. Pharmacokinetic parameters after a single intravenous dose of OBV

Animal species	Dose (mg/kg)	Sex (n)	$t_{1/2}$ (h)[a)]	V_{ss} (L/kg)	CL_p (L/h·kg)	$AUC_{0-\infty}$ (μg·h/mL)
Mouse	3	Male (6)	11.1	1.7	0.11	26.4
Rat	3	Male (6)	11.4	4.8 ± 1.6	0.46 ± 0.22	8.07 ± 3.90
Monkey	1	Female (3)	4.4	1.5 ± 0.3	0.38 ± 0.07	2.72 ± 0.51
Dog	1	Male and female (3 in total)	7.9	1.8 ± 0.2	0.18 ± 0.01	5.58 ± 0.40

Mean ± standard deviation
a) Harmonic mean

Table 17. Pharmacokinetic parameters after a single oral dose of OBV

Animal species	Dose (mg/kg)	Sex (n)	$t_{1/2}$ (h)[a)]	C_{max} (μg/mL)	T_{max} (h)	$AUC_{0-\infty}$ (μg·h/mL)	F (%)[b)]
Mouse	3	Male (6)	11.1	0.38 ± 0.15	6.0	7.65	29.0
Rat	3	Male (3)	12.1	0.12 ± 0.06	6.0 ± 0.6	2.00 ± 0.39	24.8 ± 4.8
Monkey	2.5	Female (3)	5.0	0.29 ± 0.10	3.3 ± 0.6	2.40 ± 1.13	35.3 ± 16.5
Dog	2.5	Male and female (3 in total)	7.3	0.64 ± 0.08	3.3 ± 1.2	8.00 ± 1.44	57.3 ± 10.3

Mean ± standard deviation
a) Harmonic mean
b) Calculated using $AUC_{0-\infty}$ after an oral or intravenous dose ($AUC_{0-\infty}$ values in monkeys and dogs after oral administration were converted to their equivalent values at OBV 1 mg/kg).

Table 18 shows the pharmacokinetic parameters in rats, monkeys, and dogs after a single oral dose of OBV as a single agent or in combination with RTV. The OBV exposure in plasma after administration of OBV as a single agent was similar to that after administration of OBV in combination with RTV.

Table 18. Pharmacokinetic parameters after a single oral dose of OBV with or without RTV coadministration

Animal species	Dose (mg/kg/day)		Sex (n)	$t_{1/2}$ (h)[a)]	C_{max} (μg/mL)	T_{max} (h)	AUC (μg·h/mL)
	OBV	RTV					
Rat	3	0	Male (3)	9.3	0.12 ± 0.04	3.7± 0.6	1.56 ± 0.37
	3	10	Male (3)	7.7	0.08 ± 0.03	5.7 ± 2.9	1.55 ± 0.58
Monkey	2.5	0	Female (3)	2.7	0.14 ± 0.03	6.0 ± 0.0	0.88 ± 0.35
	2.5	10	Female (3)	3.7	0.18 ± 0.09	6.0 ± 0.0	1.63 ± 0.95
Dog	2.5	0	Male and female (3 in total)	6.6	0.50 ± 0.37	4.3 ± 1.5	4.37 ± 2.24
	2.5	10	Male and female (3 in total)	5.5	0.47 ± 0.27	3.7 ± 0.6	4.73 ± 2.79

Mean ± standard deviation
a) Harmonic mean

Table 19 shows the pharmacokinetics of OBV in mice during repeated oral administration once daily, and Table 20 shows those in rats, rabbits, and dogs receiving the same dosage. No gender-related differences were observed in rats or in dogs. While OBV exposure increased in rats and dogs after repeated doses from that on Day 1, no accumulation of OBV was observed in mice or rabbits.

Table 19. Pharmacokinetic parameters of OBV in mice during repeated oral administration

Sex	Dose (mg/kg)	n	Day of administration	C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL)
Male	1	3	Day 1	0.075 ± 0.013	1.12 (0.05)
			Day 25	0.089 ± 0.049	1.15 (0.11)
	5	3	Day 1	0.349 ± 0.043	5.93 (0.24)
			Day 25	0.476 ± 0.097	7.64 (0.60)
	20	3	Day 1	1.64 ± 0.98	26.2 (1.94)
			Day 25	2.16 ± 0.23	33.8 (4.3)
	60	3	Day 1	5.48 ± 2.02	80.5 (5.42)
			Day 25	6.33 ± 1.61	103 (6.97)
Female	2	3	Day 1	0.149 ± 0.041	1.74 (0.12)
			Day 25	0.0896 ± 0.022	1.48 (0.14)
	10	3	Day 1	0.809 ± 0.18	9.77 (0.65)
			Day 25	0.551 ± 0.070	9.02 (0.77)
	40	3	Day 1	2.56 ± 0.41	40.1 (1.77)
			Day 25	2.43 ± 0.70	32.6 (2.53)
	120	3	Day 1	5.42 ± 1.04	80.3 (6.75)
			Day 25	4.51 ± 1.64	67.4 (5.12)

Mean ± standard deviation, or mean (standard error)

Table 20. Pharmacokinetic parameters of OBV during repeated oral administration

Animal species	Dose (mg/kg)	Sex (n)	Day of administration	C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL)
Rat	2.5	Male and female (6/sex)	Day 1	0.090 ± 0.024	0.829 (0.046)
			Day 14	0.15 ± 0.038	1.42 (0.13)
	5	Male and female (6/sex)	Day 1	0.18 ± 0.034	1.65 (0.075)
			Day 14	0.25 ± 0.058	2.60 (0.20)
	15	Male and female (6/sex)	Day 1	0.58 ± 0.074	5.62 (0.29)
			Day 14	0.79 ± 0.21	8.00 (0.74)
	30	Male and female (6/sex)	Day 1	0.77 ± 0.16	9.94 (0.96)
			Day 14	1.11 ± 0.36	16.0 (0.64)
Rabbit	10	Female (2)	Day 7	0.38 ± 0.053	3.42 ± 0.58
			Day 19	0.39 ± 0.074	3.29 ± 0.93
	60	Female (2)	Day 7	0.67 ± 0.28	7.92 ± 5.00
			Day 19	0.81 ± 0.27	10.0 ± 8.20
	200	Female (2)	Day 7	0.52 ± 0.15	5.41 ± 1.34
			Day 19	0.59 ± 0.21	5.15 ± 1.71
Dog	4	Male and female (4/sex)	Day 1	0.38 ± 0.12	4.24 ± 1.45
			Day 189	0.60 ± 0.12	7.23 ± 1.72
	20	Male and female (4/sex)	Day 1	2.21 ± 0.44	27.3 ± 5.87
			Day 189	3.46 ± 0.59	46.8 ± 12.2
	100	Male and female (4/sex)	Day 1	2.57 ± 1.01	39.5 ± 16.0
			Day 189	5.18 ± 1.47	83.3 ± 21.3

Mean ± standard deviation, or mean (standard error)

3.(ii).A.(7) Distribution (OBV)

3.(ii).A.(7).1) Plasma protein binding and distribution in red blood cells (4.2.2.3-7 to 9, 4.2.2.3-2, 4.2.2.3-3)

The plasma protein unbound fraction of OBV (1 μmol/L) in the plasma of mice, rats, rabbits, dogs, monkeys, and humans was 0.018%, 0.037%, <0.014%, 0.034%, 0.036%, and 0.021%, respectively, showing no dose-dependent changes within a range from 0.1 to 10 μmol/L. The plasma protein unbound

fraction of m29 and m36, the main human-specific metabolites [see "3.(ii).A.(8) Metabolism (OBV)"], was 0.21% to 1.6% and 0.40% to 2.3%, respectively, within a range from 0.1 to 10 μmol/L.

The blood-to-plasma concentration ratio of OBV in the range from 0.008 to 0.400 μg/mL (0.008 to 0.41 μg/mL) in rats, dogs, monkeys, and humans ranged from 0.44 to 0.79, showing no dose-dependent changes in any species.

3.(ii).A.(7).2) Tissue distribution (4.2.2.3-10)

The radioactivity levels in tissues of rats (pigmented, male, n = 1/time point) were determined after a single oral dose of ^{14}C-OBV 5 mg/kg. C_{max} was observed at 4 to 8 hours post-dose in all tissues. Radioactivity levels were high in the adrenal gland, liver, pancreas, renal cortex, and gastric mucosa.[38)] The radioactivity level fell below the LLOQ (49.2 ng·eq./g) in all tissues by 168 hours post-dose. Distributions in the melanin-containing portions and in melanin-free portions were similar in the same tissue.

3.(ii).A.(7).3) Placental transfer (4.2.2.3-11)

The radioactivity levels in tissues in maternal animals and fetuses were determined after a single oral dose of ^{14}C-OBV 5 mg/kg to pregnant rats on gestation day 18 (n = 1/time point). In fetuses, a negligible level of radioactivity was detected in the liver at 8 and 12 hours post-dose (52.5 and 62.4 ng·eq./g, respectively) but not in any other tissues or in the amniotic fluid. Radioactivity in maternal animals reached C_{max} at 4, 8, or 12 hours post-dose in most tissues, and was detected until 24 hours post-dose in the amniotic sac, placenta, and uterus and until 48 hours post-dose in the mammary gland. The radioactivity level in all tissues decreased to below the LLOQ (49.2 ng·eq./g) by 72 hours post-dose.

3.(ii).A.(8) Metabolism (OBV)[39)]

3.(ii).A.(8).1) *In vivo* metabolism (4.2.1.1-11, 4.2.1.1-12, 4.2.1.2-3 to 5, 4.2.2.2-20, 4.2.2.3-8, 4.2.2.4-14, 4.2.2.4-15, 4.2.2.4-17, 4.2.2.4-18, 4.2.2.4-20, 4.2.2.4-21, 4.2.2.4-23 to 26)

After a single oral dose of OBV 200 mg/kg was given to mice (male, n = 10/time point), unchanged OBV, m1, m2, m3, m6, m7, m23, m24, m26, and m30 were identified in plasma.

38) Radioactivity levels were as follows: 9200 ng·eq./g in the adrenal gland (at 4 hours post-dose), 4850 ng·eq./g in the liver (at 4 hours post-dose), 2710 ng·eq./g in the pancreas (at 8 hours post-dose), 2530 ng·eq./g in the renal cortex (at 4 hours post-dose), and 2390 ng·eq./g in the gastric mucosa (at 4 hours post-dose).

39) The metabolites presented in this section are as follows:
m1 to m5, monoxides; m6, monoanilide; m7, pyrrolidine carboxylic acid; m9, hydrate; m10, dehydrogenated oxide; m11, dehydrogenate; m13, dehydrogenate of m6; m15, diacetamide of m23; m16, t-butylhydroxy N-acetyl monoanilide; m18, t-butyryl diacetamide; m19, t-butylhydroxyacetamide, m21, t-butyl-O-glucuronate conjugate of m15; m22, t-butyryl glucuronate conjugate of m15; m23, dianilide; m24, monoacetamide of m23; m26, t-butylhydroxy dianilide; m29, acetophenone dianilide; m30, dehydrogenate of m23; m36, t-butyl demethylketo-hydroxy dianilide; m37, t-butyl dimethyl dihydroxy dianilide; m38, oxidized anilide (monoxide of m23)

After a single oral dose of ^{14}C-OBV 30 mg/kg was given to rats (n = 3/sex), unchanged OBV, m19, m23, and m24 were identified in plasma. After repeated oral doses of ^{14}C-OBV 30 mg/kg were given to rats (n = 6/sex), unchanged OBV, m1, m2, m6, m7, m9, m15, m18/m19, m23, m24, m26, and m30 were identified in plasma. After a single oral dose of ^{3}H-OBV 3 mg/kg was given to rats with biliary cannulation (male, n = 3), unchanged OBV, m3, m16, m18/m19, m21/m22,[40)] and an unknown metabolite were identified in bile and m7 in urine.

After a single oral dose of OBV 60 mg/kg was given to rabbits (female, n = 3), unchanged OBV, m6, m7, m9, m23, m24, m26, m30, m32, and m38 were identified in plasma.

After a single oral dose of ^{14}C-OBV 1 mg/kg was given to dogs (male, n = 2), the following metabolites were identified: unchanged OBV, m23, m26, and m30 in plasma; unchanged OBV, m9, and an unknown metabolite in feces; and an unknown metabolite in urine. After repeated oral doses of ^{14}C-OBV 100 mg/kg were given to dogs (female, n = 3), unchanged OBV, m6, m7, m9, m23, m26, and m30 were identified in plasma.

After a single oral dose of ^{14}C-OBV 25 mg was administered to healthy men (n = 4), the following metabolites were identified: unchanged OBV, m23, m25, m26, m29, m36, and m37 in plasma; unchanged OBV, m2, m3, m5, m6, and m9 in feces; and unchanged OBV and multiple unknown metabolites in urine.

Based on the above results, metabolic pathways of OBV deduced from metabolites identified in the plasma of mice, rats, dogs, and humans are as shown in Figure 2.

40) m18 and m19 as well as m21 and m22 coeluted.

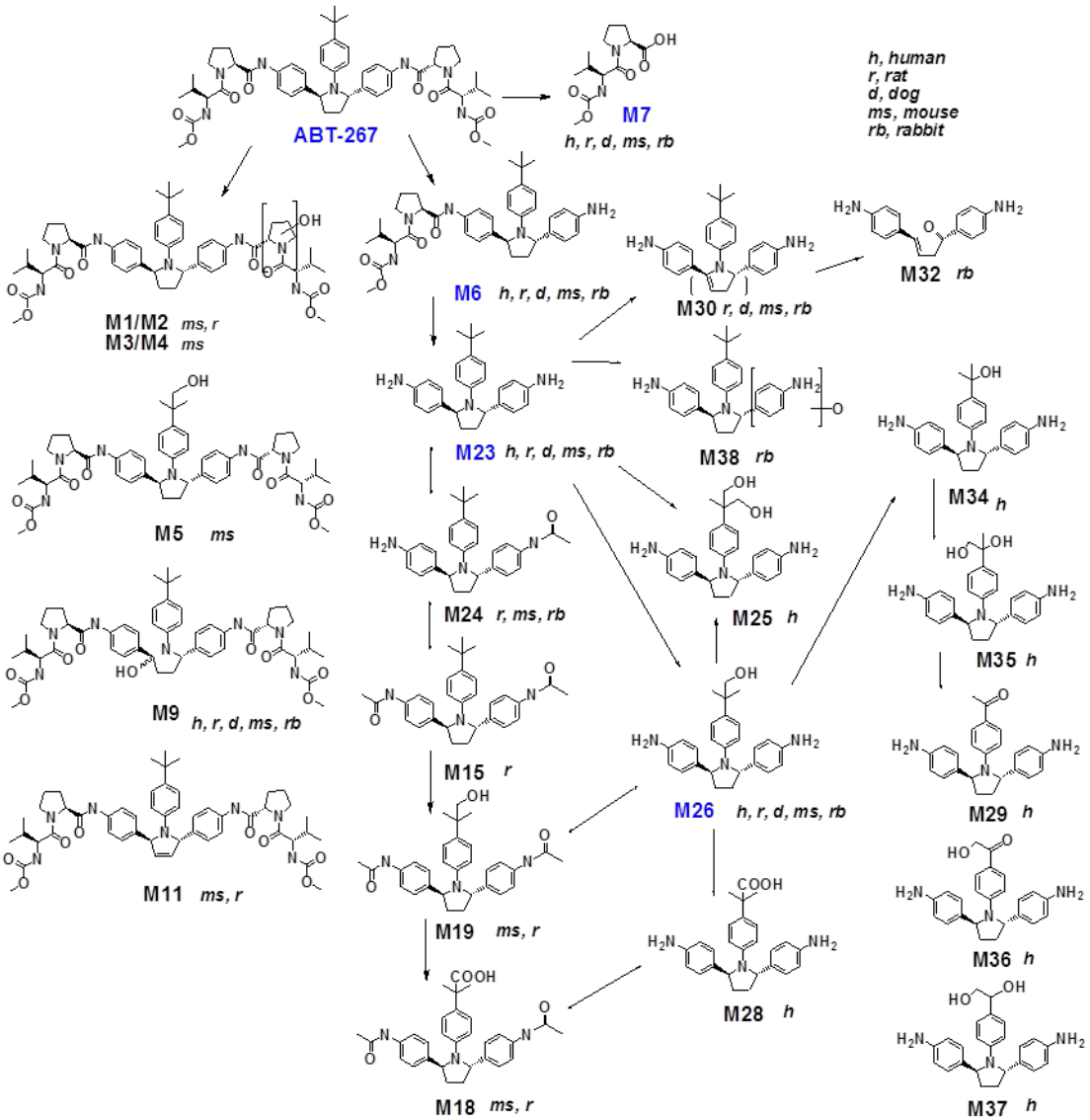

Figure 2. Possible metabolic pathways of OBV (ABT-267) in the plasma of various animal species and humans

3.(ii).A.(8).2) *In vitro* metabolism (4.2.2.4-11, 4.2.2.4-13)

The intrinsic clearance of OBV was determined using liver microsomes and hepatocytes in rats, dogs, monkeys, and humans. The intrinsic clearance in liver microsomes in rats, dogs, monkeys, and humans was 1.9, 3.0, 18.4, and 3.4 μL/min/mg tissue, respectively, and that in hepatocytes was 0.11×10^{-6}, 0.83×10^{-6}, 1.16×10^{-6}, and 0.47×10^{-6} μL/min/cells, respectively. The following metabolites were identified in hepatocytes: m1 to m3, m4/m9, m6, m7, m10, m11, and m13 in rats; m1 to m3, m4/m9, m6, m7, m8, m10, m11, and m13 in dogs and monkeys; and m1 to m3, m4/m9, m5, m6, m7, m10, m11, and m13 in humans.[41)]

41) m4 and m9 were coeluted.

Evaluation of the metabolism of OBV in the expression systems of human CYPs[42] and flavin-containing monooxygenases[43] suggested that OBV is slightly metabolized by CYP3A4/5 and CYP2C8. K_{m1} and K_{m2} of CYP3A4 were 7.1 and 71 μmol/L, respectively, and V_{max1} and V_{max2} per 1 mol of CYP were 0.1 and 4 mol/min, respectively. K_m of CYP2C8 was 79.1 μmol/L and the V_{max} per 1 mol of CYP was 1 mol/min.

3.(ii).A.(9) Excretion (OBV)

3.(ii).A.(9).1) Excretion in bile, urine, and feces (4.2.2.4-14, 4.2.2.7-2, 4.2.2.2-20, 4.2.2.4-18, 4.2.2.4-20)

After a single oral dose of ^{14}C-OBV 30 mg/kg to mice (male, n = 9), the cumulative excretion of radioactivity in feces and urine up to 48 hours post-dose was 98.1% and 0.8%, respectively, of the administered radioactivity.

Following a single oral dose of ^{3}H-OBV 3 mg/kg to rats with biliary cannulation (male, n = 2), the cumulative excretion of radioactivity in bile, feces, and urine up to 72 hours post-dose was 9.0%, 98.2%, and 0.2%, respectively. After a single oral dose of ^{14}C-OBV 30 mg/kg to rats (n = 3/sex), radioactivity was detected mainly in feces, and the cumulative excretion of radioactivity in feces up to 72 hours post-dose was 93.3% in males and 99.8% in females.

After a single oral dose of ^{14}C-OBV 1 mg/kg to dogs (male, n = 2), the cumulative excretion of radioactivity in feces and urine up to 72 hours post-dose was 96.0% and 0.8%, respectively, of the administered radioactivity.

3.(ii).A.(9).2) Excretion in milk (4.2.2.3-11, 4.2.2.4-17)

Following a single oral dose of ^{14}C-OBV 5 mg/kg to rats on postpartum day 8 to 12 (n = 3/time point), radioactivity was detected in milk until 24 hours post-dose, and the C_{max}, $AUC_{0-\infty}$, and $t_{1/2}$ were 931 ng·eq./g, 10,500 ng·eq·h/g, and 4.5 hours, respectively. The mean milk-to-plasma radioactivity ratio in individual animals was 0.267 (at 1 hour post-dose) to 5.17 (at 8 hours post-dose). The radioactivity excreted in milk was primarily unchanged OBV (91.2% of radioactivity in milk), which was followed by m19 (5.5%) and an unknown metabolite (3.2%).

3.(ii).A.(10) Pharmacokinetic drug interactions (OBV)

3.(ii).A.(10).1) Enzyme inhibition and induction (4.2.2.6-29, 4.2.2.6-32, 4.2.2.6-33)

Human liver microsomes was used to evaluate the inhibitory effect of OBV on CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) and UGT1A1. The obtained IC_{50} values were 7.4 and 2.12 μmol/L, respectively, demonstrating the inhibitory effect of OBV on CYP2C8

42) CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9*1, CYP2C18, CYP2C19, CYP2D6*1, CYP2E1, CYP2J2, CYP3A4, and CYP3A5

43) Flavin-containing monooxygenases 1, 3, and 5

and UGT1A1. OBV did not show any inhibitory effects on CYP isoforms (IC_{50} values >30 μmol/L) other than CYP2C8.

Cultured human hepatocytes were used to evaluate the induction effects of OBV (0.03-3 μmol/L) on CYP isoforms (CYP1A2, CYP2B6, and CYP3A4). OBV, at a concentration up to 3 μmol/L, did not exhibit any induction effects on any of these CYP isoforms.

3.(ii).A.(10).2) Substrate of drug transporters and inhibitory effects (4.2.2.2-17, 4.2.2.6-15, 4.2.2.6-34 to 39, 4.2.2.7-2)

HEK cells expressing OATP1B1 and OATP1B3 and MDCKII cells expressing P-gp (MDR1) and BCRP were used to examine the transport of OBV mediated by these transporters. The results suggested that OBV is not a substrate of OATP1B1, OATP1B3, P-gp, or BCRP *in vitro*. Meanwhile, the AUC_{0-t} of OBV in the plasma, liver, and brain in Mdrl/Bcrp knockout mice after an intravenous injection of OBV at 3 mg/kg, was 2.7-, 2.5, and 17-fold, respectively, those in wild-type mice and 9.5-, 8.8-, and 29-fold, respectively, those in wild-type mice after an oral administration of OBV at the same dose. These results suggested that OBV is a substrate of P-gp or BCRP *in vivo* and that P-gp or BCRP may be involved in the absorption, distribution, and excretion of OBV.

Cells expressing OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, P-gp (MDR1), BCRP, MRP2, or BSEP were used to evaluate the inhibitory effects of OBV on human drug transporters.[44)] Taking into account the IC_{50} values of the transporters and plasma OBV concentrations (C_{max}, 154 ng/mL[34)]) obtained in a clinical study, the applicant considers that OBV has no inhibitory effects on transporters when used in a clinical setting.[35,45)]

3.(ii).A.(11) Pharmacokinetic drug interactions (RTV)

3.(ii).A.(11).1) Enzyme inhibition and induction (4.2.2.4-10, 4.2.2.6-17)

Human liver microsomes were used to evaluate the inhibitory effects of RTV on CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). The results showed that the IC_{50} values of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 were >20, 1.00, 1.52, 0.57, 4.28, and 1.04 μmol/L, respectively, and IC_{50} values of CYP3A4 were 0.0055 and 0.0246 μmol/L,[46)] suggesting that RTV has inhibitory effects on the above CYP isoforms except for CYP1A2.

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44) Due to the low water solubility of OBV, a solution of OBV has not been successfully prepared at a concentration sufficient to conduct *in vitro* studies to evaluate its inhibitory effects on transporters.

45) When 100 μmol/L of OBV was added, OATP1B1, OATP1B3, P-gp (MDR1), BCRP, and MRP2 were inhibited by <50%. When 30 μmol/L of OB was added, OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2K were inhibited by <50%. Based on these results, the IC_{50} values of OBV against the above 2 groups of transporters were estimated to be >100 μmol/L and >30 μmol/L, respectively.

46) Midazolam and testosterone were used as substrates of CYP3A4.

Cultured human hepatocytes were used to evaluate the induction effects of RTV (1-30 μmol/L) on CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4). RTV, at 1 μmol/L, induced CYP2B6, CYP2C8, and CYP3A4.[47)]

3.(ii).A.(11).2) Substrate of drug transporters and inhibitory effects (4.2.2.6-20, 4.2.2.6-21, 4.2.2.6-22, 4.2.2.6-23, 4.2.2.6-24, 4.2.2.6-25 to 28)

HEK cells expressing OATP1B1 and OATP1B3 were used to examine the uptake of RTV mediated by these transporters. The results suggested that RTV is not a substrate of OATP1B1 or OATP1B3.

The efflux ratio[31)] of RTV in MDCK-II cells expressing P-gp (MDR1) and BCRP was 26.1 and 0.7, respectively, indicating that RTV is a substrate of P-gp though not a substrate of BCRP.

Cells expressing OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, P-gp (MDR1), BCRP, MRP2, or BSEP were used to evaluate the inhibitory effects of RTV on human drug transporters. Taking into account the IC_{50} values against the transporters and plasma RTV concentrations (C_{max}, 1748 ng/mL[34)]) obtained in a clinical study, the applicant considers that RTV may have an inhibitory effect on OATP2B1 (only in the intestinal tract), P-gp (MDR1), BCRP, and BSEP when used in the clinical settings.[35,48)]

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Rationale for coadministering PTV with RTV

The applicant admitted that it is difficult to justify the coadministration of PTV with RTV from non-clinical data because the liver/plasma concentration ratio of PTV differed among the animal species studied (371:1-633:1 in mice, 6:1-19:1 in dogs, 134:1 in rats), and consequently, the efficacy of PTV used in combination with RTV in humans cannot be explained by its plasma concentrations or doses from the data on *in vitro* antiviral activity.[49)]

Given that non-clinical data cannot justify the coadministration of PTV with RTV, PMDA will discuss the rationale for coadminstering PTV with RTV in "4.(ii).B.(1) Rationale for coadministering RTV with anti-HCV drugs and selecting RTV dose."

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47) In the presence of 1 μmol/L of RTV, the mRNA level of CYP2B6, CYP2C8, and CYP3A4 was increased by 6.4%, 3.1%, and 23%, respectively. This mRNA induction ratio of RTV (1 μmol/L) was 72%, 89%, and 73%, respectively, of that of the positive control (phenytoin 50 μmol/L for CYP2B6; rifampicin 10 μmol/L for CYP2C8 and CYP3A4).

48) OCT2 was inhibited by <50% when 30 μmol/L of RTV was added, and MRP2 was inhibited by <50% when 100 μmol/L of RTV was added. Based on these results, the IC_{50} values of RTV against these transporters were estimated to be >30 μmol/L and >100 μmol/L, respectively.

49) In an *in vitro* replicon cell culture assay, the EC_{50} values of PTV against genotype 1a (H77) and 1b (Con 1) replicon cells in the presence of 40% human plasma were 18 ng/mL (23 nmol/L) and 6.7 ng/mL (8.7 nmol/L), respectively.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

The data of the following toxicology studies of PTV and OBV were submitted: single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, and other toxicity studies[50)] (e.g., studies on impurities, coadministration toxicity studies). In the repeated-dose toxicity studies, reproductive and developmental toxicity studies, and carcinogenicity studies of PTV, PTV was evaluated in combination with RTV. A mixed solution of Cremophor EL, PEG-400, and oleic acid (weight ratio, 1:1:8) was used in studies related to PTV, and a mixed solution of PEG-400, Tween 20, Poloxamer-124, and d-alpha-tocopherol polyethylene glycol succinate (weight ratio, 5:2:1:2) was used as vehicles of the tested compounds in studies related to OBV, unless otherwise noted.

Concentrations and doses of PTV and OBV are expressed as free base.

3.(iii).A.(1) Single-dose toxicity

3.(iii).A.(1).1) PTV (4.2.3.1-450-1, 4.2.3.1-450-2)

Following a single oral dose of PTV 0 (vehicle), 50, 300, or 600 mg/kg to SD rats (n = 10/sex/group) and 0 (vehicle), 10, 30, or 100 mg/kg to beagle dogs (n = 3/sex/group), no abnormal findings were observed. Based on the above results, the approximate lethal dose of PTV given as a single agent was determined to be >600 mg/kg in rats and >100 mg/kg in dogs.

3.(iii).A.(1).2) OBV

No single-dose toxicity studies of OBV were conducted. Based on the results of a micronucleus test in mice (4.2.3.3.2-267-1) and the results on Day 1 of repeated-dose toxicity studies in rats and dogs (4.2.3.2-267-8 and 4.2.3.2-267-12, respectively), the approximate lethal dose of OBV was determined to be >2000 mg/kg in mice, >300 mg/kg in rats, and >100 mg/kg in dogs.

3.(iii).A.(2) Repeat-dose toxicity

PTV and RTV (PTV/RTV) were coadministered in repeated oral dose toxicity studies to mice for 4 weeks, 3 months, or 6 months; to rats for 4 weeks or 3 months; and to dogs for 4 weeks, 3 months, or 9 months. The following findings were observed in these studies: effects on the gallbladder (e.g., erosion/ulcer, epithelial necrosis, inflammation, hypertrophy/hyperplasia) in mice and dogs; and salivation, gastrointestinal symptoms (vomiting and abnormal feces), and vacuolation of the small-intestinal epithelia and other tissues in dogs. The applicant explained that the above findings were PTV-induced changes. The following findings were also observed: effects on the liver (e.g., hypertrophy of hepatocytes, increased liver weight) and on the thyroid (increased thyroid weight, follicular epithelial cell hypertrophy) in mice and rats. The applicant explained that they were highly likely to be related to

50) Including the results of the toxicity and phototoxicity studies of metabolites of OBV (m 29 and m36).

RTV[51] but toxicologically insignificant and attributable to liver drug-metabolizing enzyme induction[52] because they had also been observed in CD-1 mice in a dose-dependent manner after administration of RTV as a single agent (4.3.4-6), but no clear relationship has been observed between these changes and the dose of PTV.

OBV was administered in repeated oral dose studies to mice for 4 weeks, 3 months, or 6 months; to rats for 3 months; and to dogs for 4 weeks, 3 months, or 6 months. The maximum dose in each study was selected as the dose estimated to achieve maximum possible exposure (at which plasma OBV was expected to saturate). While no abnormalities were found in mice or rats, dilated villus lacteals and vacuolated epithelia in the small intestine (duodenum and/or jejunum) were observed in dogs. The applicant regards these effects on the small intestine in dogs as toxicologically insignificant because they were non-injurious changes with no impact on laboratory values.

The exposure in plasma ($AUC_{0\text{-}24h}$) at the no observed adverse effect level (NOAEL) of PTV during long-term administration of PTV/RTV (30 mg/kg/day in mice and 80 mg/kg/day in dogs) and at the NOAEL of OBV during long-term administration (200 mg/kg/day in mice and 100 mg/kg/day in dogs) was 1.7-fold (mice) and 76-fold (dogs) the PTV exposure in human plasma[53] and 23-fold (mice) and 53-fold (dogs) the OBV exposure in human plasma.[53]

3.(iii).A.(2).1) PTV

(a) Four-week repeated oral dose toxicity study in wild-type TgHras mice (4.2.3.2-450-3)

PTV/RTV 0/0 (vehicle), 30/30, 100/30, 300/30, or 450/30 mg/kg/day was orally administered to wild-type TgHras mice (n = 15/sex/group) for 4 weeks. No PTV/RTV-related deaths occurred in the study. Increased serum cholesterol level and liver weight were observed in ≥30/30 mg/kg groups, and slightly increased serum alkaline phosphatase (ALP) was observed in ≥100/30 mg/kg groups. The above findings in ≥30/30 mg/kg groups were considered to be secondary effects of RTV, taking into account that no aggravation was noted with the increase in the dose of PTV. Given that all the findings were mild in severity and that no histopathological findings were observed in the liver, bone, or small intestine, the applicant regards the above findings as toxicologically insignificant changes. Based on the above, the NOAEL of PTV given in combination with RTV was determined to be 450 mg/kg/day.

(b) Three-month repeated oral dose toxicity study in mice (4.2.3.2-450-4)

PTV/RTV 0/0 (vehicle), 30/30, 100/30, or 300/30 mg/kg/day was orally administered to CD-1 mice (n = 15/sex/group) for 3 months. Increased serum cholesterol and triglyceride (TG) levels and

51) Given that the plasma exposure to RTV contained in the PTV/RTV/OBV combination tablet administered at the clinical dose (100 mg/day; AUC, 9.7 μg·h/mL) was lower than that to RTV, the approved drug, administered at the clinical dose (600 mg/day; AUC, 145 μg·h/mL), the applicant explained that RTV is unlikely to be of toxicological concern.

52) Capen CC et al., *Toxicol Pathol*. 2001;29:8-33; Klaassen CD et al., *Toxicol Pathol*. 2001;29:34-40; Lewandowski TA et al., *Regul Toxicol Pharmacol*. 2004;29:348-362.

53) A comparison with the plasma exposure in the phase I study for healthy Japanese adult subjects (Study M[redacted]-247) conducted to evaluate the steady-state pharmacokinetics of PTV or OBV during once-daily multiple-dose administration of PTV/RTV/OBV at 150/100/25 mg ($AUC_{0\text{-}24h}$, 19.6 μg·h/mL for PTV and 1.56 μg·h/mL for OBV)

hepatocellular hypertrophy were observed in ≥30/30 mg/kg groups. The applicant regarded the above findings observed in ≥30/30 mg/kg groups as effects of RTV because no aggravation was noted with the increase in the dose of PTV. Based on the above, the NOAEL of PTV given in combination with RTV was determined to be 300 mg/kg/day.

(c) Six-month repeated oral dose toxicity study in mice with 1-month recovery period (4.2.3.2-450-5)

PTV/RTV 0/0 (vehicle), 30/30, 100/30, or 300/30 mg/kg/day was orally administered to CD-1 mice (n = 50/sex/group for the vehicle and 300/30 mg/kg groups; n = 40/sex/group for the 30/30 and 100/30 mg/kg groups) for 6 months (with a 1-month recovery period after the final dose). Increased liver weight was observed in ≥30/30 mg/kg groups, and localized erosion or ulcer (minor to moderate in severity), acute or chronic inflammation (minor to mild), and epithelial hypertrophy or hyperplasia (minor to mild) were observed in the gallbladder in ≥100/30 mg/kg groups. In the recovery period, acute inflammation and epithelial hypertrophy or hyperplasia in the gallbladder was persistent in the 300/30 mg/kg group; however, all the findings were mild in severity and showed a tendency towards improvement. Based on the above, the NOAEL of PTV given in combination with RTV was determined to be 30 mg/kg/day.

(d) Four-week repeated oral dose toxicity studies in rats with 1-month recovery period (4.2.3.2-450-6, 4.2.3.2-450-7)

PTV/RTV 0/0 (vehicle), 100/15, 300/15, or 520/15 mg/kg/day[54)] was orally administered to SD rats (n = 15/sex/group) for 4 weeks (with a 1-month recovery period after the final dose). No abnormal findings were observed, and the NOAEL of PTV given in combination with RTV 15 mg/kg/day was determined to be 520 mg/kg/day. In another 4-week repeated oral dose study (with a 1-month recovery period after the final dose), PTV/RTV 0/0 (vehicle), 0/45, 100/15, 300/30, or 450/45 mg/kg/day was administered to SD rats (n = 15/sex/group). No abnormal findings were observed, and the NOAEL in this study was determined to be 450/45 mg/kg/day. The plasma exposure of PTV ($AUC_{0\text{-}24h}$) following the administration of PTV/RTV 300/15 and 520/15 mg/kg was 36.7 and 31.0 μg·h/mL, respectively, showing saturation of PTV exposure, and that following the administration of PTV/RTV 300/30 and 450/45 mg/kg was 144 and 187 μg·h/mL, respectively, showing an increase in exposure.

(e) Three-month repeated oral dose toxicity study in rats (4.2.3.2-450-9)

PTV/RTV 0/0 (vehicle), 0/15, 0/45, 100/15, 300/30, or 450/45 mg/kg/day was orally administered to SD rats (n = 10/sex/group) for 3 months. In all groups including the single-agent RTV groups, the following changes were observed: decreases in erythroid parameters; increases in serum cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), liver weight, and thyroid weight; and hypertrophy of hepatocytes and thyroid follicular epithelial cells. Given that no aggravation of these findings was observed in PTV/RTV combination groups compared with single-agent RTV groups, the applicant explained that the above changes were attributable to RTV. Based on the above, the NOAEL

54) PTV/RTV was administered at 600/15 mg/kg on Days 1 and 2. Due to a deposit detected in the test solution, the dose of PTV was reduced to 520 mg/kg from Day 3 and coadministered with RTV.

of PTV given in combination with RTV was determined to be 450 mg/kg/day. The plasma exposure of PTV ($AUC_{0\text{-}24h}$) following the administration of PTV/RTV 300/30 and 450/45 mg/kg was 104 and 91.1 μg·h/mL, respectively, showing saturation of PTV exposure.

(f) Four-week and 3-month repeated oral dose toxicity studies of PTV/RTV/ribavirin in rats (4.2.3.2-450-8, 4.2.3.2-450-10)

SD rats (n = 10/sex/group) orally received PTV/RTV/ribavirin 450/50/0, 0/0/60, 0/45/60, 100/15/60, or 450/45/60 mg/kg/day in a 4-week study and 450/45/0, 100/15/60, or 450/45/60 mg/kg/day in a 3-month study. Increases in liver weight and thyroid weight and hypertrophy of hepatocytes and thyroid follicular epithelial cells were observed in the groups receiving treatment including RTV, and decreases in erythroid parameters, thymic weight, and lymphocyte count in the thymus (cortex or medulla) were observed in the groups receiving treatment including ribavirin. Coadministration of PTV caused no aggravation of the above findings or new toxic findings.

(g) Four-week repeated oral dose toxicity study in dogs with 1-month recovery period (4.2.3.2-450-13)

PTV/RTV 0/0 (vehicle), 5/5, 10/5, or 20/10 mg/kg/day was orally administered to beagle dogs (n = 5/sex/group) for 4 weeks (with a 1-month recovery period after the final dose). The following changes were observed in the 20/10 mg/kg group: increased incidence of vomiting and abnormal feces (e.g., loose stool, diarrhea), minor epithelial degeneration in the gallbladder, and minor oedemas in the lamina propria. None of these findings was observed in the recovery period. Taking into account that the findings in the gallbladder were minor, localized, and reversible and that the vomiting and abnormal feces (e.g., loose stool, diarrhea) did not affect body weight and were not accompanied by histopathological findings in the digestive tract, the applicant explained that they were toxicologically insignificant changes. Based on the above, the NOAEL of PTV given in combination with RTV was determined to be 20 mg/kg/day.

(h) Three-month repeated oral dose toxicity study in dogs (4.2.3.2-450-14)

PTV/RTV 0/0 (vehicle), 5/5, 10/5, 20/10 mg/kg/day, or 40/20 mg/kg/day (20/10 mg/kg/dose twice daily) was orally administered to beagle dogs (n = 3/sex/group) for 3 months. The following changes were observed in the study: salivation in ≥10/5 mg/kg groups; increased incidence of vomiting and abnormal feces (e.g., loose stool, diarrhea) and decreased erythroid parameters in ≥20/10 mg/kg groups; and increased serum ALP in the 40/20 mg/kg group. The applicant regards the above findings as toxicologically insignificant changes for the following reasons: the vomiting and abnormal feces (e.g., loose stool, diarrhea) did not affect body weight; the decreases in erythroid parameters were minor; the increased ALP was not accompanied by relevant histopathological findings; and the salivation was unlikely to be attributable to any effect of PTV on the nervous system because PTV distribution to the brain is expected to be low (4.2.2.2-7) and PTV's binding to or inhibition of various receptors has not been observed (4.2.1.2-1). Based on the above, the NOAEL of PTV given in combination with RTV was determined to be 40 mg/kg/day.

(i) Nine-month repeated oral dose toxicity study in dogs with 1-month recovery period (4.2.3.2-450-15)

PTV/RTV 0/0 (vehicle), 5/5, 20/10, or 80/20 (40/10 mg/kg/dose twice daily) mg/kg/day was orally administered to beagle dogs (n = 6/sex/group for the vehicle and 80/20 mg/kg groups; n = 4/sex/group for the 5/5 and 20/10 mg/kg groups) for 9 months (with a 1-month recovery period after the final dose). The following changes were observed in the study: salivation, increased incidence of vomiting and abnormal feces (e.g., loose stool, diarrhea), increased liver weight, and vacuolated villus tips in the duodenum and jejunum (minor to moderate [55)]) in ≥20/10 mg/kg groups; and decreased food consumption, increased platelet count, necrosis and oedemas of epithelial cells in the gallbladder (minor), vacuolated hepatic sinusoidal cells (mild), and vacuolated renal tubular epithelium (minor to mild) in ≥80/20 mg/kg groups. During the recovery period, the vacuolation of hepatic sinusoidal cells, renal tubular epithelium, and duodenojejunal epithelium continued to be observed. However, the vacuolation of the renal tubular epithelium and duodenojejunal epithelium was minor and showed improvement. All the findings in the gallbladder were minor and showed improvement, and the vacuolation observed in the liver, kidney, and small intestine were not injurious changes and had no effects on test values of hematology or clinical chemistry. Therefore, the applicant regards these changes as toxicologically insignificant. Given that increased liver weight was also observed following the administration of RTV as a single agent (4.3.4-13, 4-3.4-14), the applicant views this change as related to RTV. Based on the above, the NOAEL of PTV given in combination with RTV was determined to be 80 mg/kg/day.

3.(iii).A.(2).2) OBV

(a) Four-week repeated oral dose toxicity study in mice (4.2.3.2-267-3)

In this study in CD-1 mice (n = 13/sex/group), OBV 0 (vehicle), 1, 5, 20, or 60 mg/kg/day was orally administered to males, and 0 (vehicle), 2, 10, 40, or 120 mg/kg/day to females for 4 weeks. No abnormal findings were observed, and the NOAEL in the study was determined to be 60 mg/kg/day for males and 120 mg/kg/day for females. The plasma exposure at the NOAEL was similar between sexes.

(b) Four-week repeated oral dose toxicity study in wild-type TgHras mice (4.2.3.2-267-4)

In this study in wild-type TgHras mice (n = 12/sex/group), OBV 0 (vehicle[56)]), 5, 25, or 150[57)] mg/kg/day was orally administered to males, and at 0 (vehicle[56)]), 10, 50, or 150[57)] mg/kg/day to females for 4 weeks. No abnormal findings were observed, and the NOAEL in the study was determined to be 150 mg/kg/day.

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55) Moderate vacuolation was observed only in the 80/20 mg/kg group.

56) A mixed solution of Phosal 53 MCT, PEG-400, Poloxamer 124, and Cremophor RH40 (ratio by weight, 4:2:2:2)

57) In the 5-day repeated oral dose study in wild-type TgHras mice (4.2.3.2-1), the plasma exposure levels (C_{max} and $AUC_{0\text{-}24h}$) after administration of OBV 150, 200, and 300 mg/kg were similar and showed saturation.

(c) Three-month repeated oral dose toxicity study in mice (4.2.3.2-267-5)

In this study in CD-1 mice (n = 16/sex/group), OBV 0 (vehicle), 2.5, 20, or 400 mg/kg/day was orally administered to males, and 0 (vehicle), 5, 40, or 400 mg/kg/day to females for 3 months. An increase in the incidence of mucification of the vaginal epithelium was observed in females in the 400 mg/kg group. The applicant explained that this finding was unlikely to be related to OBV for the following reasons: the finding was not observed in a 6-month repeated oral dose toxicity study in mice conducted in a similar OBV exposure[58)] (4.2.3.2-267-6); other female genital organs (uterus, ovary) appeared to be unaffected; and the finding had been reported as a naturally occurring change.[59)] Based on the above, the NOAEL in the study was determined to be 400 mg/kg/day.

(d) Six-month repeated oral dose toxicity study in mice with 1-month recovery period (4.2.3.2-267-6)

In this study in CD-1 mice (n = 20/sex/group), OBV 0 (vehicle), 5, 20, or 200 mg/kg/day was orally administered to males and 0 (vehicle), 10, 40, or 200 mg/kg/day to females for 6 months (with a 1-month recovery period after the final dose). A decrease in or decreasing tendency of body weight gain was observed in females in ≥10 mg/kg groups and in both sexes in the 200 mg/kg group. However, the applicant views this finding as toxicologically insignificant because the difference in body weight between these groups and the control group was as little as approximately 4% at the end of treatment, and there were no effects on clinical condition. Based on the above, the NOAEL in the study was determined to be 200 mg/kg/day.

(e) Three-month repeated oral dose toxicity study in rats (4.2.3.2-267-8)

OBV 0 (vehicle[56)]), 10, 30, or 300 mg/kg/day was orally administered to SD rats (n = 12/sex/group) for 3 months. Although a decreasing tendency of serum TG was observed in ≥10 mg/kg groups, the applicant views this as a toxicologically insignificant change because no associated histopathological findings were noted. Based on the above, the NOAEL in the study was determined to be 300 mg/kg/day.

(f) Four-week repeated oral dose toxicity study in dogs (4.2.3.2-267-10)

OBV 0 (vehicle), 2, 10, or 60 mg/kg/day was orally administered to beagle dogs (n = 3/sex/group) for 4 weeks. No abnormal findings were noted, and the NOAEL in the study was determined to be 60 mg/kg/day.

(g) Three-month repeated oral dose toxicity study in dogs (4.2.3.2-267-11)

OBV 0 (vehicle), 2, 10, or 100 mg/kg/day was orally administered to beagle dogs (n = 4/sex/group) for 3 months. Although a dilated lacteal in the jejunal villus (minor to mild) was observed in the 100 mg/kg group, the applicant views this finding as a toxicologically insignificant change because it was localized

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58) The plasma exposure ($AUC_{0\text{-}24h}$, 47.7 μg·h/mL) on Day 84 in females in the 200 mg/kg group in the 6-month repeated oral dose toxicity study in mice with a 1-month recovery period (4.2.3.2-267-6) was similar to that ($AUC_{0\text{-}24h}$, 37.0 μg·h/mL) on Day 91 in females in the 400 mg/kg group in the 3-month repeated oral dose toxicity study in mice (4.2.3.2-267-5).

59) Westwood FR et al., *Toxicol Pathol*. 2008;36:375-384

with no injurious changes or effects on fecal condition or laboratory values and no similar findings were observed at the end of the 6-month treatment. Based on the above, the NOAEL in the study was determined to be 100 mg/kg/day.

(h) Six-month repeated oral dose toxicity study in dogs (4.2.3.2-267-12)

OBV 0 (vehicle), 4, 20, or 100 mg/kg/day was orally administered to beagle dogs (n = 4/sex/group) for 6 months. Although vacuolated duodenal or jejunal villus (minor to mild) was observed in ≥20 mg/kg groups, the applicant views this finding as a toxicologically insignificant change based on the following: no associated injurious changes were noted; neither the incidence nor severity of the finding increased with increasing dose; and there were no effects on fecal condition or laboratory values. Based on the above, the NOAEL in the study was determined to be 100 mg/kg/day.

3.(iii).A.(3) Genotoxicity (4.2.3.3.1-450-1, 4.2.3.3.1-450-2, 4.2.3.3.2-450-1, 4.2.3.3.2-450-2 (reference data), 4.2.3.3.1-267-1, 4.2.3.3.1-267-2, 4.2.3.3.2-267-1)

A bacterial reverse mutation assay (Ames), a chromosomal aberration assay using human lymphocytes (chromosomal aberration assay), and a rat micronucleus assay were conducted on PTV and OBV, and a rat comet assay was conducted on PTV. In the chromosomal aberration assay on PTV, structurally abnormal cells increased during the short treatment period with or without metabolic activation. Meanwhile, PTV was negative for genotoxicity in both the rat micronucleus assay and rat comet assay, indicating that PTV is unlikely to pose a genotoxic hazard *in vivo*. OBV was negative for genotoxicity in any of the assays performed. Based on the above, PTV/RTV/OBV combination product was considered unlikely to be genotoxic *in vivo*.[60)]

3.(iii).A.(4) Carcinogenicity

A 6-month oral dose carcinogenicity study in hemizygous TgHras mice and a 2-year oral dose carcinogenicity study in rats were conducted on PTV, and no neoplastic lesions were observed. A 6-month oral dose carcinogenicity study in hemizygous TgHras mice and a 2-year oral dose carcinogenicity study in rats were also conducted on OBV, and no neoplastic lesions were observed. Compared with the plasma exposure ($AUC_{0\text{-}24h}$)[53)] in humans at the recommended clinical dose (150/100/25 mg/day as PTV/RTV/OBV), the plasma PTV exposure ($AUC_{0\text{-}24h}$) at the non-carcinogenic dose of PTV/RTV (300/30 mg/kg/day for TgHras mice, 300/30 mg/kg/day for rats) was 14-fold and 2.7-fold in mice and rats, respectively, and the plasma OBV exposure ($AUC_{0\text{-}24h}$) at the non-carcinogenic dose of OBV (150 mg/kg/day for TgHras mice, 30 mg/kg/day for rats) was 24-fold and 15-fold in mice and rats, respectively.

60) RTV was negative for genotoxicity in all the genotoxicity studies (4.3.2-1, 4.3.4-2, 4.3.4-3, and 4.3.4-4).

3.(iii).A.(4).1) PTV

(a) Six-month oral dose carcinogenicity study in hemizygous TgHras mice (4.2.3.4.2-450-1)

PTV/RTV 0/0 (vehicle alone or water alone), 6/30, 60/30, or 300/30 mg/kg/day was orally administered to hemizygous TgHras mice (n = 35/sex/group for the control and PTV/RTV groups, n = 15/sex/group for the positive control group[61)]) for 6 months. No neoplastic lesions or effects on the survival, body weight, food consumption, or clinical condition were observed. The following non-neoplastic lesions occurred: epithelial hypertrophy or hyperplasia (minor to moderate) and subacute or chronic inflammation (minor to mild) in the gallbladder in ≥60/30 mg/kg groups; and erosion or ulcer (mild) in the gallbladder in the 300/30 mg/kg group.

(b) Two-year oral dose carcinogenicity study in rats (4.2.3.4.1-450-1)

PTV/RTV 0/0 (vehicle alone or water alone), 6/30, 60/30, or 300/30 mg/kg/day was orally administered to SD rats (n = 80/sex/group) for 2 years.[62)] No effects were observed on the survival, food consumption, or clinical condition. A decreasing tendency of body weight gain was observed in males in ≥6/30 mg/kg groups and in females in ≥60/30 mg/kg groups. There were no neoplastic lesions. As for non-neoplastic lesions, the incidence and severity of multinucleated hepatocytes and chronic progressive nephritis increased in ≥6/30 mg/kg groups. However, the applicant views these findings as attributable to RTV based on the following: the incidence of multinucleated hepatocytes and chronic progressive nephritis also increased after administration of RTV as a single agent;[63)] and no relationship was noted between the incidence of these findings and the dose of PTV.

3.(iii).A.(4).2) OBV

(a) Six-month oral dose carcinogenicity study in hemizygous TgHras mice (4.2.3.4.2-267-1)

OBV 0 (vehicle alone[56)] or water alone), 2.5, 10, or 150 mg/kg/day was orally administered to male hemizygous TgHras mice (n = 25/sex/group for the control and OBV groups, n = 15/sex/group for the positive control group[61)]) and 0 (vehicle alone[56)] or water alone), 5, 20, or 150 mg/kg/day to females for 6 months. No neoplastic lesions or effects on the survival, body weight, food consumption, or clinical condition were observed.

61) A single dose of N-nitroso-N-methylurea was intraperitoneally administered to the positive control group on Day 1.
62) The study had 2 vehicle-control groups. Since the number of female rats in the water-control group decreased to 20 on Day 693, the treatment was terminated in all the groups.
63) Two-year dietary carcinogenicity study of ABBOTT-84538 in rats. R&D1981136 - Study No. TA95-297

(b) Two-year oral dose carcinogenicity study in rats (4.2.3.4.1-267-1)

OBV 0 (vehicle alone or water alone), 3, 10, or 30 mg/kg/day was orally administered to SD rats (n = 65/sex/group) for 2 years.[64] No effects were observed on the body weight, food consumption, or clinical condition. Survival of females decreased in ≥3 mg/kg/day groups. The main cause of death was pituitary tumor. The incidence of fatal pituitary tumor tended to increase in OBV groups (25 of 65 rats [38%] in the water alone group, 49 of 130 rats [38%] in the vehicle alone group, 33 of 65 rats [51%] in the 3 mg/kg/day group, 32 of 65 rats [49%] in the 10 mg/kg/day group, and 37 of 65 rats [57%] in the 30 mg/kg/day group). Although the incidence of fatal pituitary tumor in females of the 30 mg/kg/day group was higher than the laboratory's historical data[65] (18%-50%), the applicant views it as an accidental change based on the following: pituitary tumors commonly occur in female rats of related strains[66]; the incidence of fatal pituitary tumors in female rats of related strains has been reported to be approximately 60%;[67] and there were no differences in the size or form of the pituitary tumor or time of death between the control group and OBV groups. No other neoplastic or non-neoplastic lesions were observed.

3.(iii).A.(5) Reproductive and developmental toxicity

Studies of fertility and early embryonic development to implantation (using rats for PTV and mice for OBV), embryo-fetal development studies (using rats and mice[68] for PTV, and mice and rabbits for OBV), and studies for effects on pre- and postnatal development, including maternal function (using rats for PTV and mice for OBV) were conducted for PTV and OBV. There were no effects on fertility, early embryonic development, embryo-fetal development, or postnatal development in any of these studies. Although salivation was observed in parent animals of both sexes and maternal animals in studies of PTV in rats, the applicant explained that this change was unlikely to be attributable to the effect on the nervous system and was toxicologically insignificant for the following reasons: the same finding was not found in repeated-dose toxicity studies; PTV distribution to the brain is low (4.2.2.2-7); and PTV's binding to or inhibition of various receptors has not been observed (4.2.1.3-1). The plasma PTV exposure ($AUC_{0\text{-}24h}$) for embryo-fetal development at the NOAEL of PTV (300 mg/kg/day in mice and 450 mg/kg/day in rats) when administered in combination with RTV were 35-fold and 3.0-fold in mice and rats, respectively, over the plasma PTV exposure[53] following administration at the recommended human dose (PTV/RTV/OBV, 150/100/25 mg/day). The plasma OBV exposure ($AUC_{0\text{-}24h}$) at the NOAEL of OBV (150 mg/kg/day in mice and 60 mg/kg/day in rabbits) when administered in

64) This study had 2 vehicle-control groups. In males, since the number of surviving animals had dropped to 15 in the 30 mg/kg/day group by Day 644, the treatment was discontinued in this group. Treatment in males was discontinued in all the groups on Day 693 because the number of surviving animals had dropped to ≤15 between Days 681 and 693 in the vehicle-only group, 3 mg/kg/day group, and 10 mg/kg/day group. In females, since the number of surviving animals had dropped to 15 in the 3 and 30 mg/kg/day groups by Days 626 and 603, respectively, the treatment in these groups was discontinued. Treatment in females was discontinued in all the groups on Day 644, when the number of surviving animals had dropped to ≤15 in the 10 mg/kg/day group. Consequently, the duration of treatment was 92 to 99 weeks for males and 87 to 92 weeks for females.

65) Data from carcinogenicity studies in SD rats conducted from 2009 to 2014 at a study center (20 studies; 26 groups)

66) Giknis MLA et al., *Compilation of spontaneous neoplastic lesions and survival in Crl:CD®(SD) rats from control groups*. 2004; Charles River Laboratories

67) Molon-Noblot S et al., *Toxicol Pathol*. 2003;31:310-320

68) No embryo-fetal development studies of PTV were conducted in non-rodents, taking into account that sufficient exposure was not obtained in rabbits, and that rabbits were considered to be highly sensitive to vehicles.

combination with RTV were 26-fold and 3.8-fold in mice and rabbits, respectively, over the plasma OBV exposure[53] following administration at the recommended human dose.

3.(iii).A.(5).1) PTV

(a) Study of fertility and early embryonic development to implantation in rats (4.2.3.5.1-450-1)

PTV/RTV 0/0 (vehicle), 6/30, 60/30, or 300/30 mg/kg/day was orally administered to SD rats (n = 25/sex/group) for 59 days in males from 28 days before mating, through the mating period, until the day before necropsy, and for 23 to 37 days in females from 15 days before mating to the mating period and gestation day 7. Incidence of salivation increased in maternal animals in ≥60/30 mg/kg/day groups and in paternal animals in the 300/30 mg/kg group. No effects were observed on fertility or early embryonic development. Based on the above, the NOAEL of PTV in combination with RTV was determined to be 300 mg/kg/day for general toxicity and fertility in the parent animals of both sexes and early embryonic development.

(b) Embryo-fetal development studies

i) Embryo-fetal development study in mice (4.2.3.5.2-450-2)

PTV/RTV 0/0 (vehicle), 30/30, 100/30, or 300/30 mg/kg/day was orally administered to pregnant CD-1 mice (n = 25/group) from gestation days 6 to 15. No effects were observed on maternal animals, embryos, or fetuses. Based on the above, the NOAEL of PTV in combination with RTV was determined to be 300 mg/kg/day for maternal toxicity and embryo-fetal development.

ii) Embryo-fetal development study in rats (4.2.3.5.2-450-4)

PTV/RTV 0/0 (vehicle), 30/15, 100/15, or 450/45 mg/kg/day was orally administered to pregnant SD rats (n = 25/group) from gestation days 6 to 17. Reddish staining around the mouth and nose was observed in maternal animals in the 100/15 mg/kg group. No effects were observed on embryos or fetuses. The reddish staining around the mouth and nose was considered toxicologically insignificant for the following reasons: the finding was transient and was highly likely to be secretion from the harderian gland seen often in rats under stress;[69] and there were no histopathological findings indicating hemorrhage. Based on the above, the NOAEL of PTV in combination with RTV was determined to be 450 mg/kg/day for maternal toxicity and embryo-fetal development.

(c) Rat study to ascertain effects on pre- and postnatal development, including maternal function (4.2.3.5.3-450-1)

PTV/RTV 0/0 (vehicle), 6/30, 30/30, or 300/30 mg/kg/day was orally administered to pregnant SD rats (n = 25/group) from gestation day 7 to postpartum day 20. In maternal animals, salivation was observed in the 30/30 mg/kg group and stained abdominal fur was seen in the 300/30 mg/kg group. No effects were observed on offspring (F_1) or fetuses (F_2). Based on the above, the NOAEL of PTV in combination with RTV was determined to be 300 mg/kg/day in maternal animals and offspring (F_1) of both sexes.

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69) Taradach C et al., *Crit Rev Toxicol*. 1984;12:121-147; Harkness JE et al., *Lab Anim Sci*. 1984;30:841-848

3.(iii).A.(5).2) OBV

(a) Study of fertility and early embryonic development to implantation in mice (4.2.3.5.1-267-1)

OBV 0 (vehicle), 5, 20, or 200 mg/kg/day was orally administered to CD-1 mice (n = 30/sex/group) for 43 days in males from 14 days before mating to the mating period and the day before necropsy, and for 21 to 34 days in females from 14 days before mating, through the mating period, until gestation day 6. In paternal animals, increased prostate weight was observed in ≥20 mg/kg groups and increased seminal vesicle weight in the 200 mg/kg group. No effects were observed on fertility or early embryonic development. The applicant regarded the increased prostate and seminal vesicle weights as toxicologically insignificant because they had no effects on fertility and were within the laboratory historical range data, and were therefore unlikely to be related to OBV. Based on the above, the NOAEL of OBV in the study was determined to be 200 mg/kg/day for toxicity in parent animals of both sexes and early embryonic development.

(b) Embryo-fetal development studies

i) Embryo-fetal development studies in mice (4.2.3.5.2-267-1, 4.2.3.5.2-267-2)

In a preliminary study in which OBV 0 (vehicle), 15, 50, 150, or 500 mg/kg/day was orally administered to pregnant CD-1 mice (n = 10/group) from gestation days 6 to 15, the maximum plasma exposure (C_{max} and AUC) in maternal animals was obtained in the 150 mg/kg group. In the main study, therefore, OBV 0 (vehicle), 15, 50, or 150 mg/kg/day was orally administered to pregnant CD-1 mice (n = 25/group) from gestation days 6 to 15. No effects were observed on maternal animals, embryos, or fetuses. Based on the above, the NOAEL of OBV in the study was determined to be 150 mg/kg/day for maternal toxicity and embryo-fetal development.

ii) Embryo-fetal development studies in rabbits (4.2.3.5.2-267-3, 4.2.3.5.2-267-4)

In a preliminary study in which OBV 0 (vehicle[56)]), 10, 60, or 150 mg/kg/day was orally administered to pregnant NZW rabbits (n = 7/group) from gestation days 7 to 19, the maximum plasma exposure (C_{max} and AUC) in maternal animals was obtained in the 60 mg/kg group. In the main study, therefore, OBV 0 (vehicle[56)]), 10, or 60 mg/kg/day was orally administered to pregnant NZW rabbits (n = 23/group) from gestation days 7 to 19. No effects were observed on maternal animals, embryos, or fetuses. Based on the above, the NOAEL of OBV in the study was determined to be 60 mg/kg/day for maternal toxicity and embryo-fetal development.

(c) Mouse study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3-267-1)

OBV 0 (vehicle), 10, 40, or 200 mg/kg/day was orally administered to pregnant CD-1 mice (n = 25/group) from gestation day 6 to postpartum day 20. No effects were observed on maternal animals or offspring (F_1). Based on the above, the NOAEL of OBV in the study was determined to be 200 mg/kg/day in maternal animals and offspring (F_1).

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) PTV

(a) Toxicity studies of Impurities

i) Four-week oral dose toxicity study in rats (4.2.3.7.6-450-1)

PTV/RTV 0/0 (vehicle) or 300/30 mg/kg/day was orally administered to SD rats (n = 15/group) (with or without impurities[70]) added) for 4 weeks. No effects of impurities were observed on the toxicological profile[71]) in the 300/30 mg/kg group. Taking into account the content of impurities added and the specifications for the respective impurities in batches produced on a manufacturing scale, potential impurities contained in PTV/RTV/OBV combination product given at a recommended dose were considered not to pose any safety concerns.

ii) Genotoxicity (4.2.3.7.6-450-2 to 4)

Some of the impurities in PTV (Impurities A, B, and C) were found structurally alerting. These impurities were tested by Ames assay, and negative results were obtained. The impurities with specifications exceeding the safety threshold specified in "Impurities in New Drug Substances" (PMSB/ELD Notification No. 1216001 dated December 16, 2002; hereinafter, ICH Q3A Guideline) and "Impurities in New Drug Products" (PMSB/ELD Notification No. 0624001 dated June 24, 2003; hereinafter, ICH Q3B Guideline) were determined to be of no genotoxic concern because the expected amount of their intake was <1 mg/day and because no structural alerts were identified when structure activity correlation was examined as recommended in "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk"[72]) (hereinafter, ICH M7 Guideline [Step 4]).

3.(iii).A.(6).2) OBV

(a) Toxicity studies of metabolites

Repeated-dose toxicity, genotoxicity, and embryo-fetal development studies were conducted on m29 (acetophenone dianilide) and m36 (t-butyl demethylketo-hydroxy dianilide), the major metabolites in humans. No abnormal findings were observed in repeated-dose toxicity studies and embryo-fetal development studies, and genotoxicity studies yielded negative results. The plasma m29 exposure ($AUC_{0\text{-}24h}$) at the NOAEL of m29 for general toxicity (3.5 or 3 mg/kg/day [males or females]) and embryo-fetal development (4.5 mg/kg/day) were both 25-fold over the plasma m29 exposure[73]) following the administration at the recommended human dose (PTV/RTV/OBV, 150/100/25 mg/day).

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70) Impurities (D, E, F, G, H, I, J, K, L, M, and N) that may be synthesized during the manufacturing process were added at [redacted]% to [redacted]%.

71) Although vacuolation of the small intestine was observed in both groups, with and without impurities, this finding was minor to mild and was not aggravated by added impurities. Therefore, the applicant views it as a toxicologically insignificant change.

72) http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf. Accessed January, 2015

73) A comparison with the plasma exposure ($AUC_{0\text{-}24hr}$, 0.669 μg·hr/mL for m29 and 0.442 μg·hr/mL for m36) in Study M[redacted]-394

The plasma m36 exposure ($AUC_{0\text{-}24h}$) at the NOAEL of m36 for general toxicity and embryo-fetal development (6 mg/kg/day) were 38-fold and 27-fold, respectively, over the plasma m36 exposure[73] following the administration at the recommended human dose (PTV/RTV/OBV, 150/100/25 mg/day).

i) Four-week oral dose toxicity study of m29 in mice with 4-week recovery period (4.2.3.7.5-267-1)

m29 (0 [vehicle[74]], 1, 2, or 3.5 mg/kg/day for males and 0 [vehicle[74]], 1, 2, or 3 mg/kg/day for females) was orally administered to CD-1 mice (n = 16/sex/group for the vehicle and high-dose groups; n = 11/sex/group for the low- and intermediate-dose groups) for 4 weeks (including micronucleus induction assay and a 4-week recovery period[75]). No abnormalities or micronucleus induction was observed. Based on the above, the NOAEL of m29 in the study was determined to be 3.5 mg/kg/day for males and 3 mg/kg/day for females.

ii) Four-week oral dose toxicity study of m36 in mice with 4-week recovery period (4.2.3.7.5-267-2)

m36 (0 [vehicle[74]], 1.5, 3, or 6 mg/kg/day) was orally administered to CD-1 mice (n = 15/sex/group for the control and high-dose groups; n = 10/sex/group for the low- and intermediate-dose groups) for 4 weeks (including micronucleus induction assay and a 4-week recovery period[75]). No abnormalities or micronucleus induction was observed. Based on the above, the NOAEL of m36 in the study was determined to be 6 mg/kg/day.

iii) Genotoxicity studies (4.2.3.7.5-267-3, 4.2.3.7.5-267-4)

Ames assays and chromosomal aberration assays were conducted on m29 and m36. In the chromosomal aberration assay of m36 performed with metabolic activation, structurally abnormal cells were slightly increased (3.5%) during the 3-hour treatment at 400 μg/mL, but the value only slightly exceeded the upper limit of historical data (2.5%) with no reproducibility. This finding was therefore considered to be biologically insignificant, and m36 was assessed as being non-genotoxic in the study. Since other findings were also negative for both m29 and m36, these metabolites were determined to be non-genotoxic.

iv) Embryo-fetal development study of m29 in mice (4.2.3.7.5-267-6)

m29 (0 [vehicle], 1, 2.5, or 4.5 mg/kg/day) was orally administered to pregnant CD-1 mice (n = 50 for the control group, n = 30/group for the m29 groups) from gestation days 6 to 15. No effects were observed on maternal animals, embryos, or fetuses, and the NOAEL of m29 in the study was determined to be 4.5 mg/kg/day for maternal toxicity and embryo-fetal development.

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74) A mixed solution of HPMC-AS and Copovidone (ratio by weight; 29.4:70.6) and sodium phosphate buffer solution

75) Histopathological test was not conducted in the recovery period because no effects of treatment were observed at the end of the administration period.

v) Embryo-fetal development study of m36 in mice (4.2.3.7.5-267-7)

m36 (0 [vehicle], 1.5, 3, or 6 mg/kg/day) was orally administered to pregnant CD-1 mice (n = 55/group for the control group, n = 30/group[76)] for m36 groups) from gestation days 6 to 15. No effects were observed on maternal animals, embryos, or fetuses, and the NOAEL of m36 in the study was determined to be 6 mg/kg/day for maternal toxicity and embryo-fetal development.

(b) Toxicity studies of impurities (4.2.3.7.6-267-1)

In a study on impurities with specifications exceeding the safety threshold specified in the ICH Q3A Guideline and ICH Q3B Guideline, OBV 0 or 200 mg/kg/day (with or without impurities[77)]) was orally administered to SD rats (n = 10/sex/group) for 4 weeks. No effects of impurities were observed on the toxicological profile in the 200 mg/kg group. Taking into account the content of impurities added and the specifications for the respective impurities in batches produced on a manufacturing scale, impurities potentially contained in PTV/RTV/OBV combination product used in medical practice would not be considered to raise any safety concerns on general toxicity. The applicant explained that these impurities are of no genotoxicity concern because the expected amount of their intake is <1 mg/day and no structural alerts were identified when structure activity correlation was examined as recommended in the ICH M7 Guideline (Step 4).[72)]

(c) Phototoxicity (4.2.3.7.7-267-2)

Female SKH1 hairless mice (n = 6/group) orally received either OBV 0 (vehicle) or 200 mg/kg/day for 3 days or a single dose of 50 mg/kg of 8-methoxypsoralen, the positive control substance, and then were exposed to ultraviolet light.[78)] When skin reactions to UV radiation were examined, no effects were observed on the clinical condition, body weight, or skin of OBV-treated mice. Based on the above, OBV was considered to have no phototoxicity.

3.(iii).A.(6).3) Combination toxicity (4.2.3.7.7-267-1)

PTV/RTV/OBV 0/0/0 (vehicle[79)]) or 30/20/2 mg/kg/day was orally administered to CD-1 mice (n = 10/sex/group) for 4 weeks. No combination toxicity was observed, and PTV/RTV/OBV was considered to be of little toxicity concern.

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76) Due to a low pregnancy rate in the low-dose group, the test substance was administered to an additional 6 mice (n = 36 in total).

77) The impurity-added groups in the study consisted of groups containing approximately [redacted]% of Impurity O, approximately [redacted]% of Impurity P, Impurity Q, and Impurity R.

78) Mice were exposed to UVR at 0.5 MED (minimal erythema dose) for approximately 30 minutes from 6 hours after dosing on Day 3 in the vehicle-control and 200 mg/kg groups and from 1 hour after dosing in the positive-control group.

79) A solution of excipients contained in the PTV/RTV/OBV combination product (copovidone, d-alpha-tocopherol polyethylene glycol succinate, sorbitan monolaurate, lauroglycol FCC, colloidal silicon dioxide at a mass ratio of 89.8:4.5:3.5:1.1:1.1) prepared with 0.1% medical antiform C

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Effects on gallbladder

PMDA asked the applicant to explain whether there are any concerns about safety in humans associated with effects on the gallbladder observed in animals that received PTV/RTV (such as erosion/ulceration, inflammation, and epithelial hypertrophy/hyperplasia).

The applicant's response:

The observed effects on the gallbladder included erosion/ulceration, inflammation, and epithelial hypertrophy/hyperplasia in mice that received repeated doses for 6 months and epithelial degeneration/necrosis and oedema of the lamina propria in dogs that received repeated doses for 4 weeks or 9 months. The mode of action of these findings are unknown, but they are possibly attributable to the local effects of PTV and its metabolites, since both of them are subject to biliary excretion. The effects on the gallbladder have approximately 1.7-fold and ≥14-fold safety margin in mice and dogs, respectively, and all findings resolved or were resolving. Epithelial hypertrophy/hyperplasia observed in mice did not evolve into neoplastic lesions in a carcinogenicity study in TgHras mice, and were assessed as reversible. Epithelial degeneration/necrosis and oedema of the lamina propria observed in dogs were localized, slight in severity, and without effects on the laminar structure, and were therefore assessed to be of low toxicological significance. Although these findings cannot be directly monitored in clinical practice, bile duct abnormalities are expected to be detectable by symptoms and laboratory test results (such as serum γ-glutamyltransferase, ALP, and bilirubin levels), etc. In clinical studies of a combination of PTV/RTV and OBV (phase II study [M[redacted]-536] and phase III study [M13-004] in Japanese patients), bilirubin levels increased transiently, but ALP levels and other relevant parameters did not. On the basis of the above findings and discussions, it can be concluded that the effects on the gallbladder observed in mice and dogs are unlikely to raise safety concerns in humans.

PMDA's view:

The mechanisms of the effects on the gallbladder observed in mice and dogs have not been investigated, and the safety margin for the changes in the gallbladder of mice cannot be considered sufficient. Consequently, it cannot be ruled out that the changes observed in mice (such as erosion/ulceration, inflammation, and epithelial hypertrophy/hyperplasia) could occur in humans. On the other hand, given that PTV/RTV/OBV combination product is to be administered for 12 weeks according to the current proposal on its clinical use, and that the changes in mice were observed not in the 3-month study but only in the 6-month study, and were reversible by treatment withdrawal, it is considered from a toxicological viewpoint that the findings under discussion are unlikely to raise serious safety concerns in humans. The review results on the increases in bilirubin levels observed in clinical studies will be described in "4.(iii).B.(3).3) Hepatic impairment."

3.(iii).B.(2) Effects on gastrointestinal tract

Vacuolization of the small intestinal epithelium was observed in dogs receiving PTV and OBV (4.2.3.2-450-15, 4.2.3.2-267-15). Therefore, PMDA asked the applicant to explain the mode of action of this finding, its reversibility, and the occurrence of any relevant adverse events in clinical studies.

The applicant's explanation:

Vacuolization of the small intestinal epithelium was observed in dogs, with the severity being slight to moderate in the 9-month repeated-dose oral toxicity study of PTV and slight to mild in the 6-month repeated-dose oral toxicity study of OBV. The content of small intestinal vacuoles observed during PTV administration was identified as lipids by special staining, while the content of those observed during OBV administration was not investigated. Although the mode of action of vacuolization during administration of these test substances are unknown, neither destructive epithelial changes nor laboratory test abnormalities were observed. During PTV administration, fecal abnormalities (such as soft feces and diarrhea) increased in frequency. However, there was no correlation between the frequency of soft feces and pathological findings of vacuolization or reduced body weight gain secondary to fecal abnormalities (such as soft feces and diarrhea). Vacuolization observed during PTV administration tended to resolve after a 1-month recovery period. Vacuolization observed during OBV administration was not investigated for reversibility after recovery period, but given its mild findings, a preserved histological structure, and the absence of inflammation or other relevant changes, this vacuolization is considered to be a reversible change. On the basis of the above findings and discussions, vacuolization of the small intestinal epithelium is considered to be of low toxicological significance. The findings of vacuolization had 4.2-fold safety margin for PTV and 4.9-fold safety margin for OBV. Furthermore, in clinical studies, no serious adverse events were observed in association with the gastrointestinal tract, and the incidence of adverse events was similar between treated groups and placebo groups.

PMDA considered the applicant's explanation to be acceptable

4. Clinical data

Doses and plasma concentrations of paritaprevir hydrate (PTV) and ombitasvir hydrate (OBV) are presented based on the amounts of paritaprevir (anhydride) and ombitasvir (anhydride).

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

In the clinical development of PTV, 2 formulations (Formulations 1 and 2[80)]) were first used and then a combination preparation of PTV and ritonavir (RTV) (Formulation 3) was developed. In the clinical

80) [redacted]

development of OBV, 4 formulations (Formulations 4-7[81]) were used. [redacted][82] [redacted]. This section presents the results of biopharmaceutic studies (comparative bioavailability [BA] study and a food-effect study) of the PTV/RTV/OBV combination product in the proposed commercial formulation. Concentrations of PTV, RTV, and OBV in human plasma and urine were determined by high performance liquid chromatography/tandem mass spectrometry (lower limit of quantitation [LLOQ]: 0.5–10.2 ng/mL for PTV, 4.73–10.2 ng/mL for RTV, and 0.1–1.72 ng/mL for OBV).

4.(i).A.(1) Comparative BA (5.3.3.3-4, Study M[redacted]-505 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Comparative BA of a single oral dose of PTV/RTV/OBV combination product (2 tablets of either 50/50/12.5 mg tablet or 75/50/12.5 mg tablet) relative to single combination dosing (hereinafter, triple regimen) of Formulation 2 (2 or 3 PTV 50 mg tablets), approved RTV formulation, and Formulation 6 (OBV 12.5 mg tablet) was evaluated in healthy Japanese subjects (24 subjects included in pharmacokinetic [PK] analysis).[83] The results are shown in Table 21. The maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve from time 0 to infinity (AUC_{inf}) after treatment with PTV/RTV/OBV combination product tended to be similar or higher for PTV and nearly the same for RTV and OBV, compared with those after treatment with the triple regimen.

Table 21. Ratio of least squares means of PK parameters for active ingredients following the administration of PTV/RTV/OBV combination product relative to those of the 3-formulation combination

PTV/RTV/OBV Dose (mg)	n		Ratio of least squares means [90% confidence interval (CI)]	
			C_{max}	AUC_{inf}
100/100/25	22	PTV	1.30 [1.01, 1.69]	1.08 [0.89, 1.30]
		RTV	1.16 [0.99, 1.37]	0.99 [0.90, 1.10]
		OBV	0.79 [0.75, 0.84]	0.79 [0.76, 0.83]
150/100/25	24	PTV	1.70 [1.32, 2.19]	1.53 [1.27, 1.84]
		RTV	1.23 [1.05, 1.44]	1.08 [0.98, 1.19]
		OBV	0.94 [0.89, 0.99]	0.93 [0.88, 0.97]

81) [redacted]

82) [redacted]
The individual formulations used in clinical studies were as follows:
Formulation 1, phase I studies (M[redacted]-749, M[redacted]-384, and M[redacted]-603); Formulation 2, phase I studies (M[redacted]-196, M[redacted]-198, M[redacted]-200, M[redacted]-201, M[redacted]-215, M[redacted]-221, M[redacted]-680, M[redacted]-688, M[redacted]-997, M[redacted]-100, M[redacted]-103, M[redacted]-104, M[redacted]-392, M[redacted]-491, M[redacted]-492, M[redacted]-505, M[redacted]-506, and M[redacted]-783), and phase II study (M[redacted]-536); Formulation 3, phase I studies (M[redacted]-193, M[redacted]-394, M[redacted]-782, and M[redacted]-013); Formulation 4, phase I study (M[redacted]-116); Formulation 5, phase I studies (M[redacted]-116, M[redacted]-181, M[redacted]-215, and M[redacted]-221); Formulation 6, phase I studies (M[redacted]-193, M[redacted]-198, M[redacted]-200, M[redacted]-201, M[redacted]-680, M[redacted]-997, M[redacted]-100, M[redacted]-103, M[redacted]-392, M[redacted]-394, M[redacted]-491, M[redacted]-492, M[redacted]-505, M[redacted]-506, M[redacted]-782, M[redacted]-783, and M[redacted]-013) and phase II study (M[redacted]-536); Formulation 9, phase I studies (M[redacted]-189, M[redacted]-199, M[redacted]-202, M[redacted]-204, M[redacted]-205, M[redacted]-997, M[redacted]-100, M[redacted]-505, M[redacted]-771, M[redacted]-027, M[redacted]-229, M[redacted]-247, M[redacted]-324, and M[redacted]-325) and phase III study (M13-004).

83) The study was conducted as a 4-treatment, 4-period crossover study with a minimum 7-day washout period between treatments.

4.(i).A.(2) Food effect (5.3.1.1-1, Study M[redacted]-771 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The effect of food was evaluated on the PK of PTV/RTV/OBV combination product (two 75/50/12.5 mg tablets) in healthy Japanese subjects (20 subjects included in PK analysis) who received a single oral dose of PTV/RTV/OBV combination product under fasting or fed (30 minutes after a high-fat meal [approximately 900 kcal; fat ≥35%]) conditions.[84)] The results are shown in Table 22. The ratios of least squares means [90% confidence interval; CI] of C_{max} and AUC_{inf} in the fed state to those in the fasted state were 4.98 [3.25, 7.63] and 3.28 [2.36, 4.56], respectively, for PTV; 1.37 [1.03, 1.81] and 1.34 [1.10, 1.65], respectively, for RTV; and 1.95 [1.68, 2.27] and 1.73 [1.52, 1.96], respectively, for OBV, showing that the C_{max} and AUC_{inf} of each active ingredient were higher in the fed than in the fasted state. Time to maximum plasma drug concentration (t_{max}) was longer in the fed than in the fasted state.

Table 22. PK parameters of the active ingredients following administration of PTV/RTV/OBV combination product in the fasted or fed state

	n	C_{max} (ng/mL)	t_{max} a) (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ b) (h)	CL/F (L/h)	Vd/F (L)
In the fasted state							
PTV	20	542 ± 669	4.0 [2.0-6.0]	3360 ± 3920	5.7 [3.3-11.1]	80.6 ± 55.5	674 ± 406
RTV		1090 ± 675	4.0 [2.0-5.0]	6450 ± 3370	4.3 [3.3-5.5]	21.7 ± 16.0	144 ± 114
OBV		61.2 ± 16.7	4.0 [3.0-6.0]	876 ± 224	24.2 [18.6-41.6]	30.6 ± 9.13	1090 ± 305
In the fed state							
PTV	20	2040 ± 1390	5.0 [4.0-8.0]	9860 ± 6750	5.4 [4.0-8.9]	24.4 ± 17.5	210 ± 185
RTV		1290 ± 475	5.0 [4.0-6.0]	8020 ± 3040	3.9 [3.1-6.3]	14.4 ± 5.86	83.1 ± 37.9
OBV		119 ± 31.0	5.0 [4.0-6.0]	1490 ± 304	23.5 [18.5-36.1]	17.4 ± 3.33	602 ± 136

Mean ± standard deviation; $t_{1/2}$, elimination half-life; CL/F, apparent oral clearance; Vd/F, apparent volume of distribution
a) Median [range]; b) Harmonic mean [range]

4.(i).B Outline of the review by PMDA

4.(i).B.(1) Food effect

PMDA asked the applicant to explain the mechanism of the C_{max} and AUC_{inf} of each active ingredient in the fed state being higher than those in the fasted state and to justify the proposed dosage and administration requiring PTV/RTV/OBV combination product to be given "during or immediately after meal" while PTV/RTV/OBV combination product was administered after meal in the Japanese phase III study (M13-004).

The applicant's explanation:

The C_{max} and AUC_{inf} of each active ingredient in the fed state were greater than those in the fasted state probably for the following reasons:

(i) Intake of food prolonged gastric retention time, resulting in the absorption time of each active ingredient being prolonged.

(ii) Fat contained in the meal and bile salts in bile secreted by food intake enhanced the solubilization of PTV, RTV, and OBV, which are lipid-soluble compounds, and therefore enhanced the BA of PTV/RTV/OBV combination product.

84) The study was conducted as a 2-treatment, 2-period crossover study with a minimum 7-day washout period between treatments.

Considering that PTV, RTV, and OBV were administered 30 minutes after the start of food consumption in Japanese and foreign phase I studies including the food-effect study [see "4.(i).A.(2) Food effect"] and with food in foreign phase II and III studies, the proposed dosage and administration requires PTV/RTV/OBV combination product to be given "during or immediately after meal" based on clinical data obtained in Japan and overseas. However, the proposed dosage and administration with regard to meal time will be changed to "after meal," taking into account that the efficacy and safety of PTV/RTV/OBV combination product given after meal were evaluated in the Japanese phase III study (M13-004).

PMDA considers the applicant's explanation to be acceptable.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The results of a population pharmacokinetic (PPK) analysis using data from foreign phase I studies (e.g., PK studies in healthy subjects, PK studies in subjects with hepatic or renal impairment, PK interaction studies) and Japanese phase III study were submitted. The results of *in vitro* studies using human biomaterials are presented in the following sections in "3.(ii).A": (2) Distribution (PTV), (3) Metabolism (PTV), (5) Pharmacokinetic drug interactions (PTV), (7) Distribution (OBV), (8) Metabolism (OBV), (10) Pharmacokinetic drug interactions (OBV), and (11) Pharmacokinetic drug interactions (RTV).

PK parameters are expressed as mean values unless otherwise noted.

4.(ii).A.(1) Studies in healthy subjects

4.(ii).A.(1).1) Phase I clinical study in Japanese subjects (5.3.3.3-2, Study M[redacted]-384 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK of PTV and RTV was evaluated in healthy Japanese subjects (40 subjects included in PK analysis), who received a single oral dose of or once daily (hereinafter, QD) 14-day multiple oral doses of PTV 50 to 200 mg in combination with RTV 100 mg. The results are shown in Table 23. The C_{max} and AUC of PTV after single or multiple doses increased more than dose-proportionally within the range from 50 to 200 mg. The C_{max} and AUC of RTV after single or multiple doses of PTV and RTV increased with increasing dose of PTV.

The applicant's explanation:

This increase in the C_{max} and AUC of RTV with the increase in dose of PTV was thought to be induced by the inhibitory effect of PTV on P-glycoprotein.

Table 23. PK parameters of each active ingredient after single or multiple oral doses of PTV and RTV

Dosage	Dose (mg)		n	C_{max} (ng/mL)	t_{max}[a] (h)	AUC[b] (ng·h/mL)	$t_{1/2}$[c] (h)	CL/F (L/h)	Vd/F (L)	Accumulation index[d]
Single dose	PTV	50	8	41.3 ± 22.9	5.0 [3.0-6.0]	349 ± 129	6.4 [4.4-9.5]	169 ± 81.4	1560 ± 554	–
	RTV	100		706 ± 223	4.5 [2.0-10.0]	4660 ± 1420	4.9 [4.1-5.9]	23.8 ± 9.31	169 ± 71.7	–
	PTV	100	8	287 ± 183	5.0 [4.0-6.0]	1760 ±962	6.4 [5.1-9.3]	69.5 ± 29.9	671 ± 366	–
	RTV	100		1090 ± 533	4.5 [4.0-5.0]	6860 ± 3920	4.7 [4.0-6.9]	18.3 ± 7.85	122 ± 49.0	–
	PTV	200	8	4870 ± 2600	4.0 [4.0-6.0]	24,600 ± 13,400	4.3 [3.5-5.5]	12.7 ± 10.4	81.4 ± 64.5	–
	RTV	100		1500 ± 422	4.5 [2.0-5.0]	8180 ± 2920	3.5 [2.8-4.9]	13.9 ± 5.61	76.8 ± 47.6	–
Multiple doses (14 days)	PTV	50	8	48.6 ± 17.4	5.0 [2.0-8.0]	380 ± 167	7.0 [5.7-11.1]	156 ± 72.1	1628 ± 850	1.13 ± 0.48
	RTV	100		1210 ± 267	4.0 [1.0-8.0]	7260 ± 1030	5.3 [4.7-6.9]	14.1 ± 2.48	109 ± 20.5	1.52 ± 0.50
	PTV	200	8	6770 ± 2330	4.0 [3.0-6.0]	32,500 ± 15,100	4.2 [2.8-7.1]	8.03 ± 5.64	50.3 ± 34.2	1.40 ±0.56
	RTV	100		1710 ± 470	4.0 [2.0-5.0]	10,000 ± 2830	3.8 [2.9-4.9]	10.9 ± 3.8	59.8 ± 20.4	1.00 ± 0.18

Mean ± standard deviation
a) Median [range]; b) Single dose, AUC_{inf}; multiple doses, AUC from time 0 to 24 hours (AUC_{0-24}); c) Harmonic mean [range]
d) Ratio of AUC_{0-24} on Day 14 to AUC_{0-24} on Day 1

4.(ii).A.(1).2) Phase I clinical studies in Japanese and non-Japanese subjects

(a) Phase I study (5.3.3.3-1, Study M[redacted]-688 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK of PTV and RTV was evaluated in healthy subjects (10 each of Japanese subjects living abroad, Han Chinese subjects, and Caucasian subjects included in PK analysis) after a single oral dose of PTV 250 mg in combination with RTV 100 mg. The results are shown in Table 24. The C_{max} and AUC_{inf} of PTV and RTV in Japanese subjects were greater than those in Caucasian subjects.

Table 24. PK parameters of each active ingredient after a single oral dose of PTV and RTV

	n	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$[b] (h)
PTV					
Japanese	10	5530 ± 5190	3.5 [2.0-5.0]	25,100 ± 24,000	4.5 [3.0-8.4]
Chinese	10	3450 ± 4030	2.5 [2.0-5.0]	15,900 ± 21,200	5.8 [3.8-9.8]
Caucasian	10	2920 ± 2040	4.0 [2.0-5.0]	12,900 ± 10,300	5.9 [4.4-9.2]
RTV					
Japanese	10	1060 ± 499	6.5 [4.0-12.0]	6990 ± 2760	3.8 [3.0-4.8]
Chinese	10	1040 ± 497	5.0 [3.0-10.0]	6120 ± 2670	4.1 [2.8-5.5]
Caucasian	10	788 ± 322	6.0 [4.0-24.0]	6080 ± 2780	4.5 [3.6-5.9]

Mean ± standard deviation
a) Median [range]; b) Harmonic mean [range]

(b) Phase I study (5.3.3.3-3, Study M[redacted]-181 [redacted] 20[redacted] to [redacted] 20[redacted])

The PK of OBV was evaluated in in healthy subjects (12 each of Japanese subjects living abroad, Han Chinese subjects, and Caucasian subjects included in PK analysis) during treatment with multiple oral doses of 25 or 200 mg of OBV QD for 7 days. The results are shown in Table 25. The C_{max} and AUC from time 0 to 24 hours (AUC_{0-24}) of OBV in Japanese subjects were greater than those in Caucasian subjects.

Table 25. PK parameters during treatment with multiple oral doses of OBV

Dose (mg)	Ethnic Group	n	Time point	C_{max} (ng/mL)	t_{max} [a)] (h)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ [b)] (h)	Accumulation index[d)]
25	Japanese	6	Day 1	60.0 ± 26.0	5.0 [4.0-5.0]	503 ± 182	–	–
			Day 7	72.0 ± 33.0	5.0 [4.0-5.0]	704 ± 351	25.1 [19.4-37.7]	1.38 ± 0.37
	Chinese	6	Day 1	58.5 ± 23.7	4.5 [3.0-5.0]	486 ± 156	–	–
			Day 7	76.4 ± 20.1	4.5 [3.0-5.0]	646 ± 166	26.7 [21.2-33.9]	1.37 ± 0.25
	Caucasian	6	Day 1	40.1 ± 3.48	5.0 [3.0-6.0]	363 ± 50.2	–	–
			Day 7	44.8 ± 12.9	5.0 [3.0-5.0]	463 ± 137	25.3 [14.6-37.3]	1.29 ± 0.42
200	Japanese	6	Day 1	688 ± 244	5.0 [4.0-5.0]	6310 ± 2810	–	–
			Day 7	797 ± 312	5.0 [5.0-5.0]	8570 ± 4320	26.7 [19.5-34.3]	1.34 ± 0.11
	Chinese	6	Day 1	637 ± 130	5.0 [4.0-5.0]	5260 ± 921	–	–
			Day 7	683 ± 167	5.0 [4.0-5.0]	6640 ± 1480	31.4 [21.3-57.4]	1.27 ± 0.23
	Caucasian	6	Day 1	451 ± 94.8	5.0 [4.0-5.0]	4070 ± 839	–	–
			Day 7	475 ± 114	4.5 [3.0-5.0]	5110 ± 1220	23.1 [17.6-34.8]	1.26 ± 0.16

Mean ± standard deviation
a) Median [range]; b) Harmonic mean [range]; c) Ratio of AUC_{0-24} on Day 7 relative to AUC_{0-24} on Day 1

(C) Phase I study (5.3.3.3-5, Study M[redacted]-221 [redacted] 20[redacted] to [redacted] 20[redacted])

A phase I study was conducted to assess the effect of coadministration of PTV and RTV on the PK of OBV (cohort 1) and the effect of coadministration of OBV on the PK of PTV and RTV (cohort 2) in healthy subjects (24[85)] each of Japanese subjects living abroad, Han Chinese subjects, and Caucasian subjects included in PK analysis).[86)] The results are shown in Table 26 and Table 27. The C_{max} and AUC_{0-24} of OBV coadministered with PTV and RTV were greater than those of OBV administered as a single agent. The C_{max} and AUC_{0-24} of PTV 250 mg coadministered with OBV were similar to those after administration of PTV without OBV in any of these ethnic groups. Meanwhile, C_{max} and AUC_{0-24} of PTV 200 mg coadministered with OBV in Japanese subjects were less than those of PTV administered without OBV. The C_{max} and AUC_{0-24} of RTV were not affected by coadministration with OBV.

Table 26. Effects of coadministration of PTV and RTV on the PK of OBV (cohort 1)

	Ethnic group	n	Ratio of least squares means [90% CI][a)]	
			C_{max}	AUC_{0-24}
OBV	Japanese	12	1.46 [1.29, 1.64]	1.63 [1.48, 1.80]
	Chinese	12	1.46 [1.29, 1.64]	1.63 [1.48, 1.80]
	Caucasian	12	1.27 [1.13, 1.43]	1.45 [1.31, 1.60]

a) Using PK data after coadministration (Day 21) and after non-coadministration (Day 7), ratio of PK after coadministration to PK after non-coadministration was calculated.

85) In this study, the effect of coadministration with dasabuvir, a component that is not contained in the product, was also evaluated, but its results are not presented in this review report.

86) Cohort 1 received multiple oral doses of 25 mg of OBV QD for 7 days and then multiple oral doses of 250 or 200 mg of PTV, 100 mg of RTV, and 25 mg of OBV QD for 14 days.
Cohort 2 received multiple oral doses of 250 or 200 mg of PTV and 100 mg of RTV QD for 14 days and then multiple oral doses of 250 or 200 mg of PTV, 100 mg of RTV, and 25 mg of OBV QD for 7 days.

Table 27. Effects of OBV on the PK of PTV and RTV (cohort 2)

Dose of PTV/RTV (mg)		Ethnic group	n	Ratio of least squares means [90% CI][a)]	
				C_{max}	AUC_{0-24}
200/100	PTV	Japanese	6	0.43 [0.25, 0.74]	0.50 [0.29, 0.84]
		Chinese	6	0.88 [0.51, 1.53]	0.77 [0.46, 1.31]
		Caucasian	6	0.73 [0.42, 1.27]	0.88 [0.52, 1.49]
	RTV	Japanese	6	0.79 [0.61, 1.02]	0.79 [0.66, 0.95]
		Chinese	6	1.05 [0.81, 1.36]	1.02 [0.84, 1.23]
		Caucasian	6	0.78 [0.60, 1.01]	0.88 [0.73, 1.07]
250/100	PTV	Japanese	6	0.98 [0.57, 1.71]	0.98 [0.58, 1.66]
		Chinese	6	0.92 [0.53, 1.60]	0.84 [0.50, 1.42]
		Caucasian	6	0.95 [0.54, 1.65]	0.93 [0.55, 1.58]
	RTV	Japanese	6	1.12 [0.86, 1.46]	1.11 [0.92, 1.34]
		Chinese	6	1.09 [0.84, 1.41]	0.99 [0.82, 1.19]
		Caucasian	6	1.29 [0.99, 1.68]	1.20 [0.99, 1.44]

a) Using PK data after coadministration (Day 21) and after non-coadministration (Day 14), ratio of PK after coadministration to PK after non-coadministration was calculated.

4.(ii).A.(1).3) Phase I clinical studies in non-Japanese subjects

(a) Phase I study (Reference data 5.3.3.3-1, Study M[redacted]-749 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK of PTV and RTV was evaluated in healthy subjects (65 subjects included in PK analysis), who received a single oral dose of PTV 300 to 900 mg as a single agent or PTV 25 to 400 mg in combination with RTV 50 to 200 mg. The results are shown in Table 28. The C_{max} and AUC_{inf} of PTV after coadministration of PTV 300 mg and RTV 100 mg were approximately 28-fold and 48-fold, respectively, over those after administration of PTV 300 mg as a single agent. The C_{max} and AUC_{inf} of PTV increased with increasing dose of RTV. The C_{max} and AUC_{inf} of RTV after coadministration with PTV 100 mg increased more than dose-proportionally when the dose of RTV ranged from 50 to 200 mg. The plasma concentration of PTV at 24 hours after administration of PTV 300 mg as a single agent and after coadministration of PTV 300 mg and RTV 100 mg was 0.126 and 42.5 ng/mL, respectively.

Table 28. PK parameters of each active ingredient after a single oral dose of PTV alone or in combination with RTV

Dosage	Dose (mg)		n	C_{max} (ng/mL)	t_{max} [a)] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ [b)] (h)	CL/F (L/h)	Vd/F (L)
Single agent	PTV	300	6	121 ± 68.2	2.0 [2.0-3.0]	391 ± 189	2.7 [2.1-4.2]	948 ± 502	3775 ± 2096
	PTV	600	6	780 ± 599	2.0 [1.0-2.0]	1651 ± 729	2.7 [1.7-4.2]	434 ± 205	1745 ± 644
	PTV	900	6	5120 ± 3581	2.0 [2.0-3.0]	8758 ±7401	3.1 [1.8-9.7]	234 ± 242	945 ± 612
Coadministration	PTV	100	6	48.2 ± 28.7	2.5 [0.5-5.0]	322 ± 85.0	6.4 [3.7-8.0]	329 ± 85.2	3172 ± 773
	RTV	50		90.3 ± 70.3	5.0 [0.5-12.0]	779 ± 407	6.5 [3.9-18.6]	96.2 ± 82.1	1574 ± 2556
	PTV	100	6	115 ± 78.4	4.5 [3.0-5.0]	970 ± 542	5.7 [4.8-8.0]	150 ± 121	1307 ± 1148
	RTV	100		586 ± 305	5.0 [2.0-5.0]	3589 ± 1414	5.0 [4.5-5.8]	31.7 ± 11.8	230 ± 94.1
	PTV	100	6	223 ± 170	5.0 [2.0-8.0]	1622 ± 1240	5.5 [4.8-6.8]	96.3 ± 67.0	835 ± 694
	RTV	200		2925 ± 1452	5.0 [3.0-10.0]	23,301 ± 12,270	5.4 [4.5-7.1]	11.8 ± 8.50	86.9 ± 50.8
	PTV	300	6	3397 ± 3297	5.0 [2.0-8.0]	18,543 ± 17,672	4.6 [3.4-6.5]	67.3 ± 108	478 ± 790
	RTV	100		675 ± 331	6.5 [3.0-12.0]	6994 ± 5816	4.0 [3.3-6.0]	22.5 ± 14.5	131 ± 92.0

Mean ± standard deviation; a) Median [range]; b) Harmonic mean [range]

(b) Phase I study (Reference data 5.3.3.1-5, Study M[redacted]-116 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK of OBV was evaluated in healthy subjects (32 subjects included in PK analysis) who received multiple oral doses of OBV 5 to 200 mg QD for 10 days. Subjects in the OBV 5 mg group received a single oral dose of OBV 5 mg and RTV 100 mg 1 day after the completion of multiple dose administration of OBV to evaluate the PK of OBV. The results are shown in Table 29. The C_{max} and AUC_{0-24} during multiple dose administration of OBV were nearly dose-proportional when the dose of OBV was within the range from 5 to 100 mg. The C_{max} and AUC_{0-24} after coadministration of OBV 5 mg and RTV 100 mg increased by approximately 70% and 59%, respectively, compared to those after administration of OBV 5 mg as a single agent.

Table 29. PK parameters during multiple oral doses of OBV

Dose (mg)	n	Time point	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$[b)] (h)	CL/F (L/h)	Vd/F (L)
5	8	Day 1	5.10 ± 2.00	5.0 [2.0-6.0]	45.3 ± 18.1	–	–	–
		Day 10	7.09 ± 2.42	5.0 [3.0-5.0]	64.3 ± 23.6	–	85.8 ± 26.0	1420 ± 459
		Day 11[c)]	11.9 ± 3.41	5.0 [5.0-5.0]	99.9 ±23.8	22.5 [14.4-31.2]	–	–
25	8	Day 1	37.6 ± 13.0	5.0 [2.0-5.0]	326 ± 111	–	–	–
		Day 10	56.2 ± 21.2	5.0 [3.0-5.0]	529 ± 192	28.1 [21.8-45.9]	51.9 ± 15.3	2140 ± 601
100	8	Day 1	122 ± 35.2	5.0 [3.0-5.0]	1070 ± 245	–	–	–
		Day 10	156 ± 51.3	5.0 [3.0-5.0]	1670 ± 448	24.7 [16.9-42.2]	65.5 ± 24.9	2450 ± 792
200[d)]	8	Day 1	388 ± 64.4	5.0 [3.0-6.0]	3510 ± 718	–	–	–
		Day 10	581 ± 181	5.0 [5.0-5.0]	5470 ± 1700	33.8 [24.3-49.6]	39.9 ± 12.9	1970 ± 463

Mean ± standard deviation; a) Median [range]; b) Harmonic mean [range]; c) Coadministration with RTV 100 mg; d) Use of Formulation 5 in the 200 mg group only (Formulation 4 for the other treatment groups)

(c) Phase I study (Reference data 5.3.3.1-8, Study M[redacted]-603 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK of PTV and RTV was evaluated in healthy subjects (26 subjects included in PK analysis), who received multiple oral doses of PTV, RTV, and dasabuvir (an NS5B polymerase inhibitor).[87)] The results are shown in Table 30. The C_{max} and AUC_{0-24} of PTV after coadministration with dasabuvir (Day 17) were greater than those after administration without dasabuvir (Day 20). The PK of RTV was not affected by coadministration with dasabuvir.

Table 30. PK parameters during multiple oral doses of PTV, RTV, and dasabuvir

	Time point	Coadministration with [redacted] mg of dasabuvir				Coadministration with [redacted] mg of dasabuvir			
		n	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{0-24} (ng·h/mL)	n	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{0-24} (ng·h/mL)
PTV	Day 17	14	3140 ± 1840	4.0 [2.0-6.0]	14,400 ± 9790	12	3170 ±2320	4.0 [3.0-6.0]	13,000 ± 9270
	Day 20		2520 ± 1800	4.0 [2.0-4.0]	9890 ± 6970		2150 ± 1690	4.0 [2.0-4.0]	8080 ± 6320
RTV	Day 17		1360 ± 330	4.0 [2.0-6.0]	8160 ± 1550		1410 ± 444	4.0 [2.0-8.0]	9080 ± 2380
	Day 20		1280 ± 508	4.0 [4.0-6.0]	7140 ± 1520		1340 ± 539	4.0 [4.0-6.0]	7700 ± 2200

Mean ± standard deviation; a) Median [range]

(d) Absolute BA (5.3.1.1-2, Study M[redacted]-229 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The absolute BA of PTV and OBV was evaluated in healthy subjects (16 subjects included in PK analysis) who received a single oral dose of PTV/RTV/OBV combination product (150/100/25 mg) and, after 4.75 hours, received a single intravenous infusion of ^{14}C-PTV (100 μg) or ^{14}C-OBV (25 μg) over

87) A single oral dose of dasabuvir was administered on Day 1, and after a 2-day washout period, multiple QD oral doses of PTV 200 mg and RTV 100 mg and multiple BID oral doses of dasabuvir [redacted] or [redacted] mg were coadministered for 14 days from Day 4. From Day 18, multiple QD oral doses of PTV 200 mg and RTV 100 mg were coadministered for 3 days.

15 minutes. The AUC_{inf} of PTV and ^{14}C-PTV was 3040 ng·h/mL and 3890 pg·h/mL, respectively, and the AUC_{inf} of OBV and ^{14}C-OBV was 1600 ng·h/mL and 3330 pg·h/mL, respectively. Based on the above, the absolute BA of PTV and OBV after oral administration of PTV, RTV, and OBV was determined to be 52.6% and 48.1%, respectively.

(e) Mass balance study of PTV (reference data 5.3.3.1-4, Study M[redacted]-798 [redacted] 20[redacted] to [redacted] 20[redacted])

The mass balance was investigated in healthy subjects (4 subjects included in PK analysis), who received a single oral dose of ^{14}C-PTV 200 mg in combination with RTV 100 mg. Within 192 hours of administration, 96.5% of the administered radioactivity was recovered (8.76% and 87.8% of radioactivity excreted in urine and feces, respectively).The unchanged PTV accounted for 88.9% of the AUC of total radioactivity in plasma from time 0 to the last measurable time point (AUC_t), and 5 different metabolites[88)] were detected in plasma. Unchanged PTV (1.10% of administered radioactivity) and 11 different metabolites[89)] (mainly M29, M2, and M3/18) were detected in feces, and unchanged PTV (0.05% of administered radioactivity) and 3 different metabolites[90)] (mainly M13) were detected in urine.

(f) Mass balance study of OBV (reference data 5.3.3.1-6, Study M[redacted]-186 [redacted] 20[redacted] to [redacted] 20[redacted])

The mass balance was investigated in healthy subjects (4 subjects included in PK analysis), who received a single oral dose of ^{14}C-OBV 25 mg. Within 192 hours after administration, 92.2% of the administered radioactivity was recovered (1.91% and 90.2% of radioactivity excreted in urine and feces, respectively). The unchanged OBV accounted for 8.85% of the AUC of total radioactivity in plasma from time 0 to 192 hours after administration ($AUC_{0\text{-}192}$), and 13 different metabolites[91)] (mainly, m23, m29, m36, and m37) were detected in plasma. Unchanged OBV (87.8% of administered radioactivity) and 5 different metabolites[92)] were detected in feces, and unchanged OBV (0.03% of administered radioactivity) and 5 different metabolites[93)] were detected in urine.

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88) M2 (monohydroxide) and M29 (acetylcyclopropane-sulfonamide hydrolysate) accounted for 7.8% and 3.2%, respectively, of AUC_t for plasma radioactivity.
M3 (dihydroxide), M6 (monohydroxide), and M13 (5-methylpyrazine-2- carboxylic acid) were detected in minute amounts.

89) M2, M3/M18 (M18, monoxide of M29 [acetylcyclopropane-sulfonamide hydrolysate]), and M29 accounted for 8.55%, 7.47%, and 59.9%, respectively, of administered radioactivity.
M6, M13, M14 (monoxide of M29 [acetylcyclopropane-sulfonamide hydrolysate]), M17 (dioxide), M22/23 (unknown metabolite/dioxide of M29 [acetylcyclopropane-sulfonamide hydrolysate]), and M24 (cysteine conjugate of an oxide) were all ≤3.3% of administered radioactivity.

90) M13 accounted for 8.57% of administered radioactivity, and M2 and M29 accounted for <3% of administered radioactivity.

91) m23 (dianilide), m29 (acetophenone dianilide), m36 (t-butyl demethylketo-hydroxy dianilide), and m37 (t-butyl demethyl dihydroxy dianilide) accounted for 15.0%, 31.2%, 21.4%, and 13.9%, respectively, of radioactivity in plasma.
m5 (monoxide), m6 (monoanilide), m7 (pyrrolidine carboxylic acid), m9 (hydrate), m25 (t-butyl dihydroxide of m23 [dianilide]), m26 (t-butyl hydroxy dianilide), m28 (t- butyl acid of m23 [dianilide]), m34 (t-butyl demethyl hydroxy dianilide), and m35 (t-butyl demethyl dihydroxy dianilide) were all <5% of radioactivity in plasma.

92) m2, m3, m5, m6, or m9 were all <1% of administered radioactivity.

93) mu1 to 5 (unknown metabolites) were all <1% of administered radioactivity.

4.(ii).A.(2) Studies in patients

4.(ii).A.(2).1) Japanese phase II clinical study (5.3.5.1-2, Study M[redacted]-536 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Of patients with chronic hepatitis C enrolled in this study, 73 patients with genotype 1b HCV infection received multiple oral doses of 100 or 150 mg of PTV QD in combination with 100 mg of RTV and 25 mg of OBV. The PK of each active ingredient on Day 1 of coadministration was evaluated. In patients with chronic hepatitis C (genotype 1b) in the PTV 150 mg group, the geometric mean C_{max}, t_{max}, and $AUC_{0\text{-}24}$ were 1920 ng/mL, 3.9 hours, and 16,000 ng·h/mL, respectively, for PTV; 821 ng/mL, 6.6 hours, and 8850 ng·h/mL, respectively, for RTV; and 125 ng/mL, 4.3 hours, and 1430 ng·h/mL, respectively, for OBV.

4.(ii).A.(2).2) PPK analysis (5.3.3.5-1)

PPK analysis (software used, NONMEM version 7.3) was performed using PK data (257 subjects; 1755 time points for PTV, 1754 time points for RTV, and 1762 time points for OBV) obtained from chronic hepatitis C patients with or without compensated cirrhosis (both genotype 1b) in the Japanese phase III study (M13-004). A one-compartment model with first-order absorption and first-order elimination was used as the final model for PTV, RTV, and OBV. Candidate covariates included the presence or absence of hepatic cirrhosis for CL/F of PTV and RTV, and sex, presence or absence of hepatic cirrhosis, and creatinine clearance (CL_{cr}) for CL/F of OBV.[94)] The steady-state PK parameters in chronic hepatitis C patients with or without compensated cirrhosis after multiple QD oral doses of PTV/RTV/OBV combination product (150/100/25 mg) were estimated using the final model as shown in Table 31.

Table 31. Steady-state PK parameters of individual active ingredients estimated using the final model in chronic hepatitis C (CHC) patients

Dose (mg)		C_{max} (ng/mL)		$AUC_{0\text{-}24}$ (ng·h/mL)		C_{trough} (ng/mL)	
		CHC patients with compensated cirrhosis	CHC patients without compensated cirrhosis	CHC patients with compensated cirrhosis	CHC patients without compensated cirrhosis	CHC patients with compensated cirrhosis	CHC patients without compensated cirrhosis
PTV	150	489 (141)	200 (179)	7004 (155)	3015 (156)	71.6 (186)	36.9 (173)
RTV	100	258 (109)	154 (140)	4169 (103)	2521 (118)	63.1 (96.2)	40.0 (86.9)
OBV	25	48.5 (56.3)	58.6 (59.6)	979 (47.5)	1213 (50.6)	29.1 (39.6)	37.7 (39.7)

Geometric mean (CV%); C_{trough}, Trough plasma concentration

The C_{max}, $AUC_{0\text{-}24}$, and trough plasma concentration (C_{trough}) of OBV in females were estimated to be greater than those in males by 58% to 81%. However, the applicant explained that exposure-response analysis detected no relationship between the AUC of OBV and the incidence of adverse events and that there were no gender-related differences in the safety profile of PTV/RTV/OBV combination product in any Japanese and foreign clinical studies.

94) Candidate covariates included age, sex, body weight, BMI, body surface area, CL_{cr}, estimated glomerular filtration rate (eGFR), and presence or absence of cirrhosis for CL/F; and age, sex, body weight, BMI, and body surface area for apparent volume of distribution (Vc/F) of the central compartment.

4.(ii).A.(2).3) Exposure-response analysis

Relationships between virologic response and the steady-state C_{max}, $AUC_{0\text{-}24}$, and C_{trough} of PTV and OBV were investigated using data obtained from chronic hepatitis C patients with or without compensated cirrhosis (both genotype 1b) in the Japanese phase III study (M13-004). The geometric means of C_{max}, $AUC_{0\text{-}24}$, and C_{trough} in patients who experienced virologic failure[95)] were 140 ng/mL, 2123 ng·h/mL, and 25 ng/mL, respectively, for PTV, and 48 ng/mL, 992 ng·h/mL, and 30 ng/mL, respectively, for OBV. Meanwhile, the C_{max}, $AUC_{0\text{-}24}$, and C_{trough} in other patients (who achieved absence of detectable virus at 12 weeks after the end of therapy [a 12-week sustained virologic response; hereinafter, SVR12] or who did not achieve SVR12 for reasons other than virologic failure) were 235 ng/mL, 3522 ng·h/mL, and 42 ng/mL, respectively, for PTV; and 57 ng/mL, 1179 ng·h/mL, and 36 ng/mL, respectively, for OBV. These results showed that PTV exposure tended to be lower in patients who experienced virologic failure than in other patients (who achieved SVR 12 or who did not achieve SVR12 for reasons other than virologic failure), and OBV exposure was similar.

Relationships between safety and the AUC of PTV, RTV, and OBV were investigated using data obtained from chronic hepatitis C patients with or without compensated cirrhosis (both genotype 1b) in the Japanese phase III study (M13-004). The results showed that there was a relationship between the increase in AUC of PTV and the increase in the incidence of ≥Grade 2 drug-induced rash[96)] and increased total bilirubin.

The dose in the Japanese phase II study was determined to be 100 or 150 mg for PTV, 100 mg for RTV, and 25 mg for OBV in consideration of the following:

- Modeling and simulation[97)] were conducted based on the results of a total of 5 foreign phase I and II studies,[98)] and the relationship between plasma concentrations of PTV and levels of HCV RNA was assessed using a sigmoid maximum effect (E_{max}) model. As a result, the SVR12 rate in Japanese patients was estimated to be approximately 80% when ≥100 mg of PTV was administered once daily in combination with 100 mg of RTV and 25 mg of OBV.
- In an analysis of the relationship between the AUC and C_{trough} of OBV and changes from baseline in HCV RNA level based on data from foreign phase I study (M[redacted]-116) and phase II study (M[redacted]-386), the dose of OBV needed for a sufficient decrease in HCV RNA level was estimated to be 25 mg.

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95) Virologic failure was defined as subjects who met any one of the following criteria:
(1) After a decrease in HCV RNA to <LLOQ, HCV RNA of ≥LLOQ was observed at 2 consecutive time points during treatment.
(2) An increase from the minimum level in HCV RNA by >1 $\log_{10}$ IU/mL was observed at 2 consecutive time points during treatment.
(3) HCV RNA did not decrease to <LLOQ at any time during a ≥36-day treatment.

96) An event defined by the sponsor based on MedDRA PT, including skin eruption and dermatitis.

97) A one-compartment model with dose-dependent BA was used for PTV and a two-compartment model with first-order absorption was used for OBV.

98) Studies M[redacted]-351, M[redacted]-380, M[redacted]-602, M[redacted]-116, and M[redacted]-267

4.(ii).A.(3) Intrinsic factors

4.(ii).A.(3).1) Foreign PK study in patients with hepatic impairment (reference data 5.3.3.3-6, Study M[redacted]-215 [[redacted] 20[redacted] to [redacted] 20[redacted]])

After a single oral dose of PTV 200 mg in combination with RTV 100 mg, OBV 25 mg, and an NS5B Inhibitor [redacted] mg, was administered to subjects with hepatic impairment[99] (mild, 6; moderate 6; severe, 5) and 7 subjects with normal hepatic function, the PK of each active ingredient was evaluated. The results are shown in Table 32.

The applicant provided the following explanations of the effect of hepatic impairment on the PK of each active ingredient:

- No notable increase was observed in the C_{max} and AUC_{inf} of PTV and OBV in subjects with mild or moderate hepatic impairment compared with those in subjects with normal hepatic function. Therefore, there is no need to adjust the dose of PTV/RTV/OBV combination product for patients with mild or moderate hepatic impairment.
- The C_{max} and AUC_{inf} of PTV in subjects with severe hepatic impairment were 4.25-fold and 10.5-fold, respectively, over those in subjects with normal hepatic function. Therefore, the use of PTV/RTV/OBV combination product in patients with severe hepatic impairment is not recommended.

In a plasma protein binding assay, the unbound fraction (f_u) of PTV, RTV, and OBV in subjects with severe hepatic impairment was 2.24-fold that in subjects with normal hepatic function.

Table 32. PK parameters of PTV, RTV, and OBV in subjects with hepatic impairment and subjects with normal hepatic function after a single oral dose of PTV/RTV in combination with OBV and dasabuvir

Hepatic impairment status	n	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$[a] (h)	f_u (%)	Least squares means [90% CI]	
						C_{max}	AUC_{inf}
PTV							
Normal	7	2530 ± 2810	13,900 ± 17,100	5.8 [4.4-10.6]	1.13 ± 0.273	–	–
Mild	6	1650 ± 2140	11,000 ± 15,600	5.9 [4.1-9.9]	0.779 ± 0.134	0.52 [0.21, 1.27]	0.71 [0.27, 1.84]
Moderate	6	2970 ± 2230	23,300 ± 24,700	6.4 [5.4-7.4]	0.754 ± 0.141	1.26 [0.51, 3.11]	1.62 [0.62, 4.24]
Severe	5	5580 ± 1970	73,000 ± 29,300	7.9 [6.3-9.4]	1.19 ± 0.163	4.25 [1.66, 10.9]	10.5 [3.83, 28.6]
RTV							
Normal	7	2100 ± 1400	12,700 ± 8050	5.2 [3.9-10.4]	0.634 ± 0.163	–	–
Mild	6	1100 ± 604	7190 ± 3150	5.4 [3.9-8.9]	0.524 ± 0.228	0.60 [0.33, 1.08]	0.66 [0.36, 1.22]
Moderate	6	1250 ± 380	7340 ± 2830	6.7 [5.1-9.2]	0.599 ± 0.250	0.67 [0.37, 1.23]	0.70 [0.38, 1.29]
Severe	5	1090 ± 590	12,200 ± 6850	18.3 [8.4-32.9]	0.687 ± 0.183	0.65 [0.35, 1.21]	1.13 [0.59, 2.16]
OBV							
Normal	7	108 ± 45.0	1720 ± 877	55.1 [37.3-75.4]	0.021 ± 0.005	–	–
Mild	6	104 ± 24.8	1500 ± 550	46.9 [35.3-63.1]	0.023 ± 0.008	1.00 [0.77, 1.31]	0.92 [0.67, 1.27]
Moderate	6	83.1 ± 30.8	1290 ± 538	42.8 [25.7-61.2]	0.020 ± 0.007	0.71 [0.54, 0.93]	0.70 [0.51, 0.97]
Severe	5	32.9 ± 11.4	737 ± 303	45.4 [40.0-57.5]	0.047 ± 0.011	0.32 [0.24, 0.42]	0.46 [0.33, 0.64]

Mean ± standard deviation; a) Harmonic mean [range]

99) Severity of hepatic impairment was classified according to the Child-Pugh Classification (Class A, mild; Class B, moderate; Class C, severe).

4.(ii).A.(3).2) Foreign PK study in patients with renal impairment (reference data 5.3.3.3-7, Study M[redacted]-193 [[redacted] 20[redacted] to [redacted] 20[redacted]])

After a single oral dose of 150 mg of PTV in combination with 100 mg of RTV and 25 mg of OBV, the PK of each active ingredient was evaluated in subjects with renal impairment[100] (mild, 6; moderate 6; severe, 6) and 6 subjects with normal renal function. The results are shown in Table 33. Taking into account that there was no notable difference in the C_{max}, AUC_{inf}, and f_u of PTV, RTV, and OBV between subjects with normal renal function and those in subjects with renal impairment of any severity and that the excretion ratio of unchanged PTV, RTV, and OBV in urine is low, the applicant explained that there was no need for the dose of PTV/RTV/OBV combination product to be adjusted for patients with renal impairment.

Table 33. PK parameters of PTV, RTV, and OBV in subjects with renal impairment and subjects with normal renal function after a single oral dose of PTV/RTV in combination with OBV

Renal impairment status	n	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$[a] (h)	f_u (%)	Least squares means [90% CI][b]	
						C_{max}	AUC_{inf}
PTV							
Normal	6	401 ± 473	1890 ± 1610	6.0 [4.3-11.2]	0.78 ± 0.19	–	–
Mild	6	1800 ± 1180	8590 ± 4520	6.6 [4.9-10.0]	0.78 ± 0.24	0.89 [0.56, 1.43]	1.11 [0.77, 1.60]
Moderate	6	787 ± 909	4850 ± 4400	6.6 [3.8-14.7]	0.89 ± 0.22	0.83 [0.38, 1.82]	1.19 [0.64, 2.19]
Severe	6	470 ± 348	4250 ± 2770	7.9 [5.2-12.6]	0.86 ± 0.19	0.78 [0.28, 2.18]	1.25 [0.56, 2.78]
RTV							
Normal	6	709 ± 429	3710 ± 2160	5.1 [4.4-6.1]	0.54 ± 0.19	–	–
Mild	6	2190 ± 1050	14,000 ± 8020	4.9 [4.1-6.5]	0.50 ± 0.18	1.28 [1.03, 1.60]	1.40 [1.13, 1.75]
Moderate	6	1540 ± 652	10,700 ± 4320	4.4 [2.6-7.8]	0.56 ± 0.20	1.51 [1.05, 2.18]	1.76 [1.22, 2.54]
Severe	6	918 ± 315	6460 ± 2380	5.3 [3.7-9.1]	0.53 ± 0.10	1.71 [1.07, 2.76]	2.08 [1.30, 3.35]
OBV							
Normal	6	121 ± 33	1590 ± 304	40.7 [29.3-55.1]	0.014 ± 0.007	–	–
Mild	6	138 ± 25	2240 ± 451	45.6 [30.8-66.1]	0.016 ± 0.007	0.91 [0.82, 1.02]	1.01 [0.89, 1.15]
Moderate	6	121 ± 29	2020 ± 549	47.0 [35.2-66.6]	0.019 ± 0.007	0.86 [0.72, 1.03]	1.02 [0.83, 1.25]
Severe	6	125 ± 44	2110 ± 835	46.1 [38.9-51.7]	0.014 ± 0.005	0.82 [0.65, 1.04]	1.02 [0.78, 1.34]

Mean ± standard deviation; a) Harmonic mean [range];
b) Estimated using an analysis of covariance model including C_{cr} and body weight as covariates for PTV and OBV, and C_{cr} and sex as covariates for RTV.

4.(ii).A.(4) Pharmacokinetic interactions[101]

Twenty five studies were conducted to evaluate the pharmacokinetic interactions between PTV, RTV, and OBV and concomitant drugs. Table 34 and Table 35 show the ratios of least squares means [90%

100) Severity of renal impairment was classified based on CL_{cr} using the Cockcroft-Gault formula (CL_{cr} of ≥ 90 mL/min, normal; CL_{cr} of 89 to 60 mL/min, mild; CL_{cr} of 59 to 30 mL/min, moderate; CL_{cr} of 29 to 15 mL/min, severe).

101) 5.3.3.4-1, M[redacted]-247 [[redacted], 20[redacted] to [redacted], 20[redacted]]; reference data 5.3.3.4-2, M[redacted]-196 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-3, M[redacted]-198 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-4, M[redacted]-199 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-5, M[redacted]-189 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-6, M[redacted]-027 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-7, M[redacted]-201 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-8, M[redacted]-200 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-9, M[redacted]-492 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-10, M[redacted]-013 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-11, M[redacted]-506 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-12, M[redacted]-202 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-13, M[redacted]-394 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-14, M[redacted]-783 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-15, M[redacted]-104 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-16, M[redacted]-782 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-17, M[redacted]-392 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-18, M[redacted]-103 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-19, M[redacted]-491 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-20, M[redacted]-997 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-21, M[redacted]-100 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-22, M[redacted]-205 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-23, M[redacted]-204 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-24, M[redacted]-324 [[redacted] 20[redacted] to [redacted] 20[redacted]]; reference data 5.3.3.4-25, M[redacted]-325 [[redacted] 20[redacted] to [redacted] 20[redacted]]

CI] of the C_{max}, AUC (AUC over the dosing interval [AUC_{tau}] or AUC_{inf}), and C_{trough} of PTV, RTV, and OBV or a concomitant drug when these drugs were coadministered relative to those when not coadministered.

Table 34. Effects of concomitant drugs on the PK parameters of PTV, RTV, and OBV

Concomitant drug	Regimen of concomitant drug	n	Regimen	Ratio of least squares means[a] [90% CI]		
				C_{max}	AUC [b]	C_{trough}
Ursodeoxycholic acid	50 mg TID	12	PTV 150 mg QD	1.01 [0.81, 1.25]	0.91 [0.78, 1.07]	0.74 [0.65, 0.85]
			RTV 100 mg QD	1.04 [0.93, 1.16]	0.98 [0.93, 1.03]	0.74 [0.66, 0.83]
			OBV 25 mg QD	0.95 [0.91, 1.00]	0.97 [0.94, 1.00]	0.95 [0.92, 0.99]
Monoammonium glycyrrhizinate	80 mg QD as glycyrrhizic acid	12	PTV 150 mg QD	0.92 [0.75, 1.13]	0.94 [0.81, 1.10]	1.03 [0.94, 1.14]
			RTV 100 mg QD	0.91 [0.84, 0.09]	0.96 [0.92, 0.99]	0.93 [0.86, 1.01]
			OBV 25 mg QD	1.03 [0.96, 1.09]	1.03 [0.99, 1.06]	1.04 [1.01, 1.07]
Gemfibrozil [c]	600 mg BID	11	PTV 150 mg (single dose)	1.21 [0.94, 1.57]	1.38 [1.18, 1.61]	–
			RTV 100 mg (single dose)	0.84 [0.69, 1.03]	0.90 [0.78, 1.04]	–
Warfarin sodium	5 mg (single dose)	11	PTV 150 mg QD	1.15 [0.86, 1.54]	1.11 [0.94, 1.31]	0.99 [0.89, 1.11]
			RTV 100 mg QD	1.02 [0.86, 1.21]	1.00 [0.89, 1.12]	0.91 [0.85, 0.97]
			OBV 25 mg QD	1.03 [0.95, 1.11]	1.05 [0.99, 1.11]	1.03 [0.98, 1.09]
Omeprazole	40 mg QD	12	PTV 150 mg QD	1.02 [0.64, 1.62]	0.93 [0.64, 1.34]	0.83 [0.67, 1.04]
			RTV 100 mg QD	1.06 [0.95, 1.18]	1.07 [0.96, 1.21]	1.07 [0.97, 1.18]
			OBV 25 mg QD	0.96 [0.81, 1.14]	1.00 [0.88, 1.12]	0.97 [0.89, 1.07]
Ketoconazole	400 mg QD	12	PTV 150 mg (single dose)	1.72 [1.32, 2.26]	2.16 [1.76, 2.66]	–
			RTV 100 mg (single dose)	1.27 [1.11, 1.45]	1.51 [1.36, 1.68]	–
			OBV 25 mg (single dose)	0.98 [0.92, 1.04]	1.26 [1.20, 1.32]	–
Carbamazepine [c]	200 mg BID	12	PTV 150 mg (single dose)	0.34 [0.25, 0.48]	0.30 [0.23, 0.38]	–
			RTV 100 mg (single dose)	0.17 [0.12, 0.24]	0.13 [0.093, 0.17]	–
			OBV 25 mg (single dose)	0.69 [0.61, 0.78]	0.69 [0.64, 0.74]	–
Digoxin	0.5 mg (single dose)	11	PTV 150 mg QD	1.15 [0.97, 1.36]	1.12 [1.00, 1.25]	0.97 [0.84, 1.13]
			RTV 100 mg QD	1.06 [0.99, 1.13]	1.01 [0.98, 1.05]	0.95 [0.86, 1.04]
			OBV 25 mg QD	0.99 [0.95, 1.04]	1.02 [0.98, 1.06]	1.01 [0.98, 1.05]
Pravastatin	10 mg QD	10	PTV 150 mg QD	1.44 [1.15, 1.81]	1.33 [1.09, 1.62]	1.28 [0.83, 1.96]
			RTV 100 mg QD	1.37 [1.05, 1.79]	1.37 [0.84, 2.24]	0.85 [0.76, 0.96]
			OBV 25 mg QD	0.98 [0.90, 1.06]	0.94 [0.88, 1.02]	0.97 [0.90, 1.03]
Rosuvastatin	5 mg QD	12	PTV 150 mg QD	1.40 [1.12, 1.74]	1.22 [1.05, 1.41]	1.06 [0.85, 1.32]
			RTV 100 mg QD	1.05 [0.91, 1.22]	0.94 [0.84, 1.05]	0.77 [0.65, 0.85]
			OBV 25 mg QD	0.89 [0.81, 0.97]	0.88 [0.83, 0.92]	0.87 [0.83, 0.91]
LPV/RTV	400/100 mg BID	18	PTV 150 mg QD	4.76 [3.54, 6.39]	6.10 [4.30, 8.67]	12.3 [7.30, 20.8]
			RTV 100 mg QD	1.74 [1.39, 2.17]	2.78 [2.42, 3.20]	10.0 [7.66, 13.1]
			OBV 25 mg QD	1.07 [1.01, 1.13]	1.25 [1.19, 1.32]	1.48 [1.39, 1.57]
LPV/RTV	800/200 mg QPM	11	PTV 150 mg QD	1.78 [1.26, 2.52]	3.55 [2.37, 5.32]	14.8 [9.41, 23.2]
			RTV 100 mg QD	1.80 [1.30, 2.48]	3.09 [2.36, 4.06]	23.2 [15.5, 34.5]
			OBV 25 mg QD	0.97 [0.87, 1.08]	1.09 [1.00, 1.19]	1.24 [1.13, 1.35]
DRV	800 mg QD	9	PTV 150 mg QD	2.09 [1.35, 3.24]	1.94 [1.36, 2.75]	1.85 [1.41, 2.42]
			RTV 100 mg QD	0.83 [0.68, 1.01]	0.80 [0.73, 0.87]	0.91 [0.78, 1.06]
			OBV 25 mg QD	1.01 [0.87, 1.17]	1.01 [0.91, 1.11]	1.06 [0.99, 1.13]
DRV/RTV [d]	600 mg BID/100 mg QPM	7	PTV 150 mg QD	0.70 [0.43, 1.12]	0.59 [0.44, 0.79]	0.83 [0.69. 1.01]
			OBV 25 mg QD	0.76 [0.65, 0.88]	0.73 [0.66, 0.80]	0.73 [0.64, 0.83]
DRV/RTV [d]	800/100 mg QPM	12	PTV 150 mg QD	0.70 [0.50, 0.99]	0.81 [0.60, 1.09]	1.59 [1.23, 2.05]
			RTV 100 mg QD	1.19 [1.06, 1.33]	1.70 [1.54, 1.88]	14.2 [11.7, 17.2]
			OBV 25 mg QD	0.87 [0.82, 0.93]	0.87 [0.81, 0.93]	0.87 [0.80, 0.95]
ATV	300 mg QD	10	PTV 150 mg QD	2.74 [1.76, 4.27]	2.87 [2.08, 3.97]	3.71 [2.87, 4.79]
			RTV 100 mg QD	0.85 [0.72, 0.99]	0.97 [0.84, 1.13]	1.45 [1.29, 1.64]

Concomitant drug	Regimen of concomitant drug	n	Regimen	Ratio of least squares means[a] [90% CI]		
				C_{max}	AUC [b]	C_{trough}
			OBV 25 mg QD	0.83 [0.74, 0.94]	0.91 [0.81, 1,02]	0.98 [0.87, 1.64]
FTC/TDF	200/300 mg QD	9	PTV 150 mg QD	1.02 [0.63, 1.64]	1.04 [0.74, 1.47]	1.09 [0.88, 1.35]
			RTV 100 mg QD	0.95 [0.67, 1.34]	0.94 [0.78, 1.14]	0.92 [0.68, 1.24]
			OBV 25 mg QD	0.97 [0.89, 1.05]	1.00 [0.94, 1.06]	1.02 [0.97, 1.08]
RPV [d]	25 mg QD	10	PTV 150 mg QD	1.30 [0.94, 1.81]	1.23 [0.93, 1.64]	0.95 [0.84, 1.07]
			RTV 100 mg QD	1.10 [0.98, 1.24]	1.08 [0.93, 1.27]	0.97 [0.91, 1.04]
			OBV 25 mg QD	1.11 [1.02, 1.20]	1.09 [1.04, 1.14]	1.05 [1.01, 1.08]
RPV [d]	25 mg QPM [e]	10	PTV 150 mg QD	1.22 [0.96, 1.55]	1.19 [0.92, 1.53]	1.24 [0.90, 1.71]
			RTV 100 mg QD	0.95 [0.82, 1.09]	0.96 [0.84, 1.10]	0.99 [0.85, 1.16]
			OBV 25 mg QD	1.06 [1.00, 1.13]	1.05 [0.99, 1.12]	1.06 [1.00, 1.13]
Cyclosporine	10 mg (single dose)	12	PTV 150 mg QD	1.39 [1.10, 1.75]	1.46 [1.29, 1.64]	1.18 [1.08, 1.30]
			RTV 100 mg QD	1.13 [0.94, 1.35]	1.20 [1.10, 1.30]	1.11 [0.89, 1.37]
			OBV 25 mg QD	1.06 [1.02, 1.11]	1.10 [1.07, 1.12]	1.10 [1.06, 1.14]
Tacrolimus	0.5 mg (single dose)	11	PTV 150 mg QD	0.71 [0.55, 0.91]	0.79 [0.69, 0.92]	0.84 [0.74, 0.97]
			RTV 100 mg QD	0.84 [0.76, 0.93]	0.89 [0.85, 0.93]	1.04 [0.96, 1.13]
			OBV 25 mg QD	0.94 [0.89, 1.00]	0.95 [0.91, 1.00]	0.95 [0.92, 0.99]
Ethinylestradiol /norgestimate [f]	35/250 µg QD	7	PTV 150 mg QD	0.70 [0.40, 1.21]	0.66 [0.42, 1.04]	0.87 [0.67, 1.14]
			RTV 100 mg QD	0.80 [0.53, 1.21]	0.71 [0.54, 0.94]	0.79 [0.68, 0.93]
			OBV 25 mg QD	1.05 [0.81, 1.35]	0.97 [0.81, 1.15]	1.00 [0.88, 1.12]
Norethindrone [d]	0.35 mg QD	12	PTV 150 mg QD	1.24 [0.95, 1.62]	1.23 [0.96, 1.57]	1.43 [1.13, 1.80]
			RTV 100 mg QD	1.01 [0.89, 1.13]	1.08 [0.95, 1.23]	1.27 [1.06, 1.51]
			OBV 25 mg QD	1.00 [0.93, 1.08]	0.99 [0.94, 1.04]	0.97 [0.90, 1.03]
Escitalopram	10 mg (single dose)	11	PTV 150 mg QD	1.19 [0.84, 1.68]	1.02 [0.82, 1.27]	0.80 [0.71, 0.89]
			RTV 100 mg QD	1.38 [1.15, 1.66]	1.25 [1.07, 1.46]	0.94 [0.83, 1.06]
			OBV 25 mg QD	1.16 [1.09, 1.23]	1.0 [1.00, 1.06]	1.00 [0.97, 1.03]
Duloxetine	60 mg (single dose)	12	PTV 150 mg QD	1.07 [0.63, 1.81]	0.96 [0.70, 1.32]	0.93 [0.76, 1.14]
			RTV 100 mg QD	1.05 [0.78, 1.42]	1.10 [0.93, 1.31]	0.88 [0.76, 1.02]
			OBV 25 mg QD	1.04 [0.92, 1.16]	1.04 [1.00, 1.09]	1.00 [0.97, 1.03]
Alprazolam [d]	0.5 mg (single dose)	12	PTV 150 mg QD	0.91 [0.64, 1.31]	0.96 [0.73, 1.27]	1.12 [1.02, 1.23]
			RTV 100 mg QD	0.92 [0.84, 1.02]	0.96 [0.89, 1.03]	1.01 [0.94, 1.09]
			OBV 25 mg QD	0.98 [0.93, 1.04]	1.00 [0.96, 1.04]	0.98 [0.93, 1.04]
Zolpidem tartrate [d]	5 mg (single dose)	12	PTV 150 mg QD	0.63 [0.46, 0.86]	0.68 [0.55, 0.85]	1.23 [1.10, 1.38]
			RTV 100 mg QD	0.98 [0.88, 1.09]	0.97 [0.88, 1.06]	1.03 [0.97, 1.10]
			OBV 25 mg QD	1.07 [1.00, 1.15]	1.03 [1.00, 1.07]	1.04 [1.00, 1.08]
Furosemide [d]	20 mg (single dose)	12	PTV 150 mg QD	0.93 [0.63, 1.36]	0.92 [0.70, 1.21]	1.26 [1.16, 1.38]
			RTV 100 mg QD	1.10 [0.96, 1.27]	1.04 [0.92, 1.18]	1.07 [0.99, 1.17]
			OBV 25 mg QD	1.14 [1.03, 1.26]	1.07 [1.01, 1.12]	1.12 [1.08, 1.16]
Amlodipine besylate [d]	5 mg (single dose)	14	PTV 150 mg QD	0.77 [0.64, 0.94]	0.78 [0.68, 0.88]	0.88 [0.80, 0.95]
			RTV 100 mg QD	0.96 [0.87, 1.06]	0.93 [0.89, 0.98]	0.95 [0.89, 1.01]
			OBV 25 mg QD	1.00 [0.95, 1.06]	1.00 [0.97, 1.04]	1.00 [0.97, 1.04]

TID, 3 times daily; QD, once daily (morning); BID, twice daily; QPM, once daily (evening); –, not evaluated
LPV, lopinavir; DRV, darunavir; ATV, atazanavir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; PRV, rilpivirine
a) Estimated by mixed-model repeated-measures analysis with measurement day as a fixed effect and subject as a random effect.; b) Single dose administration, AUC_{inf}; multiple dose administration, AUC_{tau}; c) Single dose coadministration of dasabuvir; d) Coadministration of dasabuvir BID; e) Administration during supper; f) Coadministration of dasabuvir BID to 3 of 7 subjects

Table 35. Effects of PTV, RTV, and OBV on PK parameters of concomitant drugs

Drug	Regimen		n	Ratio of least squares means[a] [90% CI]		
	Concomitant drug	PTV/RTV/OBV		C_{max}	AUC [b]	C_{trough}
Ursodeoxycholic acid	50 mg TID	150/100/25 mg QD	12	0.90 [0.72, 1.14]	0.81 [0.69, 0.95]	0.57 [0.41, 0.80]
Glycyrrhizic acid	Monoammonium glycyrrhizinate, 80 mg as glycyrrhizic acid	150/100/25 mg QD	12	1.01 [0.99, 1.03]	1.49 [1.38, 1.61]	1.34 [1.17, 1.54]
Glycyrrhetinic acid			12	0.88 [0.75, 1.04]	1.04 [0.89, 1.21]	0.73 [0.63, 0.83]
R-warfarin	Warfarin sodium, 5 mg (single dose)	150/100/25 mg QD	11	0.96 [0.88, 1.05]	0.87 [0.82, 0.91]	0.87 [0.84, 0.91]
S-warfarin			11	0.90 [0.82,0.99]	0.85 [0.76,0.95]	0.89 [0.84, 0.93]
Omeprazole	40 mg (single dose)	150/100/25 mg QD	12	0.48 [0.29, 0.78]	0.93 [c] [0.53, 1.64]	–
Ketoconazole	400 mg QD	150/100/25 mg (single dose)	12	1.10 [1.05, 1.16]	2.05 [1.93, 2.18]	–
carbamazepine	Carbamazepine 200 mg BID	150/100/25 mg (single dose)[d]	12	1.10 [1.07, 1.14]	1.17 [1.13, 1.22]	1.35 [1.27, 1.45]
Carbamazepine-10, 11-epoxide			12	0.84 [0.82, 0.87]	0.75 [0.73, 0.77]	0.57 [0.54, 0.61]
Digoxin	0.5 mg (single dose)	150/100/25 mg QD	11	1.58 [1.43, 1.73]	1.36 [1.21, 1.54]	1.24 [1.07, 1.43]
Pravastatin	10 mg QD	150/100/25 mg QD	10	1.43 [1.09, 1.88]	1.76 [1.46, 2.13]	–
Rosuvastatin	5 mg QD	150/100/25 mg QD	12	2.61 [2.01, 3.39]	1.33 [1.14, 1.56]	0.65 [0.57, 0.74]
LPV	LPV/RTV, 400/100 mg BID	150/100/25 mg QD	18	1.06 [0.99, 1.14]	1.13 [1.09, 1.17]	1.34 [1.26, 1.42]
RTV			18	2.26 [1.95, 2.61]	2.01 [1.88, 2.16]	1.40 [1.23, 1.59]
LPV	LPV/RTV, 800/200 mg QPM	150 mg 150/100/25 mg QD	11	1.05 [0.95, 1.17]	1.17 [1.09, 1.26]	3.50 [2.69, 4.56]
RTV			12	1.32 [1.16, 1.50]	1.61 [1.48, 1.76]	7.13 [5.70, 8.92]
DRV	DRV/RTV, 800/100 mg QD [f]	150/100/25 mg QD	7	0.99 [0.92, 1.08]	0.92 [0.84, 1.00]	0.74 [0.63, 0.88]
RTV			7	1.86 [1.43, 2.41]	1.44 [1.30, 1.59]	0.58 [0.49, 0.69]
DRV	DRV/RTV [g], 600 mg BID/100 mg QPM	150/100/25 mg QD [e]	7	0.87 [0.79, 0.96]	0.80 [0.74, 0.86]	0.57 [0.48, 0.67]
RTV			7	1.61 [1.30, 2.00]	1.28 [1.12, 1.45]	0.88 [0.79, 0.99]
DRV	DRV/RTV, 800/100 mg QPM	150/100/25 mg QD [e]	10	0.79 [0.70, 0.90]	1.34 [1.25, 1.43]	0.54 [0.48, 0.62]
RTV			10	2.54 [2.19, 2.94]	2.77 [2.41, 3.17]	8.81 [7.33, 10.6]
ATV	ATV/RTV, 300/100 mg QD [h]	150/100/25 mg QD	11	0.90 [0.83, 0.97]	0.93 [0.85, 1.02]	0.81 [0.72, 0.91]
RTV			11	0.81 [0.70, 0.95]	0.93 [0.85, 1.03]	0.96 [0.80, 1.14]
FTC	FTC/TDF. 200/300 mg QD	150/100/25 mg QD	9	0.94 [0.84, 1.06]	1.07 [1.00, 1.15]	1.25 [1.13, 1.38]
TDF			9	0.80 [0.71, 0.90]	1.01 [0.96, 1.07]	1.13 [1.06, 1.21]
RPV	25 mg QD	150/100/25 mg QD [e]	8	2.55 [2.08, 3.12]	3.25 [2.80, 3.77]	3.62 [3.12, 4.21]
RPV	25 mg QPM [i]	150/100/25 mg QD [e]	10	3.00 [2.50, 3.59]	3.43 [3.03, 3.89]	3.73 [3.16, 4.40]
RPV	25 mg QPM [j]	150/100/25 mg QD [e]	9	2.16 [1.79, 2.61]	2.50 [2.05, 3.06]	2.87 [2.28, 3.62]
RAL	400 mg BID	150/100/25 mg QD	11	1.22 [0.78, 1.89]	1.20 [0.74, 1.95]	1.13 [0.51, 2.51]
Cyclosporine	10 mg (single dose)	150/100/25 mg (single dose)	12	0.67 [0.59, 0.76]	2.83 [2.42, 3.31]	6.72 [5.55, 8.13]

Drug	Regimen		n	Ratio of least squares means[a)] [90% CI]		
	Concomitant drug	PTV/RTV/OBV		C_{max}	AUC [b)]	C_{trough}
Cyclosporine	10 mg (single dose)	150/100/25 mg QD	12	0.83 [0.72, 0.94]	4.28 [3.66, 5.01]	12.8 [10.6, 15.6]
Tacrolimus	0.5 mg (single dose)	150/100/25 mg QD	11	4.27 [3.49, 5.22]	85.8 [67.9, 108]	24.6 [19.7, 30.8]
R-methadone	Methadone, 20-120 mg QD	150/100/25 mg QD	12	0.94 [k)] [0.90, 0.98]	0.97 [l)] [0.91, 1.03]	0.99 [m)] [0.90, 1.08]
S-methadone			12	0.94 [k)] [0.90, 0.99]	0.96 [l)] [0.89, 1.03]	0.93 [m)] [0.84, 1.02]
Buprenorphine	Buprenorphine/naloxone, 4-24/1-6 mg QD	150/100/25 mg QD	11	1.19 [k)] [1.01, 1.40]	1.51 [l)] [1.27, 1.78]	1.65 [m)] [1.30, 2.08]
Norbuprenorphine			11	1.82 [k)] [1.41, 2.36]	2.11 [l)] [1.65, 2.70]	1.87 [m)] [1.48, 2.36]
Naloxone			11	0.99 [k)] [0.84, 1.16]	1.11 [n)] [0.91, 1.37]	–
Ethinylestradiol	Ethinylestradiol /norgestimate, 35/250 μg QD	150/100/25 mg QD [o)]	8	1.16 [0.90, 1.50]	1.06 [0.96, 1.17]	1.12 [0.94, 1.33]
Norelgestromin			9	2.01 [1.77, 2.29]	2.60 [2.30, 2.95]	3.11 [2.51, 3.85]
Norgestrel			9	2.26 [1.91, 2.67]	2.54 [2.09, 3.09]	2.93 [2.39, 3.57]
Norethindrone	0.35 mg QD	150/100/25 mg QD [e)]	12	0.83 [0.69, 1.01]	0.91 [0.76, 1.09]	0.85 [0.64, 1.13]
Ethinylestradiol	Ethinylestradiol /norethindrone, 35/400 μg QD	150/100/25 mg (single dose) [e)]	12	1.17 [1.09, 1.25]	1.22 [1.18, 1.26]	1.36 [1.26, 1.47]
Norethindrone			12	1.12 [0.97, 1.28]	1.29 [1.24, 1.35]	1.62 [1.52, 1.73]
Escitalopram	Escitalopram, 10 mg (single dose)	150/100/25 mg QD	11	0.92 [0.85, 0.99]	0.75 [0.67, 0.84]	–
S-didesmethylcitalopram			11	1.17 [1.08, 1.26]	1.07 [1.01, 1.13]	–
Duloxetine	60 mg (single dose)	150/100/25 mg QD	12	0.83 [0.72, 0.96]	0.80 [0.71, 0.90]	–
Alprazolam	0.5 mg (single dose)	150/100/25 mg QD [e)]	12	1.09 [1.03, 1.15]	1.34 [1.15, 1.55]	–
Zolpidem	Zolpidem tartrate, 5 mg (single dose)	150/100/25 mg QD [e)]	12	0.94 [0.76 1.16]	0.95 [0.74, 1.23]	–
Furosemide	20 mg (single dose)	150/100/25 mg QD [e)]	12	1.42 [1.17, 1.72]	1.08 [1.00, 1.17]	–
Amlodipine	Amlodipine besylate, 5 mg (single dose)	150/100/25 mg QD [e)]	14	1.26 [1.11, 1.44]	2.57 [2.31, 2.86]	–

TID, 3 times daily; QD, once daily (morning); BID, twice daily; QPM, once daily (evening); –, not evaluated
LPV, lopinavir; DRV, darunavir; ATV, atazanavir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; RPV, rilpivirine; RAL, raltegravir
a) Estimated by mixed-model repeated-measures analysis with measurement day as a fixed effect and subject as a random effect.; b) Single dose administration, AUC_{inf}; multiple dose administration, AUC_{tau}; c) 5 subjects; d) Coadministration of PTV, RTV, and OBV, with a single dose of dasabuvir; e) Coadministration of PTV, RTV, and OBV with dasabuvir BID; f) Coadministration of PTV, RTV, and OBV with DRV only without additional administration of RTV; g) Coadministration of PTV, RTV, and OBV with BID administration of DRV and QPM administration of additional RTV; h) Coadministration of PTV, RTV, and OBV with only ATV and without additional RTV; i) When PTV, RTV, and OBV were not coadministered, PRV was administered about 30 minutes after a meal; when PTV, RTV, and OBV were coadministered, PRV was administered about 4 hours after a meal; j) Administration with supper; k) C_{ma}x/dose; l) $AUC_{0\text{-}24}$/dose; m) Plasma concentration at 24 hours after administration/dose; n) AUC_t/dose; o) Coadministration of PTV, RTV, and OBV with [redacted] mg of dasabuvir BID in 3 of 7 subjects.

A study on coadministration of PTV/RTV/OBV (150/100/25 mg) QD, [redacted] mg of dasabuvir BID, and other drugs was conducted,[102)] and an interim report was obtained on Part 1 in which the effects of coadministration of a single dose of diazepam 2 mg were evaluated. The effects of a single dose of diazepam on steady-state PK parameters of PTV, RTV, and OBV are shown in Table 36.

102) A drug interaction study (M[redacted]-197) that is ongoing as of [redacted] 20[redacted]. This study has investigated the pharmacokinetic interactions with diazepam in Part 1 and with hydrocodone bitartrate/acetaminophen in Part 2. In Part 1, subjects received a single oral dose of diazepam on Day 1, and after a 20-day washout period, received multiple oral doses of PTV 200 mg, RTV 100 mg, and OBV 25 mg QD and dasabuvir [redacted] mg BID for 24 days from Day 22. On Day 36, subjects received a single oral dose of diazepam concomitantly with these drugs.

Table 36. Effects of diazepam on PK parameters of PTV, RTV, and OBV

Dosage regimen of diazepam	n	Dosage regimen	Ratio of least squares mean [90% CI]		
			C_{max}	AUC_{tau}	C_{trough}
2 mg (single dose)	15	PTV 150 mg QD	0.95 [0.77, 1.18]	0.91 [0.78, 1.07]	0.92 [0.82, 1.03]
		RTV 100 mg QD	1.10 [0.98, 1.14]	1.06 [0.98, 1.14]	0.98 [0.92, 1.03]
		OBV 25 mg QD	1.00 [0.93, 1.08]	0.98 [0.93, 1.03]	0.93 [0.88, 0.98]

4.(ii).A.(5) QT/QTc study (5.3.4.1.1, Study M[redacted]-680 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A 4-treatment, 4-period crossover study was conducted in healthy non-Japanese subjects (60 subjects[103]) to assess the effect of a single oral dose of placebo or a combination of PTV, RTV, OBV, and dasabuvir (350, 150, 50, and [redacted] mg, respectively) on QT/QTc intervals, using single oral dose of moxifloxacin 400 mg as a positive control.[104] A maximum change from baseline in QT interval corrected for heart rate using Fridericia's formula was observed 5 hours after coadministration of PTV, RTV, OBV, and dasabuvir, and the difference [90% CI] from that in the placebo group was 5.9 [4.1, 7.7] ms. The applicant interpreted the upper 90% confidence interval limit of <10 ms as demonstrating that PTV, RTV, and OBV at doses of up to 350, 150, and 50 mg, respectively, do not prolong QTc interval.[105] The C_{max} of PTV, RTV, and OBV were 10,100, 2330, and 239 ng/mL, respectively, and the AUC_{inf} of those were 80,600, 21,000, and 2900 ng·h/mL, respectively.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Rationale for coadministering RTV with anti-HCV drugs and for selecting its dose

PMDA asked the applicant to justify administration of RTV in combination with an anti-HCV product from a pharmacodynamic viewpoint.

The applicant's explanation:

Coadministration of PTV 300 mg and RTV 100 mg was compared with administration of PTV as a single-agent in a foreign phase I study (M[redacted]-749). C_{max}, AUC, and C_{trough} of PTV when coadministered with RTV increased to approximately 28-, 48-, and 300-fold, respectively, over those of PTV when administered alone and $t_{1/2}$ was also prolonged [see "4.(ii).A.(1).3).(a) Phase I study"].

An exposure-response analysis showed that C_{max}, $AUC_{0\text{-}24}$, and C_{trough} were less in subjects who experienced virologic failure than in the other subjects [see "4.(ii).A.(2).3) Exposure-response analysis"], which was interpreted as indicating an association between these PK parameters and virologic treatment outcomes. On the other hand, given that the safety analysis revealed a correlation between the AUC of

103) A combination of PTV, RTV, OBV, and dasabuvir was administered to 59 of 60 subjects; moxifloxacin was administered to 59 of 60 subjects; and placebo was administered to 59 of 60 subjects.

104) The study also evaluated the effect of a combination of PTV, RTV, OBV, and dasabuvir at therapeutic dose (200, 150, 25, and [redacted] mg, respectively) on QT/QTc interval; however, the results are not presented in this report. There was a washout period of ≥10 days between the 2 administration periods.

105) Concerning changes from baseline in QT interval corrected for heart rate by Fridericia's formula, the difference between the moxifloxacin and placebo groups was greatest at 3 hours after dosing. The maximum difference [90% CI] between the 2 groups was 10.8 [9.0, 12.6] ms.

PTV and the incidence of adverse events [see "4.(ii).A.(2).3) Exposure-response analysis"], it was considered important to maintain C_{trough} at the optimum level for efficacy while keeping AUC within a certain range by coadministration of RTV.

In the Japanese phase III study (M13-004), PTV (150 mg QD) was found to be effective. In 6 phase I studies in which the same dosage regimen was employed, C_{trough} was 12.15 ng/mL and $AUC_{0\text{-}24}$ was 2720 ng·h/mL following administration of PTV 150 mg QD in combination with RTV 100 mg QD.[106)] Then PPK modeling and simulation was performed based on the obtained C_{trough} of PTV (12.15 ng/mL) as an effective exposure level to estimate the dose of PTV that would exhibit efficacy. The dose of PTV required to yield the C_{trough} (12.15 ng/mL) when administered alone was estimated to be 1629 mg QD and 769 mg twice daily (BID), with the estimated $AUC_{0\text{-}24}$ being 66,996 and 11,266 ng·h/mL, respectively.[107)] These results suggested that coadministration of PTV and RTV allows PTV to reach the effective exposure level at a dose lower than that of PTV alone, thereby reducing the necessary pill counts. This would also lead to a reduction in the incidence of adverse events because AUC is decreased while C_{trough} is maintained around the same level in the effective exposure range. Coadministration of PTV and RTV also allows the dosing interval to be extended from BID to QD due to the increases in its C_{trough} and $t_{1/2}$ of PTV.

RTV interacts with anti-HIV agents such as atazanavir and darunavir, which are mainly metabolized by CYP3A, thereby increasing the blood concentration of these anti-HIV agents, and it has been used widely. Therefore, no particular concerns were identified in the concomitant use of RTV to increase the exposure to PTV that is metabolized by CYP3A.

PMDA found the applicant's justification for the administration of RTV in combination with PTV to be persuasive, and went on to ask the applicant to justify the dose selected for RTV.

The applicant's explanation:
In a foreign phase I study (M[redacted]-749), PTV 300 mg was coadministered with RTV 50 to 200 mg, and the AUC_{inf} of PTV achieved with RTV 100 mg was approximately 3-fold that with RTV 50 mg, but the AUC_{inf} of PTV achieved with RTV 200 mg was only 1.7-fold that with RTV 100 mg (the C_{trough} of PTV achieved with RTV 100 mg was 1.9-fold that with RTV 50 mg and that with RTV 200 mg was 1.8-fold that with RTV 100 mg) [see "4.(ii).A.(1).3).(a) Phase I study"]. Moreover, when PTV 50 to 200 mg was coadministered with RTV 100 mg in 4 phase I studies, the AUC_{inf} of PTV 100 mg was 4- to 5-fold that of PTV 50mg and the AUC_{inf} of PTV 200 mg was 5- to 9-fold that of PTV 100 mg (the C_{trough} of PTV 100 mg was 2- to 3-fold that of PTV 50 mg and the C_{trough} of PTV 200 mg was 3- to 5-fold that PTV 100 mg). Given that RTV 100 mg or higher was to be coadministered, those results indicated that increased

106) Calculated using the pooled PK data from 6 phase I studies (M[redacted]-392, M[redacted]-492, M[redacted]-783, M[redacted]-506, M[redacted]-103, and M[redacted]-491)

107) There were no clinical studies in which PTV was administered as a single agent to patients with chronic hepatitis C. Therefore, the effective dose of PTV was estimated by PPK modeling and simulation using PK data from the phase I study (M[redacted]-749) in healthy subjects who received PTV as a single agent.

dose of PTV itself was expected to contribute more to increase PTV exposure than increased dose of RTV was expected to, and therefore a dose of 100 mg was selected for RTV. This RTV dose of 100 mg is also used to increase the exposure to anti-HIV agents such as atazanavir and darunavir.

PMDA's view:

Given that the applicant rationalized the selected RTV dose on the basis of AUC_{inf} of PTV and that they discussed the significance of RTV coadministration on the basis of C_{trough} of PTV on the other hand, it is difficult to accept the applicant's explanation that the optimal dose of RTV is 100 mg. However, since the Japanese phase III study (M13-004) demonstrated the efficacy of PTV 150 mg and OBV 25 mg in combination with RTV 100 mg with an acceptable safety profile, 100 mg can be considered as an acceptable dose for RTV.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

As the efficacy and safety evaluation data, the results from 10 clinical studies (5 Japanese clinical studies and 5 foreign clinical studies) were submitted. These studies, results of which were submitted as evaluation data, are summarized in Table 37.

Table 37. Summary of clinical studies (evaluation data)

	Phase	Study identifier	Subjects	Primary objective(s)	n	Dosage and administration
Japanese	I	M[redacted]-384	Healthy adult male subjects	Pharmacokinetics Safety Tolerability	54	A single dose of 50/100, 100/100, or 200/100 mg of PTV/RTV or placebo; Multiple doses of 50/100 or 200/100 mg of PTV/RTV or placebo QD for 14 days
		M[redacted]-771	Healthy adult subjects	Food effect	20	A single dose of PTV/RTV/OBV combination product in the fasted or fed state
		M[redacted]-247	Healthy adult subjects	Drug interaction	24	Coadministration of PTV/RTV/OBV combination product and ursodeoxycholic acid 50 mg TID or glycyrrhizin 80 mg QD
Foreign	I	M[redacted]-181	Healthy adult subjects (including Japanese subjects)	Pharmacokinetics Safety Tolerability	48	Multiple doses of placebo, OBV 25 mg, or 200 mg QD for 7 days
		M[redacted]-221	Healthy adult subjects (including Japanese subjects)	Pharmacokinetics Safety	90	Coadministration of OBV and PTV/RTV QD; or OBV QD, PTV/RTV QD, and dasabuvir BID
		M[redacted]-688	Healthy adult subjects (including Japanese subjects)	Pharmacokinetics Safety	30	A single dose of 250/100 mg of PTV/RTV
		M[redacted]-505	Healthy adult subjects (including Japanese subjects)	Pharmacokinetics Safety Tolerability	48	[redacted]
		M[redacted]-680	Healthy adult subjects	QT/QTc	57	A single dose of a combination of PTV 350 mg, RTV 150 mg, OBV 50 mg, and dasabuvir [redacted] mg; or placebo; or 400 mg of moxifloxacin
Japanese	II	M[redacted]-536	Treatment-experienced patients with genotype 1b or 2 chronic hepatitis C	Pharmacokinetics Efficacy Safety	110	Coadministration of PTV/RTV 100/100 or 150/100 mg and OBV 25 mg QD for 12 or 24 weeks
Japanese	III	M13-004	Treatment-naïve or treatment-experienced genotype 1b chronic hepatitis C patients with or without compensated cirrhosis	Pharmacokinetics Efficacy Safety	363	Multiple doses of PTV/RTV/OBV combination product or placebo QD for 12 weeks

TID, 3 times daily

4.(iii).A.(1) Japanese phase II study (5.3.5.1-2, Study M[redacted]-536 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, crossover, parallel-group, comparative study[108)] was conducted at 18 centers in Japan to evaluate the efficacy and safety of the combination regimen of PTV 100 or 150 mg, RTV 100 mg, and 25 mg of OBV in treatment-experienced[109)] patients with chronic hepatitis C[110)] (73 genotype 1b subjects and 37 genotype 2 subjects).

In this study, PTV 100 or 150 mg was orally administered once daily in combination with RTV 100 mg and OBV 25 mg for 12 or 24 weeks to genotype 1b subjects and for 12 weeks to genotype 2 subjects.

All of the 110 randomized and treated subjects (73 genotype 1b subjects [18 in the 12-week PTV 100 mg group, 18 in the 12-week PTV 150 mg group, 19 in the 24-week PTV 100 mg group, and 18 in the 24-week PTV 150 mg group]; 37 genotype 2 subjects [19 in the 12-week PTV 100 mg group, 18 in the 12-week PTV 150 mg group]) were included in the safety analysis population and the intent-to-treat (ITT) population, which was defined as the efficacy analysis population.

The SVR24 rates,[111)] the primary endpoint, are shown in Table 38.

Table 38. SVR24 rates (ITT population)

	Genotype 1b				Genotype 2	
	12-week 100 mg group	12-week 150 mg group	24-week 100 mg group	24-week 150 mg group	12-week 100 mg group	12-week 150 mg group
SVR24 rate	100 (18/18)	88.9 (16/18)	100 (19/19)	100 (18/18)	57.9 (11/19)	72.2 (13/18)
[95% CI]	[81.5, 100.0]	[65.3, 98.6]	[82.4, 100.0]	[81.5, 100.0]	[33.5, 79.8]	[46.5, 90.3]

% (number of subjects)

The incidence of adverse events (including laboratory abnormalities) was 77.8% (14 of 18 subjects) in the 12-week PTV 100 mg group, 83.3% (15 of 18 subjects) in the 12-week PTV 150 mg group, 84.2%

108) Subjects were randomized, stratified in the genotype 1b cohort with response to prior treatment (null response or partial response) and in the genotype 2 cohort with response to prior treatment (null response, partial response, or relapse).

109) Patients who had a history of treatment with peginterferon (PegIFN)/ribavirin (RBV) and met any of the following:
- Null responders: Patients who received PegIFN/RBV for ≥10 weeks and showed a decrease in HCV RNA by <2 $\log_{10}$ IU/mL at Week 12
- Partial responders: Patients who received PegIFN/RBV for ≥20 weeks and showed a decrease in HCV RNA by ≥2 $\log_{10}$ IU/mL at Week 12 and from whom HCV RNA was detected at the end of treatment
- Relapse: Patients who received ≥1 treatment unit of PegIFN/RBV and from whom HCV RNA was not detected at the end of treatment but was detected during the 24-week follow-up period

110) The absence of hepatic cirrhosis was defined as follows:
1) Patients with a METAVIR score or fibrosis score according to the new Inuyama classification system of ≤3 or with Ishak score of ≤4 from a liver biopsy performed within 24 months before screening or during screening; or
2) Patients with no available data from liver biopsy who met any of the following criteria:
- Fibro Test score of ≤0.72 and aspartate aminotransferase-to-platelet ratio (APRI) score of ≤2
- Severity of cirrhosis assessed by Fibroscan of <9.6 kPa
- The following chronic hepatitis and cirrhosis discriminant score of <0:
$0.124 \times (\gamma\text{-globulin [\%]}) + 0.001 \times (\text{hyaluronic acid [}\mu\text{g/L]}) - 0.075 \times (\text{platelet count [}\times 10^4/\text{mm}^3\text{]}) - 0.413 \times \text{sex (male, 1; female, 2)} - 2.005$

111) Proportion of subjects with HCV RNA level in blood less than the LLOQ (25 IU/mL) at 24 weeks after the final dose of the study drug

(16 of 19 subjects) in the 24-week PTV 100 mg group, and 83.3% (15 of 18 subjects) in the 24-week PTV 150 mg group in genotype 1b subjects; and 73.7% (14 of 19 subjects) in the 12-week PTV 100 mg group and 88.9% (16 of 18 subjects) in the 12-week PTV 150 mg group in genotype 2 subjects. The incidence of adverse drug reactions (including laboratory abnormalities)[112] was 33.3% (6 of 18 subjects) in the 12-week PTV 100 mg group, 33.3% (6 of 18 subjects) in the 12-week PTV 150 mg group, 36.8% (7 of 19 subjects) in the 24-week PTV 100 mg group, and 44.4% (8 of 18 subjects) in the 24-week PTV 150 mg group in genotype 1b subjects; and 42.1% (8 of 19 subjects) in the 12-week PTV 100 mg group and 50.0% (9 of 18 subjects) in the 12-week PTV 150 mg group in genotype 2 subjects. The adverse events reported in ≥2 subjects in any group are shown in Table 39.

Table 39. Adverse events reported in ≥2 subjects in any group (safety analysis population)

Event	Genotype 1b				Genotype 2	
	12-week 100 mg group	12-week 150 mg group	24-week 100 mg group	24-week 150 mg group	12-week 100 mg group	12-week 150 mg group
Number of subjects	18	18	19	18	19	18
Overall	14 (77.8)	15 (83.3)	16 (84.2)	15 (83.3)	14 (73.7)	16 (88.9)
Conjunctivitis	0	0	2 (10.5)	0	0	0
Diarrhoea	3 (16.7)	0	1 (5.3)	1 (5.6)	0	0
Dyspepsia	2 (11.1)	0	1 (5.3)	0	0	2 (11.1)
Nausea	2 (11.1)	1 (5.6)	0	0	2 (10.5)	0
Vomiting	3 (16.7)	0	0	0	0	0
Malaise	2 (11.1)	0	1 (5.3)	1 (5.6)	1 (5.3)	0
Oedema peripheral	1 (5.6)	0	0	0	2 (10.5)	1 (5.6)
Pyrexia	1 (5.6)	0	2 (10.5)	0	1 (5.3)	0
Bronchitis	2 (11.1)	0	0	0	0	1 (5.6)
Gastroenteritis	0	0	2 (10.5)	2 (11.1)	2 (10.5)	0
Influenza	0	0	0	2 (11.1)	0	1 (5.6)
Animal bite	0	0	0	0	0	2 (11.1)
Nasopharyngitis	1 (5.6)	6 (33.3)	4 (21.1)	9 (50.0)	5 (26.3)	7 (38.9)
Muscle spasms	0	0	0	0	2 (10.5)	0
Back pain	3 (16.7)	1 (5.6)	2 (10.5)	2 (11.1)	0	0
Myalgia	2 (11.1)	0	0	0	0	0
Headache	2 (11.1)	1 (5.6)	3 (15.8)	1 (5.6)	3 (15.8)	5 (27.8)
Somnolence	1 (5.6)	0	0	0	2 (10.5)	0
Eczema	1 (5.6)	0	0	0	2 (10.5)	1 (5.6)
Rash	0	0	2 (10.5)	3 (16.7)	0	1 (5.6)
Hypertension	1 (5.6)	2 (11.1)	2 (10.5)	1 (5.6)	1 (5.3)	1 (5.6)

Number of subjects (%)

No deaths were reported. Serious adverse events were reported in 2 genotype 1b subjects (fluid retention and tibia fracture reported in 1 subject each) in the 12-week PTV 150 mg group, 2 genotype 1b subjects (femur fracture and autoimmune hepatitis in 1 subject each) in the 24-week PTV 100 mg group, and 1 genotype 2 subject (colitis ischaemic) in the 12-week PTV 100 mg group. All of these serious adverse events were assessed as not related to the study drug except for fluid retention and autoimmune hepatitis, and the outcome was “recovered/resolved” for all these events except for tibia fracture.[113] The adverse event leading to study discontinuation occurred in 1 genotype 1b subject (fluid retention) in the 12-week

112) Events assessed by the investigator or subinvestigator as related to the study drug

113) The subject fell and broke his/her tibia and was hospitalized to undergo open reduction and internal fixation for stabilization of the fracture. After its stabilization, the subject continued to receive treatment as an outpatient.

PTV 150 mg group and was assessed as related to the study drug. The outcome of the event was "recovered/resolved."

4.(iii).A.(2) Japanese phase III study (5.3.5.1-1, Study M13-004 [December 2013 to October 2014])

A randomized, placebo-controlled, double-blind, parallel-group, comparative study (substudy 1 in chronic hepatitis C patients without compensated cirrhosis)[114] and an open-label, uncontrolled study (substudy 2 in chronic hepatitis C patients with compensated cirrhosis) were conducted at 54 centers in Japan to evaluate the efficacy and safety of PTV/RTV/OBV combination product in chronic hepatitis C patients with or without compensated cirrhosis[115] (genotype 1b; target sample size of 312).

In substudy 1, subjects orally received 2 tablets of PTV/RTV/OBV combination product (150/100/25 mg) or placebo QD for 12 weeks. Then, subjects in the placebo group orally received an open-label regimen of 2 tablets of PTV/RTV/OBV combination product (150/100/25 mg) QD for another 12 week. In substudy 2, subjects orally received 2 tablets of PTV/RTV/OBV combination product (150/100/25 mg) QD for 12 weeks (Figure 3).

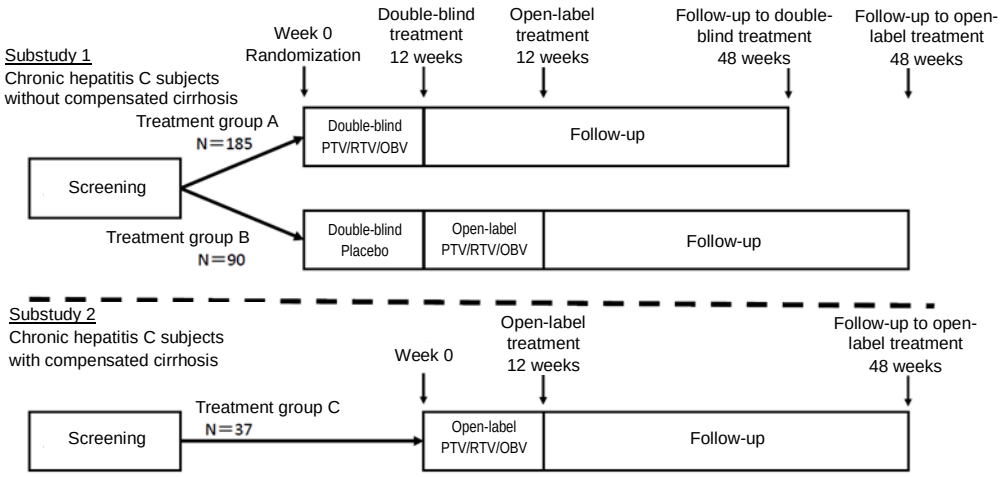

Figure 3. Study design

114) Subjects were randomized into the PTV/RTV/OBV group or the placebo group at a ratio of 2:1 based on the status of prior treatment (IFN treatment-naïve or IFN treatment-experienced). Subjects were further stratified by prior IFN treatment response (null response, relapse, intolerance to IFN) for treatment-experienced subjects and by viral load (low viral load, high viral load) for treatment-naïve subjects. Subjects with a high viral load were stratified by eligibility for IFN therapy (eligible, ineligible). Low viral load was defined as HCV RNA of <100,000 IU/mL, and high viral load was defined as HCV RNA of ≥100,000 IU mL. Eligibility for IFN therapy was evaluated by the investigator or subinvestigator based on the subject's medical history or current illness.

115) Hepatic cirrhosis was defined as satisfying the following conditions; and if the Child-Pugh score was ≤6, it was defined as compensated cirrhosis.
If liver biopsy had been conducted: A METAVIR score or fibrosis score of >3 according to the new Inuyama classification systemor Ishak score of >4
If no liver biopsy had been conducted:(1) A Fibro Test score of ≥0.73 and APRI of >2; (2) Severity of cirrhosis assessed by elasticity imaging (e.g., Fibroscan) being ≥14.6 kPa; or (3) A chronic hepatitis and cirrhosis discriminant score of >0 (see Footnote #110)

In substudy 1, all of the 321 randomized and treated chronic hepatitis C subjects without compensated cirrhosis (207 treatment-naïve subjects[116] [139 in the PTV/RTV/OBV combination product group and 68 in the placebo group] and 114 treatment-experienced subjects[117] [76 in the PTV/RTV/OBV combination product group and 38 in the placebo group]) were included in the ITT population, the safety analysis population, and the efficacy analysis population. In substudy 2, all of the 42 treated chronic hepatitis C subjects with compensated cirrhosis (9 treatment-naïve subjects and 33 treatment-experienced subjects) were included in the safety analysis population and the ITT population, which was defined as the efficacy analysis population.

The SVR12 rate[118] [95% CI] in treatment-naïve subjects with chronic hepatitis C who were eligible for interferon (IFN) therapy and who had a high viral load, the primary endpoint, was 94.6% [90.5%, 98.8%] (106 of 112 subjects), and the lower limit of the 95% confidence interval was above the pre-specified threshold for SVR12 (63%[119]), demonstrating the efficacy of PTV/RTV/OBV combination product. The SVR12 rate [95% CI] in treatment-naïve and treatment-experienced chronic hepatitis C subjects without compensated cirrhosis was 94.2% [89.1%, 97.1%] (131 of 139 subjects) and 96.1% [89.0%, 98.6%] (73 of 76 subjects), respectively. The SVR12 rate [95% CI] in treatment-naïve and treatment-experienced chronic hepatitis C subjects with compensated cirrhosis was 100% [70.1%, 100%] (9 of 9 subjects) and 87.9% [72.7%, 95.2%] (29 of 33 subjects), respectively. The SVR12 rate in treatment-naïve subjects and treatment-experienced chronic hepatitis C subjects without compensated cirrhosis who received an open-label regiment of PTV/RTV/OBV combination product after completing treatment with placebo in substudy 1 was 98.5% (67 of 68 subjects) and 97.4% (37 of 38 subjects), respectively.

The incidence of adverse events (including laboratory abnormalities) was 68.8% (148 of 215 subjects) in the PTV/RTV/OBV combination product group and 56.6% (60 of 106 subjects) in the placebo group in substudy 1 (blind phase), designed for chronic hepatitis C subjects without compensated cirrhosis, and 73.8% (31 of 42 subjects) in substudy 2, designed for chronic hepatitis C subjects with compensated cirrhosis. The incidence of adverse drug reactions (including laboratory abnormalities)[112] was 30.7% (66 of 215 subjects) in the PTV/RTV/OBV combination product group and 14.2% (15 of 106 subjects)

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116) Patients who had never received treatment with any IFN products (with or without RBV) irrespective of being eligible or ineligible for IFN therapy

117) Treatment-experienced subjects were defined as those who had been treated with an IFN product and who met any of the following criteria.
- Null responders: Patients whose HCV RNA in blood did not fall below the detection limit at the end of a ≥12-week treatment with an IFN product
- Relapsed: Patients whose HCV RNA fell below the detection sensitivity limit as a result of treatment with an IFN product but whose HCV RNA became detectable within 52 weeks after the end of treatment
- Intolerance to IFN therapy: Patients withdrawn from treatment with an IFN product due to intolerance to the treatment

118) Proportion of subjects with HCV RNA level of <LLOQ at 12 weeks after the final dose of treatment. SVR12 rates, which have been reported to be highly consistent with SVR24 rates (Chen J et al., *Gastroenterology*. 2013;144:1450-1455), were selected as the primary endpoint. The FDA Guidance (*Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Drugs for Treatment. Guidance for industry*, 2013), which was published at the time the study started, recommends the use of SVR12 rate as the primary endpoint.

119) Based on the results of a clinical study of a triple regimen of telaprevir and PegIFN/RBV in treatment-naïve Japanese patients with chronic hepatitis C (genotype 1) (Kumada H et al., *J Hepatol*. 2012;56:78-84), the calculated SVR rate for the external control was 73%. From the viewpoints of safety profile improvement and a reduction in treatment period, the threshold SVR was determined to be 63%.

in the placebo group among chronic hepatitis C subjects without compensated cirrhosis and 40.5% (17 of 42 subjects) of chronic hepatitis C subjects with compensated cirrhosis. The adverse events and adverse drug reactions that occurred at an incidence of ≥2% in any group in substudy 1 (blind phase) or in ≥2 subjects in substudy 2 are shown in Table 40.

Table 40. Adverse events and adverse drug reactions that occurred at an incidence of ≥2% or in ≥2 subjects in any group (substudies 1 and 2; safety analysis population; 12 weeks after end of study treatment)

Event	Adverse event			Adverse drug reaction		
	Chronic hepatitis C (CHC) subjects without compensated cirrhosis		CHC subjects with compensated cirrhosis	CHC subjects without compensated cirrhosis		CHC subjects with compensated cirrhosis
	PTV/RTV/OBV combination product	Placebo	PTV/RTV/OBV combination product	PTV/RTV/OBV combination product	Placebo	PTV/RTV/OBV combination product
Number of subjects	215	106	42	215	106	42
Overall	148 (68.8)	60 (56.6)	31 (73.8)	66 (30.7)	15 (14.2)	17 (40.5)
Abdominal pain upper	3 (1.4)	0	2 (4.8)	0	0	0
Constipation	2 (0.9)	2 (1.9)	2 (4.8)	2 (0.9)	0	0
Diarrhoea	8 (3.7)	3 (2.8)	1 (2.4)	3 (1.4)	1 (0.9)	1 (2.4)
Nausea	9 (4.2)	4 (3.8)	3 (7.1)	7 (3.3)	1 (0.9)	2 (4.8)
Stomatitis	5 (2.3)	3 (2.8)	0	2 (0.9)	0	0
Vomiting	2 (0.9)	2 (1.9)	2 (4.8)	1 (0.5)	1 (0.9)	0
Fatigue	6 (2.8)	1 (0.9)	1 (2.4)	2 (0.9)	1 (0.9)	0
Malaise	9 (4.2)	3 (2.8)	2 (4.8)	5 (2.3)	3 (2.8)	2 (4.8)
Oedema peripheral	11 (5.1)	0	3 (7.1)	10 (4.7)	0	2 (4.8)
Pyrexia	4 (1.9)	1 (0.9)	4 (9.5)	1 (0.5)	0	1 (2.4)
Cystitis	2 (0.9)	4 (3.8)	1 (2.4)	1 (0.5)	0	0
Nasopharyngitis	36 (16.7)	14 (13.2)	6 (14.3)	2 (0.9)	0	1 (2.4)
Blood triglycerides increased	0	0	2 (4.8)	0	0	1 (2.4)
Haemoglobin decreased	2 (0.9)	0	2 (4.8)	1 (0.5)	0	2 (4.8)
Platelet count decreased	0	0	3 (7.1)	0	0	2 (4.8)
Decreased appetite	2 (0.9)	1 (0.9)	2 (4.8)	1 (0.5)	0	1 (2.4)
Arthralgia	3 (1.4)	1 (0.9)	2 (4.8)	1 (0.5)	0	0
Back pain	7 (3.3)	2 (1.9)	0	0	0	0
Musculoskeletal stiffness	6 (2.8)	1 (0.9)	0	1 (0.5)	1 (0.9)	0
Dizziness	6 (2.8)	2 (1.9)	2 (4.8)	0	0	0
Headache	19 (8.8)	10 (9.4)	3 (7.1)	9 (4.2)	3 (2.8)	1 (2.4)
Insomnia	4 (1.9)	2 (1.9)	2 (4.8)	1 (0.5)	0	0
Upper respiratory tract inflammation	4 (1.9)	2 (1.9)	2 (4.8)	1 (0.5)	0	0
Eczema	3 (1.4)	0	2 (4.8)	0	0	0
Pruritus	10 (4.7)	4 (3.8)	0	4 (1.9)	2 (1.9)	0
Pruritus generalised	0	0	2 (4.8)	0	0	0
Rash	4 (1.9)	2 (1.9)	2 (4.8)	3 (1.4)	0	2 (4.8)
Hypotension	2 (0.9)	0	2 (4.8)	2 (0.9)	0	2 (4.8)

Number of subjects (%)

No deaths were reported during the adverse event evaluation period (for 30 days after the end of treatment). After the adverse event evaluation period, 2 chronic hepatitis C subjects with compensated

cirrhosis died (each due to lymphangiosis carcinomatosa and metastases to bone; and hepatocellular carcinoma).[120)] Both cases of death were assessed as not related to the study drug.

Serious adverse events were reported in 7 chronic hepatitis C subjects without compensated cirrhosis in the PTV/RTV/OBV combination product group (hypotension, anuria, hepatocellular carcinoma, anal abscess, myelitis, gastric cancer, and tendon rupture in 1 subject each), 2 chronic hepatitis C subjects without compensated cirrhosis in the placebo group (colon adenoma and rectosigmoid cancer in 1 subject each), and 2 chronic hepatitis C subjects with compensated cirrhosis (pulmonary oedema; and lymphangiosis carcinomatosa and metastases to bone in 1 subject each). Of these events, hypotension, anuria, and pulmonary oedema were assessed as related to the study drug. While the hepatocellular carcinoma, myelitis, gastric cancer, and tendon rupture in chronic hepatitis C subjects without compensated cirrhosis in the PTV/RTV/OBV combination product group, rectosigmoid cancer in 1 chronic hepatitis C subject without compensated cirrhosis in the placebo group, and lymphangiosis carcinomatosa and metastases to bone in chronic hepatitis C subjects with compensated cirrhosis persisted, the other events resolved. Adverse events leading to study discontinuation were reported in 2 chronic hepatitis C subjects without compensated cirrhosis in the PTV/RTV/OBV combination product group (hypotension and anuria in 1 subject each) and in 1 chronic hepatitis C subject with compensated cirrhosis (pulmonary oedema) and were all assessed as related to the study drug, but their outcome was reported as “recovered/resolved.”

In substudy 1, adverse events (including laboratory abnormalities) and adverse drug reactions (including laboratory abnormalities) were reported in 64.2% (68 of 106) and 20.8% (22 of 106), respectively, of subjects treated with an open-label regimen of PTV/RTV/OBV combination product. The adverse events and adverse drug reactions that occurred at an incidence of ≥2% are shown in Table 41.

120) Lymphangiosis carcinomatosa and metastases to bone (woman 71 years of age):
The subject died of lymphangiosis carcinomatosa 76 days after completion of 12-week treatment. This event occurred 65 days after treatment completion and was attributed to bone metastases (metastases of a cancer of unknown primary), an adverse event. Hepatocellular carcinoma had not been detected by ultrasonography performed at screening or 1 day after treatment completion.
Hepatocellular carcinoma (woman 65 years of age):
The subject died of hepatocellular carcinoma 253 days after completion of 12-week treatment. Hepatocellular carcinoma had not been detected by ultrasonography performed at screening or 1 day after treatment completion, but was detected by ultrasonography and computed tomographic (CT) scan performed 85 days after treatment completion.

Table 41. Adverse events and adverse drug reactions that occurred at an incidence of ≥2% in subjects treated with an open-label regimen of PTV/RTV/OBV combination product

Event	Adverse event	Adverse drug reaction
Number of subjects	106	106
Overall	68 (64.2)	22 (20.8)
Abdominal discomfort	3 (2.8)	1 (0.9)
Diarrhoea	5 (4.7)	2 (1.9)
Stomatitis	3 (2.8)	3 (2.8)
Oedema peripheral	4 (3.8)	3 (2.8)
Urinary tract infection	3 (2.8)	0
Nasopharyngitis	8 (7.5)	0
Pharyngitis	3 (2.8)	1 (0.9)
Contusion	3 (2.8)	0
Headache	7 (6.6)	2 (1.9)
Eczema	3 (2.8)	2 (1.9)
Pruritus	4 (3.8)	2 (1.9)
Rash	4 (3.8)	2 (1.9)

Number of subjects (%)

There were no deaths or adverse events leading to study discontinuation. Serious adverse events occurred in 3 subjects (breast cancer, necrotising retinitis, and large intestine polyp in 1 subject each). These events were assessed as not related to the study drug. The outcome of the large intestine polyp was "recovered/resolved," and that of breast cancer and necrotising retinitis was "not recovered/not resolved."

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Significance of combining antiviral agents

The applicant provided the following rationale for combining 2 different anti-HCV agents, OBV and PTV:

OBV was administered as a single agent in 2 foreign studies (M[redacted]-116 and M[redacted]-386), and among the subjects who were sampled for resistance analysis, resistance-related mutations were found in 8 of 8 subjects and 7 of 8 subjects, respectively.[121)] In another foreign study (M[redacted]-602), RTV was coadministered with PTV for 3 days in an attempt to increase the blood concentration of PTV. Among the samples obtained from 13 subjects, a resistance-related mutation was found in 1 of 5 subjects who received PTV/RTV 200/100 mg despite poor anti-HCV activity of RTV, while subjects who received PTV/RTV 50/100 or 100/100 mg showed various resistance-related mutations. As shown by these findings, resistance-related mutations occurred early in treatment with OBV or PTV alone. These 2 active substances differ in terms of their anti-HCV mechanism of action and resistance profiles [see "3.(i).A.(1).1).(d) Resistance profiles" and "3.(i).A.(4).1).(c) Resistance profiles"], and therefore the combined administration of OBV and PTV makes sense because they are expected to reduce the development of resistance-related mutations. In the Japanese phase III study, SVR12 was achieved by

121) OBV was administered as a single agent at 5, 50, or 200 mg for 3 days (Study M[redacted]-116) or at 1.5 or 25 mg for 2 days (Study M[redacted]-386).

subjects who received the PTV/RTV/OBV combination product, even by those carrying viral mutants associated with OBV or PTV resistance at baseline [see "4.(iii).B.(2).2 Resistant viral mutations"].

In addition, the relationship between efficacy and improved treatment adherence owing to the use of a combination product containing multiple agents in treating patients with HCV infection has not been elucidated, and the relationship between the occurrence of mutations associated with OBV or PTV resistance and levels of exposure to these agents has not been investigated. However, the use of a combination product containing OBV and PTV may reduce the emergence of resistant viral mutations due to low exposure levels caused by poor treatment adherence.

An overview in various treatment categories including hypotensive and hypoglycemic treatment suggests that the use of fixed-dose combination drugs enhances treatment adherence and outcomes.[122)] Moreover, given that treatment adherence increases in association with the pill counts,[123,124,125)] the availability of fixed-dose combination of multiple agents is expected to increase treatment adherence.

On the basis of above findings and discussions, the combination product containing OBV and PTV is regarded clinically significant.

PMDA's view:
The applicant's rationale for coadministering OBV and PTV is understandable. However, the relationship between efficacy and degree of adherence to fixed-dose combination products in the treatment of patients with HCV infection has not been elucidated, and the reports on the association between improved treatment adherence and efficacy are based on the information from therapeutic categories that differ from HCV treatment in terms of, for example, treatment duration. Therefore, it is difficult to accept the applicant's explanation that the clinical significance for developing combination drugs necessarily applies to the treatment of patients with HCV infection. Nevertheless, there is a certain level of clinical significance that supports combining OBV and PTV because a regimen combining daclatasvir hydrochloride (DCV) and asunaprevir (ASV), which are analogous to OBV and PTV, respectively, in terms of mechanism of action, has already been approved for the treatment of patients with HCV infection, and is recommended in the Japanese treatment guidelines and other references.[126)] Inclusion of RTV in the fixed-dose combination is also considered rational [see "4.(ii).B.(1) Rationale for coadministering RTV with anti-HCV drugs and selecting its dose"]. Therefore, the applicant's rationale for developing a fixed-dose combination drug consisting of OBV, PTV, and RTV has some basis.

122) Connor J et al., *Bull World Health Organ*. 2004;82:935-939
123) Cohen CJ et al., *BMJ Open*. 2013;3:e003028. doi:10.1136/bmjopen-2013-003028
124) Airoldi M et al., *Patient Prefer Adherence*. 2010;4:115-125
125) Nachega JB et al., *HIV/AIDS*. 2014; 58:1297-1307
126) Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. *JSH guidelines for the management of hepatitis C virus infection*, 3.3th ed. 2015

4.(iii).B.(2) Efficacy

PMDA concluded that treatment with the PTV/RTV/OBV combination product alone is expected to be effective in patients with HCV infection based on the review presented in the sections, 4.(iii).B.(2).1) and 2).

However, given that clinical studies have provided only limited information on the relationships between resistance-related mutations and efficacy, it is necessary to collect post-marketing information from sources including the published literature on the relationship between the baseline status of resistance-related mutations and the efficacy of the PTV/RTV/OBV combination product and the status of resistance-related mutations in patients failing to achieve SVR despite treatment with PTV/RTV/OBV combination product, and any new findings should be promptly provided to healthcare professionals in clinical settings.

The above conclusion of PMDA will be discussed in the Expert Discussion.

4.(iii).B.(2).1) Efficacy

PMDA asked the applicant to explain the background and rationale for not having used any existing treatment regimen as a control in the Japanese phase III study (M13-004).

The applicant's explanation:

As of the starting date of the Japanese phase III study ([redacted] 20[redacted]), IFN-containing regimens such as a triple regimen of telaprevir (TVR) and peginterferon (PegIFN)/ribavirin (RBV) and a dual regimen of PegIFN/RBV were recommended in Japan as treatment options for chronic hepatitis C patients with or without compensated cirrhosis (genotype 1).[127] However, use of any of these regimens as a control was considered to be inappropriate for the following reasons:

- An interim report of the Japanese phase II study (M[redacted]-536) in treatment-naïve patients with chronic hepatitis C (genotype 1b) shows that the SVR24 rate for 12-week treatment was 88.9% (16 of 18 subjects) in the PTV/RTV 150/100 mg group and 100% (18 of 18 subjects) in the PTV/RTV 100/100 mg group. The main adverse events reported in the study were nasopharyngitis (29.1%), headache (13.6%), back pain (7.3%), hypertension (7.3%), gastroenteritis (5.5%), pruritus (5.5%), and rash (5.5%). An adverse event leading to discontinuation and a ≥Grade 3 adverse event were reported in only 1 subject each. These results demonstrated that the safety of PTV/RTV/OBV combination product is acceptable.
- The SVR24 rate for a triple regimen of TVR, PegIFN, and RBV in Japan[128,129] was 88.1% (96 of 109 patients) among patients relapsing after successful prior treatment and 34.4% (11 of 32 patients) among null responders to prior treatment. Adverse events such as severe skin disorder and

127) Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. *JSH guidelines for the management of hepatitis C virus infection*, 2012
128) Hayashi N et al., *J Viral Hepatitis.* 2012;19:e134-e142,
129) TELAVIC Tablets 250 mg [package insert] 14th ed.; April 2015

anaemia were reported in patients treated with TVR. In patients treated with a combination of PegIFN and RBV, adverse events and laboratory abnormalities such as flu-like symptoms, anaemia, haemoglobin decreased, neutropenia, and thrombocytopenia were reported.

- Taking into account the efficacy data and safety profile of PTV/RTV/OBV combination product verified at the start of the study, it was assumed that a study design using any regimen containing PegIFN/RBV as a control would be unacceptable to both patients and investigators. Therefore, the applicant considered it impractical to conduct a substudy using any IFN-containing regimen as a control in the Japanese phase III study (M13-004).

In the Japanese phase III study, in the same way as in previous foreign clinical studies, placebo was used as a control in substudy 1 in patients with chronic hepatitis C, and either PTV/RTV/OBV combination product or placebo was administered under double-blind conditions for 12 weeks, enabling adverse events occurring after administration of the combination product to be compared with events occurring in the natural course of chronic hepatitis C. The study was also designed to enable subjects in the placebo group to be treated with PTV/RTV/OBV combination product after completion of placebo treatment; that is, all subjects enrolled in the study were able to receive the same treatment with or without a 12-week delay. Designed as such, the study seemed more feasible than a study using a PegIFN/RBV-containing regimen, which requires administration for at least 24 weeks. In the Japanese phase III study, the SVR12 rate in treatment-naïve and treatment-experienced patients with chronic hepatitis C who received PTV/RTV/OBV combination product after completing placebo treatment under open-label conditions was 98.5% (67 of 68 subjects) and 97.4% (37 of 38 subjects), respectively, demonstrating the efficacy of PTV/RTV/OBV combination product. Therefore, this study design was considered to be appropriate for investigating the safety of the PTV/RTV/OBV combination product without causing particular disadvantage to subjects.

The applicant's explanation on the efficacy of the PTV/RTV/OBV combination product in Japanese chronic hepatitis C patients with or without compensated cirrhosis (both genotype 1b):
In the Japanese phase III study, the lower limit of the 95% confidence interval for the SVR12 rate in treatment-naïve subjects with chronic hepatitis C (high viral load) who were eligible for IFN therapy, the primary endpoint, in the PTV/RTV/OBV combination product group was above the pre-specified threshold [see "4.(iii).A.(2) Japanese phase III study"]. The results of subgroup analysis of the PTV/RTV/OBV combination product group in the study demonstrated the efficacy of PTV/RTV/OBV combination product as shown in Table 42. The SVR24 rate was 93.8% (105 of 112 subjects) in IFN-eligible, treatment-naïve subjects with chronic hepatitis C (high viral load), 93.5% (130 of 139 subjects) in treatment-naïve subjects with chronic hepatitis C, and 96.1% (73 of 76 subjects) in treatment-experienced subjects with chronic hepatitis C. All chronic hepatitis C subjects with compensated cirrhosis who had achieved SVR12 also achieved SVR24.

Based on the above, the PTV/RTV/OBV combination product is expected to be effective for treating Japanese chronic hepatitis C patients with or without compensated cirrhosis (both genotype 1b).

Table 42. SVR12 rates in a subgroup analysis of chronic hepatitis C patients in the Japanese phase III study (ITT)

Baseline characteristics		PTV/RTV/OBV combination product group	
		Treatment-naïve (148 subjects)	Treatment-experienced (109 subjects)
Overall		140/148 (94.6)	102/109 (93.6)
Severity of liver fibrosis	CHC subjects without compensated cirrhosis	131/139 (94.2)	73/76 (96.1)
	CHC subjects with compensated cirrhosis	9/9 (100)	29/33 (87.9)
Age	< 65 years	91/95 (95.8)	52/55 (94.5)
	≥ 65 years	49/53 (92.5)	50/54 (92.6)
Eligibility for IFN	Eligible	112/118 (94.9)	–
	Ineligible	28/30 (93.3)	–
Response to prior treatment	Null	–	44/47 (93.6)
	Relapsed	–	28/30 (93.3)
	Intolerant to IFN	–	29/31 (93.5)
	Unknown	–	1/1 (100)
HCV RNA	< 100,000 IU/mL	5/5 (100)	–
	≥ 100,000 IU/mL	135/143 (94.4)	102/109 (93.6)
IL28B gene polymorphism rs12979860	CC	84/92 (91.3)	51/55 (92.7)
	Non CC	56/56 (100)	51/54 (94.4)

Number of subjects (%); –, not applicable

PMDA's view:

The applicant explained that from a viewpoint of feasibility, a comparative study using an IFN-containing regimen such as TVR/PegIFN/RBV as a control was not designed because (i) at the starting date of the Japanese phase III study, data had been obtained from a Japanese clinical study of a triple regimen of TVR/PegIFN/RBV in patients with chronic hepatitis C (genotype 1) and from an interim analysis of a Japanese phase II study (M[redacted]-536) of PTV/RTV/OBV combination product in patients with chronic hepatitis C (genotypes 1b and 2), and (ii) these data showed that the SVR24 rate for PTV/RTV/OBV combination product was higher than that for the combination regimen of TVR/PegIFN/RBV, indicating that PTV/RTV/OBV combination product was better tolerated than TVR/PegIFN/RBV. This explanation is understandable to some extent.

The lower limit of the 95% confidence interval for the SVR12 rate in IFN-treatment-eligible, treatment-naïve chronic hepatitis C subjects without compensated cirrhosis (genotype 1b) with a high viral load in the PTV/RTV/OBV combination product group was above the pre-specified threshold in the Japanese phase III study. The SVR12 rate was 96.1% (73 of 76 subjects) in treatment-experienced chronic hepatitis C subjects without compensated cirrhosis, 100% (9 of 9 subjects) in treatment-naïve chronic hepatitis C subjects with compensated cirrhosis, and 87.9% (29 of 33 subjects) in treatment-experienced subjects with compensated cirrhosis. Given these data, PMDA concluded that PTV/RTV/OBV combination product could be expected to be effective in treatment-naive or treatment-experienced chronic hepatitis C patients with or without compensated cirrhosis (both genotype 1b).

4.(iii).B.(2).2) Resistant viral mutations

The applicant's explanation for the development of resistant viruses and the effect of resistant viruses on the efficacy of the PTV/RTV/OBV combination product:

An analysis of PTV- and OBV-resistant viruses was performed in 13 subjects who had experienced virologic failure[130)] and 416 subjects who had achieved SVR24 or SVR12 among chronic hepatitis C subjects with or without compensated cirrhosis (both genotype 1b) treated with a combination regimen of PTV/RTV/OBV or PTV/RTV/OBV combination product in the Japanese phase II study (M[redacted]-536) and the Japanese phase III study (M13-004).

The SVR12 rates in subjects treated with PTV/RTV/OBV combination in the Japanese phase III study (M13-004) are tabulated in Table 43 by baseline status of resistance-related mutations[131)] occurring in the NS3 or NS5A domain [see "3.(i).A.(1) Primary pharmacodynamics (PTV), 3.(i).A.(1).1).(d) Resistance profiles" and "3.(i).A.(4) Primary pharmacodynamics (OBV), 3.(i).A.(4).1).(c) Resistance profiles"]. The SVR12 rates in subjects in whom resistance-related mutations in the NS3 or NS5A domain were detected were similar to those in subjects who were negative for mutation at any amino acid position. The SVR12 rate in subjects with Y93H/S mutation in the NS5A domain (83.0% [39 of 47 subjects]) was lower than that in subjects without Y93H/S mutation (99.0% [301 of 304 subjects]). In the Japanese phase II study (M[redacted]-536), resistance-related mutations were also detected at baseline in the NS3 and NS5A domains. The SVR24 rate in subjects who were positive for Y93H mutation was 100% (4 of 4 subjects), and that in subjects who were negative for Y93H mutation was 97.1% (68 of 70 subjects). In terms of other mutations, there were no marked differences in SVR12 rate or SVR24 rate among subjects with or without mutations.

130) Subjects treated with the PTV/RTV/OBV combination product who had not achieved SVR24 or SVR12 and who met any of the following criteria:
- Patients who experienced rebound during treatment (patients with HCV RNA level once dropped to < LLOQ and then returned to ≥ LLOQ during the treatment or patients experiencing an increase in HCV RNA from its minimum value [an increase from the minimum by >1 $\log_{10}$ IU/mL] at a given time point during treatment)
- Patients in the 12-week treatment group who relapsed after completion of ≥77-day treatment, or patients in the 24-week treatment group who relapsed after completion of ≥154-day treatment
- Patients whose HCV RNA level did not fall below the LLOQ (HCV RNA level was above the LLOQ at any time point during treatment) despite having received treatment for ≥6 weeks

131) A resistance-related mutation against PTV was defined as a mutation in the NS3 domain that was detected in genotype 1b replicon cells in the presence of low-concentration PTV or an NS3/4A protease inhibitor-resistant mutation in the NS3 domain that had been reported and that was confirmed *in vitro*.
A resistance-related mutation against OBV was defined as a mutation in the NS5A domain that was detected in genotype 1b replicon cells in the presence of low-concentration OBV and that was confirmed *in vitro*.

Table 43. SVR12 rates by baseline status of resistance-related mutations occurring in the NS3 or NS5A domain (M13-004)

	CHC patients without compensated cirrhosis				CHC patients with compensated cirrhosis	
	Patients treated with the PTV/RTV/OBV combination product in the blind phase		Patients treated with the PTV/RTV/OBV combination product in the open-label phase			
	Mutation-positive	Mutation-negative	Mutation-positive	Mutation-negative	Mutation-positive	Mutation-negative
NS3 domain						
T54S	100 (12/12)	96.9 (188/194)	100 (1/1)	98.0 (100/102)	100 (1/1)	91.7 (33/36)
V551	100 (1/1)	97.1 (199/205)	–	–	–	–
Y56F	97.4 (76/78)	96.9 (124/128)	97.4 (37/38)	98.5 (64/65)	90.9 (10/11)	92.3 (24/26)
Q80H/K/L/R	96.3 (26/27)	97.2 (174/179)	91.7 (11/12)	98.9 (90/91)	100 (4/4)	90.9 (30/33)
S122X/A/C/G/I/N/T/V/Y [a)]	96.2 (76/79)	97.6 (124/127)	97.3 (36/37)	98.5 (65/66)	83.3 (15/18)	100 (19/19)
D168E	100 (3/3)	97.0 (197/203)	–	–	100 (1/1)	91.7 (33/36)
NS5A domain						
L281/M/V	100 (18/18)	96.8 (183/189)	92.3 (12/13)	98.9 (90/91)	100 (4/4)	91.7 (33/36)
R30G/L/Q	100 (25/25)	96.7 (176/182)	94.7 (18/19)	98.8 (84/85)	100 (4/4)	91.7 (33/36)
L31F/I/M	100 (5/5)	97.0 (196/202)	100 (2/2)	98.0 (100/102)	50.0 (1/2)	94.7 (36/38)
Q54*/A/C/D/E/H/K/L/N/P/R/S/V/Y [b)]	98.8 (81/82)	96.0 (120/125)	97.8 (45/46)	98.3 (57/58)	95.2 (20/21)	89.5 (17/19)
P58A/L/Q/R/S/T	100 (14/14)	96.9 (187/193)	100 (9/9)	97.9 (93/95)	100 (2/2)	92.1 (35/38)
Q62A/C/D/E/H/L/M/N/P/R/S/Y	96.3 (26/27)	97.2 (175/180)	100 (6/6)	98.0 (96/98)	100 (2/2)	92.1 (35/38)
A92E/M/S/T/V	100 (14/14)	96.9 (187/193)	100 (7/7)	97.9 (95/97)	80.0 (4/5)	94.3 (33/35)
Y93H/S	86.7 (26/30)	98.9 (175/177)	80.0 (8/10)	100 (94/94)	71.4 (5/7)	97.0 (32/33)

(%) Number of subjects; –, not applicable
a) X, unidentified amino acid sequence; b) *, stop codon

Table 44 shows the resistance-related mutations in the NS3 and NS5A domains detected at baseline and at the time of virologic failure in 13 subjects who experienced virologic failure in the Japanese phase II study (M[redacted]-536) and the Japanese phase III study (M13-004). In the NS3 domain, PTV-resistance-related mutations were detected in none of the 13 subjects at baseline, but in 12 subjects at position D168 and in 5 subjects at position Y56 at time points where virologic failure was confirmed. In the NS5A domain, OBV-resistance-related mutations were detected in 10 of 13 subjects at baseline and in all the 13 subjects (mutation at Y93 in 12 subjects and at L31 in 3 subjects) at time points where virologic failure was confirmed. In 12 of 13 subjects who experienced virologic failure, resistance-related mutations were detected in both NS3 and NS5A domains at time points where virologic failure was confirmed.

Table 44. Resistance-related mutations in the NS3 and NS5A domains in subjects who experienced virologic failure

Study	Subjects	NS3 domain			NS5A domain		
		Baseline resistance mutation	At virologic failure		Baseline resistance mutation	At virologic failure	
			Resistance mutation[a)]	Fold-change in EC_{50}[b)]		Resistance mutation[a)]	Fold-change in EC_{50}[b)]
M[redacted]-536	CHC subjects without compensated cirrhosis	None	D168V	159	L28M+R30Q	L28M+R30Q +Y93H	ND
M13-004	CHC subjects without compensated cirrhosis	None	Y56H+D168V	2472	None	Y93H	77
		None	Y56H+D168V	2472	Y93H/Y	Y93H	77
		None	D168V	159	None	Y93H	77
		None	D168D/V	159	Y93H	Y93H	77
		None	D168V	159	Y93H/Y	P58S+Y93H	1401
		None	None	1	Y93H/Y	R30Q+Y93H	284
		None	D168V	159	Y93H/Y	Y93H	77
		None	Y56H, D168V	NA, 159	Y93H	P58S, Y93H	0.8, 77
		None	Y56H, D168A	NA, 27	L28M, R30Q, Y93H/Y	L28M, R30Q, Y93H	2, 0.4, 77
	CHC subjects with compensated cirrhosis	None	D168D/V	159	L31M, Y93H/Y	L31M+Y93H	142
		None	Y56H/Y, D168A	NA, 27	Y93H	L31V+Y93H	12,328
		None	D168V	159	None	L31F	10

NA, EC_{50} not calculated (replicon cells did not have sufficient replication capacity); ND, not discussed
a) "+" indicates a mutation identified in the same virus. "," indicates a mutation identified in the same specimen.
b) Fold-change in antiviral activity (EC_{50}) for each variant compared with wild-type determined using genotype 1b replicon cells

PMDA's view:

In the subjects who experienced virologic failure in the Japanese phase II study (M[redacted]-536) and phase III study (M13-004), mutations were detected at D168 and Y56 in the NS3 domain and at Y93 and L31 in the NS5A domain at time points where virologic failure was confirmed. Resistance-related mutations were detected in both the NS3 and NS5A domains in 12 of 13 subjects (Table 44). In the Japanese phase III study (M13-004), the SVR12 rate in subjects with a mutation at Y93 in the NS5A domain at baseline (83.0% [39 of 47 subjects]) was lower than that in subjects without the mutation at baseline (99.0% [301 of 304 subjects]). However, given that the SVR12 rate in chronic hepatitis C subjects with or without compensated cirrhosis was 83.0% (39 of 47 subjects) even in subjects in whom resistance-related mutations were detected at Y93 in the NS5A domain but not detected in the NS3 domain at baseline, the presence of these mutations at baseline are not necessarily responsible for virologic failure.

Taking into account that clinical studies have provided only limited information on the relationships between resistance-related mutations and the efficacy of PTV/RTV/OBV combination product, it is necessary to collect post-marketing information from sources including the published literature, on the baseline status of resistance mutations, the status of resistance-related mutations in patients failing to achieve SVR despite treatment with PTV/RTV/OBV combination product, and other relevant matters, and any new findings should be promptly provided to healthcare professionals in the clinical settings.

4.(iii).B.(3) Safety

PMDA concluded that the safety of PTV/RTV/OBV combination product in Japanese chronic hepatitis C patients with or without compensated cirrhosis (both genotype 1b) is acceptable based on the results of review in the following sections, 4.(iii).B.(3).1) to 5).

However, given that there is limited clinical experience with PTV/RTV/OBV combination product in elderly patients, further post-marketing safety information in this patient population should be collected. In addition, taking into account the high incidence of oedema-related events and the occurrence of hepatic impairment in patients treated with PTV/RTV/OBV combination product coadministered with a calcium antagonist (Ca antagonist), it is necessary to collect post-marketing information on the occurrence of these events.

The above conclusion of PMDA will be discussed at the Expert Discussion.

4.(iii).B.(3).1) Safety profile

The applicant's explanation on the safety of the PTV/RTV/OBV combination product in chronic hepatitis C patients with or without compensated cirrhosis (both genotype 1b):

Safety data from the Japanese phase III study (M13-004) are summarized in Table 45.

Table 45. Summary of the safety results of chronic hepatitis C patients in the Japanese phase III study (safety analysis population)

Event	Without compensated cirrhosis		With compensated cirrhosis	Without compensated cirrhosis
	PTV/RTV/OBV combination product	Placebo	PTV/RTV/OBV combination product	PTV/RTV/OBV combination product in the open-label phase
Number of subjects	215	106	42	106
Overall number of adverse events	148 (68.8)	60 (56.6)	31 (73.8)	68 (64.2)
Grade[132)] 3 adverse event [a)]	12 (5.6)	2 (1.9)	2 (4.8)	2 (1.9)
Serious adverse event	7 (3.3)	1 (1.9)	2 (4.8)	3 (2.8)
Death [b)]	0	0	0	0
Adverse event leading to discontinuation	2 (0.9)	0	1 (2.4)	0

Number of subjects (%)

a) No ≥Grade 4 adverse events were reported.

b) After the adverse event evaluation period, 2 deaths were reported in patients with compensated cirrhosis [see 4.(iii).A.(2) Japanese phase III study].

Serious adverse events were reported in 2 chronic hepatitis C subjects without compensated cirrhosis in the PTV/RTV/OBV combination product group (hypotension and anuria in 1 subject each) and in 1 chronic hepatitis C subject with compensated cirrhosis (pulmonary oedema). They were assessed as

132) Severity of adverse events was assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grading System (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf; Accessed June 2015) in the Japanese phase III study (M13-004), and according to the following definitions of mild, moderate, and severe in the Japanese phase II study (M[redacted]-536):
Mild, an event causing temporary and tolerable discomfort;
Moderate, an event causing anxiety or pain in the subject and interfering with their activities of daily living; and
Severe, an event making it impossible to perform usual activities of daily living, which may cause functional impairment or which is potentially life-threatening.

related to the study drug and led to study discontinuation, but their outcomes were "resolved." All Grade 3 adverse events other than serious adverse events (nausea, vomiting, headache; hypertension; urethritis; renal impairment; and presyncope in 1 subject each) resolved except for hypertension in 1 subject. Among chronic hepatitis C subjects without compensated cirrhosis, the adverse event that occurred in the PTV/RTV/OBV combination product group at an incidence higher than that in the placebo group by ≥5% was oedema peripheral (5.1% [11 of 215 subjects] in the PTV/RTV/OBV combination product group and 0% [0 of 106 subjects] in the placebo group).

PMDA's view:

Taking into account the incidences of Grade 3 adverse events and serious adverse events reported in the PTV/RTV/OBV combination product group in Japanese clinical studies, PTV/RTV/OBV combination product appears to be well tolerated when prescribed by physicians with knowledge and experience in viral hepatic disorders. Detailed review of oedema-related events, hepatic impairment, and the safety in elderly patients is presented in the sections below.

4.(iii).B.(3).2) Oedema-related events

The applicant provided the following explanation of oedema-related events.

(a) Oedema-related adverse events in Japanese and foreign clinical studies

Table 46 shows the oedema-related adverse events[133)] reported in subjects treated with a combination regimen of PTV/RTV/OBV, the PTV/RTV/OBV combination product, or a combination regimen of PTV/RTV/OBV/dasabuvir in Japanese clinical studies (pooled analysis of the phase II study [M[redacted]-536] and the phase III study [M13-004]) and foreign clinical studies.[134)]

133) Events that are classified into "face oedema," "fluid retention," "localised oedema," "oedema," "oedema peripheral," or "pulmonary oedema" according to PT of MedDRA ver. 17

134) Subjects treated with a combination regimen of PTV/RTV/OBV (200/100 mg of PTV/RTV and 25 mg of OBV QD for 12 weeks) in Study M[redacted]-998 (cohorts IV, V, and VI); subjects treated with a combination regimen of PTV/RTV/OBV (150/100 mg of PTV/RTV and 25 mg of OBV QD for 12 or 24 weeks) in Study M[redacted]-393 (groups 1, 2, 3, 7, and 8); and subjects treated with a combination regimen of PTV/RTV/OBV/dasabuvir (100/100 or 150/100 mg of PTV/RTV, 25 mg of OBV QD, and [redacted] mg of dasabuvir BID for 8 to 24 weeks) in Studies M[redacted]-652, M[redacted]-389, M[redacted]-961, and M[redacted]-002.

Table 46. Oedema-related events reported in clinical studies

MedDRA PT	Japanese clinical studies	Foreign clinical studies	
	2-DAA regimen	2-DAA regimen	3-DAA regimen
Number of subjects	473	256	588
Overall oedema-related events	30 (6.3)	9 (3.5)	12 (2.0)
Oedema peripheral	22 (4.7)	7 (2.7)	9 (1.5)
Oedema	6 (1.3)	1 (0.4)	1 (0.2)
Face oedema	3 (0.6)	0	0
Localised oedema	0	1 (0.4)	2 (03)
Fluid retention	1 (0.2)	0	0
Pulmonary oedema	1 (0.2)	0	0

Number of subjects (%)
2-DAA regimen group, subjects treated with a combination regimen of PTV/RTV/OBV or the PTV/RTV/OBV combination product
3-DAA regimen group, subjects treated with a combination regimen of PTV/RTV/OBV/dasabuvir

Most of the oedema-related events reported in Japanese and foreign clinical studies were Grade 1 or 2 in severity. However, 2 Grade 3 oedema-related events (pulmonary oedema[135)] and fluid retention[136)] in 1 subject each) occurred in 2 subjects in the Japanese clinical studies. Both events were serious and assessed as related to the study drug, though their outcomes were "recovered/resolved." The incidence of overall oedema-related events tended to be higher in the Japanese clinical studies than in foreign clinical studies.

(b) Risk of oedema-related events

Subject characteristics in Japanese clinical studies (pooled analysis of phase II study [M[redacted]-536] and phase III study [M13-004]) are summarized in Table 47 by presence or absence of oedema-related events.

135) A 67-year-old male chronic hepatitis C patient with compensated cirrhosis received the PTV/RTV/OBV combination product (M13-004). Pulmonary oedema occurred on Day 25, and oedema peripheral and increased body weight (by 3 kg) were observed on Day 29. The study treatment was discontinued on Day 28; however, the subject developed acute respiratory distress syndrome on Day 30. The pulmonary oedema was assessed by the investigator as related to the study drug. The subject recovered from these events on Day 111. Glycyrrhizic acid and a Ca antagonist had been administered before and during treatment with the PTV/RTV/OBV combination product.

136) A 72-year-old male patient with chronic hepatitis C received PTV/RTV/OBV at 150/100/25 mg (Study M[redacted]-536). Dyspnoea occurred on Day 5, and the study treatment was discontinued on Day 9. The subject developed fluid retention (an increase in body weight of 5.2 kg, pleural effusion, and cardiac failure congestive) on Day 10. The fluid retention was assessed by the investigator as related to the study drug, but was considered to be induced by renal impairment (secondary nephrotic syndrome attributable to HCV). The subject recovered from these events on Day 36. Glycyrrhizic acid and a Ca antagonist had been administered before and during treatment with the PTV/RTV/OBV combination product.

Table 47. Subject characteristics by presence or absence of oedema-related events (pooled analysis of the Japanese phase II and phase III studies)

		Oedema-related event	
		Occurred	Not occurred
Total number of subjects [a)]		30	443
Clinical profile	Age (median)	67.5	62.0
	Sex ratio (male: female)	7:23	191:252
	Number of subjects with compensated cirrhosis (%)	4 (13.3)	38 (8.6)
	Number of subjects with hypertension (%)	26 (86.7)	146 (33.0)
	Number of subjects with cardiac failure (%)	0	0
	Number of subjects with renal impairment (%)	0	6 (1.4)
Laboratory values	Platelet count ($\times 10^9$/L)	185.0	191.0
	Serum creatinine (μmol/L)	66.1	68.0
	Serum urea nitrogen (mmol/L)	5.07	5.18
	Serum albumin (g/L)	41.8	41.5
	Serum sodium (mmol/L)	140.5	140.1
	Serum potassium (mmol/L)	3.89	3.99
	eGFR (mL/min/BSA)	66.50	70.02
Concomitant drug	Number of subjects concomitantly using a Ca antagonist (%)	27 (90.0)	73 (16.5)

a) Number of subjects treated with a combination regimen of PTV/RTV/OBV or the PTV/RTV/OBV combination product

Subjects with oedema-related events had concurrent hypertension or concomitantly received a Ca antagonist in a higher proportion than those without oedema-related events. The mechanisms underlying the oedemas induced by Ca antagonists are considered as follows: Ca antagonists dilate the artery and increase intracapillary pressure, and thereby dilate the capillary and increase capillary permeability, leading to the development of oedemas.[137)] RTV, a drug with an inhibitory effect on CYP3A, has been known to inhibit the metabolism of drugs that are to be metabolized by CYP3A and increase the blood concentration of drugs and thereby enhance the action of Ca antagonists.[138)]

In an analysis of oedema-related events by the dose of a Ca antagonist, the incidence of oedema-related events was 14.3% (5 of 35 subjects) in the low-dose group and 33.8% (22 of 65 subjects) in the intermediate- to high-dose group, indicating that the incidence was higher when a Ca antagonist was coadministered at an intermediate to high dose.

On the basis of the above, concomitant use of a Ca antagonist for the treatment of hypertension was likely to be a factor causing oedema-related events during the use of PTV/RTV/OBV combination product. Healthcare professionals in the clinical settings need to be informed of oedema-related events reported during treatment with PTV/RTV/OBV combination product and precautions against administering PTV/RTV/OBV combination product in combination with a Ca antagonist.

PMDA's view:

The applicant's explanation is acceptable and due attention should be paid to the occurrence of oedema-related events during treatment with PTV/RTV/OBV combination product regardless of with or without a Ca antagonist.

137) Aellig WH et al., *Cardiovasc Drugs Ther*. 1998;12:189-196; Makani H et al., *J Hypertension*. 2011;29:1270-1280

138) Norvir Tablets 100 mg [package insert] 6th ed.; October 2014

4.(iii).B.(3).3) Hepatic impairment

The applicant's explanation on the occurrence of hepatic impairment during treatment with PTV/RTV/OBV combination product:

Bilirubin levels in Japanese clinical studies (pooled analysis of the phase II study [M[redacted]-536] and the phase III study [M13-004]) were analyzed based on the CTCAE ver. 4 grading system to investigate the severity and frequency of blood bilirubin increased in subjects treated with a combination regimen of PTV/RTV/OBV or the PTV/RTV/OBV combination product. The results of the analysis are shown in Table 48.

Table 48. Blood bilirubin increased reported in Japanese clinical studies (pooled analysis of patients with chronic hepatitis C in the Japanese phase II and phase III studies)

	Chronic hepatitis 2-DAA regimen (431 subjects)	Compensated cirrhosis 2-DAA regimen (42 subjects)	Chronic hepatitis Placebo (106 subjects)
Total number of affected subjects	55 (12.8)	14 (33.3)	4 (3.8)
Grade 1	40 (9.3)	10 (23.8)	4 (3.8)
Grade 2	15 (3.5)	3 (7.1)	0
Grade 3	0	1 (2.4)	0
Grade 4	0	0	0

Number of subjects (%)
2-DAA regimen group, subjects treated with a combination regimen of PTV/RTV/OBV or PTV/RTV/OBV combination product
Grade 1 > upper limit of normal [ULN] to 1.5 × ULN; Grade 2 > 1.5 to 3 × ULN; Grade 3 > 3 to 10 × ULN; Grade 4 > 10 × ULN

The incidence was higher in chronic hepatitis C subjects with compensated cirrhosis than in subjects without compensated cirrhosis, but most cases were Grade 1 or 2 and the outcomes of all cases were "recovered/resolved" except for a Grade 3 case in 1 subject.[139)]

Figure 4 shows the mean changes from baseline in bilirubin level among subjects with chronic hepatitis C in the Japanese phase III study (M13-004). In subjects treated with PTV/RTV/OBV combination product, the mean change from baseline in total bilirubin transiently increased and reached its peak (+ 2.4 μmol/L) at Week 1, decreased (to + 0.4 μmol/L) at Week 2, and fell below the baseline value at and after Week 4. Similarly in chronic hepatitis C subjects with compensated cirrhosis, the mean change from baseline in total bilirubin reached its peak (+ 2.4 μmol/L) at Week 1, decreased (to + 0.2 μmol/L) at Week 2, and fell below the baseline value at and after Week 4. The mean changes from baseline in direct and indirect bilirubin levels are shown in Figure 5. It was indirect bilirubin that increased in subjects treated with PTV/RTV/OBV combination product.

139) A chronic hepatitis C subject with compensated cirrhosis enrolled in Study M13-004. The grade of the event had fallen to ≤ Grade 2 by the last visit in the treatment period.

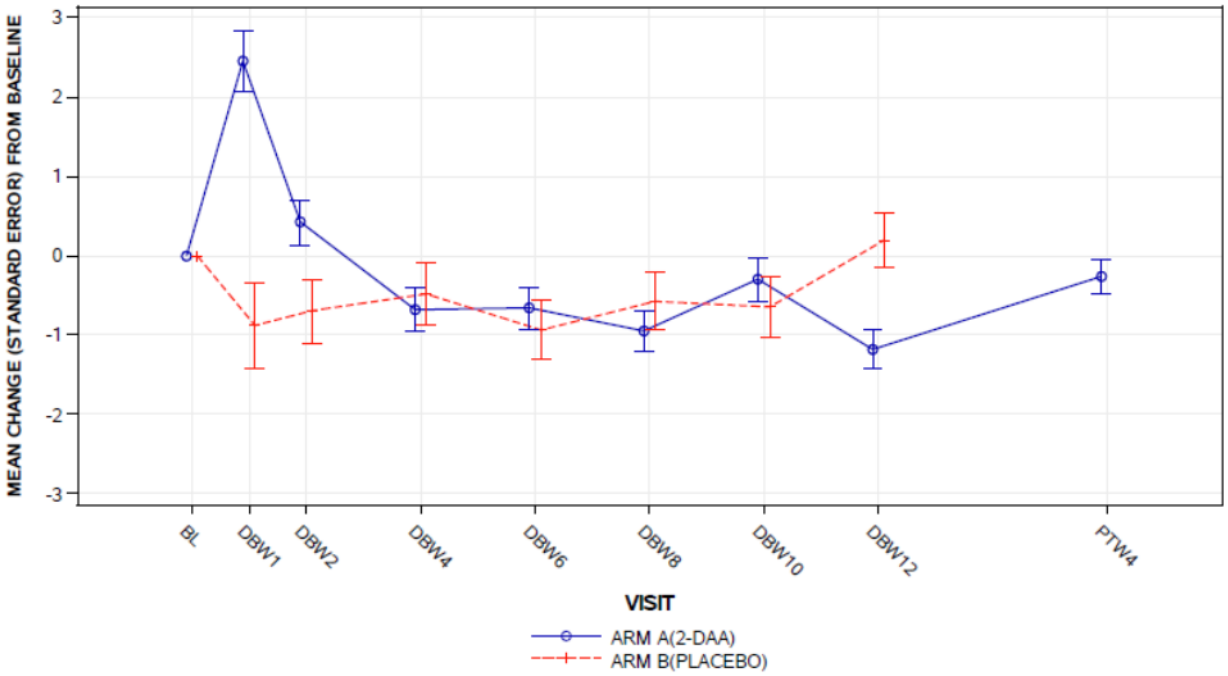

Figure 4. Change from baseline in total bilirubin (mean ± standard error)
Subjects with chronic hepatitis C (M13-004; safety analysis population); unit, µmol/L

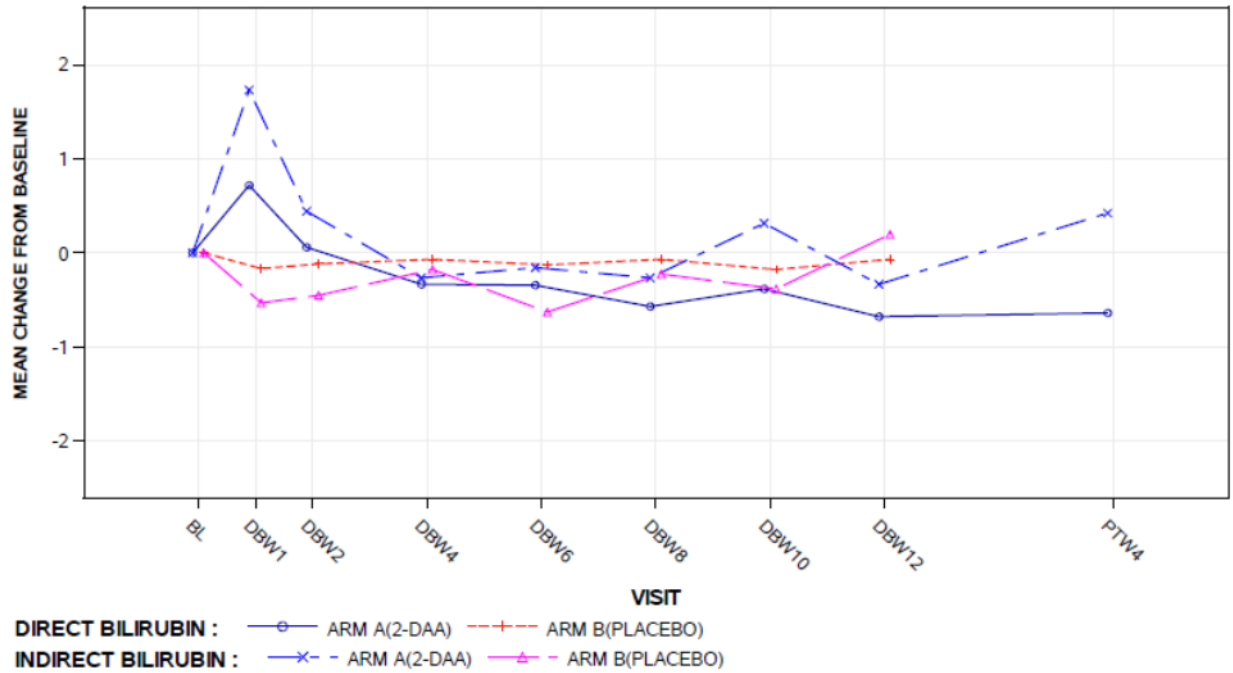

Figure 5. Changes from baseline in direct and indirect bilirubin (mean)
Subjects with chronic hepatitis C (M13-004; safety analysis population); unit, µmol/L

Blood bilirubin increased is considered to have resulted from the inhibition of OATP1B1, a transporter involved in the excretion of bilirubin, for the following reasons:

- PTV inhibits OATP1B1 [see “3.(ii).A.(5).2) Substrate of drug transporters and inhibitory effects”]

- Faldaprevir (an NS3/4A protease inhibitor that has not been approved in Japan), a similar drug known to have an inhibitory action on OATP1B1, has also been reported to cause a transient increase in bilirubin at an early stage of treatment.[140)]
- In the Japanese phase III study, blood bilirubin increased observed at an early stage of treatment with PTV/RTV/OBV combination product was a transient event, and all the events resolved except for one Grade 3 event in 1 subject with compensated cirrhosis.

Given that the blood bilirubin increased observed during treatment with PTV/RTV/OBV combination product remained nearly asymptomatic and was not accompanied by ALT increased or AST increased, this event is unlikely to be a safety concern.

In Japanese clinical studies (the phase II study [M[redacted]-536] and the phase III study [M13-004]), Grade 3 ALT increased (>5-fold to ≤20-fold the upper limit of normal [ULN]) occurred in 0.4% (2 of 471 subjects) and Grade 3 AST increased (>5-fold to ≤20-fold the ULN) occurred in 0.2% (1 of 471 subjects) without any Grade 4 ALT or AST increased. All these events were reported in subjects with chronic hepatitis C and resolved during treatment with PTV/RTV/OBV combination product.[141)] Taking into account that drug-induced liver injury is more closely associated with ALT increased than with AST increased as shown in published literature and relevant guidelines,[142)] a precautionary statement will be provided on the risk of ALT increased and the need to perform liver function tests as done in foreign countries.

PMDA's view:
Although bilirubin increased occurred in Japanese clinical studies, they were transient and in most cases were asymptomatic, and resolved or improved without causing elevated liver enzymes. Therefore, bilirubin increased related to PTV/RTV/OBV combination product is considered tolerable. However, given that Grade 3 bilirubin increased, ALT increased, and AST increased were reported and that the incidence of these events was higher in chronic hepatitis C patients with compensated cirrhosis than in those without compensated cirrhosis, information on the occurrence of hepatic impairment and the need to perform periodic liver function tests should be cautioned appropriately and relevant information in the post-marketing setting should be collected continuously.

140) Kiser JJ et al., *Nat Rev Gastroenterol Hepatol*. 2013;10:596-606
141) One subject had had Grade 2 ALT increased (120 U/L) at baseline and had Grade 3 ALT increased (174 U/L) 44 days after treatment completion, and was hospitalized for liver biopsy on Day 311 (143 days after treatment completion). The subject was diagnosed as having autoimmune hepatitis based on the results of the liver biopsy and was assessed as recovered at the final visit, when the ALT level was 58 U/L.
142) Ozer JF et al., *Regul Toxicol Pharmacol*. 2010;56:237-246; Food and Drug Administration. *Guidance for Industry Drug-Induced Liver Injury Premarketing Clinical Evaluation*. *July 2009*. U.S. Dept of Health and Human Services; 2009

4.(iii).B.(3).4) Safety in elderly patients

The applicant's explanation on the safety of the PTV/RTV/OBV combination product in elderly patients:
Safety data from Japanese clinical studies (pooled analysis of the phase II study [M[redacted]-536] and the phase III study [M13-004]) in non-elderly patients (aged <65 years) and in elderly patients (aged ≥65 years) are summarized in Table 49.

Table 49. Summary of safety results in non-elderly (<65 years) and elderly (≥65 years) patients (pooled analysis of patients with chronic hepatitis C in the Japanese phase II and phase III studies)

	2-DAA regimen group		Placebo group	
	<65 years (272 subjects)	≥65 years (201 subjects)	<65 years (59 subjects)	≥65 years (47 subjects)
Overall adverse events	180 (66.2)	158 (78.6)	34 (57.6)	26 (55.3)
Grade 3 adverse events [a)]	6 (2.2)	11 (5.5)	1 (1.7)	1 (2.1)
Serious adverse events	7 (2.6)	10 (5.0)	1 (1.7)	1 (2.1)
Death	0	0	0	0
Adverse events leading to discontinuation	0	4 (2.0)	0	0

Number of subjects (%)
2-DAA regimen group, subjects treated with a combination regimen of PTV/RTV/OBV or the PTV/RTV/OBV combination product
a) No ≥Grade 4 adverse events were reported.

Comparison of safety profiles between elderly patients (≥65 years) and non-elderly patients (<65 years) showed that the incidences of overall adverse events, Grade 3 adverse events, serious adverse events, and adverse events leading to discontinuation in elderly patients were higher than those in non-elderly patients. However, given that the difference in incidence of any adverse event between the 2 age groups was <5%, the use of PTV/RTV/OBV combination product in patients aged ≥65 years is considered to raise no particular safety concerns.

PMDA's view:
Taking into account that adverse events occurred at a higher incidence in elderly patients than in non-elderly patients in Japanese clinical studies and that, in general, adverse events can be more severe in elderly patients with deteriorating physiological function, safety information should be continuously collected in elderly patients further in post-marketing settings.

4.(iii).B.(4) Indications

PMDA's conclusion:
Based on the review in "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety," indications of similar drugs, and the review presented in the sections below, 4.(iii).B.(4).1) to 4), the appropriate indications for PTV/RTV/OBV combination product should be as follows:

Suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis

The above conclusion of PMDA will be discussed at the Expert Discussion.

4.(iii).B.(4).1) Genotype

PMDA asked the applicant to justify the selection of genotype 1 chronic hepatitis C patients as the target patients of PTV/RTV/OBV combination product.

The applicant's explanation:

In the Japanese phase III study (M13-004), the efficacy of PTV/RTV/OBV combination product was demonstrated in genotype 1b chronic hepatitis C patients with or without compensated cirrhosis. The efficacy of PTV/RTV/OBV combination product in Japanese patients with genotype 1a chronic hepatitis C was not evaluated because patients with genotype 1b infection account for approximately 99% of those with genotype 1 infection in Japan, and the proportion of patients with genotype 1a infection is extremely small.[143)] However, in the foreign phase II study (M[redacted]-998), PTV/RTV/OBV (200/100/25 mg) was administered once daily for 12 weeks to patients with genotype 1a chronic hepatitis C, and the SVR12 rate was 62.5% (5 of 8 subjects). *In vitro* studies demonstrated that PTV and OBV have anti-viral activity in patients with genotype 1a and 1b hepatitis [see "3.(i).A.(1).1) *In vitro* studies,"]. These results suggest that it is possible to define the intended population for PTV/RTV/OBV combination product as patients with genotype 1 infection.

PMDA's view:

Although it is possible to administer PTV/RTV/OBV combination product to patients with genotype 1 HCV infection, healthcare professionals in the clinical settings should be appropriately informed of clinical data on genotype 1a from foreign clinical studies and the fact that the efficacy of the drug product in Japanese patients with genotype 1a HCV infection has not been evaluated. It is also necessary to collect as much information as possible on the efficacy and safety of PTV/RTV/OBV combination product in patients with genotype 1a HCV infection in the post-marketing surveillance.

4.(iii).B.(4).2) Use in chronic hepatitis C patients with compensated cirrhosis

The applicant's explanation on the efficacy and safety of PTV/RTV/OBV combination product in patients with compensated cirrhosis:

In the Japanese phase III study (M13-004), the SVR12 rate in treatment-naïve and treatment-experienced chronic hepatitis C subjects with compensated cirrhosis was 100% (9 of 9 subjects) and 87.9% (29 of 33 subjects), respectively. The 4 chronic hepatitis C subjects with compensated cirrhosis who did not achieve SVR12 consisted of 1 subject who experienced on-treatment virologic failure, 2 subjects who experienced relapse, and 1 subject with missing data for post-treatment Week 12.[144)]

143) Takada A et al., *J Gastroenerol and Hepatol*. 1996;11:201-207

144) The SVR12 rate was 90.6% (29 of 32 subjects) in treatment-experienced chronic hepatitis C patients with compensated cirrhosis excluding those who did not achieve SVR12 for reasons other than virologic failure, a patient population similar to the efficacy analysis population in substudy 1 of Study M13-004.

Table 50 shows the summary of safety data from subjects with chronic hepatitis C with or without compensated cirrhosis in the PTV/RTV/OBV combination product group in the Japanese phase III study (M13-004).

Table 50. Summary of safety data from chronic hepatitis C subjects with or without compensated cirrhosis in the PTV/RTV/OBV combination product group (Japanese phase III study)

	CHC subjects with compensated cirrhosis (42 subjects)	CHC subjects without compensated cirrhosis (215 subjects)
Overall adverse events	31 (73.8)	148 (68.8)
Grade 3 adverse events [a)]	2 (4.8)	12 (5.6)
Serious adverse events	2 (4.8)	7 (3.3)
Death	0	0
Adverse events leading to discontinuation	1 (2.4)	2 (0.9)
Adverse events leading to suspension of treatment	0	1 (0.5)

Number of subjects (%)
a) No ≥Grade 4 adverse events were reported.

The adverse events that occurred at an incidence higher in chronic hepatitis C subjects with compensated cirrhosis than that in those without compensated cirrhosis by ≥5% were pyrexia (9.5% [4 of 42 subjects]) and platelet count decreased (7.1% [3 of 42 subjects]). All these adverse events were Grade 1 or 2 in severity, and there was no marked difference in the incidence of ≥Grade 3 adverse events between these 2 patient populations, indicating that PTV/RTV/OBV combination product is well tolerated in patients with compensated cirrhosis.

Based on the above, PTV/RTV/OBV combination product is expected to be equally effective in chronic hepatitis C patients with compensated cirrhosis as in those without compensated cirrhosis, with an acceptable safety profile.

PMDA considers as follows:
The efficacy of PTV/RTV/OBV combination product has been demonstrated by the SVR12 rates achieved in treatment-naïve and treatment experienced chronic hepatitis C subjects with compensated cirrhosis in the Japanese phase III study (M13-004). In the safety analysis, the incidence of adverse events was higher in subjects with compensated cirrhosis than in those without compensated cirrhosis. However, taking into account the types of adverse events reported and their severities, the safety of PTV/RTV/OBV combination product is acceptable if it is prescribed by physicians with sufficient knowledge and experience in the treatment of viral liver diseases, and appropriate measures are taken including monitoring and management of adverse events, suspension and discontinuation of treatment based on a full understanding of the safety profile.

However, given that there is limited clinical experience with PTV/RTV/OBV combination product in Japanese chronic hepatitis C patients with compensated cirrhosis, it is necessary to collect information on the safety and efficacy of PTV/RTV/OBV combination product in this patient population in the post-

marketing setting, and any new findings should be promptly provided to healthcare professionals in clinical settings.

4.(iii).B.(4).3) Use in patients who have been treated with an NS3/4A protease inhibitor or an NS5A inhibitor

The applicant has not conducted clinical studies on the efficacy in patients who have experienced virologic failure with an NS3/4A protease inhibitor or an NS5A inhibitor. Nevertheless, the applicant justified the use in patients who have been treated with an NS3/4A protease inhibitor or an NS5A inhibitor as follows.

(a) Use in patients who have been treated with an NS3/4A protease inhibitor

Non-responders to triple regimens combining PegIFN/RBV with simeprevir sodium, vaniprevir, or TVR have been reported to carry frequent D168 mutations in the NS3 domain.[145)] Therefore, anti-HCV agents with other mechanisms of action can be offered as subsequent treatment options for patients who failed to achieve SVR with previous NS3/4A protease inhibitor regimens. In the Japanese phase III study (M13-004), all subjects who carried the D168E mutation in the NS3 domain at baseline achieved SVR12 (100%, 4 of 4 subjects). The resistance profile is not uniform among NS3/4A protease inhibitors,[145)] and non-clinical studies revealed the existence of viruses with drug-resistant NS3 mutants that were susceptible to the anti-HCV activity of PTV [see "3.(i).A.(1).1).(d) Resistance profiles"]. Therefore, PTV/RTV/OBV combination product is expected to show anti-HCV activity against some existing viral mutants resistant to NS3/4A protease inhibitors.

(b) Use in patients who have been treated with an NS5A inhibitor

Patients who failed to achieve SVR with previous NS5A protease inhibitor regimens are considered to require treatment with anti-HCV agents with other mechanisms of action. In the Japanese phase III study (M13-004), SVR12 was achieved by 83.0% (39 of 47 subjects) and 88.9% (8 of 9 subjects) of subjects who carried the Y93H/S and L31F/I/M mutations, respectively, in the NS5A domain at baseline (Table 43). Therefore, PTV/RTV/OBV combination product is expected to be effective in some patients who have failed to achieve SVR with previous NS5A protease inhibitor regimens.

PMDA's view:

PTV and OBV have been shown to be cross-resistant to existing NS3/4A protease inhibitors and NS5A inhibitors, respectively [see "3.(i).B.(2) Resistance to PTV and OBV"]. In Japanese clinical studies, the PTV/RTV/OBV combination product was not administered to subjects who had been treated with an NS3/4A protease inhibitor or an NS5A inhibitor, therefore due to lack of information, PTV/RTV/OBV combination product cannot be recommended in the treatment of non-responders to regimens containing an NS3/4A protease inhibitor or an NS5A inhibitor.

145) Telavic Tablets 250 mg [package insert] 12th ed.; September 2014, Sovriad Capsules 100 mg [package insert] 4th ed.; October 2014, Vanihep Capsules 150 mg [package insert]; September 2014

Nevertheless, the use of PTV/RTV/OBV combination product in patients previously treated with an NS3/4A protease inhibitor or an NS5A inhibitor may be considered after taking into full account the following issues concerning resistance-related mutations:

- Resistance profile is not necessarily uniform among NS3/4A protease inhibitors, and non-clinical studies revealed some drug-resistant NS3 mutants were susceptible to the anti-HCV activity of PTV.
- PTV/RTV/OBV combination product contains OBV, an NS5A inhibitor, and is therefore expected to exert the anti-HCV activity of OBV even in patients who were resistant to an NS3/4A protease inhibitor during previous treatment.
- The Japanese phase III study (M13-004) demonstrated that PTV/RTV/OBV combination product was effective in subjects who carried the resistance-related mutation in the NS3 or NS5A domain at baseline (Table 43).

The above discussions illustrate the importance of physicians with sufficient knowledge and experience in the treatment of viral liver diseases deciding carefully that PTV/RTV/OBV combination product be indicated in patients previously treated with an NS3/4A protease inhibitor or an NS5A inhibitor, on the basis of the presence of any resistance-related mutations and the patients' conditions. Furthermore, healthcare professionals in clinical settings should be provided in an appropriate manner with not only the currently available information on resistance-related mutations but also information obtained in the post-marketing surveillance. Such information includes those on resistance-related mutations, the efficacy of PTV/RTV/OBV combination product, and other relevant factors when the patients previously treated with an NS3/4A protease inhibitor or an NS5A inhibitor start receiving PTV/RTV/OBV combination product.

4.(iii).B.(5) Dosage and administration

Based on the review in "4.(i).B.(1) Food effect" and the following review, PMDA concluded that the following statements should be included in the dosage and administration section:

The usual adult dosage is 25 mg of ombitasvir, 150 mg of paritaprevir, and 100 mg of ritonavir (2 tablets) once daily, given orally after a meal for 12 weeks.

The above conclusion of PMDA will be discussed in the Expert Discussion.

Doses and duration of the treatment with PTV and OBV

The applicant's rationale of the doses and duration of the treatment with PTV and OBV is as follows:

The doses in the Japanese phase II study were determined to be PTV 100 or 150 mg, RTV 100 mg, and OBV 25 mg in consideration of the pharmacological results of foreign phase I and II studies [see "4.(ii).A.(2) Studies in patients" and "4.(ii).B.(1) Rationale for coadministering RTV with anti-HCV drugs and selecting its dose"].

The duration of treatment was determined as follows:

In a foreign study (M[redacted]-746), the 12-week combination regimen of PTV/RTV 150/100 or 250/100 mg and RBV QD with [redacted] mg of dasabuvir BID was studied in treatment-naïve patients with genotype 1 infection. The SVR24 rate was 85.7% (12 of 14 subjects) in the 150/100 mg of PTV/RTV + dasabuvir group and 94.7% (18 of 19 subjects) in the 250/100 mg of PTV/RTV + dasabuvir group, demonstrating the antiviral activity of the 12-week regimen of PTV/RTV with dasabuvir. In a foreign study (M[redacted]-267) conducted to evaluate the 12-week combination regimen of PTV/RTV 150/100 mg and RBV QD with [redacted] mg of Compound A (an NS5B polymerase inhibitor) QD, the SVR24 rate was 90.9% (10 of 11 subjects). Given that the antiviral activity of dasabuvir and Compound A is lower than that of OBV,[146)] a combination of PTV/RTV and OBV was expected to enable patients to achieve a high SVR rate. Using an exposure-response model constructed based on the data on PK and viral load from a 2- or 3-day study of single-agent treatment with PTV/RTV, OBV, dasabuvir, or Compound A and the evaluable data from a study of combination treatment of PTV/RTV with RBV and Compound A or dasabuvir, simulation was conducted to investigate optimal durations of treatment and the effect of the doses of direct-acting antiviral agents on SVR. The results showed that the SVR24 rate was >80% in patients with genotype 1b HCV infection treated with a ≥12-week combination regimen of PTV 100, 150, or 200 mg, RTV 100 mg, and OBV 25 mg QD. Because no further improvement in the SVR24 rate was expected with >12-week treatment, the optimal duration of treatment was considered to be 12 weeks. These results suggested that it was appropriate to administer the combination of PTV/RTV with OBV for 12 weeks in treatment-naïve Japanese patients with genotype 1b HCV infection. However, taking into account that the Japanese phase II study was to be conducted in treatment-experienced patients, the effect of a 24-week treatment was decided to be evaluated as well in patients with genotype 1b HCV infection. In the Japanese phase II study (M[redacted]-536), the SVR24 rate in patients with genotype 1b HCV infection was 100% (19 of 19 subjects in the PTV 100 mg group and 18 of 18 subjects in the PTV 150 mg group) when treatment was given for 24 weeks; 88.9% (16 of 18 subjects) in the 12-week PTV 150 mg group; and 100% (18 of 18 subjects) in the 12-week PTV 100 mg group. Considering that 1 of the 2 subjects in the 12-week PTV 150 mg group who failed to achieve SVR had been withdrawn from the study due to an adverse event, 24-week treatment was unlikely to produce any clinically meaningful benefits, and thus the optimal duration of treatment was considered to be 12 weeks.

Based on the above and the results of the Japanese phase III study (M13-004) in which the efficacy of a 12-week treatement with PTV/RTV/OBV 150/100/25 mg (2 fixed-dose combination tablets) QD was demonstrated, the proposed dosage and administration of PTV/RTV/OBV combination product in chronic hepatitis C patients with or without compensated cirrhosis C (genotype 1) was determined to be PTV 150 mg, RTV 100 mg, and OBV 25 mg, administered once daily for 12 weeks.

PMDA's view:

Based on the available data, the following dosage and administration of PTV/RTV/OBV combination product in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) is acceptable:

146) After a single-agent administration of OBV 25 mg QD, dasabuvir [redacted] mg BID, or Compound A [redacted] mg QD to patients with HCV genotype 1 infection, the decrease in viral load was 3.33, 1.08, and 1.57 $\log_{10}$ IU/mL, respectively.

PTV/RTV/OBV 150/100/25 mg (2 fixed-dose combination tablets) given once daily for 12 weeks. Given that no studies have been conducted in Japan to evaluate PTV/RTV/OBV combination product in combination with other anti-HCV agents, healthcare professionals in the clinical settings should be appropriately advised that PTV/RTV/OBV combination product alone be used to treat HCV at this point.

4.(iii).B.(6) Clinical positioning

The applicant's explanation on the clinical positioning of PTV/RTV/OBV combination product for the treatment in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1):

Japanese clinical guidelines recommend triple regimen of PegIFN/RBV with simeprevir sodium or vaniprevir and the DCV/ASV dual regimen for IFN-eligible patients with a high viral load and the DCV/ASV dual regimen for IFN-ineligible patients with a high viral load.[126)] The SVR12 rate in treatment-naïve patients was 88.6% to 91.7% for the PegIFN/RBV/simeprevir sodium triple regimen and 83.7% for the PegIFN/RBV/vaniprevir triple regimen,[147, 148, 149)] and the SVR12 rate for the DCV/ASV dual regimen was 89.1% in IFN-eligible, treatment-naïve patients with a high viral load and 88.1% in IFN-ineligible patients with a high viral load.[150,151)] In the Japanese phase III study (M13-004), the SVR12 rate for a 12-week treatment with PTV/RTV/OBV 150/100/25 mg (2 fixed-dose combination tablets) QD was 94.6% in IFN-eligible, treatment-naïve subjects and 91.3% in IFN-ineligible subjects.

For the treatment of chronic hepatitis C, PegIFN, IFN monotherapy, and the DCV/ASV dual regimen are recommended in patients with a low viral load. The SVR rate in patients with a low viral load has not been reported for the DCV/ASV dual regimen, but was reported to be 57.1% for PegIFN.[152)] In the Japanese phase III study (M13-004), the SVR12 rate for a 12-week treatment with PTV/RTV/OBV 150/100/25 mg (2 fixed-dose combination tablets) QD was 100% in treatment-naïve subjects with a low viral load, and the SVR rate was 95.5% in previously treated and relapsed subjects and 100% in previously treated non-responders.

For the treatment of chronic hepatitis C patients with compensated cirrhosis, irrespective of viral load, the DCV/ASV dual regimen and the PegIFN/RBV dual regimen are recommended in IFN-eligible patients and the DCV/ASV dual regimen is recommended in IFN-ineligible patients. The SVR24 rate in chronic hepatitis C patients with compensated cirrhosis was 90.9% for the DCV/ASV dual regimen,[150)] and was 21.7% for the PegIFN/RBV dual regimen.[153)] In the Japanese phase III study (M13-004), the SVR12 rate for a 12-week treatment with PTV/RTV/OBV 150/100/25 mg (2 fixed-dose combination tablets) QD was 90.5% (38 of 42 subjects) in subjects with compensated cirrhosis.

147) Hayashi N et al., *J Hepatol*. 2014;61:219-227
148) Kumada H et al., *Hepatol Res*. 2014;doi:10.1111/hepr.12375
149) Vanihep Capsules 150 mg [package insert] 3rd ed.; January 2015
150) Daklinza Tablets 60 mg [package insert] 3rd ed.; March 2015
151) Kumada H et al., *Hepatology*. 2014;59:2083-2091
152) Sakai T et al., *Medicine and Pharmacology*. 2003;50:655-672
153) Rebetol Capsules 200 mg [package insert] 18th ed.; July 2014

The above findings and discussions demonstrate that a 12-week treatment with PTV/RTV/OBV combination product QD is effective in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) irrespective of baseline patient characteristics or viral factors, and its safety is acceptable. Thus, PTV/RTV/OBV combination product is expected to be the first-line drug for the treatment of chronic hepatitis C patients with or without compensated cirrhosis (genotype 1).

PMDA's view:

The applicant's expectation that PTV/RTV/OBV combination product will be the first-line drug for the treatment of chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) is not supported by the evidence because PTV/RTV/OBV combination product has not been compared with currently available therapeutic regimens in Japanese clinical studies. Nevertheless, the available study results suggest a certain degree of efficacy in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) [see "4.(iii).B.(2) Efficacy"], and there appear to be no particular concerns regarding PTV/RTV/OBV combination product's tolerability except for oedema-related adverse events that warrant careful monitoring. Therefore, if it is prescribed by physicians with sufficient knowledge and experience in the treatment of viral liver diseases, and appropriate measures are taken including monitoring and management of adverse events, and suspension and discontinuation of treatment based on a full understanding of the safety profile, PTV/RTV/OBV combination product can be a new option for the treatment of chronic hepatitis C with or without compensated cirrhosis (both genotype 1).

4.(iii).B.(7) Post-marketing investigations

The applicant plans to conduct the post-marketing surveillance as follows:

Use-results survey

- Objectives

  To collect and evaluate information on the safety and efficacy of PTV/RTV/OBV combination product used in clinical practice
- Target number of patients

  3000 patients

  Rationale:

  The number of patients needed to detect unknown adverse drug reactions that occur at a frequency of 0.1% with the power of 95% was calculated to be 3000. Patients will be registered in this survey with a goal of 1000 chronic hepatitis C patients with compensated cirrhosis being included.
- Observation period

  36 weeks (12 weeks of treatment with PTV/RTV/OBV combination product and 24 weeks of follow-up)
- Survey period

  27 months from the date of market launch (18 months of registration period)

Specified use-results survey (follow-up)

Follow-up will be performed in subjects enrolled in Japanese clinical studies to collect information on resistance-related mutations against PTV and OBV, which are acquired after treatment with PTV/RTV/OBV combination product. In addition, information will be collected on hepatic cirrhosis and hepatocellular carcinoma observed during the 5 years following completion of treatment with PTV/RTV/OBV combination product.

PMDA considers that the following information should be collected in the post-marketing setting:

- Efficacy and safety in patients with genotype 1a HCV infection
- Efficacy and safety in elderly patients and chronic hepatitis C patients with compensated cirrhosis
- Occurrence of oedema-related events and hepatic impairment
- Resistance-related mutations, efficacy, and other findings observed after treatment with PTV/RTV/OBV combination product in patients who have been treated with an NS5A inhibitor or an NS3/4A protease inhibitor

The above conclusion of PMDA will be discussed in the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

The assessments are currently underway. The results and PMDA's conclusion will be reported in Review Report (2).

IV. Overall Evaluation

Based on the submitted data, the efficacy of PTV/RTV/OBV combination product in the treatment of chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) has been demonstrated and the safety is acceptable in view of its observed benefits.

PMDA considers that PTV/RTV/OBV combination product may be approved if it is not considered to have any particular problems based on the comments from the Expert Discussion.

Review Report (2)

August 20, 2015

I. Product Submitted for Registration

[Brand name] Viekirax Combination Tablets
[Non-proprietary name] Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir
[Applicant] AbbVie GK
[Date of application] February 12, 2015

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

In response to the opinions expressed by the expert advisors in the Expert Discussion, PMDA discussed the following additional issues and took necessary measures. The expert advisors supported PMDA's conclusions about efficacy and dosage and administration as described in Review Report (1).

(1) Safety

The conclusion of PMDA on safety [see "4.(iii).B.(3) Safety" in Review Report (1)] was supported by the expert advisors. The following comments concerning the precautionary statement on oedema-related events and hepatic impairment were made by the expert advisors:

- Because treatment with Viekirax Combination Tablets (hereinafter, "PTV/RTV/OBV combination product" or "Viekirax") may cause oedema-related events irrespective of concomitant use of a calcium (Ca) antagonist, an appropriate precautionary statement should be included in the package insert.
- Although bilirubin increased related to PTV/RTV/OBV combination product occurred mostly during the first 4 weeks of treatment, the package insert should recommend that liver function tests be performed even after the first 4 weeks.
- Taking into account that Grade 3 bilirubin increased, alanine aminotransferase (ALT) increased, and aspartate aminotransferase (AST) increased have been reported in patients treated with PTV/RTV/OBV combination product, appropriate precautions should be provided regarding the occurrence of hepatic impairment and the necessity of conducting regular liver function tests.

Based on the above comments from the expert advisors, PMDA conducted the following review:
In the Japanese phase II and III studies, oedema-related events occurred in 30 subjects, and 90% of them (27 of 30 subjects) had concomitantly received a Ca antagonist. While concomitant Ca antagonist was

considered to be one factor for the onset of these events associated with PTV/RTV/OBV combination product, oedema-related events were also reported during treatment with PTV/RTV/OBV combination product without concomitant use of any Ca antagonists. Therefore, patients treated with PTV/RTV/OBV combination product should be carefully monitored for oedema-related events irrespective of concomitant use of a Ca antagonist, and appropriate measures, such as discontinuation of treatment, should be taken if any abnormalities are observed.

Although bilirubin increased occurred mostly within 4 weeks from the start of treatment, liver function tests should be performed on a regular basis during the entire treatment period, taking into account that those who receive the product are patients with chronic hepatitis C with or without compensated cirrhosis. Also considering that Grade 3 bilirubin increased, ALT increased, and AST increased have been reported, the following caution statement should be included in the "Important Precautions" section of the package insert:
Hepatic impairment may occur. Liver function tests should be performed on a regular basis during treatment with PTV/RTV/OBV combination product. Since hepatic impairment mainly occurs during the first 4 weeks of treatment, liver function tests should be performed more frequently as needed during the early stage of treatment.

PMDA instructed the applicant to include the above precautionary statement in the package insert and the applicant accepted the instruction.

(2) Indications

The expert advisors supported the conclusion of PMDA on indications [see "4.(iii).B.(4) Indications" of Review Report (1)] and added the following comment:

- Given that the product contains ritonavir, an HIV protease inhibitor, the effect on HIV infection treatment should be examined when PTV/RTV/OBV combination product is administered to HCV/HIV co-infected patients.

Based on the above comment from the expert advisors, PMDA conducted the following review:
In the foreign clinical study[154)] of PTV/RTV/OBV combination product in HCV/HIV co-infected patients who had achieved HIV virologic suppression by anti-HIV therapy, PTV/RTV/OBV combination product did not affect the treatment for HIV infection. However, it is unknown what effects PTV/RTV/OBV combination product containing 100 mg of ritonavir may have on HIV protease genotype and subsequently on HIV infection treatment when administered once daily to HCV/HIV co-infected patients with no prior anti-HIV therapy.

154) In a foreign clinical study, PTV/RTV/OBV combination product, dasabuvir, and RBV were coadministered for 12 or 24 weeks to 63 HCV/HIV co-infected chronic hepatitis C patients with or without compensated cirrhosis (genotype 1). These patients had achieved HIV virologic suppression by anti-HIV therapy containing 2 nucleoside reverse transcriptase inhibitors including atazanavir or raltegravir. The SVR12 rate in the subjects in the 12-week treatment group was 93.5% (29 of 31 subjects). No subjects had HIV RNA of >200 copies/mL. No subjects required a change in their anti-HIV agent due to virologic failure.

Taking into account the above, PMDA instructed the applicant to include the following precautionary statement in the "Precautions for Indications" section of the package insert:
Among HCV/HIV co-infected patients, PTV/RTV/OBV combination product should be administered only to those who have achieved HIV virologic suppression by an anti-HIV drug regimen (ritonavir contained in the combination product may induce resistance to protease inhibitors).

The applicant accepted this instruction.

The labels of PTV/RTV/OBV combination product approved in Europe and the USA state that ritonavir contained in this combination product may induce resistance to HIV protease inhibitors in HCV/HIV co-infected patients without prior anti-HIV therapy and that the PTV/RTV/OBV combination product should be used in HCV/HIV co-infected patients who have achieved HIV virologic suppression.

(3) Proposed risk management plan

The conclusion of PMDA on post-marketing investigations [see "4.(iii).B.(7) Post-marketing investigations" of Review Report (1)] was supported by the expert advisors.

Also taking into account the comment from the expert advisors included in the section, "(2) Indications," PMDA concluded that it is necessary to collect the following information including efficacy and safety in HCV/HIV co-infected patients and that any new findings should be provided promptly to healthcare professionals in the clinical settings:

- Efficacy and safety in patients with genotype 1a HCV infection
- Efficacy and safety in elderly patients and patients with compensated cirrhosis
- Occurrence of oedema-related events and hepatic impairment
- Resistance-related mutations, efficacy, and other findings observed during treatment with PTV/RTV/OBV combination product in patients who have a history of treatment with an NS5A inhibitor or an NS3/4A protease inhibitor
- Efficacy and safety in HCV/HIV co-infected patients

Only limited amount of information may be collected from Japanese patients on the above issues. Therefore, any new findings including those from non-Japanese patients should be promptly provided to healthcare professionals in clinical settings. Patients without sustained negative HCV RNA despite treatment with PTV/RTV/OBV combination product should be followed up as much as possible to collect information on resistance mutations including the clinical course after treatment, and any findings should be promptly provided to healthcare professionals in clinical settings.

PMDA asked the applicant to consider the above issues, and the applicant followed this instruction accordingly.

Based on the above discussion, PMDA concluded that the risk management plan (draft) of PTV/RTV/OBV combination product should include the safety and efficacy specifications shown in Table 51 and that additional pharmacovigilance activities and risk minimization activities shown in Table 52 should be conducted. The synopsis (draft) for a use-results survey and a specified use-results survey has been submitted as shown in Table 53.

Table 51. Safety and efficacy specifications in the proposed risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Fluid retention • Hepatic impairment	None	None
Efficacy specifications		
• Efficacy in clinical practice • Drug resistance		

Table 52. Outline of additional pharmacovigilance activities and risk minimization activities in the proposed risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey	• Early post-marketing phase vigilance

Table 53. Outline of the proposed post-marketing surveillance (draft)

Use results survey	
Objectives	To evaluate the efficacy and safety of the product in clinical practice
Survey method	Central registration system
Target patients	Chronic hepatitis C patients with or without compensated cirrhosis
Survey period (follow-up period)	2 years and 3 months [36 weeks (24 weeks after completion of treatment)]
Target number of patients	3,000 patients (including 1,000 chronic hepatitis C patients with compensated cirrhosis)
Main survey items	Fluid retention, hepatic impairment, patients with genotype 1a HCV infection, efficacy and safety in elderly patients and patients with compensated cirrhosis, severities and frequencies of resistance-related mutations, efficacy and safety in HCV/HIV co-infected patients, and other relevant matters
Specified use-results survey (follow-up survey)	
Objectives	To collect information on the acquisition of resistance-related mutations against PTV and OBV, and to collect information on the occurrence of hepatic cirrhosis and hepatocellular carcinoma during the 5 years following completion of treatment with PTV/RTV/OBV combination product
Survey period	Up to 5 years after completion of study treatment in the last patient in the Japanese clinical study (M13-004)
Target patients	Patients who have been enrolled in Japanese clinical studies (M[redacted]-536, M13-004)
Main survey items	Occurrence of resistance-related mutations, hepatic cirrhosis, and hepatocellular carcinoma, and other relevant matters

PTV, paritaprevir hydrate; OBV, ombitasvir hydrate

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP assessments and data integrity assessment

Document-based compliance inspection and data integrity assessment of the data submitted in the new drug application were conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products,

Gene Therapy Products, and Cosmetics. PMDA concluded that there should be no problem in conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the new drug application (5.3.5.1-1, 5.3.5.1-2). From the results, PMDA concluded that there should be no problem in conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that Viekirax may be approved for the indications and dosage and administration as shown below, with the following conditions. As it is a new combination drug with new active ingredients, the re-examination period is 8 years. The drug product is classified as a powerful drug, while ombitasvir hydrate and paritaprevir hydrate, the drug substances, are not classified as a poisonous drug, a powerful drug, a biological product, or a specified biological product.

[Indications]

Suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis

[Dosage and administration]

The usual adult dosage is 25 mg of ombitasvir, 150 mg of paritaprevir, and 100 mg of ritonavir (2 tablets) once daily, administered orally after a meal for 12 weeks.

[Conditions for approval]

The applicant is required to develop and appropriately implement a risk management plan.