Report on the Deliberation Results

September 14, 2016
Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health 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	December 17, 2015

Results of Deliberation

In the meeting held on September 9, 2016, the Second Committee on New Drugs concluded that the partial change application for 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 re-examination period of the product is the time to the expiration date of the re-examination period specified at the initial approval (until September 27, 2023).

Conditions for Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

August 23, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical products submitted for marketing approvals conducted by the Pharmaceuticals and Medical Devices Agency.

Brand Names	(a) Viekirax Combination Tablets
	(b) Rebetol Capsules 200 mg
Non-proprietary Names	(a) Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir
	(b) Ribavirin
Applicants	(a) AbbVie GK
	(b) MSD K.K.
Dates of Applications	(a) December 17, 2015
	(b) December 25, 2015
Dosage Forms/Strengths	(a) Each tablet contains 13.6 mg of ombitasvir hydrate (as 12.5 mg of ombitasvir), 78.5 mg of paritaprevir hydrate (as 75 mg of paritaprevir), and 50 mg of ritonavir
	(b) Each capsule contains 200 mg of ribavirin
Application Classifications	(a) Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
	(b) Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Review

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the combination regimen of Viekirax Combination Tablets and Rebetol Capsules 200 mg in the treatment of chronic hepatitis C (genotype 2) and acceptable safety in view of the benefits indicated by the data submitted, as shown in the Attachment.

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

Indications (a) Viekirax Combination Tablets

1. Suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis
2. Suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients

(Underline denotes additions.)

(b) Rebetol Capsules 200 mg

1. In combination with Interferon Alfa-2b (Genetical Recombination), Peginterferon Alfa-2b (Genetical Recombination), or interferon beta for the suppression of viremia in either of the following patients with chronic hepatitis C:
   (1) patients with high blood HCV-RNA levels, or
   (2) patients who have failed to respond to or relapsed after interferon monotherapy
2. In combination with Peginterferon Alfa-2b (Genetical Recombination) for the suppression of viremia in chronic hepatitis C patients with compensated cirrhosis
3. In combination with sofosbuvir for the suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients with or without compensated cirrhosis
4. In combination with ombitasvir hydrate/paritaprevir hydrate/ritonavir for the suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients

(Underline denotes additions.)

Dosages and Administration

(a) Viekirax Combination Tablets

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

   The usual adult dosage is 2 tablets (25 mg of ombitasvir, 150 mg of paritaprevir, and 100 mg of ritonavir) administered orally once daily after a meal for 12 weeks.
2. For suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients

   The usual adult dosage is 2 tablets (25 mg of ombitasvir, 150 mg of paritaprevir, and 100 mg of ritonavir) administered orally once daily after a meal in combination with ribavirin for 16 weeks.

(Underline denotes additions.)

(b) Rebetol Capsules 200 mg

The usual adult oral dosage of ribavirin is provided in the table below.
Appropriate measures, such as dose reduction and discontinuation, should be taken depending on the patient's condition.

- In combination with Interferon Alfa-2b (Genetical Recombination), interferon beta, sofosbuvir, or ombitasvir hydrate/paritaprevir hydrate/ritonavir

Body weight	Dose of ribavirin		
	Daily dose	After breakfast	After supper
≤60 kg	600 mg	200 mg	400 mg
>60 kg to ≤80 kg	800 mg	400 mg	400 mg
>80 kg	1000 mg	400 mg	600 mg

• In combination with Peginterferon Alfa-2b (Genetical Recombination)

(1) Chronic hepatitis C patients with or without compensated cirrhosis with baseline hemoglobin level ≥14 g/dL

Body weight	Dose of ribavirin		
	Daily dose	After breakfast	After supper
≤60 kg	600 mg	200 mg	400 mg
>60 kg to ≤80 kg	800 mg	400 mg	400 mg
>80 kg	1000 mg	400 mg	600 mg

(2) Chronic hepatitis C patients with compensated cirrhosis with baseline hemoglobin level <14 g/dL

Body weight	Dose of ribavirin		
	Daily dose	After breakfast	After supper
≤60 kg	400 mg	200 mg	200 mg
>60 kg to ≤80 kg	600 mg	200 mg	400 mg
>80 kg	800 mg	400 mg	400 mg

(Underline denotes additions or changes.)

Conditions of Approval

The applicants are each required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

June 10, 2016

The following is an outline of the data submitted by the applicants and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Products Submitted for Approval

Brand Names	(a) Viekirax Combination Tablets
	(b) Rebetol Capsules 200 mg
Non-proprietary Names	(a) Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir
	(b) Ribavirin
Applicants	(a) AbbVie GK
	(b) MSD K.K.
Dates of Applications	(a) December 17, 2015
	(b) December 25, 2015
Dosage Forms/Strengths	(a) Each tablet contains 13.6 mg of ombitasvir hydrate (as 12.5 mg of ombitasvir), 78.5 mg of paritaprevir hydrate (as 75 mg of paritaprevir), and 50 mg of ritonavir
	(b) Each capsule contains 200 mg of ribavirin

Proposed Indications

(a) Viekirax Combination Tablets

1. Suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis
2. Suppression of viremia in treatment-naïve patients with serogroup 2 (genotype 2) chronic hepatitis C

(Underline denotes additions.)

(b) Rebetol Capsules 200 mg

1. In combination with Interferon Alfa-2b (Genetical Recombination), Peginterferon Alfa-2b (Genetical Recombination), or interferon beta for the suppression of viremia in either of the following patients with chronic hepatitis C:
   (1) patients with high blood HCV-RNA levels, or
   (2) patients who have failed to respond to or relapsed after interferon monotherapy
2. In combination with Peginterferon Alfa-2b (Genetical Recombination) for the suppression of viremia in chronic hepatitis C patients with compensated cirrhosis

3. In combination with sofosbuvir for the suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients with or without compensated cirrhosis
4. In combination with ombitasvir hydrate/paritaprevir hydrate/ritonavir for the suppression of viremia in treatment-naïve patients with serogroup 2 (genotype 2) chronic hepatitis C

(Underline denotes additions.)

Proposed Dosages and Administration

(a) Viekirax Combination Tablets

1. Serogroup 1 (genotype 1)

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

2. Serogroup 2 (genotype 2)

The usual adult dosage is 2 tablets (25 mg of ombitasvir, 150 mg of paritaprevir, and 100 mg of ritonavir) administered orally once daily after a meal in combination with ribavirin for 16 weeks.

(Underline denotes additions.)

(b) Rebetol Capsules 200 mg

1. In combination with Interferon Alfa-2b (Genetical Recombination), Peginterferon Alfa-2b (Genetical Recombination), or interferon beta for the suppression of viremia in chronic hepatitis C patients

The usual adult oral dosage of ribavirin is provided in the table below.
Appropriate measures, such as dose reduction and discontinuation, should be taken depending on the patient's condition.

Body weight	Dose of ribavirin		
	Daily dose	After breakfast	After supper
≤60 kg	600 mg	200 mg	400 mg
>60 kg to ≤80 kg	800 mg	400 mg	400 mg
>80 kg	1000 mg	400 mg	600 mg

2. In combination with Peginterferon Alfa-2b (Genetical Recombination) for the suppression of viremia in chronic hepatitis C patients with compensated cirrhosis

The usual adult oral dosage of ribavirin is provided in the table below.
Appropriate measures, such as dose reduction and discontinuation, should be taken depending on the patient's condition.

(1) Patients with baseline hemoglobin level ≥14 g/dL

Body weight	Dose of ribavirin		
	Daily dose	After breakfast	After supper
≤60 kg	600 mg	200 mg	400 mg
>60 kg to ≤80 kg	800 mg	400 mg	400 mg
>80 kg	1000 mg	400 mg	600 mg

(2) Patients with baseline hemoglobin level <14 g/dL

Body weight	Dose of ribavirin		
	Daily dose	After breakfast	After supper
≤60 kg	400 mg	200 mg	200 mg
>60 kg to ≤80 kg	600 mg	200 mg	400 mg
>80 kg	800 mg	400 mg	400 mg

3. In combination with sofosbuvir for the suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients with or without compensated cirrhosis

The usual adult oral dosage of ribavirin is provided in the table below.
Appropriate measures, such as dose reduction and discontinuation, should be taken depending on the patient's condition.

Body weight	Dose of ribavirin		
	Daily dose	After breakfast	After supper
≤60 kg	600 mg	200 mg	400 mg
>60 kg to ≤80 kg	800 mg	400 mg	400 mg
>80 kg	1000 mg	400 mg	600 mg

4. In combination with ombitasvir hydrate/paritaprevir hydrate/ritonavir for the suppression of viremia in treatment-naïve patients with serogroup 2 (genotype 2) chronic hepatitis C

The usual adult oral dosage of ribavirin is provided in the table below.
Appropriate measures, such as dose reduction and discontinuation, should be taken depending on the patient's condition.

Body weight	Dose of ribavirin		
	Daily dose	After breakfast	After supper
≤60 kg	600 mg	200 mg	400 mg
>60 kg to ≤80 kg	800 mg	400 mg	400 mg
>80 kg	1000 mg	400 mg	600 mg

(Underline denotes additions.)

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List of Abbreviations

ALT	Alanine aminotransferase
AUC_{0-24}	Area under the plasma concentration versus time curve from 0 to 24 hours
AUC_{inf}	Area under the plasma concentration versus time curve extrapolated to infinite time
AUC_{tau}	Area under the plasma concentration versus time curve over the dosing interval
BCRP	Breast cancer resistance protein
BID	bis in die (twice daily)
BMI	Body mass index
CL_{cr}	Creatinine clearance
CL/F	Apparent oral clearance
C_{max}	Maximum plasma concentration
C_{trough}	Trough plasma concentration
CYP	Cytochrome P450
EC_{50}	50% effective concentration
HCV	Hepatitis C Virus
IFN	Interferon
ITT	Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Multidrug resistance-associated protein
OBV	Ombitasvir
OATP	Organic anion transporting polypeptide
PegIFN	Pegylated interferon
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPK	Population pharmacokinetics
PTV	Paritaprevir
QD	quaque die (once daily)
RTV	Ritonavir
SVR12	Sustained virologic response of week 12
SVR24	Sustained virologic response of week 24
T_{max}	Time to maximum plasma concentration
V_c/F	Central compartment apparent volume of distribution
V_p/F	Peripheral compartment apparent volume of distribution
PMDA	The Pharmaceuticals and Medical Devices Agency
PTV/RTV/OBV combination	Viekirax Combination Tablets
RBV	Rebetol Capsules 200 mg
PTV/RTV/OBV combination + RBV	Combination regimen of PTV/RTV/OBV combination and RBV

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Viekirax Combination Tablets (the PTV/RTV/OBV combination) is a combination drug containing 3 active ingredients—ombitasvir hydrate (OBV), paritaprevir hydrate (PTV), and ritonavir (RTV)—and was approved in Japan in September 2015 for the indication of "suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C (CHC) patients with or without compensated cirrhosis." OBV and PTV suppress the proliferation of hepatitis C virus (HCV) by inhibiting HCV NS5A and NS3/4A proteases, respectively, which are involved in HCV replication. RTV inhibits a human cytochrome P450 (CYP) isozyme, CYP3A4, and is therefore, despite its weak anti-HCV activity, contained in the PTV/RTV/OBV combination to increase the blood concentration of PTV that is metabolized mainly by CYP3A4.

The number of HCV-infected patients is estimated to be approximately 170 million worldwide and 1.5 to 2 million in Japan (The Japan Society of Hepatology Drafting Committee for Hepatitis Management. *JSH Guidelines for the Management of Hepatitis C Virus Infection.* 4.1th ed. [in Japanese]. 2015), and approximately 30% of them are infected by genotype 2 HCV (*Liver Int*. 2011;31 Supple 2:61-80). For the treatment of genotype 2 CHC patients, a regimen of an interferon (IFN) or a peginterferon (PegIFN) and a combination regimen of sofosbuvir (NS5B polymerase inhibitor) and ribavirin (RBV) are currently available in Japan.

In a Japanese phase III study in genotype 2 CHC patients with or without compensated cirrhosis, the efficacy and safety of the PTV/RTV/OBV combination + RBV were demonstrated in treatment-naïve patients with chronic hepatitis. On the basis of these results, partial change applications for the PTV/RTV/OBV combination and RBV have recently been filed.

Outside Japan, the PTV/RTV/OBV combination has been developed by AbbVie Inc. in the US and is approved in 73 countries including the US and European countries for use in combination with dasabuvir (NS5B inhibitor) or RBV as of June 2016. However, this combination regimen is not yet approved in any country or region for the indication of genotype 2 CHC with or without compensated cirrhosis. Meanwhile, RBV is approved in 96 countries or regions as of January 2016.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

No new data relating to quality were submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Data from primary pharmacodynamic studies of PTV and OBV have been submitted for this application.

3.1 Primary pharmacodynamics

3.1.1 Antiviral activities of PTV and OBV against HCV replicons (4.2.1.1-2; reference, 4.2.1.1-1, 4.2.1.1-6)

The antiviral activities (50% effective concentration [EC_{50}]) of PTV and OBV against HCV replicons were evaluated as measured by the number of HCV replicon copies in an HCV replicon assay (luciferase reporter gene assay), yielding the results shown in Table 1.

Table 1. Antiviral activities of PTV and OBV against HCV replicons

HCV genotype (virus strain)	EC_{50} (nmol/L)	
	PTV	OBV
genotype 1a (H77)	1.0	0.014
genotype 1b (Con-1)	0.21	0.005
genotype 2a (JFH-1)	9.8	0.00082[a)]
genotype 2a (Con-1)[b)]	–	0.012
genotype 2b (Con-1 or JFH-1)	107[c)]	0.0043[d)]

Mean; –, not available

a) EC_{50} was calculated as measured by the amount of HCV RNA by RT-PCR method.
b) HCV genotype 1b (Con-1) chimeric replicons containing amino-acid sequences in the NS5A region from samples of genotype 2a
c) HCV genotype 2a (JFH-1) chimeric replicons containing amino-acid sequences in the NS3 region from samples of genotype 2b
d) HCV genotype 1b (Con-1) chimeric replicons containing amino-acid sequences in the NS5A region from samples of genotype 2b

3.1.2 Effect of the combination of PTV and OBV (4.2.1.1-4)

HCV genotype 2a (JFH-1) replicons were cultured in the presence of PTV alone, OBV alone, or PTV and OBV at a concentration approximately 10-fold the respective EC_{50} values. After incubation for 3 weeks, the effect of the combination of PTV and OBV was evaluated as measured by the number of surviving colony forming units. The number of surviving colony forming units was approximately 1.0×10^6 before culture with any test drug and approximately 420 after culture with PTV only, >2000 after culture with OBV only, and zero after culture with PTV and OBV.

3.1.3 Resistance profiles

3.1.3.1 Resistance profile of PTV (4.2.1.1-2; reference, 4.2.1.1-3)

Mutations in the NS3 region were evaluated in HCV genotype 2a (JFH-1) replicons or HCV genotype 2b chimeric replicons (HCV genotype 2a [JFH-1] chimeric replicons containing amino-acid sequences in the NS3 region from samples of genotype 2b) cultured with PTV. At a concentration of approximately 10-fold the EC_{50} of PTV, the observed amino acid mutations were as follows: D168A/V/Y in HCV genotype 2a (JFH-1) replicons; and F154Y, E79G + F154Y, F154Y + E173G, and D168A/V in HCV genotype 2b chimeric replicons.

In addition, the antiviral activities of PTV were evaluated in HCV genotype 2a (JFH-1) replicons and HCV genotype 2b chimeric replicons containing the above amino acid mutations and the mutation in the NS3 region detected in Japanese phase II and III studies [see “7.R.1.3 Viral resistance mutations”], yielding the results shown in Table 2.

Table 2. Antiviral activities of PTV against wild-type and mutant replicons

Genotype 2a (JFH-1[a)])			Genotype 2b (JFH-1[a)])		
Mutation	EC_{50} (nmol/L)	Fold resistance[b)]	Mutation	EC_{50} (nmol/L)	Fold resistance[b)]
Wild-type	17	–	Wild-type	114	–
V55A	35	2.1	E79G	253	2.2
V55I	64	3.8	P146S	109	1.0
Y56H	64	3.8	A150V	111	1.0
D168A	306	18	F154Y	272	2.4
D168E	89	5.3	A160T	102	0.9
D168H	213	13	D168A	1309	11
D168V	228	13	D168E	256	2.2
D168Y	222	13	D168F	1239	11
V55A + D168E	159	9.4	D168H	1055	9.3
V55I + D168E	199	12	D168S	1008	8.8
Y56H + D168A	766	45	D168T	1165	10
Y56H + D168V	443	27	D168V	1073	9.4
			D168Y	803	7.0
			E173G	289	2.5
			A178T	116	1.0
			A178V	153	1.3
			Y56F + D168A	1381	12
			Y56F + D168E	62	0.5
			Y56F + D168V	1102	9.7
			Y56H + D168E	310	2.7
			E79G + F154Y	1214	11
			F154Y + E173G	1060	9.3
			A160T + D168V	1732	15
			A160T + D168Y	1556	14
			D168V + A178T	722	6.3
			D168V + A178V	1559	14

Mean; –, not available

a) Virus strain

b) Defined as EC_{50} value against mutant replicon/EC_{50} value against wild-type replicon

3.1.3.2 Resistance profile of OBV (4.2.1.1-2; reference, 4.2.1.1-6)

Mutations in the NS5A region were evaluated in HCV genotype 2a or 2b chimeric replicons (HCV genotype 1b [Con-1] chimeric replicons containing amino-acid sequences in the NS5A region from samples of genotype 2a or 2b) cultured with OBV. At a concentration of approximately 50-fold the EC_{50} of OBV, the observed amino acid mutations were T24A and F28S in HCV genotype 2a chimeric replicons and L28F, L31V, and Y93H in HCV genotype 2b chimeric replicons.

The antiviral activities of OBV were also evaluated in HCV genotype 2a and 2b chimeric replicons containing the above amino acid mutations and the mutation in the NS5A region detected in Japanese phase II and III studies [see “7.R.1.3 Viral resistance mutations”], yielding the results shown in Table 3.

Table 3. Antiviral activities of OBV against wild-type and mutant replicons

Genotype 2a (Con-1[a])[c, d]			Genotype 2b (Con-1[a])[c, e]		
Mutation	EC_{50} (pmol/L)	Fold resistance[b]	Mutation	EC_{50} (pmol/L)	Fold resistance[b]
Wild-type	1.3	–	Wild-type	0.71	–
T24A	50	38	L28F	33	47
T24S	87	67	L31I	20	28
F28C	652	501	L31M	1.1	1.5
F28S	15,103	11,618	L31V	361	511
K30M	0.23	0.2	V52I	0.84	1.2
M31I	25	19	C92S	5.7	8
M31V	–[f]	–	C92Y	7.8	11
C92S	16	13	Y93H	–[f]	–
Y93H	–[f]	–	Y93N	–[f]	–
T24A + M31L	20	15	L28F + L31I	1013	1427
T24A + C92S	1250	962	L28F + L31M	176	247
T24S + F28C	6026	4636	L28F + L31V	–[f]	–
F28S + Y93H	–[f]	–	L31M + C92S	27	38
			D168Y	803	23
			E173G	289	7423
			A178T	116	2088
			A178V	153	–

Mean; –, not available

a) Virus strain
b) Defined as EC_{50} value against mutant replicon/EC_{50} value against wild-type replicon
c) HCV genotype 1b (Con-1) chimeric replicons containing amino-acid sequences in the NS5A region from samples of HCV genotype 2a or 2b were used.
d) Replicons containing Met at position 31 of the NS5A region
e) Replicons containing Leu at position 31 of the NS5A region
f) Not detected because of low replication level

3.2 Secondary pharmacodynamics

No new secondary pharmacodynamics study data were submitted.

3.3 Safety pharmacology

No new safety pharmacology data were submitted.

3.R Outline of the review conducted by PMDA

3.R.1 Antiviral activities of PTV and OBV

The applicants' explanation on the antiviral activities of PTV and OBV, and the effects of the combination of PTV, OBV, and RBV:

The results of the *in vitro* study in HCV genotype 2a and 2b replicons [see "3.1.1 Antiviral activity of PTV and OBV against HCV replicons"] suggested that PTV and OBV are expected to have antiviral activities against HCV genotype 2a and 2b. The effects of the combination of PTV and RBV and those of OBV and RBV on HCV genotype 1b (Con-1) replicons were evaluated. As a result, additive or synergistic antiviral activities were observed at any concentrations evaluated in the combined use of PTV (0.1-3.2 μmol/L) and RBV (6-200 μmol/L) or in the combined use of OBV (0.4-12.5 pmol/L) and RBV (13-400 μmol/L). Although the inhibitory effects of the combination of PTV, OBV and RBV on HCV genotype 2a and 2b replicons have not been evaluated, the combination is expected to have an additive or synergistic effect on HCV genotype 2 because: (i) PTV and OBV exhibited antiviral activity against HCV genotype 2a and 2b replicons [see "3.1.1 Antiviral activity of PTV and OBV in HCV replicons"]; (ii) the combined use of PTV and OBV showed an effect on HCV genotype 2a replicons

[see "3.1.2 Effect of the combination of PTV and OBV"]; and (iii) RBV was reported to have antiviral activity against any HCV genotype (*Nature.* 2005;436:967-972).

PMDA considers that the antiviral activity of PTV and OBV against and the additive/synergistic effect of the combination of PTV, OBV, and RBV on HCV genotype 2a and 2b are promising. The efficacy of the PTV/RTV/OBV combination + RBV in HCV genotype 2a or 2b CHC patients with or without compensated cirrhosis is described in "7.R.1 Efficacy."

3.R.2 Resistance to PTV and OBV

The applicants' explanation on the resistance profiles of PTV and OBV on HCV genotype 2a and 2b :

In *in vitro* and clinical studies, the major resistance mutations[1)] to PTV were observed at amino acid position 168 in the NS3 region of both HCV genotype 2a and 2b [see "3.1.3.1 Resistance profile of PTV"], and the major resistance mutations to OBV were observed at amino acid positions 24 and 28 in the NS5A region of HCV genotype 2a and at positions 28, 31, and 92 in the NS5A region of HCV genotype 2b [see "3.1.3.2 Resistance profile of OBV"].

The major resistance mutations to PTV were observed at amino acid position 168 in the NS3 region of both HCV genotype 1 and 2. The major resistance mutations to OBV were observed at amino acid positions 28, 30, 31, 58, and 93 in the NS5A region of HCV genotype 1. The resistance mutations at amino acid positions 28 and 31 were commonly observed in HCV genotype 1 and 2. However, the fold resistance[2)] of the D168Y mutation in the NS3 region was 219 to 337 in HCV genotype 1 and 7 to 13 in HCV genotype 2, and a difference was also observed in the fold resistance of other resistance mutations between HCV genotype 1 and 2.

PMDA's view:

As shown in the results of *in vitro* studies in HCV genotype 2a and 2b replicons, mutations at amino acid position 168 in the NS3 region reduced the antiviral activity of PTV and mutations at the amino acid positions of 24, 28, 31, and 92 in the NS5A region reduced the antiviral activity of OBV. Furthermore, the resistance conferred by mutations at positions 79, 154, and 173, etc., in the NS3 region detected in *in vitro* studies and clinical studies was found to be greater when these mutations were doubled than when they occurred as single mutations [see "3.1.3 Resistance profiles"].

With respect to resistance profiles of HCV genotype 1 and genotype 2, while some of the positions of amino acid mutations were the same, fold resistance of each resistance mutation between HCV genotype 1 and genotype 2 were different as shown in the results of *in vitro* studies. Since limitations on the information from clinical studies is limited and presence or absence of any resistance mutations may

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[1)] Of amino acid mutations identified in an *in vitro* resistance selection study, those that were observed at the time of virologic failure in clinical studies with the fold resistance of mutation strains containing the relevant mutations ≥3-fold [see "3.1.3 Resistance profiles"]. Amino acid mutations at position 92 in the NS5A region of HCV genotype 2b were not observed in the *in vitro* resistance selection study. However, amino acid mutations at position 92, which had not been observed at baseline, were observed in ≥2 patients at the time of virologic failure in clinical studies. For this reason, the applicants explained, amino acid mutations at position 92 were selected as major resistance mutations.

[2)] Defined as EC_{50} value against mutant replicon/EC_{50} value against wild-type replicon

become important information in relation to the efficacy of the PTV/RTV/OBV combination + RBV, post-marketing information should be collected on resistance to PTV and OBV in CHC (genotype 2) patients including published literature, and any new findings should be promptly provided to healthcare professionals in clinical settings. Relationships between resistance mutations observed in clinical studies and the efficacy of the PTV/RTV/OBV combination + RBV are described in "7.R.1.3 Viral resistance mutations."

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

No new pharmacokinetic (PK) data were submitted.

5. Toxicology and Outline of the Review Conducted by PMDA

No new toxicology data were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

No new biopharmaceutic study data were submitted.

Concentrations of PTV, RTV, OBV, and RBV in human plasma were determined by high performance liquid chromatography/tandem mass spectrometry (lower limit of quantitation [LLOQ]; 0.601 ng/mL for PTV, 4.93 ng/mL for RTV, 0.462 ng/mL for OBV, and 98.1 ng/mL for RBV).

6.2 Clinical pharmacology

The results of a Japanese phase II study, a population pharmacokinetic (PPK) analysis of data from Japanese phase III studies, and a PK interaction study were submitted for this application. All doses and plasma concentrations of PTV and OBV are presented as paritaprevir (anhydride) and ombitasvir (anhydride) equivalents.

Unless otherwise specified, PK parameters are expressed as mean values.

6.2.1 Studies in patients

6.2.1.1 Japanese phase II study (5.3.5.2-2, Study M12-536 [July 2012 to May 2014])

Of CHC subjects enrolled in a Japanese phase II study (Study M12-536), 37 subjects with genotype 2 HCV infection received orally PTV 100 or 150 mg once daily (QD), RTV 100 mg QD, and OBV 25 mg QD in combination. The PK of each active ingredient on Day 1 was evaluated. In CHC (genotype 2) subjects in the PTV 150 mg group, the C_{max} (geometric mean), t_{max} (mean), and $AUC_{0\text{-}24}$ (geometric mean) were 2650 ng/mL, 3.8 hours, and 18,100 ng·h/mL, respectively, for PTV; 1070 ng/mL, 3.8 hours, and 9180 ng·h/mL, respectively, for RTV; and 154 ng/mL, 4.1 hours, and 1720 ng·h/mL, respectively, for OBV.

6.2.1.2 PPK analysis and exposure-response analysis (5.3.3.5-1)

PPK analysis (software used, NONMEM version 7.3) was performed on PK data (in 534 subjects for PTV, RTV and OBV; 3690 time points for PTV, 3686 samples for RTV, and 3702 samples for OBV; and in 171 subjects for RBV, 1206 samples) obtained from genotype 1b or 2 CHC subjects with or without compensated cirrhosis in Japanese phase III studies (Study M13-004 in genotype 1 CHC patients with or without compensated cirrhosis receiving the PTV/RTV/OBV combination alone, and Study M14-153 in genotype 2 CHC patients with or without compensated cirrhosis receiving the PTV/RTV/OBV combination + RBV). The final models used were a one-compartment model with first-order absorption and first-order elimination for PTV, RTV, and OBV, and a two-compartment model with first-order absorption and first-order elimination for RBV. Covariates selected were the presence or absence of hepatic cirrhosis for apparent oral clearance (CL/F) of PTV and RTV; sex, presence or absence of hepatic cirrhosis, and creatinine clearance (CL_{cr})[3] for CL/F of OBV; body weight[4] for CL/F of RBV; and age[5] and sex for the central compartment apparent volume of distribution (V_c/F) and peripheral compartment apparent volume of distribution (V_p/F) of RBV.[6] The presence or absence of concomitant RBV was not a covariate for the CL/F or V_c/F of PTV, RTV, or OBV.

The steady-state PK parameters (estimated values) in CHC subjects with or without compensated cirrhosis who received orally the PTV/RTV/OBV combination (PTV/RTV/OBV, 150/100/25 mg) QD and RBV (body weight-based dose) twice daily (BID) were estimated using the final model as shown in Table 4.

Table 4. Steady-state PK parameters of individual active ingredients estimated from the final model

Dose (mg)		Sex	C_{max} (ng/mL)		$AUC_{0\text{-}24}$ (ng·h/mL)		C_{trough} (ng/mL)	
			Compensated cirrhosis	Chronic hepatitis	Compensated cirrhosis	Chronic hepatitis	Compensated cirrhosis	Chronic hepatitis
PTV	150	Both	439 (143)	197 (184)	6380 (154)	2971 (163)	69.0 (181)	36.6 (169)
RTV	100	Both	238 (110)	154 (134)	3839 (103)	2503 (115)	57.6 (96)	38.6 (120)
OBV[a)]	25	Male	36.6 (49.1)	41.8 (51.8)	734 (39.2)	849 (42.3)	21.5 (26.4)	25.4 (31.6)
		Female	58.2 (52.5)	66.5 (53.9)	1194 (42.2)	1406 (44.1)	36.4 (30.8)	45.3 (29.9)
RBV	400-1000[b)]	Male	1067 (27.1)		47,427 (26.7)		899 (27.0)	
		Female	987 (40.5)		41,205 (31.2)		730 (35.0)	

Geometric mean (CV%);

a) Estimated value when the CL_{cr} was 78 mL/min;

b) Daily dose specified based on body weight (≤60 kg, 600 mg/day; >60 to ≤80 kg, 800 mg/day; >80 kg, 1000 mg/day) or daily dose reduced based on laboratory test values was administered in 2 divided doses as spedified in Rebetol Capsules 200 mg [package insert].

[3] The CL/F of OBV in patients with mild renal impairment (CL_{cr} of 75 mL/min) increased by 8% to 11% compared to that in patients with normal renal function (CL_{cr} of 105 mL/min).

[4] In a male aged 59 years, changes in exposure to RBV associated with a 10 kg increase or decrease in body weight were less than 15%.

[5] In a male with a body weight of 61.3 kg, changes in exposure to RBV associated with a 10 year increase or decrease in age were less than 3%.

[6] Age, sex, body weight, BMI, CL_{cr}, presence or absence of concomitant RBV, presence or absence of hepatic cirrhosis, and genotype (1b or 2) were evaluated as potential covariates for CL/F; and age, sex, body weight, BMI, presence or absence of concomitant RBV, and genotype (1b or 2) for V_c/F (V_c/F and V_p/F for RBV).

6.2.2 PK interactions[7)]

Five new studies were conducted to evaluate the drug interactions between PTV, RTV, OBV, and concomitant drugs. Table 5 and Table 6 show the ratios of least squares means [90% confidence interval (CI)] of the C_{max}, AUC, and C_{trough} of PTV, RTV, OBV and a concomitant drug administered in combination to their respective parameter values of each drug administered alone.

Table 5. 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}
Diazepam[c)]	2 mg (single dose)	13	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 [1.02, 1.19]	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]
Hydrocodone Bitartrate[d)]/ acetaminophen[c)]	5/30 mg (single dose)	15	PTV 150 mg QD	1.01 [0.80, 1.27]	1.03 [0.89, 1.18]	1.10 [0.97, 1.26]
			RTV 100 mg QD	1.01 [0.90, 1.13]	1.03 [0.96, 1.09]	1.01 [0.93, 1.10]
			OBV 25 mg QD	1.01 [0.93, 1.10]	0.97 [0.93, 1.02]	0.93 [0.90, 0.97]
Carisprodol[c, d)]	250 mg (single dose)	14	PTV 150 mg QD	0.88 [0.75, 1.03]	0.96 [0.85, 1.08]	1.14 [1.02, 1.27]
			RTV 100 mg QD	0.94 [0.87, 1.02]	0.94 [0.88, 0.99]	0.95 [0.89, 1.03]
			OBV 25 mg QD	0.98 [0.92, 1.04]	0.95 [0.92, 0.97]	0.96 [0.92, 0.99]
Cyclobenzaprine[c, d)]	5 mg (single dose)	14	PTV 150 mg QD	1.14 [0.99, 1.32]	1.13 [1.00, 1.28]	1.13 [1.01, 1.25]
			RTV 100 mg QD	0.93 [0.87, 0.99]	1.00 [0.95, 1.06]	1.13 [1.05, 1.21]
			OBV 25 mg QD	0.98 [0.92, 1.04]	1.00 [0.97, 1.03]	1.01 [0.98, 1.04]
Metformin[c)]	500 mg (single dose)	12	PTV 150 mg QD	0.63 [0.44, 0.91]	0.80 [0.61, 1.03]	1.22 [1.13, 1.31]
			RTV 100 mg QD	0.89 [0.80, 0.99]	0.92 [0.86, 0.99]	1.18 [1.07 1.29]
			OBV 25 mg QD	0.92 [0.87, 0.98]	1.01 [0.97, 1.05]	1.01 [0.98, 1.04]
Sulfamethoxazole/ trimethoprim[e)]	800/160 mg BID	11	PTV 150 mg (single dose)	0.78 [0.61, 1.01]	0.87 [0.72, 1.06]	–
			RTV 100 mg (single dose)	0.91 [0.78, 1.07]	0.95 [0.83, 1.09]	–
			OBV 25 mg (single dose)	0.88 [0.83, 0.94]	0.85 [0.80, 0.90]	–
Dolutegravir[c)]	50 mg QD	11	PTV 150 mg QD	0.89 [0.69, 1.14]	0.84 [0.67, 1.04]	0.66 [0.59, 0.75]
			RTV 100 mg QD	0.93 [0.83, 1.05]	0.85 [0.79, 0.92]	0.72 [0.68, 0.76]
			OBV 25 mg QD	0.96 [0.89, 1.03]	0.95 [0.90, 1.00]	0.92 [0.87, 0.98]
Abacavir/ lamivudine[c)]	600/300 mg QD	11	PTV 150 mg QD	0.84 [0.69, 1.02]	0.82 [0.70, 0.97]	0.73 [0.63, 0.85]
			RTV 100 mg QD	0.88 [0.77, 1.00]	0.88 [0.82, 0.94]	0.93 [0.83, 1.03]
			OBV 25 mg QD	0.82 [0.76, 0.89]	0.91 [0.87, 0.95]	0.92 [0.88, 0.96]
Sofosbuvir	400 mg QD	8	PTV 150 mg QD	0.90 [0.63, 1.28]	0.91 [0.62, 1.31]	0.99 [0.66, 1.50]
			RTV 100 mg QD	0.99 [0.91, 1.07]	0.94 [0.88, 1.00]	0.93 [0.84, 1.03]
			OBV 25 mg QD	0.96 [0.89, 1.04]	0.93 [0.87, 1.00]	0.90 [0.84, 0.96]

–, not evaluated

a) Estimated using a mixed model for repeated measures 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) Coadministration of dasabuvir (not approved in Japan) [redacted] mg BID;

d) Not approved in Japan;

e) Single dose coadministration of dasabuvir (not approved in Japan) [redacted] mg

[7)] Reference 5.3.3.4-9, Study M[redacted]-230 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference 5.3.3.4-10, Study M[redacted]-197 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference 5.3.3.4-11, Study M[redacted]-012 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference 5.3.3.4-12, Study M[redacted]-228 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference 5.3.3.4-13, Study M[redacted]-527 ([redacted] 20[redacted] to [redacted] 20[redacted])

Table 6. 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_{inf}	C_{trough}
Diazepam	Diazepam, 2 mg (single dose)	150/100/25mg QD[b]	13	1.18 [1.07, 1.30]	0.78 [0.73, 0.82]	–
Nordiazepam (metabolite)			13	1.10 [1.03, 1.19]	0.56 [0.45, 0.70]	–
Hydrocodone Bitartrate[c]	Hydrocodone Bitartrate/acetaminophen, 5/300 mg (single dose)	150/100/25mg QD[b]	15	1.27 [1.14, 1.40]	1.90 [1.72, 2.10]	–
Acetaminophen			15	1.02 [0.89, 1.18]	1.17 [1.09, 1.26]	–
Carisprodol[c]	Carisprodol, 250 mg (single dose)	150/100/25 mg QD[b]	14	0.54 [0.47, 0.63]	0.62 [0.55, 0.70]	–
Meprobamate (metabolite)			14	1.17 [1.10, 1.25]	1.09 [1.03, 1.16]	–
Cyclobenzaprine[c]	Cyclobenzaprine, 5 mg (single dose)	150/100/25 mg QD[b]	14	0.68 [0.61, 0.75]	0.60 [0.53, 0.68]	–
Norcyclobenzaprine (metabolite)			14	1.03 [0.87 1.23]	0.74 [0.64, 0.85]	–
Metformin	500 mg (single dose)	150/100/25 mg QD[b]	12	0.77 [0.71, 0.83]	0.90 [0.84, 0.97]	–
Sulfamethoxazole	Sulfamethoxazole /trimethoprim, 800/160 mg BID	150/100/25 mg (single dose)[d]	11	1.21 [1.15, 1.28]	1.17[e] [1.14, 1.20]	1.15 [1.10, 1.20]
Trimethoprim			11	1.17 [1.12, 1.22]	1.22[e] [1.18, 1.26]	1.25 [1.19, 1.31]
Dolutegravir	50 mg QD	150/100/25 mg QD[b]	11	1.22 [1.15, 1.29]	1.38[f] [1.30, 1.47]	1.36 [1.19, 1.55]
Abacavir	Abacavir/lamivudine, 600/300 mg QD	150/100/25 mg QD[b]	11	0.87 [0.78, 0.98]	0.94[f] [0.90, 0.99]	–
Lamivudine			11	0.78 [0.72, 0.84]	0.88[f] [0.82, 0.93]	1.29[g] [1.05, 1.58]
Sofosbuvir	Sofosbuvir, 400 mg QD	150/100/25 mg QD	7	1.64 [0.99, 2.71]	1.93[f] [1.41, 2.64]	–
GS-331007 (metabolite)			7	1.16 [1.04, 1.30]	1.32[f] [1.25, 1.39]	1.71 [1.49, 1.96]

–, not evaluated
a) Estimated using a mixed model for repeated measures with measurement day as a fixed effect and subject as a random effect.;
b) Coadministration of PTV, RTV, and OBV, with dasabuvir (not approved in Japan) ■ mg BID;
c) Not approved in Japan;
d) Coadministration of PTV, RTV, and OBV with a single dose of dasabuvir (not approved in Japan) ■ mg;
e) AUC from 0 to 12 hours after administration;
f) $AUC_{0\text{-}24}$;
g) 10 subjects

6.R Outline of the review conducted by PMDA

Effects of RBV on the PK of PTV, RTV, and OBV

The applicants' explanation on the effect of coadministration of RBV on the PK of PTV, RTV, and OBV: A PPK analysis was performed on the PK data from CHC patients with or without compensated cirrhosis enrolled in Japanese phase III studies (Studies M13-004 and M14-153). The results showed that the presence or absence of concomitant RBV was not a covariate for the CL/F or V_c/F of PTV, RTV, or OBV [see "6.2.1.2 PPK analysis and exposure-response analysis"]. Furthermore, no marked difference was observed between the C_{trough} of PTV, RTV, and OBV (plasma concentration at 22-26 hours post-dose at Weeks 2-12; 70.2, 48.7, and 41.0 ng/mL, respectively) following repeated administration of PTV/RTV/OBV combination (150/100/25 mg) in genotype 1b CHC patients without hepatic cirrhosis (Study M13-004) or between the C_{trough} of PTV, RTV, and OBV (47.5, 39.6, and 35.4 ng/mL, respectively) following repeated administration of the PTV/RTV/OBV combination (150/100/25 mg) + RBV, in genotype 2 CHC patients without hepatic cirrhosis (Study M14-153). In addition, RBV and its metabolites are excreted mainly in urine, RBV exhibited no inhibitory effects on CYP1A2, 2C9/10, 2D6,

2E1, or 3A4 in *in vitro* studies (Rebetol Capsules 200 mg [package insert]. 20th ed.; January 2016), and no published literature or other relevant documents suggest that RBV has an effect on transporters involved in the transportation of PTV, RTV, or OBV (e.g., P-gp, BCRP, OATP1B1/1B3, MRP2). Therefore, RBV is considered unlikely to affect the PK of PTV, RTV, or OBV

PMDA accepted the applicants' explanation.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

Japanese phase II and III study results (1 study each) have been submitted as evaluation data of efficacy and safety in genotype 2 CHC patients with or without compensated cirrhosis. These studies are summarized in Table 7. Because data from Study M12-536 were submitted at the time of the initial filing of the application of the PTV/RTV/OBV combination, this section presents a summary of the results of Study M14-153.

All doses and plasma concentrations of PTV or OBV are presented as those of paritaprevir (anhydride) or ombitasvir (anhydride), respectively.

In this section, CHC patients were classified either as "treatment-naïve" or "treatment-experienced" depending on whether they were previously treated with IFN.

Table 7. Summary of clinical studies (evaluation data)

Phase	Study identifier	Target patients	Primary objectives	N	Dosage and administration
II	M12-536	Treatment-experienced patients with HCV genotype 1b or 2 CHC	PK Efficacy Safety	110	PTV/RTV/OBV 100/100/25 mg or 150/100/25 mg QD for 12 or 24 weeks for genotype 1b CHC patients and for 12 weeks for genotype 2 CHC patients
III	M14-153	Treatment-naïve or treatment-experienced patients with HCV genotype 2 CHC with or without compensated cirrhosis	Efficacy Safety PK	171	The PTV/RTV/OBV combination QD and RBV (body-weight-based dose) BID for 12 or 16 weeks

7.1 Japanese phase III study (5.3.5.2.1, Study M14-153 [January 2014 to April 2015])

A randomized, open-label, parallel-group, comparative study was conducted at 53 study sites in Japan to evaluate the efficacy and safety of the PTV/RTV/OBV combination + RBV in genotype 2 CHC subjects with or without compensated cirrhosis (target sample size, 150 subjects [approximately 80

treatment-naïve subjects with chronic hepatitis,[8] approximately 60 treatment-experienced subjects with chronic hepatitis,[9] and approximately 10 subjects with compensated cirrhosis[10]]).

In this study, 2 tablets of PTV/RTV/OBV combination (150/100/25 mg) QD and RBV at a dose specified based on body weight (≤60 kg, 600 mg/day; >60 to ≤80 kg, 800 mg/day; and >80 kg, 1000 mg/day; administered daily in 2 divided doses in accordance with Rebetol Capsules 200 mg [package insert]) were orally administered after a meal for 12 or 16 weeks.

All 171 randomized and treated subjects (95 treatment-naïve subjects with chronic hepatitis [48 in the 12-week treatment group and 47 in the 16-week treatment group], 65 treatment-experienced subjects with chronic hepatitis [32 in the 12-week treatment group and 33 in the 16-week treatment group], and 11 subjects with compensated cirrhosis [5 in the 12-week treatment group and 6 in the 16-week treatment group]) were included in the intention-to-treat (ITT) population and the safety analysis population. The ITT population was defined as the efficacy analysis population.

The SVR12 rate (proportion of subjects with HCV RNA in blood less than the LLOQ at 12 weeks after the final dose of the study drug) [95% CI][11] in treatment-naïve subjects with CHC, the primary endpoint, was 75.0% [62.8%, 87.2%] (36 of 48 subjects) in the 12-week treatment group and 91.5% [83.5%, 99.5%] (43 of 47 subjects) in the 16-week treatment group. In treatment-naïve subjects with CHC, the lower 95% confidence limit of the SVR12 rate in the 16-week treatment group was higher than the pre-specified threshold of the SVR12 rate (67%[12]), demonstrating the efficacy of the study treatment, while that in the 12-week treatment group was not higher than the threshold, failing to show efficacy.[13] The SVR12 rates in other subject populations are shown in Table 8.

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[8] Patients who had never received treatment for HCV infection

[9] Patients who had previously been treated with a regimen containing IFN and met any of the following criteria:
- Null responders
  Patients who received a regimen containing IFN for ≥12 weeks and failed to achieve an HCV RNA level less than the detection limit at the end of treatment
- Relapsed
  Patients who received a regimen containing IFN and in whom HCV RNA level was less than the detection limit at or after the end of treatment but HCV RNA was detected during the 52-week follow-up period
- Intolerant to IFN
  Patients who were intolerant to a regimen containing IFN and discontinued the regimen

[10] Hepatic cirrhosis was defined as follows (with Child-Pugh score ≤6 at screening):
- Patients for whom liver biopsy was conducted, METAVIR score or fibrosis score by new Inuyama classification system >3 or Ishak score >4
- Patients for whom no liver biopsy was conducted, (1) Fibro Test score ≥0.73 and aspartate aminotransferase-to-platelet ratio index (APRI) >2; (2) Severity of cirrhosis assessed by elasticity imaging (e.g., Fibroscan) ≥14.6 kPa; or (3) Chronic hepatitis and cirrhosis discriminant score >0 when calculated by the formula below:
  $0.124 \times (\gamma\text{-globulin [\%]}) + 0.001 \times (\text{hyaluronic acid [}\mu\text{g/L]}) - 0.075 \times (\text{platelet count [}\times 10^4/\text{mm}^3\text{]}) - 0.413 \times \text{sex (male, 1; female, 2)} - 2.005$

[11] Determined by the normal approximation

[12] On the basis of the study results of pegIFN and RBV combination regimen in treatment-naïve patients with chronic hepatitis (genotype 2) including Japanese (*J Hepatol*. 2011;54:408-414; *J Viral Hepat*. 2010;17:336-344; and other literature), the SVR rate for the external control was calculated to be 77%. Taking into account the improvement in the safety profile from the pegIFN/RBV regimen and a reduction in the treatment period, the threshold SVR12 rate was determined to be 67%.

[13] Evaluation process was planned to involve step-down procedure to maintain the probability of type 1 error at 5%. Therefore, the 16-week treatment group was evaluated first, and then the 12-week treatment group was.

Table 8. SVR 12 rates in respective patient populations (ITT population)

Patient population	12-week treatment	16-week treatment
Overall	72.9 (62/85)	81.4 (70/86)
Chronic hepatitis patients without compensated cirrhosis	72.5 (58/80)	85.0 (68/80)
Treatment-naïve	75.0 (36/48)	91.5 (43/47)
Treatment-experienced	68.8 (22/32)	75.8 (25/33)
Chronic hepatitis patients with compensated cirrhosis	80.0 (4/5)	33.3 (2/6)

% (n/N)

The incidence of adverse events (including abnormal laboratory findings) was 81.2% (69 of 85 subjects) in the 12-week treatment group and 86.0% (74 of 86 subjects) in the 16-week treatment group. The incidence of adverse drug reactions (including abnormal laboratory findings)[14] was 54.1% (46 of 85 subjects) in the 12-week treatment group and 45.3% (39 of 86 subjects) in the 16-week treatment group. The adverse events and adverse drug reactions that occurred with an incidence of ≥2% in either treatment group are shown in Table 9.

[14] Adverse events that were assessed by the investigator as "related to the study drug"

Table 9. Adverse events and adverse drug reactions that occurred with an incidence of ≥2% in either group

Event	Adverse event		Adverse drug reaction	
	12-week treatment (N = 85)	16-week treatment (N = 86)	12-week treatment (N = 85)	16-week treatment (N = 86)
Overall	69 (81.2)	74 (86.0)	53 (62.4)	50 (58.1)
Anaemia	16 (18.8)	21 (24.4)	16 (18.8)	21 (24.4)
Blood bilirubin increased	16 (18.8)	15 (17.4)	15 (17.6)	15 (17.4)
Headache	12 (14.1)	6 (7.0)	4 (4.7)	4 (4.7)
Nasopharyngitis	10 (11.8)	13 (15.1)	1 (1.2)	1 (1.2)
Pruritus	7 (8.2)	10 (11.6)	6 (7.1)	8 (9.3)
Haemoglobin decreased	7 (8.2)	4 (4.7)	7 (8.2)	4 (4.7)
Reticulocyte count increased	6 (7.1)	5 (5.8)	6 (7.1)	5 (5.8)
Fatigue	6 (7.1)	2 (2.3)	5 (5.9)	1 (1.2)
Nausea	5 (5.9)	3 (3.5)	4 (4.7)	2 (2.3)
Malaise	4 (4.7)	7 (8.1)	4 (4.7)	6 (7.0)
Cough	4 (4.7)	5 (5.8)	2 (2.4)	3 (3.5)
Rash	4 (4.7)	4 (4.7)	3 (3.5)	4 (4.7)
Red blood cell count decreased	4 (4.7)	3 (3.5)	4 (4.7)	3 (3.5)
Diarrhoea	4 (4.7)	1 (1.2)	1 (1.2)	1 (1.2)
Blood cholesterol decreased	3 (3.5)	4 (4.7)	3 (3.5)	4 (4.7)
Oedema peripheral	3 (3.5)	2 (2.3)	2 (2.4)	1 (1.2)
Eczema	3 (3.5)	1 (1.2)	0	0
Hyperuricaemia	3 (3.5)	0	2 (2.4)	0
Pyrexia	2 (2.4)	4 (4.7)	1 (1.2)	1 (1.2)
Creatinine renal clearance decreased	2 (2.4)	3 (3.5)	2 (2.4)	2 (2.3)
Dizziness	2 (2.4)	3 (3.5)	1 (1.2)	3 (3.5)
Bilirubin conjugated increased	2 (2.4)	2 (2.3)	2 (2.4)	2 (2.3)
Decreased appetite	2 (2.4)	2 (2.3)	1 (1.2)	2 (2.3)
Thirst	2 (2.4)	1 (1.2)	1 (1.2)	0
Hypotension	2 (2.4)	1 (1.2)	1 (1.2)	1 (1.2)
Protein urine present	2 (2.4)	1 (1.2)	2 (2.4)	1 (1.2)
Urobilinogen urine increased	2 (2.4)	1 (1.2)	2 (2.4)	1 (1.2)
Somnolence	2 (2.4)	1 (1.2)	0	0
Blood triglycerides increased	2 (2.4)	0	1 (1.2)	0
Blood uric acid increased	2 (2.4)	0	2 (2.4)	0
Pollakiuria	2 (2.4)	0	1 (1.2)	0
Proteinuria	2 (2.4)	0	1 (1.2)	0
Epistaxis	2 (2.4)	0	0	0
Hypertension	2 (2.4)	0	1 (1.2)	0
Urine leukocyte esterase positive	2 (2.4)	0	2 (2.4)	0
Toothache	2 (2.4)	0	0	0
Vomiting	2 (2.4)	0	1 (1.2)	0
Neutrophil count decreased	1 (1.2)	4 (4.7)	1 (1.2)	4 (4.7)
White blood cell count decreased	1 (1.2)	4 (4.7)	1 (1.2)	4 (4.7)
Insomnia	1 (1.2)	3 (3.5)	0	2 (2.3)
Upper respiratory tract infection	1 (1.2)	3 (3.5)	0	0
Blood pressure decreased	1 (1.2)	2 (2.3)	1 (1.2)	2 (2.3)
ALT increased	1 (1.2)	2 (2.3)	1 (1.2)	2 (2.3)
Contusion	0	4 (4.7)	0	0
Abdominal discomfort	0	3 (3.5)	0	1 (1.2)
Blepharitis	0	2 (2.3)	0	0
Back pain	0	3 (3.5)	0	0
Blood triglycerides decreased	0	2 (2.3)	0	2 (2.3)
Haematocrit decreased	0	2 (2.3)	0	2 (2.3)
Lymphocyte count decreased	0	2 (2.3)	0	2 (2.3)
Specific gravity urine decreased	0	2 (2.3)	0	2 (2.3)
Weight decreased	0	2 (2.3)	0	1 (1.2)
Pain in extremity	0	2 (2.3)	0	1 (1.2)
Urticaria	0	2 (2.3)	0	1 (1.2)

n (%)
ALT, alanine aminotransferase

No deaths occurred. Serious adverse events were observed in 3 subjects (bronchopneumonia, gastritis alcoholic, and incisional hernia [1 subject each]) in the 16-week treatment group. A causal relationship to the study drug was ruled out for all these events and their outcome was resolved. No adverse events led to study discontinuation. An adverse event leading to study interruption (nausea) occurred in 1 subject in the 16-week treatment group and was assessed as related to PTV/RTV/OBV combination; however, its outcome was resolved. Adverse events leading to dose adjustment of RBV occurred in 9 subjects (4 experienced haemoglobin decreased; 3, anaemia; 1, creatinine renal clearance decreased; and 1, glomerular filtration rate decreased) in the 12-week treatment group and 8 subjects (6 experienced anaemia; and 2, haemoglobin decreased) in the 16-week treatment group. All these events were mild or moderate in severity and their outcomes were resolved.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the following review, PMDA has concluded that the 16-week treatment with the PTV/RTV/OBV combination + RBV is expected be effective for treatment-naïve patients with CHC (genotype 2), the proposed indication.

However, since clinical studies have provided only limited information on relationships between resistance-related mutations and the efficacy of the PTV/RTV/OBV combination + RBV, it is necessary to continue to collect the following information in the post-marketing setting from sources including the published literature: 1) relationships between the baseline status of resistance mutations and the efficacy of the combination regimen; and 2) the status of resistance-related mutations in patients failing to achieve SVR despite treatment with the combination regimen. Any new findings should be provided promptly to healthcare professionals in clinical settings.

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

7.R.1.1 Study design

PMDA asked the applicants to explain the background and rationale for not having used an IFN-based regimen as the control in the Japanese phase III study (Study M14-153).

The applicants' response:

The safety profiles of the PTV/RTV/OBV combination and RBV were considered unlikely to be affected by HCV genotype. The safety profile of RBV was considered already established, since it had been widely used in combination with IFN in clinical settings in Japan,. In addition, the safety of the PTV/RTV/OBV combination was planned to be examined in Study M13-004 (a Japanese phase III placebo-controlled study of the PTV/RTV/OBV combination in genotype 1 CHC patients with or without compensated cirrhosis) when the Japanese phase III Study M14-153 started. Taking the above into account, Study M14-153 was considered unnecessary to be designed as another placebo-controlled study.

At the start of Study M14-153 (January 2014), IFN-containing regimens such as PegIFN monotherapy and PegIFN/RBV combination therapy were recommended for treating CHC (genotype 2) patients (The Japan Society of Hepatology Drafting Committee for Hepatitis Management. *JSH Guidelines for the Management of Hepatitis C Virus Infection.* 2nd ed. [in Japanese]. 2013). However, such IFN-containing regimens were considered inappropriate to be included as a control in the study for the following reasons:

- The interim analysis of the Japanese phase II study (Study M12-536) showed that the SVR24 rate at Week 12 of PTV/RTV/OBV combination (150/100/25 mg) treatment was 72.2% (13 of 18 subjects) in genotype 2 CHC subjects who had previously been treated with PegIFN in combination with RBV. An adverse event leading to study discontinuation and a Grade 3 or worse adverse event was reported in only 1 subject each. These results demonstrated that the PTV/RTV/OBV combination was well tolerated in subjects in the study.
- As of the start of Study M14-153, no monotherapy regimen of antiviral agents such as sofosbuvir had been approved, and the SVR24 rate after recommended treatments in Japanese patients with CHC (genotype 2) was 76.2% (*J Hepatol*. 2011;54:408-414) in treatment-naïve patients (high viral load) (combination regimen of PegIFN and RBV), 61.5% (*Japanese Journal of Medicine and Pharmaceutical Science.* [in Japanese]. 2003;50:655-672) in treatment-naïve patients (low viral load) (monotherapy with PegIFN), and 56% to 71.4% (*J Gastroenterol*. 2011;46:1031-1037; *Dig Dis Sci*. 2011;56:3335-3342) in patients with a history of PegIFN + RBV treatment (combination regimen of PegIFN and RBV). Adverse events reported in patients treated with these IFN-containing regimens included flu-like symptoms, anaemia, haemoglobin decreased, neutropenia, and thrombocytopenia.
- Taking into account the efficacy data and safety profile of the PTV/RTV/OBV combination obtained from Japanese and foreign clinical studies before the start of the Japanese phase III (Study M14-153) and the safety profiles of IFN-containing regimens, a study controlled by an IFN-containing regimen was considered difficult to be accepted by potential participants and investigators.

PMDA's view:

At the time the Japanese phase III study (Study M14-153) was initiated, exploratory study results of the PTV/RTV/OBV combination in genotype 2 CHC patients suggested that the regimen was well tolerated and was no less effective than PegIFN monotherapy or PegIFN/RBV combination therapy. Taking them into account, the applicant's explanation is, in part, understandable in that the Japanese clinical study controlled by an IFN-containing regimen such as PegIFN/RBV was not feasible.

7.R.1.2 Efficacy

The applicants' explanation on the efficacy of the PTV/RTV/OBV combination + RBV in genotype 2 CHC patients with or without compensated cirrhosis:

(a) Treatment-naïve patients with chronic hepatitis

In the Japanese phase III study (Study M14-153), the SVR12 rate [95% CI],[11] the primary endpoint, in treatment-naïve subjects with chronic hepatitis was 75.0% [62.8%, 87.2%] (36 of 48 subjects) in

the 12-week treatment group and 91.5% [83.5%, 99.5%] (43 of 47 subjects) in the 16-week treatment group. The lower 95% confidence limit of the SVR12 rate in the 16-week treatment group was higher than the pre-specified threshold of the SVR12 rate (67%),[12] demonstrating the efficacy of the 16-week treatment with the PTV/RTV/OBV combination + RBV in this patient population. Because the lower 95% confidence limit of the SVR12 rate in the 12-week treatment group did not exceed the pre-specified threshold of SVR12 rate, the efficacy of the 12-week treatment with the PTV/RTV/OBV combination + RBV was considered not demonstrated.

(b) Treatment-experienced patients with chronic hepatitis

Currently, the Japanese guideline (The Japan Society of Hepatology Drafting Committee for Hepatitis Management. *JSH Guidelines for the Management of Hepatitis C Virus Infection.* 4.1th ed. [in Japanese]. 2015) recommends a 12-week treatment with the combination of sofosbuvir and RBV for treating genotype 2 CHC patients excluding those with severe renal impairment or renal failure requiring dialysis. In a clinical study of the combination of sofosbuvir and RBV, the SVR12 rate in treatment-experienced patients with CHC was 95.2% (60 of 63 subjects) (*J Viral Hepat*. 2014;21:762-768). Meanwhile, in the Japanese phase III study (Study M14-153), the SVR12 rate in treatment-experienced patients with chronic hepatitis receiving the 16-week treatment with the PTV/RTV/OBV combination + RBV was 75.8% (25 of 33 subjects), suggesting that this regimen is unlikely to have sufficient efficacy in treatment-experienced patients with CHC. Therefore, the treatment with the PTV/RTV/OBV combination + RBV cannot be recommended for treating this patient population.

(c) Chronic hepatitis patients with compensated cirrhosis

A 12-week treatment with the combination of sofosbuvir and RBV is recommended for the treatment of genotype 2 chronic hepatitis patients with compensated cirrhosis, as in those without compensated cirrhosis (The Japan Society of Hepatology Drafting Committee for Hepatitis Management. *JSH Guidelines for the Management of Hepatitis C Virus Infection.* 4.1th ed. [in Japanese]. 2015), and the SVR12 rate in this patient population was 94.1% (16 of 17 patients) (*J Viral Hepat*. 2014;21:762-768). Given that the SVR12 rate in patients with compensated cirrhosis receiving the 16-week treatment with the PTV/RTV/OBV combination + RBV was 33.3% (2 of 6 subjects) in the Japanese phase III study (Study M14-153), this regimen was considered unlikely to have sufficient efficacy in CHC patients with compensated cirrhosis. Therefore, the treatment with the PTV/RTV/OBV combination + RBV cannot be recommended for treating this patient population.

The SVR24 rate in treatment-naïve subjects with chronic hepatitis, treatment-experienced patients with chronic hepatitis, and subjects with compensated cirrhosis was 72.9% (35 of 48 subjects), 68.8% (22 of 32 subjects), and 80.0% (4 of 5 subjects), respectively, in the 12-week treatment group and 91.5% (43 of 47 subjects), 75.8% (25 of 33 subjects), and 33.3% (2 of 6 subjects), respectively, in the 16-week treatment group. After achieving SVR12, 1 treatment-naïve subject with chronic hepatitis in the 12-week treatment group relapsed by 24 weeks after completing the treatment. In the NS5A region in this

subject, resistance-related mutations were detected at P58S at baseline and at L28F at the time of virologic failure.[15)]

The results of subanalyses in CHC subjects are shown in Table 10. The SVR12 rate for the treatment with the PTV/RTV/OBV combination + RBV at Week 16 in treatment-naïve subjects was approximately 90% in any subgroup. The corresponding SVR12 rate in treatment-experienced subjects was 93.8% (15 of 16 subjects) in genotype 2a CHC subjects and 56.3% (9 of 16 subjects) in genotype 2b CHC subjects, showing a particularly low SVR12 rate in genotype 2b CHC subjects.

Table 10. SVR12 rates in CHC subjects (ITT population)

Baseline characteristic		Treatment-naïve		Treatment-experienced	
		12-week treatment	16-week treatment	12-week treatment	16-week treatment
Overall		75.0 (36/48)	91.5 (43/47)	68.8 (22/32)	75.8 (25/33)
Age	<65 years	74.3 (26/35)	92.3 (36/39)	63.2 (12/19)	72.2 (13/18)
	≥65 years	76.9 (10/13)	87.5 (7/8)	76.9 (10/13)	80.0 (12/15)
Eligibility for IFN (for treatment-naïve subjects only)	Eligible	75.0 (33/44)	91.1 (41/45)	–	–
	Ineligible	75.0 (3/4)	100 (2/2)	–	–
Response to prior treatment (for treatment-experienced subjects only)	Null	–	–	40.0 (2/5)	50.0 (3/6)
	Relapsed	–	–	80.0 (12/15)	93.8 (15/16)
	Intolerant to IFN	–	–	66.7 (8/12)	63.6 (7/11)
subtype	2a	82.8 (24/29)	93.9 (31/33)	86.4 (19/22)	93.8 (15/16)
	2b	63.2 (12/19)	85.7 (12/14)	22.2 (2/9)	56.3 (9/16)
HCV RNA	<100,000 IU/mL	100 (7/7)	100 (4/4)	66.7 (2/3)	100 (1/1)
	≥100,000 IU/mL	70.7 (29/41)	90.7 (39/43)	69.0 (20/29)	75.0 (24/32)
IL28B gene polymorphism rs12979860	CC	73.7 (28/38)	91.9 (34/37)	69.6 (16/23)	80.0 (20/25)
	non CC	80.0 (8/10)	90.0 (9/10)	66.7 (6/9)	62.5 (5/8)

% (n/N); –, not applicable

PMDA's view:

On the basis of the results of the Japanese phase III study (Study M14-153), PMDA concluded that the 16-week treatment with the PTV/RTV/OBV combination + RBV is expected to be effective in treatment-naïve patients with CHC (genotype 2). Taking into account the SVR12 rates in treatment-experienced subjects with chronic hepatitis with or without compensated cirrhosis of the treatment with the PTV/RTV/OBV combination + RBV in the above study and those in clinical studies of similar drugs, PMDA understands the applicants' comment that the treatment with the PTV/RTV/OBV combination + RBV cannot be recommended for these patient populations. For these patients, regimens other than the treatment with the PTV/RTV/OBV combination + RBV should be selected as the first line treatment. Indications of the proposed regimen are reviewed in "7.R.3 Indications."

7.R.1.3 Viral resistance mutations

The applicants' explanation on the emergence of viruses resistant to the PTV/RTV/OBV combination and the effect of resistant viruses on the efficacy of the PTV/RTV/OBV combination + RBV:

[15)] In this subject, no resistance mutations were detected in the NS3 region at baseline, and amino acid mutations were detected at A160T and T472I at the time of virologic failure.

Table 11 shows SVR12 rates by baseline status of resistance-related mutations[16] in the NS3 or NS5A region based on data from subjects for whom baseline sequencing data were available in the Japanese phase III study (Study M14-153). Although the subjects were identified who had resistance-related mutations at baseline at position 56 or 168 in the NS3 region, they were too few to allow a sufficient examination of the effects of these mutations on SVR12 rates. Also the subjects were identified at baseline who had resistance-related mutations at positions 24, 28, 30, 31, 58, or 92 in the NS5A region; however, no marked difference was observed in SVR12 rate between subjects with and without these mutations.

Table 11. SVR12 rates by the baseline status of resistance-related mutations in the NS3 or NS5A region (Study M14-153)

Mutations		12-week treatment		16-week treatment	
		With mutation	Without mutation	With mutation	Without mutation
Genotype 2a					
NS3 region	Y56F	–	88.2 (45/51)	0 (0/1)	95.8 (46/48)
	D168E	–	88.2 (45/51)	100 (1/1)	93.8 (45/48)
NS5A region	T24A/S	80.0 (4/5)	89.4 (42/47)	100 (6/6)	93.2 (41/44)
	F28C/L	100 (1/1)	88.2 (45/51)	100 (2/2)	93.8 (45/48)
	K30R	–	88.5 (46/52)	100 (1/1)	93.9 (46/49)
	L31I/M	87.8 (43/49)	100 (3/3)	93.5 (43/46)	100 (4/4)
	P58H/S	100 (2/2)	88.0 (44/50)	100 (1/1)	93.9 (46/49)
	C92S	50.0 (1/2)	90.0 (45/50)	–	94.0 (47/50)
Genotype 2b					
NS3 region	Y56F/H	50.0 (1/2)	51.9 (14/27)	0 (0/2)	73.3 (22/30)
NS5A region	L28F	60.0 (3/5)	50.0 (12/24)	50.0 (1/2)	66.7 (20/30)
	K30R	100 (1/1)	50.0 (14/28)	100 (1/1)	64.5 (20/31)
	M31I/L	62.5 (5/8)	47.6 (10/21)	80.0 (4/5)	63.0 (17/27)
	P58S/T	100 (1/1)	50.0 (14/28)	50.0 (1/2)	66.7 (20/30)
	C92S	66.7 (2/3)	50.0 (13/26)	–	65.6 (21/32)

% (n/N); –, not applicable

Table 12 shows the resistance-related mutations in the NS3 and NS5A regions detected at baseline and at the time of virologic failure[17] in 48 subjects (11 with genotype 2a infection[18] and 37 with genotype 2b infection) who experienced virologic failure in the Japanese phase III study (Study M14-153) and the Japanese phase II study (Study M12-536). Among subjects with genotype 2a infection, mutations were observed at the time of virologic failure in 7 subjects in the NS3 region (at D168 in 7 subjects and at Y56 in 3 subjects) and in 10 subjects in the NS5A region (at L31 in 9 subjects, at T24 and F28 in 3 subjects each, and at C92 in 1 subject). Among subjects with genotype 2b infection, mutations were observed at the time of virologic failure in 35 subjects in the NS3 region (at D168 in 35 subjects and at

16) On the basis of the results of *in vitro* studies and clinical studies in patients with genotype 1 (*Antimicrob Agents Chemother*, 2016;60:1106-1113; *Antimicrob Agents Chemother*. 2015;59:5445-5454; and other literature) and the results of *in vitro* studies and a Japanese phase II study (Study M12-536) in patients with genotype 2, mutations at positions 56, 155, 156, and 168 in the NS3 region and at positions 24, 28, 30, 31, 32, 58, 62, 92, and 93 in the NS5A region were regarded as resistance-related mutations to be analyzed.

17) Virologic failure was defined as either of the following:
- The observed HCV RNA was greater or equal to the LLOQ at 2 consecutive time points after the HCV RNA level decreased to below LLOQ during study treatment.
- The increase from the minimum HCV RNA level was ≥1 $\log_{10}$ IU/mL at 2 consecutive time points during study treatment.
- The HCV RNA level never decreased to below the LLOQ during the first 6 weeks of study treatment.

18) Because post-baseline sequence data were not obtained from 1 subject with genotype 2a infection, analysis in subjects with genotype 2a infection in the Japanese phase III study (Study M14-153) was performed on data from 11 subjects.

Y56 in 2 subjects) and in 36 subjects in the NS5A region (at L28 in 29 subjects, at L/M31 in 15 subjects, at C92 in 7 subjects, and at Y93 in 4 subjects).

Table 12. Resistance-related mutations in the NS3 and NS5A regions in subjects who experienced virologic failure in Japanese clinical studies

Study identifier	Treatment	NS3 region		NS5A region	
		Baseline resistance mutation	Resistance mutation at virologic failure[a)]	Baseline resistance mutation	Resistance mutation at virologic failure[a)]
Genotype 2a					
M12-536	12-week	None	Y56H + D168V	T24A, K30K/T	T24A
		None	D168Y	L31M	L31M
M14-153	12-week	None	Y56H/Y, D168V	T24A, L31M, C92C/S	T24A + L31M + C92S
		None	None	L31M	L31M
		None	D168Y	L31M	F28S + L31M
		None	None	L31M	L31M
		None	None	L31M	L31M
	16-week	Y56F	Y56F + D168E	L31M	T24A, L31I/M/V
		None	D168A	L31M	F28S + L31M
		None	D168E	L31M	F28S + L31M
Genotype 2b					
M12-536	12-week	None	D168Y	None	L28F, M31I
		None	D168V	None	L28F, C92Y
		None	D168V	K30R	M31V, Y93H
		None	D168V/Y	None	L28F, M31A/I/V, Y93C
		Y56F	D168F/V/Y	None	L28F
		None	D168V	None	L28F
		None	D168F/V/Y	M31L	M31V
		None	D168V	L28F	L28F
		None	D168V	None	L28F, C92S
		Y56F/Y	D168F/V/Y	None	L28F, M31I
		None	D168V	None	L28F, C92S

Study identifier	Treatment	NS3 region		NS5A region	
		Baseline resistance mutation	Resistance mutation at virologic failure[a)]	Baseline resistance mutation	Resistance mutation at virologic failure[a)]
M14-153	12-week treatment	None	D168V	None	M31V + C92S
		None	None	P58S	L28F
		None	D168A/D/F/S/V/Y	None	L28F
		None	D168V	L28F + C92S	L28F + C92S
		None	None	None	L28F
		None	D168V	M31L	M31L + C92Y
		None	D168A/D/F/S/V/Y	None	L28F
		Y56H/Y	D168A/D/F/S/V/Y	L28F	L28F
		None	D168V	None	M31V
		None	D168Y	M31L	M31L + Y93H
		None	D168A/D/F/S/V/Y	None	L28F
		None	D168D/F/V/Y	None	L28F, C92C/S/T
		None	D168Y	None	L28F
		None	D168V	M31L	L28F, M31L/V
		None	D168Y	None	L28F
	16-week treatment	Y56F	Y56F, D168A/T	None	L28F
		None	D168Y	None	L28F, M31I/M
		NA	D168D/F/V/Y	L28F/L	L28F
		None	D168Y	P58P/S/T	L28F, M31I/M
		None	D168Y	None	L28F
		None	D168A/D/H/L/P/V	None	L28F
		Y56F	Y56F, D168D/V	M31L	M31L/V, Y93H/Y
		None	D168V	None	L28F
		None	D168Y	None	L28F + M31I
		None	D168N/S/T/Y	None	L28F, M31I/M
		None	D168V	None	L28F, M31I/M

NA, sequence data were not available.
a) "+" indicates a mutation identified in the same virus, and "," indicates a mutation identified in the same specimen.

With respect to resistance-related mutations in the NS3 and NS5A regions at baseline, PMDA confirmed that no relationships were detected between the status of amino acid mutations and SVR12 rates for the PTV/RTV/OBV combination + RBV in the Japanese phase III study (Study M14-153). Among subjects who experienced virologic failure in this study or in the Japanese phase II study (Study M12-536), PMDA also confirmed the following, at the time point when virologic failure was observed: (i) mutations at Y56 or D168 in the NS3 region or at T24, F28, L31, or C92 in the NS5A region were observed in subjects with genotype 2a infection; and (ii) mutations at Y56 or D168 in the NS3 region or at L28, L/M31, C92, or Y93 in the NS5A region were observed in subjects with genotype 2b infection.

Since information from clinical studies is limited on relationships between the status of resistance-related mutations and SVR12 rates for the PTV/RTV/OBV combination + RBV, information on resistance-related mutations at baseline, the emergence of resistance-related mutations in patients failing to achieve SVR after treatment, and other relevant matters should also be collected in the post-marketing setting from sources including the published literature, and any new findings should be provided promptly to healthcare professionals in clinical settings.

7.R.2 Safety

Based on the results of review in the following sections, PMDA concluded that, although attention should be paid to anaemia-related events and to the events identified as such at the initial approval including oedema-related events and hepatic function disorder, the safety of the treatment with the PTV/RTV/OBV combination + RBV in Japanese CHC patients with or without compensated cirrhosis

(genotype 2) is supported if appropriate measures such as monitoring and management of adverse events and interruption or discontinuation of treatment are taken by a physician with sufficient knowledge and experience in treating viral liver diseases.

However, given the limited clinical experience with the treatment with the PTV/RTV/OBV combination + RBV in elderly patients, it is necessary to collect post-marketing safety and efficacy information in this patient population. In addition, information on oedema-related events, hepatic function disorder, and anaemia-related events should also be collected continuously after market launch.

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

7.R.2.1 Safety profile

The applicants' explanation on the safety of the treatment with the PTV/RTV/OBV combination + RBV in CHC patients with or without compensated cirrhosis (genotype 2):

Table 13 summarizes the safety data obtained from the Japanese phase III study (Study M14-153) in CHC subjects with or without compensated cirrhosis (genotype 2). With respect to incidence of serious adverse events and Grade 3 or worse adverse events, no marked differences were noted between data from Japanese phase III study (Study M14-153) and those from the phase III study (Study M13-004) in genotype 1 chronic hepatitis C subjects with or without compensated cirrhosis submitted for the initial application (Review Report on Viekirax Combination Tablets [August 20, 2015]) in genotype 1 CHC patients with or without compensated cirrhosis. The incidence of adverse events in chronic hepatitis patients with compensated cirrhosis (63.6% [7 of 11 subjects]) was not higher than that in patients without compensated cirrhosis (85.0% [136 of 160 subjects]), and no particular difference in the severity of reported adverse events was found between the 2 patient populations.

Table 13. Summary of the safety results of the Japanese phase III study (Study M14-153) (safety analysis population)

Event	12-week treatment group (N = 85)	16-week treatment group (N = 86)
All adverse events	69 (81.2)	74 (86.0)
Death	0	0
Serious adverse events	0	3 (3.5)
Grade 3 or worse adverse events[a)]	0	3 (3.5)
Adverse events leading to study discontinuation	0	0
Adverse event leading to study interruption	0	1 (1.2)

n (%)

a) No Grade 4 or worse adverse events occurred.

Serious adverse events were observed in 3 subjects (bronchopneumonia, gastritis alcoholic, and incisional hernia in 1 subject each) in the 16-week treatment group; however, a causal relationship was ruled out for all of them, and their outcomes were resolved. One Grade 3 adverse event other than the serious ones (uveitis) was observed in 1 subject in the 16-week treatment group; however, a causal relationship was ruled out, and its outcome was resolved.

The incidence of oedema-related events[19] and hepatotoxic events,[20] identified as requiring attention at the time of the initial approval, was 3.5% (6 of 171 subjects, 4 in the 12-week treatment group and 2 in the 16-week treatment group) and 0.6% (1 of 171 subjects, 1 in the 12-week treatment group), respectively. In liver function test, Grade 3 or worse alanine aminotransferase (ALT) increased was observed in 2.4% (2 of 85 subjects) in the 12-week treatment group and 0% in the 16-week treatment group. The incidence of Grade 2 or worse blood bilirubin increased was 24.7% (21 of 85 subjects) in the 12-week treatment group and 20.9% (18 of 86 subjects) in the 16-week treatment group and the incidence of Grade 3 or worse blood bilirubin increased was 4.7% (4 of 85 subjects) in the 12-week treatment group and 2.3% (2 of 86 subjects) in the 16-week treatment group. The incidence of blood bilirubin increased in the study was higher than that in Japanese clinical studies of the PTV/RTV/OBV combination monotherapy (a phase II study [Study M12-536] and a phase III study [Study M13-004]; Review Report on Viekirax Combination Tablets [August 20, 2015]) submitted in the initial application. Blood bilirubin increased is considered to have resulted from the inhibition of OATP1B1, a transporter involved in the excretion of bilirubin, caused by PTV (Review Report on Viekirax Combination Tablets [August 20, 2015]). Bilirubin may also be increased by hemolytic anaemia related to the use of RBV (*J Hepatol*. 1996;25:591-598; *Hepatology*. 1997;26:473-477; and other literature), which may partially explain the higher incidence of blood bilirubin increased in Japanese phase III study (Study M14-153) than in the data submitted in the initial application. However, taking into account that all events of bilirubin increased observed in the study were transient, asymptomatic and resolved while subjects continued to receive the treatment with the PTV/RTV/OBV combination + RBV, this event is considered controllable by periodic blood tests to monitor liver function test values in accordance with the precautionary statements in the package insert and by taking appropriate measures when any adverse event occurs.

Anaemia-related events are known adverse drug reactions to RBV, and some subjects in the Japanese phase III study (Study M14-153) had their dose of RBV adjusted due to anaemia and haemoglobin decreased. Careful attention should be paid to the occurrence of these events.

On the basis of the above, the safety profile of the PTV/RTV/OBV combination + RBV, excluding anaemia-related events, is considered controllable by monitoring patients carefully and taking appropriate measures as described in the current package insert for the PTV/RTV/OBV combination.

PMDA's view:
Considering the incidence of adverse events reported in the Japanese phase III study (Study M14-153), the safety of the PTV/RTV/OBV combination + RBV is acceptable, provided, as in the initial approval, that physicians with sufficient knowledge and experience of treating viral liver diseases monitor patients carefully to detect adverse drug reactions and take appropriate measures if any event occurs. However, adverse events in which careful monitoring was considered necessary in the initial application, such as

[19] Events identified via of MedDRA ver. 17 search of the following PTs: "face oedema," "fluid retention," "localised oedema," "oedema," "oedema peripheral," or "pulmonary oedema"
[20] Events identified via MedDRA search of "drug related hepatic disorders - severe events only (Standardised MedDRA Queries [SMQs]-broad)"

oedema-related events and hepatic function disorder, should be carefully monitored as in the initial approval. Since a certain incidence of anaemia-related events occurred in the Japanese phase III study (Study M14-153) and some events led to RBV dose adjustment, a detailed review was conducted in the section below.

7.R.2.2 Anaemia-related events

The applicants' explanation on anaemia-related events[21)] observed in the Japanese phase III study (Study M14-153):

In the Japanese phase III study (Study M14-153), anaemia-related events occurred in 27.1% (23 of 85 subjects; anaemia in 16 subjects, haemoglobin decreased in 7 subjects, and red blood cell count decreased in 4 subjects) in the 12-week treatment group and in 30.2% (26 of 86 subjects; anaemia in 21 subjects, haematocrit decreased in 2 subjects, haemoglobin decreased in 4 subjects, and red blood cell count decreased in 3 subjects) in the 16-week treatment group, all of which were Grade 1 or 2 in severity. In 9 of the 37 subjects who developed anaemia (16 in the 12-week treatment group and 21 in the 16-week treatment group) and in 6 of 11 subjects who developed haemoglobin decreased (7 in the 12-week treatment group and 4 in the 16-week treatment group), the RBV dose was adjusted. All of these subjects were able to complete the study treatment with the PTV/RTV/OBV combination + RBV owing to RBV dose reduction or interruption. The outcomes of these events were resolved except for anaemia in 1 subject.

PMDA asked the applicants to explain the impact of RBV dose reduction or interruption on the efficacy of the PTV/RTV/OBV combination + RBV.

The applicants' explanation:

In the Japanese phase III study (Study M14-153), adverse events leading to RBV dose reduction or interruption occurred in 17 subjects (anaemia in 9, haemoglobin decreased in 6, and creatinine renal clearance decreased and glomerular filtration rate decreased in 1 subject each). All of them completed the treatment with the PTV/RTV/OBV combination + RBV and 16 of them achieved SVR12. These results suggested that RBV dose reduction or interruption due to adverse events is unlikely to affect the efficacy of the PTV/RTV/OBV combination + RBV.

PMDA's view:

PMDA confirmed that all anaemia-related events observed in the Japanese phase III study (Study M14-153) were Grade 1 or 2 in severity and that subjects developing anaemia-related events were able to continue the treatment with the PTV/RTV/OBV combination + RBV with dose adjustment of RBV. PMDA also confirmed that RBV dose adjustment had little impact on the efficacy of the PTV/RTV/OBV combination + RBV in the study, although the data were from a small number of subjects.

21) Events were evaluated that were identified via MedDRA search of "haematopoietic cytopenias (SMQs-broad)" or PTs of "haemolytic anaemia," "coombs negative haemolytic anaemia," or "coombs positive haemolytic anaemia."

Anaemia-related events caused by the PTV/RTV/OBV combination + RBV can be controlled if periodic blood tests are performed in clinical settings to monitor hemoglobin levels and other relevant parameters, and if appropriate measures such as RBV dose reduction or interruption are taken upon the occurrence of any anaemia-related event.

Healthcare professionals in medical settings should be informed of anaemia-related events and advised that the treatment with the PTV/RTV/OBV combination + RBV be performed by physicians with sufficient knowledge and experience in treating viral liver diseases, while patients be monitored by periodic blood tests and appropriate measures be taken upon the occurrence of any anaemia-related event in reference also to RBV (Rebetol Capsules 200 mg) [package insert].

7.R.2.3 Safety in elderly patients

The applicants' explanation on the safety of the PTV/RTV/OBV combination + RBV in elderly patients:
Among CHC patients with or without compensated cirrhosis enrolled in the Japanese phase III study (Study M14-153), 53 patients were aged ≥65 years (29 in the 12-week treatment group and 24 in the 16-week treatment group). Table 14 summarizes the safety data from elderly subjects (aged ≥65 years) and non-elderly subjects (aged <65 years). No deaths or adverse events leading to study discontinuation occurred in the study. No marked difference in the incidence of serious adverse events or Grade 3 or worse adverse events was noted between elderly and non-elderly subjects.

Table 14. Summary of safety results in elderly and non-elderly patients (Study M14-153)

	12-week treatment		16-week treatment	
	<65 years (N = 56)	≥65 years (N = 29)	<65 years (N = 62)	≥65 years (N = 24)
All adverse events	46 (82.1)	23 (79.3)	53 (85.5)	21 (87.5)
Grade 3 or worse adverse events[a)]	0	0	2 (3.2)	1 (4.2)
Serious adverse events	0	0	1 (1.6)	2 (8.3)
Adverse events leading to dose interruption	0	0	1 (1.6)	0
Adverse events that occurred with an incidence of ≥5% in either group				
Anaemia	10 (17.9)	6 (20.7)	12 (19.4)	9 (37.5)
Blood bilirubin increased	9 (16.1)	7 (24.2)	10 (16.1)	5 (20.8)
Cough	2 (3.6)	2 (6.9)	3 (4.8)	2 (8.3)
Fatigue	1 (1.8)	5 (17.2)	1 (1.6)	1 (4.2)
Haemoglobin decreased	3 (5.4)	4 (13.8)	4 (6.5)	0
Headache	8 (14.3)	4 (13.8)	5 (8.1)	1 (4.2)
Malaise	1 (1.8)	3 (10.3)	4 (6.5)	3 (12.5)
Nasopharyngitis	9 (16.1)	1 (3.4)	6 (9.7)	7 (29.2)
Nausea	2 (3.6)	3 (10.3)	3 (4.8)	0
Pruritus	3 (5.4)	4 (13.8)	5 (8.1)	5 (20.8)
Rash	4 (7.1)	0	4 (6.5)	0
Reticulocyte count increased	4 (7.1)	2 (6.9)	5 (8.1)	0

n (%)
a) No Grade 4 or worse adverse events were observed.

The adverse events that occurred at a higher incidence (≥5%) in elderly patients than in non-elderly patients were nasopharyngitis, anaemia, haemoglobin decreased, malaise, pruritus, and blood bilirubin increased. Of these, in the incidence in nasopharyngitis, no specific trend was observed between dose groups; and severity of malaise and pruritus were mild. Thus, the differences in the incidence of these events were considered not to be low in clinically significant. Given that advanced age has generally

been reported to be a risk factor for anaemia (*J Viral Hepat*. 2013;20:e90-95), elderly patients should be carefully monitored for the occurrence of anaemia when treated with the PTV/RTV/OBV combination + RBV. However, anaemia-related events in elderly patients can be controlled as in non-elderly patients if periodic blood tests are performed and appropriate measures such as RBV dose reduction or interruption are taken upon the occurrence of any anaemia-related event [see "7.R.2.2 Anaemia-related events"]. Blood bilirubin increased is considered to be caused by inhibition of OATP1B1, a transporter involved in the excretion of bilirubin by PTV (Review Report on Viekirax Combination Tablets [August 20, 2015]). Bilirubin may also be increased by hemolytic anaemia related to RBV (*J Hepatol*. 1996;25:591-598; *Hepatology*. 1997;26:473-477; and other literature); in elderly patients, the high incidence of anaemia-related events may have contributed to the high incidence of blood bilirubin increased. However, most events of blood bilirubin increased observed were transient and asymptomatic. Therefore, this event is considered controllable in elderly patients as in non-elderly patients by performing periodic liver function tests and taking appropriate measures as described in the current package insert for the PTV/RTV/OBV combination.

PMDA's view:

In the Japanese phase III study (Study M14-153), while the incidence of some adverse events observed was higher in elderly patients than in non-elderly patients, no marked differences were found in the incidence of serious adverse events or Grade 3 adverse events between elderly and non-elderly patients. Considering that subjects developing anaemia-related events were able to continue to receive the treatment with the PTV/RTV/OBV combination + RBV by RBV dose reduction or treatment interruption [see "7.R.2.2 Anaemia-related events"] and that all events of blood bilirubin increased observed were transient and asymptomatic, PMDA concluded that adverse events associated with the PTV/RTV/OBV combination + RBV in elderly patients can be controlled as in non-elderly patients by performing periodic blood tests to monitor hemoglobin levels and liver function test values, and taking appropriate measures when any adverse event occurs. However, since clinical experience with the PTV/RTV/OBV combination + RBV is limited in elderly Japanese patients, and elderly patients may generally be at a higher risk of developing adverse events because of their decreased physiological function, safety and efficacy information of the regimen in this patient population should be collected continuously in the post-marketing setting.

7.R.3 Indications

Based on the review in "7.R.1 Efficacy" and "7.R.2 Safety," indications of similar drugs, and the review presented in the section below, PMDA concluded that the appropriate indications for the PTV/RTV/OBV combination + RBV should be as follows:

The PTV/RTV/OBV combination

1. Suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis
2. Suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients

(Underline denotes additions.)

RBV

1. In combination with Interferon Alfa-2b (Genetical Recombination), Peginterferon Alfa-2b (Genetical Recombination), or interferon beta for the suppression of viremia in either of the following patients with chronic hepatitis C:
   (1) patients with high blood HCV-RNA levels, or
   (2) patients who have failed to respond to or relapsed after interferon monotherapy
2. In combination with Peginterferon Alfa-2b (Genetical Recombination) for the suppression of viremia in chronic hepatitis C patients with compensated cirrhosis
3. In combination with sofosbuvir for the suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients with or without compensated cirrhosis
4. In combination with ombitasvir hydrate/paritaprevir hydrate/ritonavir for the suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients

(Underline denotes additions.)

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

7.R.3.1 Indications

The applicants' rationale of the proposed indication of "suppression of viremia in treatment-naïve patients with serogroup 2 (genotype 2) chronic hepatitis C":

The results of the Japanese phase III study (Study M14-153) showed that the 16-week treatment with the PTV/RTV/OBV combination + RBV achieved the SVR12 rate of 91.5% (43 of 47 subjects) in treatment-naïve subjects with CHC (genotype 2), suggesting efficacy of this regimen in this patient population. Among treatment-naïve subjects with chronic hepatitis, the SVR12 rate by subtype was 93.9 % (31 of 33 subjects) in genotype 2a CHC subjects and 85.7% (12 of 14 subjects) in genotype 2b CHC subjects, showing that a certain level of efficacy can be obtained in this patient population irrespective of subtype [see "7.R.1.2 Efficacy].

Meanwhile, the SVR12 rate for the 16-week treatment with the PTV/RTV/OBV combination + RBV in treatment-experienced patients with chronic hepatitis was 75.8% (25 of 33 subjects), showing that the regimen is unlikely to have sufficient efficacy in this patient population. Therefore, the PTV/RTV/OBV combination + RBV cannot be recommended for treatment-experienced patients with chronic hepatitis [see "7.R.1.2 Efficacy"].

Furthermore, given that the SVR12 rate for the 16-week treatment with the PTV/RTV/OBV combination + RBV in CHC patients with compensated cirrhosis was 33.3% (2 of 6 subjects), the regimen was considered unlikely to have sufficient efficacy in this patient population as in treatment-experienced patients with CHC. Therefore, the PTV/RTV/OBV combination + RBV cannot be recommended for CHC patients with compensated cirrhosis [see "7.R.1.2 Efficacy"].

On the basis of the above results, "suppression of viremia in treatment-naïve patients with serogroup 2 (genotype 2) chronic hepatitis C" was proposed as the indication for the PTV/RTV/OBV combination + RBV in this application.

PMDA's view:
Although available information from the study regarding the efficacy by subtype in treatment-naïve patients with chronic hepatitis was limited, a certain level of efficacy of the PTV/RTV/OBV combination + RBV can be expected in genotype 2 treatment-naïve patients irrespective of subtype, on the basis of the Japanese phase III study (Study M14-153).

Considering the SVR12 rate for the PTV/RTV/OBV combination + RBV in the Japanese phase III study (Study M14-153) and SVR12 rates and other relevant parameters in clinical studies of similar drugs in treatment-experienced patients with chronic hepatitis, the applicants' comment is understandable in that the PTV/RTV/OBV combination + RBV cannot be recommended for this patient population. For these patients, treatments other than the PTV/RTV/OBV combination + RBV should be mainly selected [see "7.R.1.2 Efficacy"]. However, given that the PTV/RTV/OBV combination + RBV is to be used by physicians with sufficient knowledge and experience in treating viral liver diseases after selecting patients appropriately, PMDA concluded that there is no need to restrict the indication of this regimen to "treatment-naïve" patients with CHC for the following reasons:

- At the time the Japanese phase III study (Study M14-153) started (January 2014), IFN-containing regimens were the only regimens approved for the indication of genotype 2 CHC patients. Under this circumstance, patients were categorized into treatment-experienced or treatment-naïve patients based only on their previous treatment experience with IFN. Currently, the combination of sofosbuvir and RBV is recommended as a first-line treatment for genotype 2 CHC patients (The Japan Society of Hepatology Drafting Committee for Hepatitis Management, *JSH Guidelines for the Management of Hepatitis C Virus Infection.* 4.1th ed. [in Japanese]. 2015). Taking into account the safety profiles of IFN-containing regimens, treatment concepts for "treatment-naïve" and "treatment-experienced" patients with CHC in clinical practice may change in the future.
- The SVR12 rate for the combination of sofosbuvir and RBV in clinical studies was >90% irrespective of the status of previous treatment with IFN (Sovaldi Tablets 400 mg [package insert]. 2nd ed.; May 2015). Considering the SVR12 rate and other clinical data from the combination of sofosbuvir and RBV, treatments other than the PTV/RTV/OBV combination + RBV are likely to be selected as a first line therapy for patients with chronic hepatitis who have previously been treated with IFN. However, since the SVR12 rate in the Japanese phase III study (Study M14-153) was 75.8% [see "7.R.1.2 Efficacy"], the PTV/RTV/OBV combination + RBV is expected to be effective.

The results of the PTV/RTV/OBV combination + RBV in compensated hepatitis C (genotype 2) subjects in Japanese phase III study (Study M14-153) showed a low SVR12 rate. Therefore, the applicants' conclusion is appropriate in that the PTV/RTV/OBV combination + RBV should not be indicated for compensated hepatitis C (genotype 2) patients.

On the basis of the above, the indication of the PTV/RTV/OBV combination + RBV should be "serogroup 2 (genotype 2) chronic hepatitis C."

If chronic hepatitis patients who have previously been treated with IFN receive the PTV/RTV/OBV combination + RBV in clinical practice after market launch, information on these patients should be collected. Therefore, the efficacy and safety information of the regimen should be collected by prior treatment status (naïve vs experienced) in the post-marketing setting. Furthermore, given the limited available data on the efficacy by subtype, information on the efficacy and safety of the PTV/RTV/OBV combination + RBV in each subtype of patients should be collected continuously in the post-marketing setting, and any new findings should be provided promptly to healthcare professionals in the clinical settings.

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

7.R.4 Dosages and administration

On the basis of the review presented in "7.R.1 Efficacy" and "7.R.2 Safety," review at the initial application (Review Report on Viekirax Combination Tablets [August 20, 2015]), and the following review, PMDA concluded that the statement below should be included in the dosage and administration section for the PTV/RTV/OBV combination + RBV:

The PTV/RTV/OBV combination

1. For suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis
   The usual adult dosage is 2 tablets (25 mg of ombitasvir, 150 mg of paritaprevir, and 100 mg of ritonavir) administered orally once daily after a meal for 12 weeks.
2. For suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients
   The usual adult dosage is 2 tablets (25 mg of ombitasvir, 150 mg of paritaprevir, and 100 mg of ritonavir) administered orally once daily after a meal in combination with ribavirin for 16 weeks.

(Underline denotes additions.)

RBV

1. to 3. (omitted)
4. In combination with ombitasvir hydrate/paritaprevir hydrate/ritonavir for the suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients
   The usual adult oral dosage of ribavirin is provided in the table below.
   Appropriate measures, such as dose reduction and discontinuation, should be taken depending on the patient's condition.

Body weight	Dose of ribavirin		
	Daily dose	After breakfast	After supper

≤60 kg	600 mg	200 mg	400 mg
>60 kg to ≤80 kg	800 mg	400 mg	400 mg
≥80 kg	1000 mg	400 mg	600 mg

(Underline denotes additions.)

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

7.R.4.1 Doses of PTV, RTV, and OBV and duration of treatment

The applicants' rationale of the doses and duration of the treatment with PTV, RTV, and OBV:
In the Japanese phase III study (Study M14-153), the doses of PTV, RTV, and OBV were selected to be 150, 100, and 25 mg, respectively, based on (i) the clinical pharmacological results in genotype 1 CHC patients[22)] submitted in the initial application; and (ii) the results of a Japanese phase II study (Study M12-536) in which treatment-experienced patients with CHC (genotype 2) were treated with PTV/RTV/OBV combination (100/100/25 mg or 150/100/25 mg) QD for 12 weeks—SVR24 rate was 57.9% (11 of 19 subjects) and 72.2% (13 of 18 subjects), respectively (Review Report on Viekirax Combination Tablets [August 20, 2015]).

An exposure-response model was constructed based on the PK and viral load data from two foreign studies in which PTV/RTV, OBV, dasabuvir (an NS5A polymerase inhibitor), or Compound A (an NS5B polymerase inhibitor) was administered for 2 or 3 days, and in which PTV/RTV with RBV was coadministered with dasabuvir or Compound A. An optimal duration of treatment was simulated based on this model. The results suggested that the SVR24 rate would be above 80% in patients with genotype 2 infection when treated with the PTV/RTV/OBV combination 150/100/25 mg QD for 12 weeks. The Japanese phase II study (Study M12-536) was designed based on the above results, which showed that the SVR24 rate in treatment-experienced subjects with CHC (genotype 2) was 72.2% (13 of 18 subjects) when treated with the PTV/RTV/OBV combination 150/100/25 mg QD for 12 weeks, demonstrating the efficacy of the 12-week treatment. However, 11.1% (2 of 18 subjects) relapsed in the above study and 20% (2 of 10 subjects) also in a foreign phase II study (Study M12-998), showing that the duration of 12 weeks may be insufficient for the PTV/RTV/OBV combination without RBV for patients with genotype 2 infection. Meanwhile, the results of an exposure-response model-based simulation on the data from foreign clinical studies suggested that the optimal duration of the PTV/RTV/OBV combination with RBV was 16 weeks in treatment-experienced patients with chronic hepatitis.

In the Japanese phase III study (Study M14-153), on the basis of the results of investigation concerning dosage regimen and duration of treatment, subjects received PTV/RTV/OBV 150/100/25 mg (2 tablets of the PTV/RTV/OBV combination) and RBV for 12 or 16 weeks. The results demonstrated the efficacy

22) 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 were conducted based on the results of a total of 5 foreign phase I and II studies, 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 (Study M12-116) and phase II study (Study M13-386), the dose of OBV needed for a sufficient decrease in HCV RNA level was estimated to be 25 mg.

in treatment-naïve subjects with chronic hepatitis in the 16-week treatment group with an acceptable safety profile [see "7.R.1 Efficacy" and "7.R.2 Safety"]. On the basis of the above, the following dosage and administration statement has been proposed for the PTV/RTV/OBV combination "The usual adult dosage is 2 tablets (25 mg of ombitasvir, 150 mg of paritaprevir, and 100 mg of ritonavir) QD administered orally after a meal in combination with ribavirin for 16 weeks."

PMDA's comment:
Based on the results of Japanese and foreign clinical studies, PMDA considers that it is acceptable to specify the dosage and administration of the PTV/RTV/OBV combination as 2 tablets (PTV/RTV/OBV 150/100/25 mg) QD in combination with RBV for 16 weeks is acceptable. The necessity of combination with RBV (Rebetol Capsules 200 mg) and the dosage and administration of RBV are discussed in the sections below.

7.R.4.2 Significance of combination with RBV
PMDA asked the applicants to explain the significance of the combination of the PTV/RTV/OBV combination and RBV.

The applicants' explanation:
In the Japanese phase III study (Study M14-153), the PTV/RTV/OBV combination was administered in combination with RBV for the following reasons:

- While relapse was observed in CHC (genotype 2) subjects treated with the PTV/RTV/OBV combination without RBV for 12 weeks in a Japanese phase II study (Study M12-536) and a foreign phase II study (Study M12-998) [see "7.R.4.1 Doses of PTV, RTV, and OBV and duration of treatment"], no relapse was observed in any subjects (0 of 10 subjects) treated with the PTV/RTV/OBV combination with RBV for 12 weeks in a foreign phase II study (Study M12-998 conducted in treatment-naïve patients with CHC [genotype 1, 2, or 3] to evaluate the safety and efficacy [SVR12 rate] of the PTV/RTV/OBV combination with or without RBV administered for 12 weeks).
- In a foreign phase II study (Study M12-998) in genotype 2 CHC patients, the SVR24 rate for the PTV/RTV/OBV combination administered for 12 weeks was 80% (8 of 10 subjects) when RBV was coadministered and 60% (6 of 10 subjects) when RBV was not, indicating that coadministration of RBV may contribute to an increase in SVR rates in patients with genotype 2 infection.

The Japanese phase III study (Study M14-153) was conducted in light of the above findings, and its results demonstrated the efficacy of 16-week treatment with 2 tablets of PTV/RTV/OBV (150/100/25 mg) in combination with RBV with an acceptable safety profile [see "7.R.1 Efficacy" and "7.R.2 Safety"]. Therefore coadministering the PTV/RTV/OBV combination with RBV is considered significant.

PMDA's view:

Taking into account the results of Japanese and foreign clinical studies and the efficacy of the PTV/RTV/OBV combination + RBV demonstrated with an acceptable safety profile in the Japanese phase III study (Study M14-153) [see "7.R.1 Efficacy" and "7.R.2 Safety"], coadministeration of the PTV/RTV/OBV combination with RBV may be specified in treatment-naïve patients with CHC (genotype 2).

7.R.4.3 Dosage and administration of RBV (Rebetol Capsules 200 mg)

The applicants' explanation on the dosage and administration of Rebetol Capsules 200 mg:

In the Japanese phase III study (Study M14-153), the dosage and administration of RBV and the criteria for RBV dose reduction or treatment discontinuation due to safety issues in the PTV/RTV/OBV combination + RBV were specified in accordance with the package insert of Rebetol Capsules 200 mg approved in a combination regimen with PegIFN.

In the Japanese phase III study (Study M14-153), adverse events leading to RBV dose adjustment occurred in 9.9% (17 of 171 subjects), and 88.2% (15 subjects) of them were anaemia-related events. However, all subjects completed the PTV/RTV/OBV combination + RBV by complying with the criteria of dose reduction or treatment interruption specified in the package insert for Rebetol Capsules 200 mg, resulting in high SVR12 rates [see "7.R.2.2 Anaemia-related events"]. On the basis of the above, the proposed dosage and administration of Rebetol Capsules 200 mg in the PTV/RTV/OBV combination + RBV in treatment-naïve patients with CHC (genotype 2) was specified in the same way as in the Japanese phase III study. The duration of treatment was determined by referring to the package insert of the coadministered Viekirax Combination Tablets in the same way as in the combination use of Rebetol Capsules 200 mg with other drugs.

Taking into account that the efficacy of the PTV/RTV/OBV combination + RBV was demonstrated with an acceptable safety profile in the Japanese phase III study (Study M14-153) with the same dosage regimen and criteria for dose reduction or treatment interruption specified in the current package insert for RBV [see "7.R.1 Efficacy" and "7.R.2 Safety"], PMDA considers the dosage and administration of RBV can be proposed in this application as those for the PTV/RTV/OBV combination + RBV is acceptable.

7.R.5 Clinical positioning

The applicants' explanation on the clinical positioning of the PTV/RTV/OBV combination + RBV in CHC (genotype 2) patients:

Currently, a Japanese guideline (The Japan Society of Hepatology Drafting Committee for Hepatitis Management, *JSH Guidelines for the Management of Hepatitis C Virus Infection.* 4.1th ed. [in Japanese]. 2015) recommends the 12-week treatment with the combination of sofosbuvir and RBV as a first-line treatment for CHC (genotype 2) patients excluding those with severe renal impairment or renal failure requiring hemodialysis. The guideline also presents as treatment options the combination regimen of PegIFN and RBV for treatment-naïve patients with a high viral load and single-agent regimen of PegIFN or IFN for treatment-naïve patients with a low viral load. In treatment-naïve patients with CHC, the

SVR12 rate was 97.3% for the combination of sofosbuvir and RBV (Sovaldi Tablets 400mg [package insert]. 2nd ed.; May 2015), and the SVR24 rate was 76.2% for the combination regimen of PegIFN and RBV (*J Hepatol*. 2011;54:408-414). The SVR24 rate for monotherapy with PegIFN or IFN was 61.5% and 100%, respectively, in treatment-naïve patients with a low viral load (*Japanese Journal of Medicine and Pharmaceutical Science*. 2003;50:655-672). In the Japanese phase III study (Study M14-153), the SVR12 rate in treatment-naïve patients with CHC (genotype 2) treated with the PTV/RTV/OBV combination + RBV for 16 weeks was 91.5%.

Major adverse events reported in the Japanese phase III study (Study M14-153) of the PTV/RTV/OBV combination + RBV were anaemia, blood bilirubin increased, nasopharyngitis, headache, and pruritus and no adverse events led to study discontinuation, suggesting the safety profile of the regimen is acceptable [see "7.R.2 Safety"].

Consequently, the PTV/RTV/OBV combination + RBV showed high efficacy and good tolerance in treatment-naïve patients with CHC (genotype 2) and is likely to be a first-line treatment for this patient population.

The 12-week treatment with the combination of sofosbuvir and RBV is currently recommended as a first-line treatment also for treatment-experienced patients with genotype 2 CHC with or without compensated cirrhosis, and the SVR12 rates in clinical studies of sofosbuvir and RBV were 95.2% (60 of 63 subjects) and 94.1% (16 of 17 subjects), respectively (*J Viral Hepat*. 2014;21:762-768). In the Japanese phase III study (Study M14-153), the SVR12 rate for the PTV/RTV/OBV combination + RBV in treatment-experienced subjects with CHC with or without compensated cirrhosis was 75.8% and 33.3%, respectively, suggesting that sufficient efficacy of the regimen cannot be expected in these patient populations. Therefore, the PTV/RTV/OBV combination + RBV should not be used in these patients.

PMDA's view:
On the basis of the results of the Japanese phase III study (Study M14-153), efficacy is expected to a certain extent in the 16-week treatment with the PTV/RTV/OBV combination + RBV for treatment-naïve patients with CHC (genotype 2) [see "7.R.1 Efficacy"]. Also, its safety is considered acceptable, although attention should be paid to the occurrence of adverse events such as oedema-related events, hepatic function disorder, and anaemia-related events.

Therefore, the PTV/RTV/OBV combination + RBV may become a new treatment option for treatment-naïve patients with CHC (genotype 2) insofar as physicians with sufficient knowledge and experience in treating viral liver diseases take appropriate measures such as monitoring and management of adverse events and dose reduction, treatment interruption or discontinuation based on a thorough understanding of the safety profile of the PTV/RTV/OBV combination.

As shown in the review in "7.R.3 Indications," the indication of the PTV/RTV/OBV combination + RBV for this application should be "chronic hepatitis C patients," and not limited to "treatment-naïve patients with chronic hepatitis C." However, the applicants commented that selecting treatment methods other than the PTV/RTV/OBV combination + RBV should be recommended for treatment-experienced patients with chronic hepatitis on the basis of the SVR12 rate of this regimen in the Japanese phase III study (Study M14-153) and SVR12 rates in clinical studies of similar drugs. Therefore, healthcare professionals in clinical settings should be informed of the results of clinical studies in treatment-experienced patients with chronic hepatitis and advised to select patients eligible for the PTV/RTV/OBV combination + RBV.

7.R.6 Post-marketing investigations

The applicants plan to conduct the following post-marketing surveillance for the PTV/RTV/OBV combination + RBV:

Specified drug use-results survey

- Objectives: To collect information on the safety and efficacy of the PTV/RTV/OBV combination + RBV in treatment-naïve patients with serogroup 2 (genotype 2) CHC in clinical practice
- Target number of patients: 480 patients
- Rationale: The number of patients needed to estimate, with an accuracy of ±2%, the width of 95% CI of the incidence of adverse events that occurred with an incidence of ≥5.0% in clinical studies was calculated to be 457. Based on this estimation, the target number of patients was determined to be 480 in consideration of dropouts during the survey period.
- Observation period: 40 weeks (16 weeks of treatment and 24 weeks of follow-up)
- Survey period: 28 months (18 months of registration period)

PMDA considers that the following information should be collected in the post-marketing setting:

- Safety and efficacy in elderly patients
- Occurrences of oedema-related events, hepatic function disorder, and anaemia-related events
- Safety and efficacy by subtype
- Safety and efficacy by prior treatment status (naïve vs experienced)

Information on the status of resistance mutations before and after the start of the PTV/RTV/OBV combination + RBV should be collected continuously from sources including published literature, and any new findings should be provided promptly to healthcare professionals in clinical settings. Patients who fail to achieve a sustained virologic response or negative HCV RNA despite treatment with the PTV/RTV/OBV combination + RBV should be followed up wherever possible to collect information on resistance mutations, and any findings should be provided promptly to healthcare professionals in clinical settings.

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

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

The assessments are currently underway. The results and PMDA's conclusion will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Prior Assessment Report (1)

On the basis of the submitted data, the efficacy of the PTV/RTV/OBV combination + RBV in CHC (genotype 2) patients is expected and its safety is acceptable in view of its observed benefits. The PTV/RTV/OBV combination + RBV provides a new treatment option for CHC (genotype 2) patients, which is considered clinically significant.

PMDA considers that the products may be approved if they are considered not to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 22, 2016

Products Submitted for Approval

Brand Names	(a) Viekirax Combination Tablets
	(b) Rebetol Capsules 200 mg
Non-proprietary Names	(a) Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir
	(b) Ribavirin
Applicants	(a) AbbVie GK
	(b) MSD K.K.
Dates of Application	(a) December 17, 2015
	(b) December 25, 2015

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc., concerning the products submitted for marketing approvals, 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).

At the Expert Discussion, the expert advisors supported PMDA's conclusions on issues presented in Review Report (1) ("7.R.2 Safety" and ""7.R.4 Dosages and administration").

PMDA also discussed the following points and took actions as necessary.

1.1 Efficacy and indications

The conclusions of PMDA on efficacy [see "7.R.1 Efficacy" of Review Report (1)] and indications [see "7.R.3 Indications" of Review Report (1)"] were mostly supported by the expert advisors. On the other hand, the expert advisors made the following comments concerning efficacy by subtype:

- It is inevitable for the combination regimen of Viekirax Combination Tablets (the PTV/RTV/OBV combination) and ribavirin (RBV) to be indicated for patients with "serogroup 2 (genotype 2) chronic hepatitis C." However, as shown in the results of SVR12 rates in CHC patients by subtype (93.9% [31 of 33 patients] in treatment-naïve patients with genotype 2a CHC, 85.7% [12 of 14 patients] in treatment-naïve patients with genotype 2b CHC, 93.8% [15 of 16 patients] in treatment-experienced patients with genotype 2a CHC, and 56.3% [9 of 16 patients] in treatment-experienced patients with genotype 2b CHC), SVR12 rates in patients with genotype 2b CHC are lower than in patients with genotype 2a CHC. The information on the efficacy of the regimen by subtype should be provided appropriately to healthcare professionals in clinical settings. Also, they should be informed that the PTV/RTV/OBV combination + RBV is not recommended for treating patients

who are unlikely to have an adequate response to the regimen in order to minimize the risk of the emergence of resistance-related mutations caused by virological treatment failure.

On the basis of the Expert Discussion, PMDA instructed the applicants to provide information on efficacy by subtype in the Clinical Studies section of the package insert, and to include a precautionary statement to the effect that the PTV/RTV/OBV combination + RBV should be carefully selected by thoroughly understanding the clinical study results by subtype and considering the potential benefits and risks in individual patients, to which the applicants agreed.

1.2 Safety

After the market launch of the PTV/RTV/OBV combination, acute renal failure-related events (including one fatal event) were reported in some genotype 1 CHC patients for which a causal relationship to the PTV/RTV/OBV combination could not be ruled out. Consequently, an instruction was given, on July 5, 2016, to revise the information contained in the package insert regarding acute renal failure (Notification No. 0705-1, Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated July 5, 2016).

PMDA confirmed that all renal function-related adverse events observed in a Japanese clinical study in CHC patients with genotype 2 with or without compensated cirrhosis (Study M14-153) were not serious [see "7.1 Japanese phase III study" of Review Report (1)] and that no new concerns on renal function-related events have been identified in patients treated with the PTV/RTV/OBV combination + RBV. Nevertheless, the regimen may have a similar risk irrespective of genotype; therefore, caution should be exercised not only to CHC patients with genotype 1 but also CHC patients with genotype 2. Furthermore, information on the safety of the PTV/RTV/OBV combination + RBV in genotype 2 CHC patients with renal impairment and the occurrence of renal function-related events including acute renal failure need to be collected in the post-marketing setting and any new findings should be provide appropriately to healthcare professionals in clinical settings.

1.3 Risk management plan (draft)

In view of the discussions presented in "7.R.6 Post-marketing investigations" of Review Report (1) and "1.2 Safety" of Review Report (2), and the expert advisors' comment that the safety of the regimen in patients with renal impairment should be evaluated in the post-marketing setting, PMDA has concluded that the applicants should also investigate the following points in the post-marketing surveillance:

- Safety and efficacy in elderly patients
- Safety in patients with renal impairment
- Occurrences of oedema-related events, hepatic function disorder, anaemia-related events, and renal function-related events
- Safety and efficacy by subtype
- Safety and efficacy by prior treatment status (naïve vs experienced)
- Safety and efficacy in HIV/HCV co-infected patients

PMDA considers that information on the status of resistance mutations before and after the start of the treatment with the PTV/RTV/OBV combination + RBV should be collected continuously from sources including the published literature, and any new findings should be provided promptly to healthcare professionals in clinical settings. In addition, patients who fail to achieve a sustained virologic response or negative HCV RNA despite treatment with the PTV/RTV/OBV combination + RBV should be followed up wherever possible to collect information on resistance mutations, and any findings should be provided promptly to the healthcare professionals.

PMDA requested the applicants to investigate the above issues during post-marketing surveillance and the applicants agreed to take such action.

In view of the discussions above, PMDA concluded that the risk management plan (draft) for the PTV/RTV/OBV combination should include the safety and efficacy specifications presented in Table 15, and that its applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 16. With respect to RBV, PMDA concluded that the risk management plan (draft) should include the safety and efficacy specifications shown in Table 17 and that tits applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 18. The applicant each prepared an outline (draft) of specified use-results survey for the PTV/RTV/OBV combination and RBV presented in Table 19.

Table 15. Safety and efficacy specifications in the risk management plan (draft) for Viekirax Combination Tablets

Safety specification		
Important identified risk	Important potential risk	Important missing information
• Fluid retention • Hepatic function disorder, hepatic failure • Reactivation of hepatitis B virus • Acute renal failure	Anaemia	Not applicable
Efficacy specification		
• Efficacy in clinical practice • Drug resistance • Efficacy in patients with CHC and concurrent renal disease who are on hemodialysis		

Table 16. Summary of additional pharmacovigilance and risk minimization activities included under the risk management plan (draft) for Viekirax Combination Tablets

Additional pharmacovigilance activities	Additional risk minimization activities
• Use-results survey (serogroup 1 [genotype 1]) • Post-marketing clinical study (serogroup 1 [genotype 1])[a)] • Specified use-results survey (serogroup 2 [genotype])	Not applicable

a) An open-label study conducted to evaluate the safety and efficacy of Viekirax Combination Tablets in Japanese patients with genotype 1b CHC and concurrent renal disease who are on hemodialysis

Table 17. Safety and efficacy specifications in the risk management plan (draft) for Rebetol Capsules 200 mg

Safety specification		
Important identified risk	Important potential risk	Important missing information
• Blood disorder; anaemia (including hemolytic anaemia), neutropenia, thrombocytopenia • Aplastic anaemia, pancytopenia • Mental disorder; depression, suicidal ideation, unsuccessful suicide, aggression toward others • Hepatic function disorder • Shock • Haemorrhage of digestive tract (e.g., melena, bloody stool), peptic ulcer, ischaemic colitis, small intestine ulcer • Lung disorder; interstitial pneumonia, pulmonary fibrosis, pulmonary oedema • Cerebrovascular disorder • Diabetes mellitus • Renal impairment • Heart disorder • Sepsis • Eye disorders • Autoimmune phenomenon • Haemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) • Skin and subcutaneous tissue disorders; toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme • Rhabdomyolysis • Effect of teratogenicity on fetuses • Hypertension	• Impaired growth in height and weight; decreased growth rate, deficient weight gain	Not applicable
Efficacy specification		
• Efficacy of the combination of sofosbuvir and Rebetol Capsules 200 mg in clinical practice • Efficacy of the combination of ombitasvir hydrate/paritaprevir hydrate/ritonavir and Rebetol Capsules 200 mg in clinical practice		

Table 18. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft) for Rebetol Capsules 200 mg

Additional pharmacovigilance activities	Additional risk minimization activities
• Use-results survey (combination therapy of sofosbuvir and Rebetol Capsules 200 mg) • Specified use-results survey (combination therapy of ombitasvir hydrate/paritaprevir hydrate/ritonavir and Rebetol Capsules 200 mg)	Not applicable

Table 19. Outline (draft) of the specified use-results survey for Viekirax Combination Tablets and Rebetol Capsules 200 mg

Objectives	Evaluation of the safety and efficacy of the regimen in serogroup 2 (genotype 2) CHC patients in clinical practice
Survey method	Central registration system
Population	Serogroup 2 (genotype 2) CHC patients
Survey period (follow-up period)	2 years and 4 months (40 weeks [24 weeks after the final dose])
Planned sample size	480 patients
Main survey items	Fluid retention, hepatic function disorder/hepatic failure, acute renal failure, reactivation of hepatitis B virus, blood disorder (anaemia, neutropenia, thrombocytopenia), aplastic anaemia/pancytopenia, safety in patients with renal impairment, safety and efficacy in elderly patients, safety and efficacy based on prior treatment status (naïve vs experienced), status of resistance-related mutations, safety and efficacy in HIV/HCV co-infected patients, and other relevant matters

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and data integrity assessment 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. The inspection revealed that the sponsor's monitor had changed or modified a part of the case report forms entered by the investigator/subinvestigator in the electronic data handling system. Despite the above finding, which should be improved, no effects on the reliability of the studies or the evaluation of the results of the studies were detected. Therefore, PMDA concluded that there should be no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.3.2-1 for Viekirax Combination Tablets and CTD 5.3.5.1.1 for Rebetol Capsules 200 mg) were subjected to an on-site GCP inspection, 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. The inspection revealed that the clinical studies had generally been conducted in accordance with the GCP principles. PMDA concluded that there should be no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following findings at some of the study sites or in the sponsor, though having little effect on the overall evaluation of the studies. These findings were notified to the heads of the relevant study sites and the applicants (sponsors) as issues to be improved.

Issues to be improved

<u>Study sites</u>

- Deviation from the protocol (did not comply with the specified dosage and administration of the study drug)
- Blood collection for analysis from subjects who did not sign the informed consent form to participate in mRNA analysis

Sponsor

- Insufficient information provided on the package (including the inner package) of the study drug

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the products may be approved after modification of the indication, and dosage and administration statements as shown below, with the following conditions. Although this application has been filed for drugs with a new indication and a new dosage, given that at least 4 years are left to the expiration of the re-examination period specified for Viekirax Combination Tablets, and that Viekirax Combination Tablets are administered in combination with Rebetol Capsules 200 mg, the re-examination period for Viekirax Combination Tablets should last to the expiration of the current re-examination period (until September 27, 2023) and the re-examination period for Rebetol Capsules 200 mg should be specified as until September 27, 2023, as with Viekirax Combination Tablets.

Indications

Viekirax Combination Tablets

1. Suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis
2. Suppression of viremia in ~~treatment-naïve~~ serogroup 2 (genotype 2) chronic hepatitis C patients

(Strikethrough denotes deletions.)

Rebetol Capsules 200 mg

1. In combination with Interferon Alfa-2b (Genetical Recombination), Peginterferon Alfa-2b (Genetical Recombination), or interferon beta for the suppression of viremia in either of the following patients with chronic hepatitis C:
   (1) patients with high blood HCV-RNA levels, or
   (2) patients who fail to respond to or relapse after interferon monotherapy
2. In combination with Peginterferon Alfa-2b (Genetical Recombination) for the suppression of viremia in chronic hepatitis C patients with compensated cirrhosis
3. In combination with sofosbuvir for the suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients with or without compensated cirrhosis
4. In combination with ombitasvir hydrate/paritaprevir hydrate/ritonavir for the suppression of viremia in ~~treatment-naïve~~ serogroup 2 (genotype 2) chronic hepatitis C patients

(Strikethrough denotes deletions.)

Dosages and Administrations

Viekirax Combination Tablets

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

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

2. For suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients

The usual adult dosage is 2 tablets (25 mg of ombitasvir, 150 mg of paritaprevir, and 100 mg of ritonavir) administered orally once daily after a meal in combination with ribavirin for 16 weeks.

(Underline denotes additions.)

Rebetol Capsules 200 mg

The usual adult oral dosage of ribavirin is provided in the table below.

Appropriate measures, such as dose reduction and discontinuation, should be taken depending on the patient's condition.

• ~~1. For suppression of viremia in chronic hepatitis C patients~~ In combination with Interferon Alfa-2b (Genetical Recombination), ~~peginterferon alfa-2b (genetical recombination), or~~ interferon beta, sofosbuvir, or ombitasvir hydrate/paritaprevir hydrate/ritonavir

~~The usual adult oral dosage of ribavirin is provided in the table below.~~

~~The dose may be reduced or discontinued, or other appropriate measures may be taken depending on the patient's condition.~~

Body weight	Dose of ribavirin		
	Daily dose	After breakfast	After supper
≤60 kg	600 mg	200 mg	400 mg
>60 kg to ≤80 kg	800 mg	400 mg	400 mg
>80 kg	1000 mg	400 mg	600 mg

• ~~2. For suppression of viremia in chronic hepatitis C patients with compensated cirrhosis~~ In combination with Peginterferon Alfa-2b (Genetical Recombination)

~~The usual adult oral dosage of ribavirin is provided in the table below.~~

~~The dose may be reduced or discontinued, or other appropriate measures may be taken depending on the patient's condition.~~

(1) Chronic hepatitis C patients or patients with compensated cirrhosis with baseline hemoglobin level ≥14 g/dL

Body weight	Dose of ribavirin		
	Daily dose	After breakfast	After supper
≤60 kg	600 mg	200 mg	400 mg
>60 kg to ≤80 kg	800 mg	400 mg	400 mg
>80 kg	1000 mg	400 mg	600 mg

(2) Chronic hepatitis C patients with compensated cirrhosis with baseline hemoglobin level <14 g/dL

Body weight	Dose of ribavirin		
	Daily dose	After breakfast	After supper
≤60 kg	400 mg	200 mg	200 mg
>60 kg to ≤80 kg	600 mg	200 mg	400 mg
>80 kg	800 mg	400 mg	400 mg

~~3. For suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients with or without compensated cirrhosis in combination with sofosbuvir~~

~~The usual adult oral dosage of ribavirin is provided in the table below.~~

~~The dose may be reduced or discontinued, or other appropriate measures may be taken depending on the patient's condition.~~

~~Body weight~~	~~Dose of ribavirin~~		
	~~Daily dose~~	~~After breakfast~~	~~After supper~~
~~≤60 kg~~	~~600 mg~~	~~200 mg~~	~~400 mg~~
~~>60 kg to ≤80 kg~~	~~800 mg~~	~~400 mg~~	~~400 mg~~
~~>80 kg~~	~~1000 mg~~	~~400 mg~~	~~600 mg~~

~~4. For suppression of viremia in treatment-naïve patients with serogroup 2 (genotype 2) chronic hepatitis C in combination with ombitasvir hydrate/paritaprevir hydrate/ritonavir~~

~~The usual adult oral dosage of ribavirin is provided in the table below.~~

~~The dose may be reduced or discontinued, or other appropriate measures may be taken depending on the patient's condition.~~

~~Body weight~~	~~Dose of ribavirin~~		
	~~Daily dose~~	~~After breakfast~~	~~After supper~~
~~≤60 kg~~	~~600 mg~~	~~200 mg~~	~~400 mg~~
~~>60 kg to ≤80 kg~~	~~800 mg~~	~~400 mg~~	~~400 mg~~
~~>80 kg~~	~~1000 mg~~	~~400 mg~~	~~600 mg~~

(Underline denotes additions, and Strikethrough denotes deletions.)

Conditions of Approval

The applicants are each required to develop and appropriately implement a risk management plan for Viekirax Combination Tablets or Rebetol Capsules 200 mg.