Report on the Deliberation Results

September 13, 2013
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Sovriad Capsules 100mg
[Non-proprietary name]	Simeprevir Sodium (JAN*)
[Applicant]	Janssen Pharmaceutical K.K.
[Date of application]	February 22, 2013

[Results of deliberation]
In the meeting held on September 13, 2013, the Second Committee on New Drugs concluded that the product may be approved, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years, the drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

**Japanese Accepted Name (modified INN)*

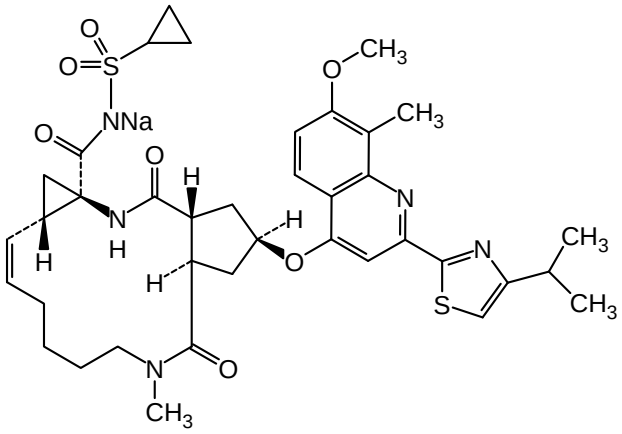
Review Report

September 3, 2013
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Sovriad Capsules 100mg
[Non-proprietary name]	Simeprevir Sodium (JAN)
[Name of applicant]	Janssen Pharmaceutical K.K.
[Date of application]	February 22, 2013
[Dosage form/Strength]	A capsule containing 102.93 mg of simeprevir sodium (100 mg of simeprevir) per capsule
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{38}H_{46}N_5NaO_7S_2$

Molecular weight: 771.92

Chemical name: Monosodium (cyclopropylsulfonyl)[(2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-2-({7-methoxy-8-methyl-2-[4-(1-methylethyl)-1,3-thiazol-2-yl]quinolin-4-yl}oxy)-5-methyl-4,14-dioxo-1,2,3,3a,4,5,6,7,8,9,11a,12,12a,13,14,14a-hexadecahydrocyclopenta[*c*]cyclopropa[*g*][1,6]diazacyclotetradecine-12a-carbonyl]azanide

[Items warranting special mention]	Priority review (Notification No. 0402-1 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated April 2, 2013)
[Reviewing office]	Office of New Drug IV

Review Results

September 3, 2013

[Brand name] Sovriad Capsules 100mg
[Non-proprietary name] Simeprevir Sodium
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] February 22, 2013
[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in improving viraemia in patients with chronic hepatitis C virus (HCV) infection has been demonstrated and its safety is acceptable in view of its observed benefits.

However, it is necessary to continue to investigate the efficacy and safety of the drug product in the following patients via post-marketing surveillance: patients infected with HCV genotype 1a, patients who have been previously treated with triple therapy including a protease inhibitor other than the drug product, and patients with low viral load who have failed to respond to or have relapsed after prior treatment. It is necessary to analyze and evaluate the data obtained from Japanese and foreign clinical studies and provide information on the resistance mutations to the drug product to those involved in clinical practice.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and dosage and administration as shown below.

[Indication]
Improvement of viraemia in any of the following patient with serogroup 1 (genotype I [1a] or II [1b]) chronic hepatitis C virus infection:
1) Treatment-naïve patients with high blood HCV RNA load
2) Patients who have failed to respond to, or have relapsed after, therapy including interferon

[Dosage and administration]
The usual adult dosage is 100 mg of simeprevir given orally once daily. The duration of treatment is 12 weeks. The drug product should be used in combination with either Peg-interferon α-2a (genetical recombination) and ribavirin or Peg-interferon α-2b (genetical recombination) and ribavirin.

Review Report (1)

July 18, 2013

I. Product Submitted for Registration

[Brand name]	Sovriad Capsules 100mg
[Non-proprietary name]	Simeprevir Sodium
[Name of applicant]	Janssen Pharmaceutical K.K.
[Date of application]	February 22, 2013
[Dosage form/Strength]	A capsule containing 102.93 mg of simeprevir sodium (100 mg of simeprevir) per capsule

[Proposed indication]

Improvement of viraemia in any of the following patient with serogroup 1 (genotype I [1a] or II [1b]) chronic hepatitis C virus infection:

1) Patients with high blood HCV RNA load who have not received interferon monotherapy or a combination therapy with interferon and ribavirin

2) Patients who have failed to respond to, or have relapsed after, interferon monotherapy or a combination therapy with interferon and ribavirin

[Proposed dosage and administration]

The usual adult dosage is 100 mg of simeprevir given orally once daily. The duration of treatment is 12 weeks. The drug product should be used in combination with either Peg-interferon α-2a (genetical recombination) and ribavirin or Peg-interferon α-2b (genetical recombination) and ribavirin.

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

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Simeprevir is a selective inhibitor of NS3/4A serine protease which is essential for replication of HCV, and was developed by Medivir and Tibotec Pharmaceuticals Ltd. (currently Janssen R&D Ireland) as a drug for hepatitis C virus (HCV) infection.

It is estimated that approximately 170 million persons have HCV infection worldwide, more than 1.5 million of whom are in Japan.[1)] If untreated after infection, HCV infection progresses to chronic hepatitis in 55% to 85% of patients, followed by gradual progression of liver fibrosis, and HCV infection leads to cirrhosis in 5% to 20% of patients over 20 to 25 years.[2)] Cirrhosis is a serious disease that finally

1) The Japan Society of Hepatology, Drafting Committee for Hepatitis Management Guidelines, Guidelines for the Management of Hepatitis C Virus Infection (First edition), 2012

2) Research group for Special Research Project for Health Labour Sciences "Formulation of guidelines for the treatment of hepatitis C," Guidelines for the Management of Hepatitis C, 2007

results in liver failure and hepatocellular carcinoma, and approximately 80% of the annual deaths due to hepatocellular carcinoma in Japan are considered to have originated from chronic hepatitis C.[1,2,3)]

Interferon (IFN), pegylated interferon (Peg-IFN), ribavirin (RBV), and telaprevir, a HCV NS3/4A serine protease inhibitor, are currently approved in Japan as drugs for the treatment of chronic hepatitis C virus infection aiming at the eradication of the virus. Dual therapy with Peg-IFN and RBV is one of therapies for treatment-refractory chronic HCV genotype 1-infected patients with high viral load, but the treatment period is as long as 48 weeks (72 weeks if the effect is insufficient) and the SVR24[4)] rate is approximately 50%.[5)] The total treatment period for triple therapy with telaprevir, Peg-IFN, and RBV is 24 weeks, and therefore the treatment is possible within a shorter period than with dual therapy using Peg-IFN and RBV. The triple therapy shows an improvement in the therapeutic effect,[6)] while producing new issues such as restriction of prescription due to safety concerns and the response to adverse drug reactions.[7,8,9)] Therefore, there is a high medical need for a novel therapeutic drug.

A marketing application has now been filed based on the findings that: co-administration of the drug product with Peg-IFN and RBV to treatment-naïve patients produced a therapeutic effect higher than dual therapy with Peg-IFN and RBV; a favorable therapeutic effect was also demonstrated in patients who had failed to respond to, or had relapsed after, prior treatment; and there was no significant safety problem.

As of June 2013, the drug product has not been approved for use in any foreign countries. The drug product has been submitted for registration in 4 counties or regions including the US, and is currently under review.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white powder. The solubility, dissociation constant, distribution coefficient, and optical rotation have been determined. The chemical structure of the drug substance has been determined by ultraviolet-visible absorption spectrometry, infrared spectrometry, nuclear magnetic resonance spectrometry (^{1}H- and ^{13}C-NMR), mass spectrmetry, and elementary analysis.

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3) Yoshida H, et al. *Ann Intern Med.* 1999;131(3):174-181

4) Sustained virological response for HCV RNA 24 weeks after completion (or discontinuation) of treatment

5) Kuboki M, et al. *J Gastroenterol Hepatol*. 2007;22(5):645-652

6) Kumada H, et al. *J Hepatol*. 2012;56(1):78-84, Hayashi N, et al. *J Viral Hepat.* 2012;19(2):e134-142

7) "Proper use of Telaprevir (request for cooperation)" (PFSB/ELD Notification No. 0926-1 dated September 26, 2011, PFSB/SD Notification No. 0926-3, issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau and Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW)

8) Telavic tablets 250 mg package insert (fourth edition), Mitsubishi Tanabe Pharma Corporation, revised in September 2012

9) Serious renal impairment including acute renal failure during treatment with Telavic tablets 250 mg, "Important announcement on the proper use of Telavic tablets 250 mg," Mitsubishi Tanabe Pharma Corporation, revised in September 2012

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

[redacted]

[redacted][10)] [redacted][11)] [redacted][12)] [redacted]

[redacted]

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

The drug substance specifications[13)] have been set for strength, description, identification (infrared spectrometry), purity (heavy metals and related substances [liquid chromatography (HPLC)]), water content, residue on ignition, and assay (HPLC).

2.A.(1).4) Stability of simeprevir[14)]

The stability studies for simeprevir are shown in the table below. The results of the photostability studies showed that simeprevir is unstable when exposed to light.

Table. Stability studies for simeprevir

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term testing	4 batches[a)]	25°C	60%RH	Double low density polyethylene bag + fiber drum	18 months
Accelerated testing	4 batches	40°C	75%RH		6 months

a) Produced using a manufacturing process different from the one that will be used in commercial production. However, the results of 3-month long-term testing and 3-month accelerated testing of simeprevir produced using that same manufacturing process that will be used in commercial production confirmed that the stability of simeprevir in commercial production will be comparable to that in these 4 batches.

Based on the above, a retest period of [redacted] months has been proposed for simeprevir when placed in a double low density polyethylene bag and stored protected from light in a fiber drum at room temperature, in accordance with the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term testing for simeprevir will be conducted for up to [redacted] months using 3 batches of simeprevir produced using the same manufacturing process that will be used for commercial production in a commercial production facility.

10) [redacted]

11) [redacted]

12) [redacted]

13) Controlled as simeprevir. [redacted]

14) Long-term testing (25ºC/60%RH) for up to [redacted] months and 6-month accelerated testing (40°C/75%RH) have been conducted for simeprevir sodium, and conformity to the in-process limits has been confirmed.

2.A.(2) Drug product

2.(2).1) Description and composition of the drug product, and formulation development

The drug product is a hard capsule containing 102.93 mg of the drug substance (100 mg as simeprevir) per capsule. The drug product contains lactose hydrate, croscarmellose sodium, magnesium stearate, sodium lauryl sulfate, and colloidal silicon dioxide as excipients.

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

[redacted]

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

The drug product specifications have been set for strength, description, identification (HPLC), purity (degradation products [HPLC]), uniformity of dosage units (HPLC), dissolution (HPLC), and assay (HPLC).

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

The stability studies for the drug product are shown in the table below. The results of the photostability study showed that simeprevir is unstable when exposed to light.

Table. Stability studies for the drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term testing	4 batches[a)]	25°C	60%RH	PTP packaging (polyvinyl chloride + polyethylene + polyvinylidene chloride film + aluminum foil)	12 months
Accelerated testing	4 batches	40°C	75%RH		6 months

Based on the above, a shelf life of 24 months has been proposed for the drug product when packaged in PTP (polyvinyl chloride/polyethylene/polyvinylidene chloride film/aluminum foil) and stored protected from light at room temperature, in accordance with ICH Q1E Guidelines. Long-term testing will be continued for up to [redacted] months.

2.B Outline of the review by PMDA

Based on the submitted data and the following review, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

2.B.(1) Related Substance C

The following specifications/control limits of **Related Substance C,** a synthetic impurity of simeprevir, were proposed for simeprevir and simeprevir sodium (≤[redacted]% and ≤[redacted]%, respectively). The limits exceeded the thresholds for qualification of impurities as specified in the ICH Q3A Guideline[15)] and

15) "Impurities in new drug substances" (PFSB/ELD Notification No. 1216001 dated December 16, 2002)

ICH Q3B Guidelines.[16)]

A toxicity test using a batch containing **Related Substance C** suggested an effect on cardiac muscle,[17)] but no effect was found in a toxicity test using a batch not containing **Related Substance C** [see "3.(iii).A.(2).7) One-month repeat gavage dose toxicity study and one-month reversibility study in dogs"]. PMDA considers that the possible effect of **Related Substance C** on cardiac muscle cannot be ruled out and that the drug product containing a maximum of [redacted]% of **Related Substance C** is not suitable for distribution. Therefore, PMDA asked the applicant to explain what measures would be implemented, including stricter control of **Related Substance C**.

The applicant explained as follows:

[redacted]18)[redacted]

Based on the above, the specification limit of **Related Substance C** in simeprevir will be changed to "≦[redacted]%."

[redacted]19)[redacted]

PMDA considered that there is no specific problem with the applicant's response as stated above.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

16) "Impurities in new drug products" (PFSB/ELD Notification No. 0624001 dated June 24, 2003)
17) Of the toxicity studies conducted using batches containing **Related Substance C**, an effect on cardiac muscle was detected in a 2-week repeat oral gavage dose toxicity study in dogs [see "3.(iii).A.(2).6) Two-week repeat oral gavage dose toxicity study in dogs"].
18) [redacted]
19) [redacted]

Primary pharmacodynamics studies conducted for this application included crystallography, action on enzyme inhibition, antiviral action on HCV, cytotoxic action on human and animal cells, action on viruses other than HCV, action on IFN production system, action in combined use with other anti-HCV drugs or anti-human immunodeficiency virus (HIV) drugs, and drug resistance. Secondary pharmacodynamics studies included interaction with various receptors, *in vitro* and *in vivo* studies on action on the autonomic nervous system, central nervous system, cardiovascular system, allergy/inflammation, and gastrointestinal system. Safety pharmacology studies included action on the cardiovascular system, central nervous system, respiratory system, human platelet aggregation, human red blood cells, and gastrointestinal system.

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

3.(i).A.(1).1) Mechanism of action (4.2.1.1.1)

Crystallography (resolution, 2.4Å) of simeprevir bound to NS3/4A protease[20)] showed that the acylsulfonamide of simeprevir forms a hydrogen bond with NS3/4A protease and the cyclopropyl group occupies the pocket region composed of phenylalanine at position 43 of NS3/4A protease. It was also shown that the macrocyclic moiety of simeprevir occupies the hydrophobic region of NS3/4A protease and that the pyridine-thiazole group of simeprevir occupies the catalytic region of NS3/4A protease together with the cyclopentyl group.

3.(i).A.(1).2) Enzymological studies (4.2.1.1.2)

(a) Inhibitory activity of simeprevir against HCV NS3/4A protease

The inhibitory activity of simeprevir against HCV NS3/4A protease was measured with the fluorescence resonance energy transfer (FRET) using the NS5A-5B site of HCV genotype 1a as a substrate. The median inhibition constant (Ki) of simeprevir was 0.5 nmol/L against genotype 1a (H77 strain) and 1.4 nmol/L against genotype 1b (Con1 strain).

The inhibitory activity of simeprevir against genotypes 1a, 1b, 2b, 3a, 4a, 4d, 5a, and 6a NS3 proteases was investigated. The 50% inhibitory concentrations (IC_{50}) of simeprevir against each genotype were compared with an IC_{50} of 5.2 nmol/L against wild-type strain genotype 1b (Con1 strain) to calculate the fold change (FC).[21)] The FCs in the IC_{50} of simeprevir were <0.04 to 0.4 for genotype 1a (4 strains), 1.1 to 2.5 for genotype 1b (3 strains), 0.6 for genotype 2b (1 strain), 0.4 to 5 for genotype 4a (3 strains), 0.4 to 0.8 for genotype 4d (3 strains), and 0.1 to 0.8 for genotype 6a (3 strains), while the FCs were 8.3 and 148 for genotype 3a (2 strains) and 71 for genotype 5a (1 strain).

(b) Inhibitory activity of simeprevir against HCV NS5B polymerase

The inhibitory activity of simeprevir against HCV genotype 1a, 1b, 2a, and 3a NS5B polymerases was investigated by primer-dependent transcription assay. The IC_{50} of simeprevir against genotypes1a, 1b, 2a, and 3a was 8.0, 7.1, 13.4, and 6.0 μmol/L, respectively. The selectivity index (SI),[22)] which represents

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20) Maxwell DC, et al. *Angew Chem Int Ed*. 2010;49:1652‑1655

21) IC_{50} against each test strain/IC_{50} against wild-type genotype 1b

22) IC_{50} against each NS5B polymerase/IC_{50} against NS3 protease

the ratios of these IC_{50} values to the inhibitory activity of simeprevir (IC_{50}, 5.2nmol/L) against genotype 1b (Con1 strain) NS3 protease, was 1162 to 2577.

(c) Action of simeprevir on human proteases

Inhibitory activity of simeprevir against 20 types of human proteases was investigated by FRET or hydrolytic activity of p-nitroaniline-labeled protein. Simeprevir did not show inhibitory activity against 14 of the 20 types of proteases tested (IC_{50} > 10 μmol/L), but simeprevir inhibited 6 proteases including cathepsin S, leucocyte-elastase, cathepsin G, thrombin, trypsin, and plasmin with IC_{50} values of 0.8, 1.5, 3.8, 5.6, 5.7, and 5.8 μmol/L, respectively. The SI[23)] for the 14 proteases against which simeprevir did not show inhibitory activity was >3846, and the SI for the 6 proteases against which simprevir showed inhibitory activity ranged from 154 to 1115.

In addition, an assessment of the action of simeprevir on cathepsin S and thrombin[24)] showed that simeprevir did not affect them even at the highest concentration assessed (cathepsin S, 10 μmol/L; thrombin, 300 μmol/L).

(d) Action of simeprevir on human kinases (4.2.1.1.3)

The effect of simeprevir on 233 types of human protein kinases and lipid kinases was investigated. Inhibitory activity of ≥50% was seen in 12 of the 233 human kinases at 10 μmol/L simeprevir. In particular, the inhibitory activity was shown to be 70% to 86% against Aurora-B, CK1γ3, Hck, JAK3, and PRAK.

3.(i).A.(1).3) Studies using cells

(a) Antiviral activity of simeprevir on HCV replicon cells (4.2.1.1.4)

Antiviral activity of simeprevir on various HCV replicon cells was investigated. The antiviral activity was measured by luciferase reporter gene assay (HCV replication level) and by RT-PCR (HCV RNA level). The results are shown in the following table.

Table. Antiviral activity and cytotoxic activity of simeprevir: luciferase reporter gene assay

Replicon cells	EC_{50} (nmol/L)		Cells	CC_{50} (nmol/L)		SI
	Number of studies	Median		Number of studies	Median	
Huh7-Luc (genotype 1b)	399	9.4	Huh7-CMV-Luc	12	33700	3585
			MT4-LTR-Luc	73	17700	1883
	EC_{90} (nmol/L)		Cells	CC_{90} (nmol/L)		SI
	Number of studies	Median		Number of studies	Median	
	401	19	Huh7-CMV-Luc	15	87400	4600
			MT4-LTR-Luc	35	31400	1653

EC_{50}, 50% effective concentration; CC_{50}, 50% cytotoxic concentration; EC_{90}, 90% effective concentration; CC_{90}, 90% cytotoxic concentration; SI, CC_{50}/EC_{50} or CC_{90}/EC_{90}

23) IC_{50} against each human protease/IC_{50} against NS3 protease

24) Inhibitory activity against cathepsin S was measured as follows: simeprevir was allowed to react with human JY-B cells for 24 hours, and the amount of invariant chain p10 fragment, which is a substrate of cathepsin S, was determined by Western blot. Inhibitory activity against thrombin was measured as follows: simeprevir was allowed to react with plasma, and the simeprevir concentration required to double the activated partial thromboplastin and prothrombin time were calculated.

Table. Antiviral activity and cytotoxic activity of simeprevir: RT-PCR

Replicon cells	Subtype	EC_{50} (nmol/L)		Control	CC_{50} (nmol/L)		SI
		Number of studies	Median		Number of studies	Median	
Huh7-Luc	1b	21	13	RPL13A	2	25900	1992
Huh-21-5	1b	2	3.7		2	>10000	>2703
Huh7-SGcon1b	1b	17	25		13	>32000	>1270
Huh7-SG1a	1a	19	28		13	>32000	>1127
Huh7-FL1a	1a	9	23		10	>32000	>1391

EC_{50}, 50% effective concentration; CC_{50}, 50% cytotoxic concentration; EC_{90}, 90% effective concentration; CC_{90}, 90% cytotoxic concentration; SI, CC_{50}/EC_{50} or CC_{90}/EC_{90}

(b) Effect of human serum proteins on antiviral activity of simeprevir (4.2.1.1.4)

The effect of human serum proteins (α1-acid glycoprotein [AGP], human serum albumin [HAS], and human serum [HS])[25] on the antiviral activity of simeprevir was measured with reporter gene expression as an index, using HCV genotype 1b replicon cells, Huh7-Luc. The EC_{50} of simeprevir against Huh7-Luc increased 0.9- to 2.4-fold after the addition of human serum proteins.

(c) Cytotoxic activity of simeprevir (4.2.1.1.5)

The cytotoxic activity of simeprevir was investigated using 13 types of human cells[26] and 4 types of animal cells.[27] The CC_{50} against human and animal cells and EC_{50} against HCV genotype 1b replicon cells (9.4 nmol/L)[28] were used to calculate the SI[29] of simeprevir. The CC_{50} of simeprevir against human cells was ≥14.1 μmol/L and the SI was >1500. In animal cells, the CC_{50} of simeprevir was 1.67 μmol/L against canine kidney-derived (MDCK) cells, but was ≥13.9 μmol/L against other animal cells. The SI of simeprevir against animal cells including MDCK cells was ≥177.

In addition, the cell proliferation inhibitory activity and cytotoxic activity of simeprevir against human peripheral blood mononuclear cells (PBMC) were investigated.[30] The 50% cell proliferation inhibitory concentration (CsC_{50}) and CC_{50} of simeprevir against PBMC were 10.3 and 33 μmol/L, respectively, and the SI of simeprevir was >1100.

(d) Action of simeprevir on other viruses (4.2.1.1.6)

The antiviral activity of simeprevir against viruses other than HCV[31] was investigated. In terms of HIV-1, enzymological assessment of the protease inhibitory activity of simeprevir was investigated, in addition to antiviral activity. The EC_{50} of simeprevir was >100 μmol/L for the Flaviviridae, >25 to >100 μmol/L for other single-stranded RNA viruses, and 16.9 and >100 μmol/L for HBV and HSV (DNA viruses), respectively. The EC_{50} of simeprevir against HIV-1 was 8.84 to 15.2 μmol/L. The IC_{50}

25) The amounts of human serum proteins added were as follows: 1 mg/mL AGP, 40 mg/mL HSA, 1mg/mL AGP + 40 mg/mL HSA, and 10 to 50% HS.
26) HeLa, Huh7, HepG2, HUT78, HEK-293T, K562, MT-4, MRC-5, SAOS-2, HT-1080, U-2 OS, and SK-MEL-5 cells
27) CV-1, MDBK, MDCK, and Vero cells
28) EC_{50} for replicon cells Huh7-Luc (luciferase reporter gene assay) is described in "3.(i).A.(1).3).(a) Antiviral activity of simeprevir on HCV replicon cells"
29) CC_{50} for each cell/EC_{50} for HCV genotype 1b replicon cells
30) The cell proliferation inhibitory activity was measured by the uptake of labeled thymidine. The cytotoxic activity was measured by the colorimetric method using tetrazolium salt (WST-1).
31) Investigated in: viruses of the Flaviviridae family, including single-stranded RNA viruses such as HCV (bovine viral diarrhea virus, yellow fever virus, and West Nile virus); other single-stranded RNA viruses (influenza A virus, respiratory syncytial virus, Coxsackie virus, vesicular stomatitis virus, and Sindbis virus; DNA viruses (hepatitis B virus [HBV] and herpes simplex virus [HSV]).

of simeprevir against HIV-1 protease was >200 μmol/L.

(e) Action of simeprevir on IFN production system (4.2.1.1.7)

HCV NS3/4A protease is not only involved in the processing of viral polyproteins but also cleaves mitochondrial antiviral signaling protein (MAVS) and toll-IL1 receptor domain-containing adaptor inducing IFNβ (TRIF) in host cells.[32,33,34,35)] MAVS and TRIF are essential adaptor proteins for retinoic acid-inducible gene I (RIG-I) and toll-like receptor 3 (TLR3), respectively. Interferon regulatory factor 3 (IRF-3) is activated via these adaptors, leading to biosynthesis of IFNα and IFNβ.

The action of simeprevir on the IFN production system via RIG-I dependent signal transduction was investigated.[36)] The results showed that 1000 nmol/L simeprevir induced comparable activation of IFNβ promoters to that in the untreated group, and protein expression of full-length MAVS was seen at 100 and 250 nmol/L of simeprevir. Similar investigation using an anti-HCV drug with a different mechanism of action (Tib-3, a nonnucleoside HCV NS5B RNA polymerase inhibitor) was conducted. As a result, the IFNβ production system did not recover at concentrations up to 10 μmol/L, and protein expression of full-length MAVS was not observed either. Moreover, the effect of simeprevir to inhibit cleavage of TRIF was investigated. As a result, the cellular TRIF level recovered at 1000 nmol/L of simeprevir before the amount of NS3 was affected.

3.(i).A.(1).4) *In vitro* resistance development studies (4.2.1.1.8)

The development of resistance against simeprevir was investigated using HCV genotype 1a and 1b replicon cells.[37)] Amino acid mutations were found at position 43, 80, 155, 156, or 168 in the NS3 protease region in 105 of 109 sequences analyzed (96.3%), and multiple mutations in 14 sequences. Of these, the D168 mutations were found most frequently (78.0% [85 of 109 sequences]): amino acid mutations of D168V[38)] and D168A occurred at rates of 40.4% (44 of 109 sequences) and 29.4% (32 of 109 sequences), respectively. Amino acid mutations at positions 43, 80, 155, and 156 in the NS3 protease region were found in 4, 14, 7, and 10 sequences, respectively. The A156V mutation was found only in genotype 1b, and Q80K and R155K mutations were found only in genotype 1a.

In genotype 1a, there was no amino acid mutation found at positions 43, 80, 155, 156, and 168 in 4 of 109 sequences selected for simeprevir. Mutations of Q89R+N174K, Q41R+E176K, Q41Q/R, and Q41Q/R+N174N/K were found.

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32) Foy E, et al. *Science*. 2003;300:1145-1148
33) Li K, et al. *Proc Natl Acad Sci U S A*. 2005;102:2992-2997
34) Li XD, et al. *Proc Natl Acad Sci U S A*. 2005;102:17717-17722
35) Meylan E, et al. *Nature*. 2005;437:1167-1172
36) IFN promoter-driven luciferase reporter plasmid was introduced into HCV genotype 1b replicon cells exposed to simeprevir and the effect on Sendai virus-induced IFNβ production was measured.
37) Resistance development studies were conducted 14 times (genotype 1a, 6 times; genotype 1b, 8 times) using HCV genotype 1b replicon cells (Huh7-Luc and Huh7-con1b) and HCV genotype 1a replicon cells (Huh7-SG1a). NS3 protease and helicase regions and the NS4A region, from the 109 RNA sequences obtained (genotype 1a, 46 sequences; genotype 1b, 63 sequences), were analyzed to determine the amino acid sequence. As a control, the amino acid sequence was determined from replicon cells (genotype 1a, 21 sequences; genotype 1b, 91 sequences) not exposed to simeprevir (in the presence of an NS5B inhibitor).
38) Amino acids before and after mutating are shown on the left and right, respectively, with the position number in-between. Amino acids were expressed in single letter codes.

Amino acid mutations at position 41 (Q41R and Q41P) were mainly observed in genotype 1a with an incidence of 18.3% (20 of 109 sequences). The amino acid mutation at position 176, which has been reported to be an adaptive mutation that increases replication of the HCV replicon,[39,40] was observed in genotype 1a with an incidence of 28.3% (13 of 46 sequence).

In clinical studies on noncyclic NS3/4A protease inhibitors, boceprevir (not approved in Japan) and telaprevir, it has been reported that there were amino acid mutations at positions 36, 54, 55, 107, 132, 155, 156, 158, 168, 170, and 175 in the NS3 protease region in patients with treatment failure.[41,42] An *in vitro* resistance development study on simeprevir revealed amino acid mutations at positions 36, 55, and 132 in addition to positions at R155, A156, and D168. However, these mutations were expressed only in a single sequence and were accompanied by simultaneous mutations at position 156 or 168.

The development of most mutations in the NS3 helicase region and NS4A region was comparable or less than that in the control group.

Huh7.5 cells transfected with HCV genotype 2a JFH-1 strain and Jc-1-Luc strain were subcultivated in the presence of simeprevir to investigate the development of resistance. As a result, amino acid mutations were found at positions 43, 156, and 168 in the NS3 protease region.

3.(i).A.(1).5) Drug resistance profile and cross-resistance

(a) Influence of site-directed mutations (SDMs) on antiviral activity of simeprevir (4.2.1.1.9)

The antiviral activity of simeprevir was investigated in: wild-type HCV genotype 1a (H77 strain), 1b (Con1 strain), and 2a (JFH-1 strain) replicon cells; replicon cells transfected with SDMs of genotype 1a and 1b. The EC_{50} of simeprevir was 2.7 and 5.2 nmol/L for the wild-type genotypes 1a and 1b, respectively, and was 275 nmol/L for wild-type genotype 2a.

The antiviral activity of simeprevir against replicon cells transfected with SDMs of genotype 1b was calculated as the FC.[43] The results are shown in the following table.[44]

39) Lohmann V, et al. *J Virol*. 2003;77:3007-3019
40) Krieger N, et al. *J Virol*. 2001;75:4614-4624
41) Highlights of Prescribing Information for VICTRELIS® (boceprevir) Capsules for oral use. Merck Sharp & Dohme Corp. Revised: 12/2012.
42) Highlights of Prescribing Information for INCIVEK™ (telaprevir) Film Coated Tablets, for oral use. Vertex Pharmaceuticals Incorporated. Revised: 12/2012.
43) EC_{50} for each SDM/EC_{50} for wild-type genotype 1b
44) Based on the sensitivity of clinically isolated strains to simeprevir and the efficacy data of combination therapy with this drug product/Peg-IFN/RBV, strains with an FC ≤2 were defined as sensitive, strains with an FC >2 and <50 were defined as mildly resistant, and strains with an FC ≥50 were defined as highly resistant [see "3.(i).A.(1).5).(b) Antiviral activity of simeprevir against clinical isolates"]

Table. Antiviral activity of simeprevir against replicon cells transfected with SDMs in the NS3 protease region of HCV genotype 1b: Single mutations

Amino acid mutation	FC
V36A, V36G, V36I, V36L, V36M	2.8, 3.6, 0.8, 1.3, 1.5
Q41R	1.8
F43C, F43I, F43L, F43S, F43V	3.6, 89, 11, 12, 99
T54A, T54C, T54G, T54S	0.6, 1.0, 0.9, 1.2
V55A, V55C, V55I	0.8, 0.9, 1.3
Q80G, Q80H, Q80K, Q80L, Q80N, Q80R	1.7, 3.6, 7.7, 1.1, 0.9, 6.9
V107I	1.0
S122A, S122C, S122G, S122K, S122N, S122R, S122T	1.1, 1.1, 0.4, 29, 1.1, 20, 0.5
S138T	4.3
R155G, R155H, R155I, R155K, R155M, R155Q, R155S, R155T, R155W	20, 1.9, 0.7, 33, 0.4, 1.6, 21, 24, 67
A156F, A156G, A156N, A156S, A156T, A156V	32, 16, 18, 0.3, 44, 181
V158I	1.0
G162R	2.6
D168A, D168C, D168E, D168G, D168H, D168I, D168N, D168Q, D168T, D168V, D168Y	948, 7.6, 43, 4.3, 368, 1800, 6.6, 385, 308, 2830, 651
F169I, F169L, F169Y	1.1, 1.0, 0.8
V170A, V170F, V170I, V170T	4.7, 1.2, 0.6, 4.7
S174A, S174G, S174K	1.0, 0.8, 7.8
M175L	1.1

FCs (median) of simeprevir against SDM replicon cells for each amino acid mutation are shown in the corresponding order.

Table. Antiviral activity of simeprevir against replicon cells transfected with SDMs in the NS3 protease region of HCV genotype 1b: Multiple mutations

Amino acid mutation	FC
Q80K+R155K, Q80R+R155K	364, 270
Q80K+D168E, Q80R+D168E	373, 361
Q80K+R155K+D168E, Q80R+R155K+D168E	1830, 1410
S122G+R155K, S122R+R155K	11, 194
R155K+D168A, R155K+D168E, R155K+D168N, R155K+D168V	552, 162, 11, 400
D168E+F169I, D168E+F169L	194, 138

FCs (median) of simeprevir against replicon cells for each amino acid mutation are shown in the corresponding order.

For amino acid mutations at positions 36, 54, 55, 107, 158, 162, 170, and 175, which are involved in the development of resistance to noncyclic NS3/4A protease inhibitors, boceprevir and telaprevir, the FC for simeprevir was ≤2 in 15 of 20 strains. In 5 of 20 strains (V36A/G, G162R, and 170A/T), mild resistance was observed with FCs of 2.6 to 4.7.

In the replicon cells transfected with mutations resistant to HCV NS5A and NS5B inhibitors, the antiviral activity of simeprevir was not affected (FC < 2) except for the mutation of C316Y (FC = 2.1).

The antiviral activity of NS5A and NS5B inhibitors was investigated in replicon cells that had been transfected with simeprevir-resistant mutations. The FCs of the non-nucleoside NS5B inhibitor TMC647055 relative to A156T and A156V mutations were 2.4 and 2.8, respectively, but the FCs for NS5A and NS5B inhibitors were <2.0 in other mutations.

(b) Antiviral activity of simeprevir against clinical isolates (4.2.1.1.10)

The antiviral activity of simeprevir against HCV genotype 1 clinical isolates obtained in foreign clinical studies (Studies C101, C201, C205, and C206) was investigated using replicon cells transfected with

the NS3 protease region from clinical isolates.[45)] The FC (median [range]) of simeprevir for genotype 1a replicon cells (78 strains) and genotype 1b replicon cells (59 strains) isolated at baseline was 1.4 [0.4, 100] and 0.4 [0.1, 26], respectively. The FC (median [range]) of simeprevir for genotype 1a with a genetic polymorphism of Q80K at baseline (33 strains) was 11 [3.6, 27]. The FC (median [range]) of simeprevir for genotype 1a with a genetic polymorphism of R155K (4 strains) was 95 [26, 100]. The FC of simeprevir for genotype 1a with a genetic polymorphism of S122G+R155K (1 strain) was 26. Genetic polymorphism of Q80K was found at baseline in 2 genotype 1b strains. One of them had a polymorphism at 1 site (Q80K, FC = 15) and the other had a polymorphism at multiple sites (S122G+Q80K, FC = 1.8). In addition, a genetic polymorphism of D168E was observed in 1 genotype 1b strain (FC 20).

The susceptibility of clinical isolates (at baseline and after starting treatments) to simeprevir was classified by mutations at positions 43, 80, 122, 155, 156, and 168 in the NS3 protease region. Strains with an FC ≥2 were defined as susceptible, strains with an FC >2 and <50 were defined as mildly resistant, and strains with an FC ≥50 were defined as highly resistant.[46)] Strains without mutations at positions 43, 80, 122, 155, 156, and 168 and most strains with a mutation of Q80L or S122G/N/T were susceptible to simeprevir. Strains with mutations of Q80K/R, D168E, S122G+R155K, or S122R were mildly resistant to simeprevir. A single mutation of R155K, multiple mutations of R155K at position 80, 122 and 168, and single mutations of A156V and D168A/Q/T/V were highly resistant to simeprevir. Amino acid mutations at position 43 found in an *in vitro* resistnace development study were not found in the clinical isolates.

3.(i).A.(1).6) Action of combined use of simeprevir with other anti-HCV drugs (4.2.1.1.11)

Simeprevir was applied in combination with other anti-HCV drugs (NS5B inhibitors, NS5A inhibitors, Peg-IFNα, and RBV) to HCV genotype 1a and 1b replicon cells to study antiviral activity. Additive and synergistic actions were observed while no antagonistic action was seen. The replicon cells resistant to simeprevir were generated and treated with simprevir. Simeprevir alone inhibited colony formation of simeprevir-resistant replicon cells in a concentration-dependent manner. The inhibition of colony formation was enhanced by combined use with other anti-HCV drugs.

3.(i).A.(1).7) Interaction between simeprevir and anti-HIV drugs (4.2.1.1.12 to 4.2.1.1.13)

The anti-HIV activity of simeprevir when used in combination with HIV protease inhibitors (amprenavir [APV], atazanavir [ATV], lopinavir [LPV], and darunavir [DRV]) was investigated based on the cytopathic effect. The anti-HIV activity of simeprevir combined with HIV protease inhibitors was not antagonistic but additive.

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45) Using the FC of simeprevir for strains with amino acid mutations at position 43, 80, 122, 155, 156, or 168 of genotype 1a and 1b, the correlation between clinical isolates and SDMs was examined. The FCs of simeprevir against clinical isolates and SDMsshowed a correlation ($r^2 = 0.8432$, $P < 0.0001$).

46) Based on the FC of simeprevir for strains without amino acid mutations at positions 43, 80, 122, 155, 156, and 168 in the NS3 protease region, the biological cut-off value (BCO) for simeprevir was set at FC = 2, and strains with an FC ≤2 were defined as susceptible to simeprevir. Based on the FC of simeprevir for R155K mutant strains, which was frequently found in treatment failure cases who had received a combination therapy with simeprevir/Peg-IFN/RBV in a foreign clinical study, the threshold between mildly and highly resistant strains against simeprevir was set at FC = 50.

The anti-HCV activity of simeprevir when used in combination with HIV protease inhibitors (APV, ATV, LPV, and DRV) was investigated using HCV genotype 1b replicon cells, Huh7-Luc. The EC_{50} was 1.9 to 2.4 nmol/L for simeprevir alone, and was 0.6 to 2.8 nmol/L even when APV, ATV, LPV, or DRV was combined up to a concentration of 20 µmol/L.

3.(i).A.(2) Secondary pharmacodynamics (4.2.1.2.1 to 4.2.1.2.2)

In vitro and *in vivo* studies were conducted to investigate the following: *in vitro* interaction between simeprevir and 50 types of receptors/channels; actions of simeprevir on the autonomic nervous system, central nervous system, cardiovascular system, allergy/inflammation, and gastrointestinal system. The results are shown in the following table.

Table. Summary of secondary pharmacodynamics studies

Animal species/line	Mode of administration	Sex and number of animals/ groups	Dose (concentration) (vehicle)	Noteworthy findings
Receptors, channels, and transporters	*in vitro*	-	30 µmol/L (22µg/mL) (0.3%DMSO)	Interaction present: Adenosine (A_1 [68%], A_3 [89%]), angiotensin type 1 (96%), cholecystokinin A (60%), endothelin A (58%), melatonin 1 (60%), muscarine 1 (56%), neurokinin 2 (51%), opioid (δ_2 [100%], κ [78%], µ [75%]), serotonin (5-HT_{1A} [55%], 5-HT_{2A} [60%], 5-HT_{5A} [87%]) receptors, and chloride channel (69%)
Cells and tissues	*in vitro*	-	3, 10, and 30 µmol/L	No effect on central nervous system, allergy/inflammation, and gastrointestinal system. Cardiovascular system: 100% inhibition of arachidonic acid induced rabbit platelet aggregation at 30 µmol/L (IC_{50}, 12.2 µmol/L) (9.1 µg/mL)
Mice/ICR	Intraperitoneal or oral	5 males/5 females or 5 males	Intraperitoneal: 100 mg/kg (2% Tween80/0.9% NaCl) Oral: 30, 100, and 300 mg/kg (2% Tween80)	
Rats/Wister	Intraperitoneal or oral	5 males/5 females	Intraperitoneal: 10 mg/kg (2% Tween80/0.9% NaCl) Oral: 100 mg/kg (2% Tween80)	

3.(i).A.(3) Safety pharmacology (reference 4.2.1.3.1 to 4.2.1.3.7, 4.2.1.3.8 to 4.2.1.3.9, reference 4.2.1.3.10)

The actions on the central nervous system, cardiovascular system, respiratory system, human platelet aggregation, human red blood cells, and gastrointestinal system were investigated in safety pharmacology studies. The results are shown in the following table.

Table. Summary of safety pharmacology studies

Tissues evaluated	Animal species/strains	Mode of administration	Sex and number of animals/groups	Dose (concentration) (vehicle)	Test results
Cardiovascular system (potassium current [I_{Kr}])	HEK293 expressing hERG	*in vitro*	-	0.1, 0.3, and 3 µmol/L (0.075, 0.22, and 2.2 µg/mL) (0.1% DMSO)	0.1 and 0.3 µmol/L: no effect 3 µmol/L: leakage of cell contents (the recovery rate of simeprevir was 13% of the tested concentration range)
Cardiovascular system (sodium current [I_{Na}])	CHO expressing human myocardial sodium channel gene	*in vitro*	-	0.1, 0.3, 1, 3, and 10 µmol/L (0.075, 0.22, 0.75, 2.2, and 7.5 µg/mL) (0.1% or 0.3% DMSO)	Inhibition of I_{Na} HP: -140 mV 0.1 µmol/L, no effect; 0.3 µmol/L, 10.4% inhibition (vehicle, 3.6%); 1 µmol/L, 27.6% inhibition (vehicle, 7.6%); 3 µmol/L, 50.2% inhibition (vehicle, 9.2%); 10 µmol/L, 60.0% inhibition (vehicle, 8.0%) HP: -40 mV 0.1 µmol/L, no effect; 0.3

Tissues evaluated	Animal species/strains	Mode of administration	Sex and number of animals/groups	Dose (concentration) (vehicle)	Test results
					µmol/L, 21.4% inhibition (vehicle, 5.4%); 1 µmol/L, 33.2% inhibition (vehicle, 8.8%); 3 µmol/L, 54.0% inhibition (vehicle, 11.4%); 10 µmol/L, 60.2% inhibition (vehicle, 8.2%)
Cardiovascular system (myocardial action potential)	Isolated guinea pig right atrium	*in vitro*	-	1, 3, and 10 µmol/L (0.75, 2.2, and 7.5 µg/mL) (0.1% DMSO)	1 and 3 µmol/L: no effect on contraction rate and contractile force of cardiac muscle 10 µmol/L: slight decrease in contraction rate, contractile force, and effective refractory period (recovery rate of simeprevir was 3% of set concentration)
Cardiovascular system (myocardial action potential)	Isolated rabbit Langendorff heart	*in vitro*	-	30-minute perfusion 0.1, 0.3, 1, 3, and 10 µmol/L (0.075, 0.22, 0.75, 2.2, and 7.5 µg/mL) (0.1% DMSO)	0.1-10 µmol/L: no effect on APD instability, reverse use-dependence of APD, and APD triangulation; no proarrhythmic effect; no EAD, VT, VF, and TdP. 1 µmol/L: increase in coronary blood flow (+16% vs. vehicle 0%) 3 µmol/L: increase in coronary blood flow (+35% vs. vehicle -4%) 10 µmol/L: APD_{60} shortening (-19% vs. vehicle +1%); IVC prolongation (+9% vs. vehicle 0%); increase in coronary blood flow (+50% vs. vehicle +2%)
				60 and 90-minute perfusion 3 and 10 µmol/L each (0.1% DMSO)	3 µmol/L: APD_{60} shortening (-19% vs. vehicle) -2%, 45 min); increase in coronary blood flow (+23% vs. vehicle -7%, 15 minutes) 10 µmol/L: APD_{60} shortening (-65% vs. vehicle -7%, 45 min); decrease in coronary blood flow (-81% vs. vehicle 0%, 45 min); IVC prolongation (+184% vs. vehicle 0%, 45 min.); VF (4/6); EAD (1/6); TdP (1/6) Concentration (median) in the cardiac tissue at the completion of the study was 597 µg/g.
Platelet aggregation	Human platelets	*in vitro*	-	30 µmol/L (22 µg/mL) (0.2% DMSO)	No direct effect No effect on arachidonic acid/ collagen/adenosine diphosphate induced human platelet aggregation
Hemolysis	Human red blood cells	*in vitro*	-	1, 3, 10, 30, 100, and 300 µmol/L (0.75, 2.2, 7.5, 22, 75, and 225 µg/mL) (0.2%-1% DMSO)	1, 3, 10, 30, and 100 µmol/L: no effect 300 µmol/L: mild hemolysis (mild hemolysis was observed also in the vehicle group)
Cardiovascular and respiratory system	Anesthetized dog/beagle	5-minute continuous cumulative intravenous infusion at 30-minute intervals	3 males/1 female	0.16, 0.32, 0.63, 1.25, 2.5, and 5 mg/kg, I.V. (20% HP-β-CD)	No effect on respiratory system at all doses 0.16, 0.32, and 0.63 mg/kg: no effect on cardiovascular system, median C_{max} = 1.23, 3.21, and 5.18 µg/mL, respectively. 1.25 mg/kg: prolonged RR interval (+21% vs. vehicle -8%), median C_{max} = 12.15

Tissues evaluated	Animal species/strains	Mode of administration	Sex and number of animals/groups	Dose (concentration) (vehicle)	Test results
					μg/mL 2.5 mg/kg: HR reduction (-19% vs. vehicle +3%); CCVR increase (+22% vs. vehicle -9%), median C_{max} = 26.05 μg/mL 5 mg/kg: SVR increase (+29% vs. vehicle -2%); PVR increase (+28% vs. vehicle +8%); CO reduction (-18% vs. vehicle +4%); QTcB shortening (-10% vs. vehicle -1%); QTcF shortening (-8% vs. vehicle -1%); QTcVDW shortening (-9% vs. vehicle -1%), median C_{max} = 67.2 μg/mL No ventricular arrhythmia, supraventricular arrhythmia, EAD, and DAD at all doses
Cardiovascular and respiratory system	Unanesthetized dog/beagle	Oral	4 males	[redacted]	No effect Maximum plasma concentration (mean) was 6.2, 51.3, and 90.8 μg/mL at 10, 40, and 160 mg/kg, respectively.
Central nervous system	Rat/SD	Oral	5 males	[redacted]	50 mg/kg: reduction in alertness, mean C_{max} = 2.3 μg/mL (2 hours post-dose) 150 mg/kg: reduction in alertness; mild blepharophimosis, mean C_{max} = 2.8 μg/mL (4 hours post-dose) 500 mg/kg: reduction in alertness; mild blepharophimosis; champing (myoclonic movement of jaw) (1/5), mean C_{max} = 3.5 μg/mL (2 hours post-dose)
Gastrointestinal system	Rat/Wistar	Oral	5 males	[redacted]	Chocolate pellets were administered orally 1 hour after oral administration of simeprevir. After 1 hour, weight of stomach content was measured (median). Control (water): 0.80 g Vehicle (PEG): 1.79 g 160 mg/kg: 4.79 g 320 mg/kg: 4.23 g 640 mg/kg: 4.57 g

HP = holding potential, APD_{60} = 60% action potential duration, CCVR = common carotid vascular resistance, CHO = Chinese hamster ovary derived cells, CO = cardiac output, DAD = delayed after depolarization, C_{max} = maximum plasma concentration, DMSO = dimethylsulfoxide, EAD = early after depolarization, HEK293 = human embryonic kidney cells, hERG = human ether-a-go-go related gene, HP-β-CD = hydroxypropyl-β-cyclodextrin, HR = heart rate, I_{Kr} = rapidly activating delayed rectifier potassium current, I_{Na} = voltage dependent sodium current, IVC = intraventricular conduction time, PEG = polyethylene glycol, QTcB = QT interval corrected by heart rate based on Bazett's formula, QTcF = QT interval corrected by Fridericia's formula, QTcVDW = QT interval corrected by Van de Water's formula, PVR = pulmonary vascular resistance, SVR = systemic vascular resistance, TdP = torsade de pointes, VF = ventricular fibrillation, VT = ventricular tachycardia

The safety margin[47)] of simeprevir for I_{Kr}, I_{Na}, and isolated rabbit Langendorff heart preparation was 52-fold, 18-fold, and 52-fold, respectively. Following intravenous (C_{max}, 67.2 μg/mL) and oral administration (C_{max}, 90.8 μg/mL) of simeprevir to anesthetized and unanesthetized dogs, the safety margin was at least 16-fold. In addition, cumulative intravenous administration up to 5 mg/kg in

47) Safety margin was calculated based on either the mean maximum plasma concentration (C_{max}, 4.26 μg/mL) obtained in the study (Study HPC3008) in which 100 mg of simeprevir were orally administered once daily for 12 weeks to Japanese chronic hepatitis C patients or the plasma concentration of unbound simeprevir (4.26 ng/mL) calculated from C_{max} and the percentage of unbound simprevir in human plasma [≤0.1%, see "3.(ii).B.(2) Distribution"].

anesthetized dogs (C_{max}, 67.2 μg/mL) and oral administration up to 160 mg/kg in unanesthetized dogs (C_{max}, 90.8 μg/mL) did not affect the respiratory system, and the safety margin was at least 16-fold. No effect on human platelets was observed, but arachidonic acid-induced rabbit platelet aggregation using rabbit platelets was inhibited 100% in a secondary pharmacodynamics study, which the applicant attributed to differences in the experimental methods[48] and species differences in platelet aggregation.[49]

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

3.(i).B.(1) Antiviral activity of simeprevir against HCV

PMDA's view on the antiviral activity of simeprevir against HCV is as follows:

Taking into account the following results from investigations presented in support of this application, the findings suggest that simeprevir selectively inhibits HCV NS3/4A protease, and therefore an antiviral activity against HCV can be expected. Nevertheless, the efficacy of simeprevir in patients with chronic hepatitis C virus infection will be discussed in "4.(iii).B.(1) Efficacy."

- Crystallography showed that simeprevir binds to HCV NS3/4A protease.
- The investigation of the inhibitory activity against HCV NS3/4A protease showed that simeprevir inhibits HCV NS3/4A protease activity.
- The investigation of antiviral activity using HCV replicon cells demonstrated inhibition of HCV replicon replication.
- No particular inhibitory action was detected for other viruses, various enzymes, receptors, or channels.

3.(i).B.(2) Resistance to simeprevir

PMDA asked the applicant to explain the presence or absence of changes in the activity of other NS3/4A protease inhibitors against HCV that express resistance mutations to simeprevir, taking account of the investigation of the drug resistance profile of simeprevir [see "3.(i).A.(1).4) *In vitro* resistance development studies"].

The applicant explained as follows:

In replicon cells with introduced amino acid mutations at position D168, which has the most significant impact on resistance to simeprevir, the activity (FC^{21}) of linear ketoamides, boceprevir and telaprevir, was 0.3 to 2.4 and 0.4 to 1.2, respectively, indicating that there is no impact on the antiviral activity of these drugs. On the other hand, the activity (FC^{21}) of BI-201335, MK-7009, and ITMN-191, which have a cyclic structure or large molecule side chain (P2 group), as with simeprevir, was 56 to 2430, 46 to 1410, and 8.1 to 391, respectively, indicating a reduction in antiviral activity. In addition, for replicon cells with amino acid mutations at positions R155 and A156, all other protease inhibitors tested demonstrated reduced activity, as with simeprevir (FC: R155 [boceprevir, 0.8-50; telaprevir, 2.5-81; BI-201335, 961; MK-7009, > 362-516; ITMN-191, 20-324]; A156 [boceprevir, 2.1-64; telaprevir, 0.6-286; BI-201335, 542-1750; MK-7009, 58-531; ITMN-191, 41-76]).

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48) Differences in the platelet aggregation reaction due to differences in the concentration of arachidonic acid added (humans, 500 μmol/L; rabbits, 100 μmol/L).

49) Packham MA, et al. *Comp Biochem Physiol Comp Physiol*. 1992;103(1):35-54

PMDA asked the applicant to explain the variations in the resistance profile of simeprevir observed in Japanese and foreign clinical studies.

The applicant explained as follows:
When the amino acid sequences at 18 evaluation sites[50)] were analyzed in patients (genotype 1a/other, 528 patients; genotype 1b, 608 patients) who received simeprevir (150 mg) in combination with Peg-IFN and RBV in foreign clinical studies (phase II studies [Studies C205 and C206] and phase III studies [Studies C208, C216, and HPC3007]), at least one amino acid mutation was found at position 80, 122, 155, or 168 in most patients with treatment failure (genotype 1a/other, 94.8% [110 of 116 patients]; genotype 1b, 86.4% [70 of 81 patients]). The major mutation in patients with genotype 1b was a single mutation of D168V, which occurred in 51.9% of patients (42 of 81 patients). The incidence of other mutations was ≤10%. Most mutations observed in patients with treatment failure were mutants highly resistant to simeprevir (FC ≥ 50).

The majority of the Japanese patients with chronic hepatitis C virus infection enrolled in the Japanese clinical studies (phase II study [Study C215] and phase III studies [Studies HPC3003, HPC3008, HPC3004, and HPC3010]) were genotype 1b patients (501 of 509 patients), of whom those with treatment failure were subjected to analysis of the amino acid sequences at 18 evaluation sites.[50)] The patients from whom samples were obtained at baseline and at the time of treatment failure included13 treatment-naïve patients, 4 patients who had relapsed after prior treatment, and 67 patients who had failed to respond to prior treatment. Mutations were found at the time of treatment failure in 92.3% (12 of 13 patients), 75.0% (3 of 4 patients) and 92.5% (62 of 67 patients) of patients, respectively, demonstrating a high mutation rate in all patient populations. Of the 18 evaluation sites, at least one mutation was found at position 41, 80, 122, 155, 168, or 174. The most common mutation was, regardless of with or without genetic polymorphism at baseline, a single mutation of D168V, which occurred in 38.5% (5 of 13 patients) of treatment-naïve patients, 75.0% (3 of 4 patients) of patients who had relapsed after prior treatment, and 61.2% (41 of 67 patients) of patients who had failed to respond to prior treatment. Other common mutations included mixed mutations at position D168 (detected as a mixture of single mutations at the same amino acid site) or multiple mutations including mutations at D168.

Based on the above, although the resistance profile of simeprevir observed in Japanese and foreign clinical studies could not be assessed sufficiently in HCV genotype 1a patients because of the small number of patients enrolled in the Japanese clinical studies, a major mutation at D168V in HCV genotype 1b patients with treatment failure suggests that the resistance profile of simeprevir is similar between Japan and foreign populations.

PMDA accepted the above explanation by the applicant. It is important to continue to collect post-

[50)] Amino acids at positions 36, 41, 43, 54, 55, 80, 107, 122, 132, 138, 155, 156, 158, 168, 169, 170, 174, and 175

marketing information on the simeprevir resistance-associated mutations and to provide information to the clinical practice when new findings become available.

3.(ii) Summary of pharmacokinetic studies

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

As the data submitted in support of this application, the pharmacokinetics of simeprevir were investigated by administration of ^{3}H-labeled, ^{14}C-labeled, and unlabeled simeprevir to mice, rats, hamsters, rabbits, dogs, and monkeys. In the studies on simeprevir, tissue radioactivity concentrations were measured by quantitative whole body radiography (QWBA) or liquid scintillation counting (LSC). Simeprevir concentrations in biological samples were measured by liquid chromatography/tandem mass spectrometry (LC/MS/MS; lower limit of quantification, 0.005 μg/mL). Metabolites were analyzed by ultraviolet absorption or radioactivity detection high-performance liquid chromatography, liquid chromatography/mass spectrometry, and LC/MS/MS.

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

3.(ii).A.(1) Absorption (4.2.2.2.2 to 4.2.2.2.10, 4.2.3.2.1, 4.2.3.2.2, 4.2.3.2.8 to 4.2.3.2.10, 4.2.3.2.15 to 4.2.3.2.19, 4.2.3.7.7.2)

A single dose of simeprevir or simeprevir sodium was administered intravenously[51)] or orally[52)] to rats, hamsters, rabbits, dogs, cynomolgus monkeys, and rhesus monkeys. Total body clearance (CL) following a single intravenous dose was 1.10 to 2.31, 2.26, 7.21, 0.073 to 0.400, 0.249, and 0.417 L/h/kg, respectively. Volume of distribution at steady state (Vd_{ss}) in rats, dogs, cynomolgus monkeys, and rhesus monkeys was 2.77 to 5.34, 0.247 to 0.795, 0.456, and 1.11 L/kg, respectively. Following a single oral dose, the exposure (area under the plasma concentration-time curve [AUC] and C_{max} for mice and rats, and C_{max} for rhesus macaques) was less than dose-proportional in mice, rats, and rhesus monkeys; elimination half-life ($t_{1/2}$) tended to prolong with increasing doses in rats and rhesus monkeys. These observations are potentially attributed to saturation of oral absorption that resulted from the low water solubility of simeprevir. On the other hand, $t_{1/2}$ prolonged with increasing doses in dogs, but, unlike in other animal species, AUC from time 0 to 24 hours (AUC_{24h}) increased in a more than dose-proportional manner. The non-linearity observed in dogs may be associated with saturation of distribution or elimination since an increase in dose was accompanied by a decrease in volume of distribution (Vd_z) calculated from CL, Vd_{ss}, and the elimination rate constant in the terminal phase following a single intravenous dose to dogs.

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51) The following doses were administered: 4 to 20 mg/kg to rats (3 males each), 8 mg/kg to hamsters (3 males per time point), 4 mg/kg to rabbits (4 females), 2 to 20 mg/kg to dogs (3 males each), 4 mg/kg to cynomolgus monkeys (3 males) and 5 mg/kg to rhesus monekys (2 males).

52) The following doses were administered: 40 mg/kg to rats (3 males per time point), 100 mg/kg to hamsters (2-3 males per time point), 40 mg/kg to rabbits (4 females), 5 mg/kg to dogs (3 males), 20 mg/kg to cynomolgus monkeys (3 males), and 20 to 300 mg/kg to rhesus monkeys (2 males each).

Following repeated oral administration of simeprevir in mice, rats, dogs and rhesus monkeys,[53] the exposure declined only in mice, while repeated administration did not affect plasma simeprevir concentrations in other animal species.

3.(ii).A.(2) Distribution (4.2.2.2.2, 4.2.2.3.1 to 4.2.2.3.7, 4.2.3.2.1, 4.2.3.2.8, 4.2.3.2.15, 4.2.3.2.18, 4.2.3.5.3.1)

A single dose of simeprevir or ^{14}C-simeprevir (mice, 150 mg/kg; rats, 40 mg/kg or 120 mg/kg) was orally administered to mice (1 male pigmented mouse/time point) and rats (3 male white rats/time point or 1 male pigmented rat/time point). Among tissues other than the intestinal tract, simeprevir concentration or radioactivity concentration remained higher in the liver than in blood. The radioactivity concentrations in melanin-containing tissues including eyeballs, uvea, and pigmented skin etc. remained low compared to blood. The radioactivity in tissues other than the liver declined below the detection limit[54] by 96 hours post-dose both in mice and rats, and the concentration in the liver declined to a low level (0.687 and 0.816 μg eq/g). Following repeated oral administration of simeprevir[55] in mice, rats, and dogs, a significantly higher concentration was detected in the liver than in plasma.

In an *in vitro* protein binding study (equilibrium dialysis method), the rate of unbound ^{3}H-simeprevir in the plasma from animals (mice, rats, rabbits, dogs, and monkeys) and humans was as low as approximately 0.1% to 0.2%, and was almost constant across the concentration range tested (animals, 0.2-20 μg/mL; humans, 0.2-10 μg/mL). The rate of unbound simeprevir in plasma was also as low as <0.1% in foreign clinical studies in patients with hepatic or renal impairments (Studies C113 and C126)[56] (patients with hepatic impairment, 0.0046 or 0.010 μg/mL; patients with renal impairment, 0.020 μg/mL). In addition, the rate of ^{3}H-simeprevir (2 μg/mL) unbound to HSA (3.0%-6.0%) and AGP (0.05%-0.20%) was 0.09% to 0.14% and 18.45% to 69.78%, respectively.

Following a single oral dose of 30 mg/kg of ^{14}C-simeprevir in dogs (3 males), the blood/plasma radioactivity concentration ratio was as low as 0.42 to 0.56 and showed no changes over time.

Following a single oral dose of 120 mg/kg of ^{14}C-simeprevir in rats on gestation day 18 (1 female/time point), the concentration remained high over time in the liver, among tissues other than the gastrointestinal tract, compared to blood. Although radioactivity was detected in the mammary gland, its concentration was lower than that in blood. The radioactivity in the fetus and fetal liver was below the detection limit at all sampling time points (<0.79 μg eq/g).

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53) The following doses were administered: in mice, 150 to 2000 mg/kg/day for 2 weeks, 150 to 2000 mg/kg/day for 3 months (3 males and 3 females per time point); in rats, 40 to 360 mg/kg/day for 2 weeks (3 males and 3 females), 50 to 500 mg/kg/day for 1 month, 50 to 500 mg/kg/day for 6 months (3 males and 3 females per time point), 1000 to 1500 mg/kg/day for 2 weeks (6 males and 6 females); in dogs, 10 to 160 mg/kg/day for 2 weeks (3 males and 3 females), 10 to 90 mg/kg/day for 1 month (2 males and 2 females), 5 to 45 mg/kg/day for 6 months (3-4 males and 3-4 females) or 9 months (4-6 males and 4-6 females); in rhesus monkeys, 20 mg/kg/day for 15 days followed by 60 mg/kg/day for 22 days (5 and 3 males).

54) The detection limit was as follows: <0.28 μg eq/g for eyeball (LSC) and <0.37 μg eq/g for other tissues (QWBA) in mice; <0.078 μg eq/g for eyeball (LSC) and <0.79 μg eq/g for other tissues (QWBA) in rats.

55) The following doses were administered: 150 to 2000 mg/kg/day for 2 weeks in mice (3 males and 3 females); 40 to 360 mg/kg/day for 2 weeks in rats (3 males and 3 females); 10 to 160 mg/kg/day for 2 weeks in dogs (3 males and 3 females), and 5 to 45 mg/kg/day for 9 months in dogs (4 males and 4 females).

56) For the details of Studies C113 and C126, see "4.(ii).A.(4) Assessment of intrinsic factors."

Repeated oral doses of 150, 500, or 1000 mg/kg/day of simeprevir were administered to rats (6 females each) from 6 or 8 days after mating to 6 days postpartum. Although simeprevir was detected in the plasma and liver of neonates, the concentration was lower than the plasma concentration in maternal animals.

3.(ii).A.(3) Metabolism (4.2.2.3.6, 4.2.2.4.1 to 4.2.2.4.12)

A single oral dose of ^{14}C-simeprevir (rats, 120 mg/kg; dogs, 30 mg/kg) was administered to rats (n = 2-3/sex) and dogs (3 males) to study *in vivo* metabolism. The proposed metabolic pathway of simeprevir based on the study results is shown in the following figure. The major component both in plasma and feces was unchanged simeprevir and the major metabolite(s) was the *O*-demethylation (M18) of the unchanged simeprevir. The glucuronide conjugate (M7) of M18 was detected in bile from rats as well. Since urinary radioactivity was low, urinary metabolites were not analyzed.

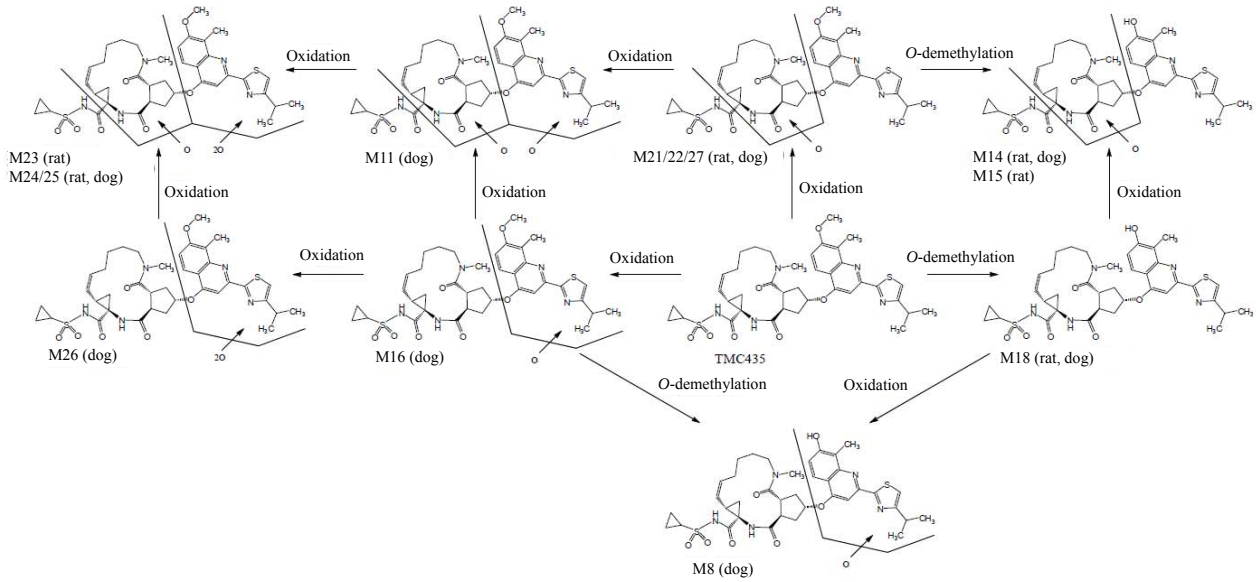

Figure. Proposed metabolic pathway of simeprevir

In vitro metabolism of simeprevir was investigated by adding simeprevir or ^{14}C-simeprevir (5 or 10 µmol/L) into hepatocytes (suspension or primary culture) or the hepatocyte fraction added with the NADPH generating system (12000 × g supernatant or microsomes) from mice, rats, rabbits, dogs, monkeys, and humans.[57] Hepatocyte samples from male and female animals were prepared separately. There was no significant sex difference in mice, but male rats had a higher metabolic rate than female rats. Human metabolites were also detected in rats and dogs except for an oxidized form of simeprevir (M22).[58]

Inhibitiory action of simeprevir for the metabolic activity of specific substrates to cytochrome P450 (CYP450) drug metabolizing enzyme isoforms (CYP1A2, CYP2A6, CYP2C8/9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A) was investigated using human liver microsomes. The

57) Sex is unknown for human samples
58) M22 was detected in feces from rats and dogs in *in vivo* studies.

activities of CYP2A6, CYP2C8, CYP2C19, CYP2D6, and CYP3A4/5 were inhibited (IC_{50}, 42.9-155 μmol/L).

The effect of simeprevir (2.5 and 10 μmol/L) on the metabolism of specific substrates to CYP1A2 and CYP3A4 was investigated using human hepatocytes. The results showed no induction of the activity of CYP1A2 or CYP3A4.

3.(ii).A.(4) Excretion (4.2.2.3.6, 4.2.2.4.4, 4.2.2.4.5, 4.2.2.5.1)

Following a single oral dose of 120 mg/kg of ^{14}C-simeprevir in rats (n = 3/sex), the urinary and fecal radioactivity excretion rates up to 96 hours post-dose were 0.016% and 98.7%, respectively, in male rats and 0.011% and 99.0%, respectively, in female rats. Following a single oral dose of 30 mg/kg ^{14}C-simeprevir in dogs (3 males), the urinary and fecal radioactivity excretion rates up to 96 hours post-dose were 0.09% and 96.0%, respectively. Following a single oral dose of 40 mg/kg simeprevir in a bile duct-cannulated rat (1 male), the biliary excretion rate of simeprevir up to 24 and 48 hours post-dose was 16.8% and 17.2%, respectively.

3.(ii).A.(5) Pharmacokinetic drug interactions (4.2.2.6.1, 4.2.2.6.2)

The effect of simeprevir on the metabolism of drugs that may be co-administered with simeprevir was investigated using human liver microsomes. The IC_{50} for the metabolism of budesonide, ^{3}H-diazepam, glibenclamide, and ^{3}H-paroxetine was approximately 50 to 100 μmol/L, and the IC_{50} of digoxin, metoprolol, and simvastatin was ≥288 μmol/L. Based on the results of the investigation of concentrations in the gastrointestinal tract and liver estimated from the plasma concentration at a clinical dose[59)] and the drug interaction study to investigate the effect on substrates for each CYP molecular species in the cocktail approach (Study C107), the applicant explained that, although simeprevir may inhibit the metabolism of CYP3A substrates (diazepam, budesonide, digoxin, and simvastatin) in the gastrointestinal tract, taking account of the dosage regimen and pharmacokinetic profile of these drugs, simeprevir is unlikely to affect metabolic drug interactions with the exception of simvastatin.

Following a single oral dose of approximately 2 to 5 mg/kg of simeprevir, alone or in combination with 10 mg/kg ritonavir (3 doses at 12-hour intervals), in dogs (3 males), $t_{1/2}$ of simeprevir tended to be prolonged and AUC_{∞} increased approximately 2- to 3-fold. However, the pharmacokinetic parameters of ritonavir remained unchanged, irrespective of the dose of simeprevir.

3.(ii).A.(6) Other pharmacokinetic studies (4.2.2.2.1, 4.2.2.7.1 to 4.2.2.7.8)

3.(ii).A.(6).1) Effect on glucuronide conjugation

The effect of simeprevir and RBV on bilirubin glucuronide conjugation was investigated using human liver microsomes. The results suggested that simeprevir inhibits bilirubin glucuronide conjugation (inhibition constant [Ki], 119 μmol/L). After addition of RBV (150 μmol/L), bilirubin glucuronide

59) In a Japanese phase III study (Study HPC3008) in which multiple oral doses of 100 mg of simeprevir were administered once daily to Japanese patients with chronic hepatitis C infection, the plasma C_{max} of simeprevir was 4.26 μg/mL (5.68 μmol/L) at Week 12.

conjugation (1.5 μmol/L) was 84% of that without RBV addition.

3.(ii).A.(6).2) Investigation of liver uptake and drug excretion transporters

The effect of simeprevir on liver uptake of ^{3}H-taurocholic acid and ^{3}H-17β-estradiol glucuronide conjugate and the effect of other drugs on the liver uptake of ^{3}H-simeprevir were investigated using both rat and human hepatocyte suspensions. The results showed that simeprevir (0.2-20 μmol/L) inhibited the liver uptake of ^{3}H-taurocholic acid (1 μmol/L) and ^{3}H-17β-estradiol glucuronide conjugate (1 μmol/L) (IC_{50}: 6.3-7 μmol/L and 5.4-6 μmol/L, respectively, in rat hepatocytes; 3.5-4 μmol/L and 0.98-1 μmol/L, respectively, in human hepatocytes). In addition, ritonavir (20 μmol/L), rifampicin (20 μmol/L), and cyclosporine A (20 μmol/L) reduced liver uptake of ^{3}H-simeprevir (1 μmol/L) in rat hepatocytes by 19%, 16%, and 36%, respectively, and in human hepatocytes by 18%, 21%, and 25%, respectively.

The effect of simeprevir on the liver uptake and bile excretion of ^{3}H-taurocholic acid and ^{3}H-17β-estradiol glucuronide conjugate was investigated using human sandwich-cultured hepatocytes. The results showed that at 0.5 μmol/L of simeprevir, there was practically no inhibition (≤6%) of the liver uptake and biliary excretion of ^{3}H-taurocholic acid (1 μmol/L), but at 5 μmol/L, inhibition was 47% and 31%, respectively. In addition, at 0.5 and 2 μmol/L of simeprevir, there was practically no inhibition (≤14%) of liver uptake and biliary excretion of ^{3}H-17β-estradiol glucuronide conjugate (1 μmol/L), but at 5 μmol/L, inhibition was 72% and 33%, respectively.

Greater uptake of ^{14}C-simeprevir and ^{3}H-17β-estradiol glucuronide conjugate (1 μmol/L each) occurred in HEK293 cells expressing organic anion transporters (OATP1B1, OATP1B1*15, OATP1B3, or OATP2B1) as compared with the control (mock-transfected HEK293 cells), and rifampicin (50 μmol/L) reduced the uptake of ^{3}H-17β-estradiol glucuronide conjugate.

Following a single oral dose of 12.5 mg/kg of ^{14}C-simeprevir in wild-type and Oatp 1a/1b deficient male mice, the plasma concentrations of simeprevir and radioactivity were higher in Oatp 1a/1b deficient mice than in wild-type mice. In addition, the liver/plasma concentration ratios of simeprevir and radioactivity were lower in Oatp 1a/1b deficient mice than in wild-type mice.

An investigation of the *in vitro* inhibitory action of simeprevir on P-glycoprotein (P-gp), Na^{+}-taurocholate cotransporting polypeptide (NTCP), OATP1B1, bile salt export pump (BSEP), and multi-drug resistance-related protein 2 (MRP2) showed that simeprevir inhibited the uptake of each substrate as shown in the following table.

Table. Transporter inhibition by simeprevir *in vitro*

Test system		Transported substance (concentration)		IC_{50} (μmol/L)
Cell	Expressed protein			
Caco-2	P-gp	^{3}H-taxol	(0.0375 μmol/L)	85.9
CHO	NTCP	^{3}H-taurocholic acid	(1 μmol/L)	0.44-2.16
	OATP1B1	^{3}H-17β-estradiol glucuronic acid conjugate	(1 μmol/L)	0.06-0.26
Inside-out vesicles	BSEP	^{3}H-taurocholic acid	(0.71 μmol/L)	1.67-1.77
	MRP2	^{3}H-17β-estradiol glucuronic acid conjugate	(50 μmol/L)	6.35-19.1
	MRP2	5/6-carboxy-2',7'-dichlorofluorescein	(5 μmol/L)	6.35-19.1

The results of an investigation of the transport of simeprevir by P-gp, breast cancer resistance protein (Bcrp1) (mouse), and MRP2, shown in the following table, indicate that simeprevir is a substrate of P-gp, Bcrp1, and MRP2.

Table. Efflux/influx ratio of simeprevir

Test system		Transported substance (concentration)	Inhibitor (concentration)	Efflux/influx ratio	
				Expression of transporter	
Cell	Expressed protein			No	Yes
Caco-2	P-gp	Simeprevir (20 μmol/L)	None	–	3.18
			Verapamil (100 μmol/L)	–	1.09
LLC-PK1	P-gp	^{14}C-simeprevir (1 μmol/L)	None	2.73	20.4
			GF120918[a] (5 μmol/L)	1.44	1.54
		^{14}C-simeprevir (1 μmol/L)	None	2.17	109
			Ritonavir (50 μmol/L)	1.10	18.2
		^{3}H-digoxin (30 nmol/L)	None	2.10	21.0
			Ritonavir (50 μmol/L)	0.99	13.1
MDCK II	Bcrp1	^{14}C-simeprevir (1 μmol/L)	None	2.98	74.3
			Ko143[b] (1 μmol/L)	3.30	0.79
		^{14}C-simeprevir (1 μmol/L)	None[c]	0.97	9.68
			Ritonavir[c] (50 μmol/L)	1.06	8.05
		^{3}H-cimetidine (1 μmol/L)	None[c]	1.31	9.95
			Ritonavir[c] (50 μmol/L)	1.19	2.88
	MRP2	^{14}C-simeprevir (1 μmol/L)	None[d]	2.27	18.2
			Ritonavir[d] (50 μmol/L)	1.86	11.6
		^{3}H-vinblastine (1 μmol/L)	None[d]	1.16	10.6
			Ritonavir[d] (50 μmol/L)	0.80	3.03

a) P-gp and Bcrp1 inhibitor; b) Bcrp1 inhibitor; c) PSC833 (10 μmol/L), a P-gp inhibitor, was added;
d) GF120918 (5 μmol/L), a P-gp and Bcrp1 inhibitor, was added.

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

3.(ii).B.(1) Mechanism for the increases in bilirubin levels

PMDA asked the applicant to explain the mechanism responsible for the increases in blood bilirubin levels in humans [see "4.(iii).B.(2).2) Increases in blood bilirubin levels"], taking account of the discussion on the concentrations investigated in various *in vitro* studies and the estimated levels of simeprevir by using the proposed dosage and administration.

The applicant explained as follows:

It is known that unconjugated and conjugated bilirubin is taken up into the liver mainly by OATP1B1. Unconjugated bilirubin then undergoes glucuronide conjugation mediated by UGT1A1, while the biliary

excretion of conjugated bilirubin is mediated by MRP2.[60)]

Following once-daily multiple oral doses of simeprevir 100 mg in Japanese patients with chronic hepatitis C virus infection (Study HPC3008), the C_{max} of the total plasma concentration of simeprevir at Week 12 was 4.26 μg/mL (5.68 μmol/L[61)]). This value was higher than the IC_{50} values against NTCP and OATP1B1 (0.06-2.16 μmol/L), which exist in the basolateral membrane of the liver. Considering that the highest liver/plasma concentration ratio of simeprevir was 64.6 in rats and that the uptake of simeprevir in human hepatic cells in the presence of 2% BSA was approximately one-third of the uptake in rat hepatic cells, the highest total concentration of simeprevir in the liver in Japanese patients with chronic hepatitis C virus infection was estimated to be 122 μmol/L (= 5.68 × 64.6 ÷ 3). It was considered that this concentration is higher than the IC_{50} values against BSEP and MRP2 (1.67-19.1 μmol/L), and is comparable to the Ki value for glucuronide conjugation and the IC_{50} value against P-gp (119 and 85.9 μmol/L, respectively). However, because the effective concentration of simeprevir for transporters including OATP1B1 and drug metabolizing enzymes is considered to be lower than the total concentration, the effective concentration of simeprevir in the liver is estimated to be lower than the Ki value for glucuronide conjugation and the IC_{50} value against P-gp. In addition, whereas simeprevir increased the exposure of substrates of OATP1B1 (rosuvastatin, atorvastatin, and simvastatin), the exposure of a substrate of UGT1A1 (raltegravir) was not increased [see "4.(ii).A.(5) Assessment of drug interactions"]. Moreover, inhibition of NTCP and BSEP may lead to intrahepatic cholestasis, resulting in increased values of not only bilirubin levels but also liver function tests including alanine aminotransferase (ALT) and aspartate aminotransferase (AST). However, the pooled data of Japanese clinical studies (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3004, HPC3008, and HPC3010) revealed no tendency for an increase in AST or ALT along with an increase in total bilirubin level [see "4.(iii).B.(2).2) Increases in blood bilirubin levels"].

Taking the above into consideration, the increases in plasma bilirubin concentration observed in the clinical studies on simeprevir is considered to be mainly mediated by the inhibition of OATP1B1 and MRP2.

PMDA considers that the applicant's explanation is acceptable. The safety of simeprevir concerning blood bilirubin increased will be discussed in "4.(iii).B.(2) Safety."

3.(iii) Summary of toxicology studies

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

The following studies were submitted as toxicology studies: single-dose toxicity studies, repeated dose toxicity studies, genotoxicity studies, reproduction toxicity studies, local tolerance studies, phototoxicity studies, skin sensitization studies, and toxicity studies on simeprevir impurities. [redacted]

60) Zhang W, et al. *Clin Exp Pharmacol Physiol*. 2007;34:1240-1244; Campbell SD, et al. *Chem Biol Interact*. 2009;182:45-51; Miners JO, et al. *Toxicology*. 2002;181-182:453-456; Jedlitschky G, et al. *Expert Opin Drug Metab Toxicol*. 2006;2:351-366.

61) Mol concentration calculated using the molecular weight of 749.94 for simeprevir

[redacted][62)][redacted]

3.(iii).A.(1) Single-dose toxicity (4.2.3.3.2.2, reference 4.2.3.2.7, reference 4.2.3.2.14, and reference 4.2.3.2.19)

Acute toxicity was evaluated by bone-marrow micronucleus test in CD-1 mice (n = 10/sex/group). In addition, the results of the following studies were submitted: single oral dose toxicity studies in SD rats (5 males in each group) and beagle dogs (1 male and 1 female); single oral and intravenous dose toxicity studies in rhesus monkeys (2 males). Following a single oral dose of 0, 500, 1000, or 2000 mg/kg of simeprevir in mice, no deaths occurred in the 2000 mg/kg group, and thus the approximate lethal dose was determined to be >2000 mg/kg. Following a single oral dose of 0, 50, 200, or 1000 mg/kg of simeprevir in SD rats and a single oral dose of 0, 10, 40, 160, or 320 mg/kg of simeprevir to beagle dogs, no deaths occurred in either study, and thus the approximate lethal dose was determined to be >1000 mg/kg in rats and >320 mg/kg in dogs. Following a single oral dose of 0, 20, 150, and 300 mg/kg of simeprevir or a single intravenous dose of 5 mg/kg of simeprevir in rhesus monkeys, no deaths occurred, and thus the approximate lethal dose was determined to be >300 mg/kg for oral administration and >5 mg/kg for intravenous administration.

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

The results of the following studies were submitted as major repeated dose toxicity studies on simeprevir: oral gavage dose toxicity studies in mice (3 months), rats (1 month and 6 months), dogs (2 weeks, 1 month, 6 months, and 39 weeks), and monkeys (14 days and 28 days); dietary administration toxicity studies in mice (13 weeks) and rats (13 weeks). Main observations related to simeprevir administration were: centrilobular hypertrophy of hepatocytes, vacuolization of pancreatic acinar cells (accompanied by reduction in zymogen granules or apoptosis), and delayed gastric emptying in mice and rats; hepatic cell necrosis in dogs; swelling and vacuolization of apical mucosa cells of the duodenum and jejunum in mice, rats, and dogs. The changes in the liver and gastrointestinal tract in dogs were reversible. Although acute myocardial necrosis occurred in the left ventricle in a 2-week oral gavage dose toxicity study in dogs, no cardiac findings were observed in other repeated dose toxicity studies in dogs and any of the other repeated dose toxicity studies in mice, rats, and monkeys. Airway inflammation was observed in the oral gavage dose toxicity studies in mice and rats, and the inflammation/necrotic changes were considered to have been induced by reflux/aspiration of the administered simeprevirinto the airway. This was probably caused by delayed gastric emptying due to inhibited gastric emptying by simeprevir and the vehicle (PEG400) or high viscosity and irritancy of the administered simeprevir.

The AUC_{24h} values of simeprevir at the no-observed-adverse-effect levels (NOAEL) (500 mg/kg/day in rat 6-month study and 15 mg/kg/day in dog 39-week study) in oral gavage dose toxicity studies[63)] were

62) A solution of PEG400 to which 2.5% vitamin E acetate-D-α-tocopheryl polyethylene glycol 1000 succinate was added.

63) AUC_{24h} was 30.2 µg·h/mL and 52.7 µg·h/mL in male and female rats (Day 181), respectively. AUC_{24h} was 47.4 µg·h/mL and 70.1 µg·h/mL in male and female dogs (Day 273), respectively.

approximately 0.4- to 0.6-fold and 0.6- to 0.8-fold, respectively, as compared with AUC_{24h} following administration of simeprevir to Japanese subjects.[64)]

3.(iii).A.(2).1) Three-month repeated oral gavage dose toxicity study in mice (4.2.3.2.2)

Oral gavage doses of 0 (vehicle, PEG400), 150, 500, or 2000 mg/kg/day of simeprevir were administered to CD-1 mice (n = 10/sex/group) for 3 months. Because deaths and sacrificed moribund occurred frequently in the 2000 mg/kg/day group, the dose was reduced to 1000 mg/kg/day after Day 8. Satellite groups (control group, n = 9/sex; simeprevir groups, n = 15/sex/group) were established to study toxicokinetics at the same doses (TK group). Deaths and sacrificed moribund occurred in all groups including the TK group and the control group. In all dose levels of simeprevir (including the TK groups), abnormal gastric content (administered formulation) and gastric or small intestinal swelling were observed in the dead or sacrificed mice, in which the deaths were considered unrelated to a dosing error. Therefore, delayed gastric emptying was considered to be the cause of death. Changes related to delayed gastric emptying included airway inflammatory/necrotic changes due to reflux/aspiration of simeprevir into the airway. Furthermore, in the dead or sacrificed mice in the 2000/1000 mg/kg/day group, swelling and darkening of the pancreas were observed, and vacuolization of pancreatic acinar cells and reduction in zymogen granules occurred frequently. The following findings were observed in the surviving mice: decreased cholesterol and increased amylase at ≥150 mg/kg; increased lymphocytes and platelets, increased incidence of centrilobular hypertrophy of hepatocytes, increased pancreas weight, and vacuolization of pancreatic acinar cells at ≥500 mg/kg; increased liver weight at 2000/1000 mg/kg/day. Based on the above reports, the NOAEL was not obtained in this study.

3.(iii).A.(2).2) Thirteen-week dietary administration toxicity studies in mice (4.2.3.2.4 and 4.2.3.2.6)

Dietary administration of 0 (powder diet only), 0.5, 2, or 5 g eq./kg/day (expressed as the free base of simeprevir) of simeprevir sodium was conducted for 13 weeks in CD-1 mice (n = 10/sex/group). TK groups (control groups, n = 9/sex/group; simeprevir groups, n = 12/sex/group) were also established. The following findings were observed at ≥0.5 g eq./kg/day: reduced body weight gain; increased bilirubin, alkaline phosphatase (ALP), AST, ALT, and inorganic phosphorus; decreased cholesterol, albumin, triglyceride, total protein, and A/G ratio; increased liver and pancreas weight; centrilobular hypertrophy of hepatocytes; hyperplasia of forestomach epithelium; swelling or vacuolization of apical enterocytes in the duodenum. The following findings were observed at 2 g eq./kg/day: low body weight; increased lipase; decreased heart and kidney weight; gastrointestinal distention; rough forestomach epithelium; increased mitoses in the liver; hyperkeratosis in forestomach; swelling and vacuolization of apical enterocytes in the jejunum. Because rapid deterioration of clinical condition and deaths occurred in the 5 g eq./kg/day group, all mice were sacrificed on Day 4 or 5. The following findings were observed in the dead or sacrificed mice: gastrointestinal distention; recess in gastric corpus; rough forestomach epithelium; forestomach hyperplasia, submucous inflammation/edema, hyperkeratosis, and ulcer;

64) In a Japanese phase III study (Study HPC3008) in which 100 mg of simeprevir was administered once daily for 12 weeks to patients who relapsed after prior treatment, AUC_{24h} was 82.8 μg·h/mL.

centrilobular hypertrophy of hepatocytes; swelling and vacuolization of apical enterocytes in the duodenum and jejunum; reduction in zymogen granules or basophilic changes in pancreatic acinar cells and acinar cell vacuolization; regression or atrophy of thyroid gland; atrophy/fatty metamorphosis and cell density reduction in mesenteric lymph node. Based on the above reports, the NOAEL was not obtained in this study.

Since the tolerability of simeprevir sodium was not observed at 5 g eq./kg/day, dietary administration of 0 (powder diet only) and 3 g eq./kg/day (expressed as the free base of simeprevir) of simeprevir sodium was conducted for 13 weeks in CD-1 mice (n = 10/sex/group) to investigate the tolerability at 3 g eq./kg/day. TK groups (control groups, n = 9/sex/group; simeprevir groups, n = 12/sex/group) were also established. In the TK group, 1 female mouse in the 3 g eq./kg/day group was sacrificed at Week 11 due to rapid deterioration of clinical condition: gastrointestinal distention, a small number of dark resesses of in the gastric corpus mucosa, patchy congestion of the lungs, and darkening of adrenal gland were observed. Surviving animals in the 3 g eq./kg/day group had hunchback position, decreased activity, thinness, pallor, abdominal distension, piloerection, and decreased body temperature. Hematological and histopathological examinations revealed the following findings in addition to the findings obtained in the 5 g eq./kg/day group in the previous study (4.2.3.2.4): decreases in red blood cells and red blood cell-related parameters; anisocytosis and microcytosis; increases in lymphocytes and total white blood cells; a decrease in vacuoles and clarification of adrenal gland X zone; atrophy of adrenal cortex; a decrease in number of corpus luteum in the ovary. Thus, the tolerability of simeprevir sodium was not observed at 3 g eq./kg/day , and the NOAEL was not obtained.

3.(iii).A.(2).3) One-month repeated oral gavage dose toxicity study and one-month reversibility study in rats (4.2.3.2.9)

Oral gavage doses of 0 (vehicle, PEG400), 50, 150, or 500 mg/kg/day of simeprevir were administered to SD rats (n = 10/sex/group) for 1 month. At 0 and 500 mg/kg/day, 5 males and 5 females were added to each group as a recovery group to study the reversibility after a 1-month recovery period. The following findings were observed: at ≥150 mg/kg/day, decreased albumin and potassium; at 500 mg/kg/day, increased ALT, decreased total protein, increased inorganic phosphorus and cholesterol, urinary occult blood by urinalysis, increased red blood cells, increased squamous cells, and increased adrenal gland weight. However, all findings completely resolved after the1-month recovery period. Based on the above reports, since the changes in clinical laboratory values observed in this study were unaccompanied by related histopathological changes, the NOAEL was determined to be 500 mg/kg/day.

3.(iii).A.(2).4) Six-month repeated oral gavage dose toxicity study in rats (4.2.3.2.10)

Oral gavage doses of 0 (vehicle, PEG400), 50, 150, or 500 mg/kg/day of simeprevir were administered to SD rats (n = 30/sex/group) for 6 months, and 10 males and 10 females in each group were sacrificed after 3 months of administration. Although deaths, cannibalism, and sacrificed moribund occurred in all groups including the control group, the number of cases was not dose-dependent, and the deaths were considered related to dosing error or airway inflammation due to aspiration of the administered

preparation. The following findings were observed: at ≥50 mg/kg/day, decreased reticulocytes, dark colored urine by urinalysis, increased urine specific gravity, and a transient decrease in urine pH; at ≥150 mg/kg/day, decreased total protein and albumin, a transient increase in creatinine, transient decreases in magnesium and potassium, increased inorganic phosphorus, and decreased urea nitrogen; at 500 mg/kg/day, increased chloride and sodium, decreased potassium, and shortening of activated partial thromboplastin time (APTT). Based on the above reports, since the changes of clinical laboratory values observed in this study were unaccompanied by related histopathological changes, the NOAEL was determined to be 500 mg/kg/day.

3.(iii).A.(2).5) Thirteen-week repeated dietary administration toxicity study in rats (4.2.3.2.13)

Dietary administration of 0 (powder diet only), 500, 1000, or 2000 mg eq./kg/day of simeprevir sodium was conducted for 13 weeks in SD rats (n = 10/sex/group). The following findings were observed: at ≥500 mg eq./mg/kg, discolored stools, increased body weight, decreased food consumption, decreased triglyceride, and centrilobular hypertrophy of hepatocytes; at ≥1000 mg eq./mg/kg, decreased feeding efficiency and increased lipase; at 2000 mg eq./mg/kg, increased bile acid and vacuolization of apical enterocytes in the jejunum. The relationship between the increase in bile acid and the administration of simeprevir was unclear because of considerable inter-individual variability. Because of the above reports, the NOAEL for this study was not obtained.

3.(iii).A.(2).6) Two-week repeated oral gavage dose toxicity study in dogs (reference 4.2.3.2.15)

Oral gavage doses of 0 (vehicle, VitE-TPGS/PEG400), 10, 40, 120 (female), or 160 (male) mg/kg/day of simeprevir were administered to beagle dogs (n = 3/sex/group) for 2 weeks. Death or sacrificed moribund occurred in 1 male and 1 female in the 40 mg/kg/day group and 1 female in the 120 mg/kg/day group, and clinical condition deteriorated markedly in 1 male in the 10 mg/kg/day group. The deaths and deterioration of clinical condition in the animals were considered related to bronchial pneumonia, which resulted from aspiration of the administered formulation into the lungs. Necrotic focus of hepatocytes was also observed in sacrificed animal (female) in the 40 mg/kg/day group. The following findings were observed: at ≥40 mg/kg/day, salivation, increases in total bilirubin, direct bilirubin, and ALT; at 120 and 160 mg/kg/day, decreased body weight and food consumption, decreased cholesterol, necrotic focus of hepatocytes, and cholestasis of the bile canaliculus. In addition, 1 male and 1 female in the 120 and 160 mg/kg/day groups experienced acute myocardial necrosis (left ventricle), and a male with myocardial necrosis had necrotizing arteriopathy (medial arteries in the adipose tissue from the stomach through rectum and around the bladder and salivary gland). Electrocardiogram (ECG) and myocardial biomarkers (cardiac troponin I and creatinine kinase-MB, etc.) did not reveal any changes related to simeprevir treatment. Based on the above reports, the NOAEL was determined to be 10 mg/kg/day in this study.

3.(iii).A.(2).7) One-month repeated oral gavage dose toxicity study and one-month reversibility study in dogs (4.2.3.2.16)

Oral gavage doses of 0 (vehicle, PEG400), 10, 30, or 90 mg/kg/day of simeprevir were administered to

beagle dogs (n = 3/sex/group) for 1 month. In the 0 and 90 mg/kg/day groups, 2 males and 2 females were added to each group as a recovery group to study the reversibility after a 1-month recovery period. The following findings were observed: at ≥30 mg/kg/day, mucous stools, decreased body weight, decreased reticulocytes, decreased cholesterol, increased ALT, and multifocal hepatic necrosis; at 90 mg/kg/day, decreased food consumption, salivation, increased frequency or severity of loose or mucous stools, bloody stools, shortening of APTT, decreased hemoglobin and hematocrit, increased total bilirubin (direct and indirect bilirubin), decreased total protein and albumin, and increased AST, ALP, and γ-glutamyl transpeptidase. Simeprevir treatment showed no changes in ECG, heart rate, cardiac troponin I, and Von Willebrand factor. All findings resolved after the 1-month recovery period. Based on the above, the NOAEL was determined to be 10 mg/kg/day in this study.

3.(iii).A.(2).8) Six-month repeat oral gavage dose toxicity study in dogs (4.2.3.2.17)

Oral gavage doses of 0 (vehicle, PEG400), 5, 15, or 45 mg/kg/day of simeprevir were administered to beagle dogs (n = 4/sex/group) for 6 months. The following findings were observed at 45 mg/kg/day: loose stools; mucous stools; discolored stools and increased frequency of salivation; decreased body weight and body weight gain; decreased reticulocytes; increased fibrinogen; increased total bilirubin (direct and indirect bilirubin); increased ALT, ALP, and AST; decreased triglyceride; transient increases in bilirubin and urobilinogen in urinalysis; increased liver weight; multifocal hepatic cell necrosis; focal or multifocal brown pigmentation (hemosiderin) of Kupffer cells and macrophages in the liver; portal or periportal mixed type inflammatory cell infiltrate in the liver, and vacuolization (fat droplets) of apical enterocytes in the duodenum and jejunum. Simeprevir treatment showed no changes in ECG and heart rate. Based on the above reports, the NOAEL was determined to be 15 mg/kg/day in this study.

3.(iii).A.(2).9) Thirty-nine-week repeated oral gavage dose toxicity study and 13-week reversibility study in dogs (4.2.3.2.18)

Oral gavage doses of 0 (vehicle, PEG400), 5, 15, or 45 mg/kg/day simeprevir were administered to beagle dogs (n = 4/sex/group) for 39 weeks. In the 0 and 45 mg/kg/day group, 2 males and 2 females were added to each group as a recovery group to study the reversibility after a 13-week recovery period. Increased ALP was observed at ≥5 mg/kg/day. The following findings were observed at ≥15 mg/kg/day: increased ALT, decreased cholesterol and an increasing trend in bile acid. Histopathological findings included vacuolization of chorionic epithelial tips and lacteal dilatation in the small intestine, all of which were considered to be of low toxicological significance. The increases in ALT, ALP, and bile acid were significant at 45 mg/kg/day. All findings resolved completely after the 13-week recovery period. ECG showed no changes attributable to simeprevir treatment. Based on the above, the NOAEL was determined to be 15 mg/kg/day in this study.

3.(iii).A.(2).10) Fourteen-and twenty eight-day repeated oral gavage dose toxicity study in monkeys (reference 4.2.3.2.19)

Oral gavage doses of vehicle (VitE-TPGS/PEG400) and 200 mg/kg/day of simeprevir were administered to 2 and 6 male rhesus monkeys, respectively. Because serious symptoms were observed in 1 animal in

the 200 mg/kg/day group at 1.5 hours after the first dose, the animal was subjected to sacrificed moribund at 2.5 hours post-dose. Deterioration of clinical condition was considered to be due to aspiration of the administered formulation into the lungs, because: serious findings were observed in the lungs (necrotizing bronchiolitis and hemorrhagic bronchopneumonia); a high concentration of simeprevir was detected in the plasma and lung; and no change had been observed in clinical condition up to 1.5 hours post-dose. Since reddish feces were observed in other surviving animals in the 200 mg/kg/day group, simeprevir treatment was discontinued on Day 4. Fecal occult blood test was negative in the surviving animals, and increased total bilirubin, direct bilirubin, and AST were detected after the first dose.

Oral gavage doses of vehicle (VitE-TPGS/PEG400) and 20 mg/kg/day of simeprevir were administered to 2 and 5 male rhesus monkeys, respectively, for 14 and 15 days. Salivation, vomiting, and increased AST occurred in the 20 mg/kg/day group. Necropsy of 2 animals in the 20 mg/kg/day group revealed multifocal bronchopneumonia and multifocal pleurisy (associated with foreign matter) in 1 animal. This finding was considered related to aspiration of the administered formulation into the lungs.

Oral gavage doses of vehicle (VitE-TPGS/PEG400) and 60 mg/kg/day of simeprevir were administered to 2 and 3 male rhesus macaques, respectively, for 28 days. Increased total bilirubin and direct bilirubin were observed in the 60 mg/kg/day group, but other parameters including ECG and echocardiography revealed no changes related to simeprevir treatment.

3.(iii).A.(3) Genotoxicity（4.2.3.3.1.1 to 4.2.3.3.1.3 and 4.2.3.3.2.2, reference 4.2.3.3.2.1)

As genotoxicity studies on simeprevir, a bacterial reverse mutation assay, mouse lymphoma TK assay, and mouse peripheral blood and bone marrow micronucleus assays were conducted. No genotoxicity was found in any study. [redacted]

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

No carcinogenicity study was conducted because the recommended duration of treatment with simeprevir does not exceed 12 weeks, genotoxicity studies were negative, and the rat and dog repeat dose toxicity studies revealed neither preneoplastic lesions nor proliferative lesions.

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

Rat study for fertility and early embryonic development to implantation, rat study for effects on pre- and postnatal development, including maternal function, and rat and mouse[65)] study for effects on embryo-fetal development were conducted as reproduction toxicity studies on simeprevir. Major findings related to the administration of simeprevir were as follows: in maternal mice and rats, clinical condition deteriorated; in mouse embryos and fetuses, total resorptions, increased number of late-stage resorptions

65) Various formulations and routes of administration were investigated assuming that rabbits would be used in an embryo-fetal study. However, mice were used in addition to rats in embryo-fetal studies because rabbits showed high clearance of and very low exposure to simeprevir.

and post-implantation losses, increases in frequency of skeletal variation and delayed ossification at doses not associated with low body weight, and decreased fetal body weight; in rat pups, low body weight at the time of weaning, decreased body weight gain after weaning, delayed acquisition of air righting reflex, decreased locomotor activity, and delayed vaginal patency. The AUC values at the NOAEL (<150 mg/kg/day in mice and 500 mg/kg/day in rats) for embryos and fetuses in the embryo-fetal development study in mice and rats were approximately <1.1-fold and 0.4-fold, respectively, as compared with the AUC following administration of simeprevir to humans.[64)]

3.(iii).A.(5).1) Rat study of fertility and early embryonic development to implantation (4.2.3.5.1.1)

Oral gavage doses of 0 (vehicle, PEG400), 50, 150, or 500 mg/kg/day simeprevir were administered once daily to SD rats (n = 24/sex/group): from 4 weeks prior to mating to the day of autopsy in males and from 2 weeks prior to mating to gestation day 7 in females. Salivation and abnormal breath sounds were sporadically observed in males in the 500 mg/kg/day group, but no effect was observed in relation to general toxicity, fertility, and early embryonic development in paternal and maternal animals. Based on the above reports, the NOAEL for general toxicity, fertility, and early embryonic development in parental animals was determined to be 500 mg/kg/day in this study.

3.(iii).A.(5).2) Embryo-fetal development studies

(a) Preliminary study in mice (reference 4.2.3.5.2.1)

Oral gavage doses of 0 (vehicle, PEG400), 150, 500, 1000, or 2000 mg/kg/day of simeprevir were administered to pregnant CD-1 mice (n = 6/group) from gestation days 6 to 15. Two maternal animals in the 1000 mg/kg/day group died on gestation days 12 and 15, but the cause of death was unknown. Loose stools were observed at ≥1000 mg/kg/day, and eyelid ptosis and decreased food consumption during the early period of treatment (gestation days 6-11) occurred at 2000 mg/kg/day, but there were no other smeprevir-related changes. Exencephalia and tongue protrusion in the fetus were observed in 6 of 50 animals in the 1000 mg/kg/day group and in 4 of 64 animals in the 2000 mg/kg/day group. Decreased fetal body weight was also observed in the 2000 mg/kg/day group.

(b) Study in mice (4.2.3.5.2.2)

Oral gavage doses of 0 (vehicle, PEG400), 150, 500, or 1000 mg/kg/day of simeprevir were administered to pregnant CD-1 mice (n = 19-23/group) from gestation day 6 to 15. Deterioration of clinical condition and decreased body weight and food consumption occurred in 2 of 22 maternal animals in the 1000 mg/kg/day group. These animals, which were subjected to emergency slaughter on gestation day 10, had total resorption of embryos. There were no other simeprevir-related changes in the surviving animals. Embryos and fetuses showed a dose-dependent increase in frequency of a skeletal abnormality (14th rib) at ≥150 mg/kg/day, increased frequency of delayed ossification (skull, thoracic vertebra, metacarpal bone, or metatarsal bone) at ≥500 mg/kg/day, and increased number of late-stage resorption and post-implantation losses as well as decreased fetal body weight in the 1000 mg/kg/day group. A relationship between delayed ossification and decreased fetal body weight was suggested in

the 1000 mg/kg/day group, but delayed ossification was not associated with decreased body weight in the 500 mg/kg group. No abnormalities were found in the number of live fetuses or in the sex ratio. Based on the above reports, the NOAEL was determined to be 500 mg/kg/day for maternal animals and <150 mg/kg/day for embryo-fetal development in this study.

(c) Study in rats (4.2.3.5.2.4)

Oral gavage doses of 0 (vehicle, PEG400), 50, 150, or 500 mg/kg/day of simeprevir were administered to pregnant SD rats (n = 21-24/group) from gestation day 6 to 17. Food consumption decreased in the early phase of treatment (gestation day 6-9) in the maternal animals in the 500 mg/kg/day group. However, the decrease was considered to be of low toxicological significance because the decrease was transient and had no effect on body weight. No other changes due to simeprevir treatment were seen in maternal animals. There was no simeprevir-related change in the fetus in any dose group. Based on the above reports, the NOAEL was determined to be 500 mg/kg/day for maternal animals and fetuses in this study.

3.(iii).A.(5).3) Rat study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.2)

Oral gavage doses of 0 (vehicle, PEG400), 150, 500, or 1000 mg/kg/day of simeprevir were administered to pregnant SD rats (n = 24/group) from gestation day 6 to lactation day 20. Dyspnoea including abnormal breath sounds or gasping respiration occurred in 2 maternal animals in the 1000 mg/kg/day group, and these animals were sacrificed on gestation days 10 and 18, respectively. The animals showed decreased body weight gain and food consumption at ≥150 mg/kg/day, and abnormal breath sounds and discolored stools at ≥500 mg/kg/day. Low body weight was observed on gestation day 20 at 1000 mg/kg/day, but body weight on gestation day 21 did not differ between the vehicle group and the simeprevir group. F1 pups showed a decreased body weight gain during the lactation period and decreased body weight at the time of weaning at ≥150 mg/kg/day. At ≥500 mg/kg/day, F1 pups had a low body weight even after reaching the age of approximately 35 days, delayed acquisition of air righting reflex, and delayed vaginal patency in females: a relationship between the delays and low body weight was suggested. There was decreased body weight gain at 1000 mg/kg/day after the age of approximately 35 days until the time of sacrifice in males and during the entire period until the day of mating in females. Decreased locomotor activity was also observed. Simeprevir treatment did not affect motor coordination after weaning, learning and memory, preputial cleavage, mating rate, fertility, and parameters for F2 early embryos. Based on the above reports, the NOAEL was determined to be <150 mg/kg/day for maternal animals and pups in this study.

3.(iii).A.(6) Local tolerance

3.(iii).A.(6).1) Bovine corneal opacity and permeability (BCOP) test (reference 4.2.3.6.1)

Isolated bovine cornea was exposed to the 20% simeprevir suspension (vehicle, physiological saline) for 4 hours, and the *in vitro* score was calculated based on the corneal opacity and pigment permeability. The results indicated a slight increase in the corneal opacity and permeability. Thus, the 20% simeprevir

suspension was considered to have mild eye irritancy.

3.(iii).A.(6).2) *In vitro* phototoxicity study (4.2.3.6.2)

BALB/c 3T3 mouse fibroblasts were exposed to 0.93 to 118.7 µg/mL of simeprevir (dissolved in DMSO and diluted with EBSS). Cell viability with or without UVA irradiation (5 J/cm^2 for 50 minutes) was measured by the uptake of neutral red. The photo-irritancy-factor (PIF) of simeprevir was 15.917 and the mean phototoxic effect (MPE) was 0.682, indicating the phototoxicity of simeprevir (PIF ≥ 5, MPE ≥ 0.15).

3.(iii).A.(6).3) *In vitro* phototoxicity study (second round) (4.2.3.6.3)

In vitro phototoxicity of simeprevir was investigated in the presence of albumin. BALB/c 3T3 mouse fibroblasts were exposed to 0.98 to 125 µg/mL of simeprevir (dissolved in DMSO and diluted with EBSS) and 0, 2, and 5 g/100 mL of bovine serum albumin (BSA) was added. The cell viability with or without UVA irradiation (5 J/cm^2 for 50 minutes) was measured by the uptake of neutral red. Simeprevir was shown to have phototoxicity (PIF ≥ 5, MPE ≥ 0.15), irrespective of addition of BSA. The PIF (50% effective dose [ED_{50}] without irradiation/ED_{50} with irradiation) and ED_{50} without irradiation increased with the amount of added BSA. However, the results were not interpreted as indicating an increase in phototoxicity because the ED_{50} with irradiation remained low when BSA was added.

3.(iii).A.(6).4) Murine local lymph node assay (4.2.3.6.4)

Simeprevir solution (25 µL) dissolved in DMF was applied once daily for 3 days to the pinnae of CBA/CaOlaHsd mice (n = 4/sex/group) at concentrations of 0%, 2.5%, 5%, and 10%. Tritium labeled thymidine (^{3}H-TdR) was administered intravenously on Day 5. The lymph nodes of the left and right pinnae were isolated after approximately 5 hours to measure the uptake of ^{3}H-TdR and to calculate the stimulation index. The results showed that the stimulation index was <3 in all simeprevir groups. Thus, the applicant considered that simeprevir is not a skin sensitizer.

3.(iii).A.(6).5) Primary skin irritation study in rabbits (4.2.3.6.5)

Simeprevir 0.5 g (1% aqueous solution) was applied to the shaved skin of NZW rabbits (2 females and 1 male) using gauze patches and left for 4 hours (application sites were covered with a semi-occlusive bandage). Skin was observed 1, 24, 48, and 72 hours after removal of the gauze patches. No response to stimuli was noted at any observation time point, and thus the applicant considered that simeprevir does not induce skin irritation.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Toxicity study of impurities

[redacted]

[redacted]

[redacted] 15,16) [redacted]

[redacted]

[redacted] Because 4 impurities, excluding **related substance C**, were contained in the test substance for the repeated dose toxicity studies in mice, rats, and dogs, safety was evaluated based on the results of the repeated dose toxicity studies. Based on the above reports, it is considered that the safety of the 5 impurities was confirmed.

(a) [redacted]

(4.2.3.7.6.1)

Oral gavage doses of 0 (vehicle, PEG400), 150, or 500 mg/kg/day of simeprevir were administered to SD rats (n = 5/sex/group) for 2 weeks. Decreased body weight, body weight gain and food consumption, and increased cholesterol were observed in the 500 mg/kg/day group, but these were considered to be of low toxicological significance because of no other findings. Therefore, the toxicological profile of the batch used in this study was considered to be similar to that of simeprevir used in preceding toxicological studies.

(b) Genotoxicity (4.2.3.7.6.2 to 9)

[redacted]

3.(iii).A.(7).2) Bovine corneal opacity and permeability (BCOP) comparative tests (reference 4.2.3.7.7.3)

Since airway inflammation occurred due to simeprevir administration in mouse 3-month and rat 6-month repeated oral gavage dose toxicity studies, the irritancy of formulated simeprevir was evaluated by BCOP tests. [redacted] A similar test was conducted using negative control (PEG400, physiological saline) and positive control (100% DMF and 20% imidazole). [redacted] When exposed to simeprevir formulation suspended in an aqueous 0.5% methylcellulose solution, the *in vitro* score could not be determined because the suspension became pasty with heavy precipitation after 4 hours of treatment. However, histopathological examination revealed mild injury to the corneal epithelium at

≥50mg/kg.

3.(iii).A.(7).3) Cytotoxicity study using hepatocytes (Reference 4.2.3.7.7.4)

[redacted] Their primary cells were exposed to 0.5 to 100 μmol/L of simeprevir for 23 to 28 hours, and lactase dehydrogenase (LDH) release, neutral red uptake, and ATP content were measured. The ED_{50} values for the parameters ranged from 5.49 to 34.5 μmol/L (4.12-25.9 μg/mL) in human cells, and did not differ significantly among animal species. Given that the amount of unbound simeprevir in plasma is extremely small, and that the media did not contain protein, it is considered that the above ED_{50} values cannot be extrapolated to humans.

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

3.(iii).B.(1) Safety of combination therapy with three drugs

PMDA asked the applicant to explain whether a combination therapy including simeprevir may enhance effects on the liver, and whether regular liver function tests are necessary in clinical practice, based on the report that hepatic cell necrosis was observed in repeated dose toxicity studies of simeprevir in dogs, in which the exposure at NOAEL was below the clinical exposure level, and that effects on the liver were also detected in non-clinical toxicity studies of RBV.[66)]

The applicant explained as follows:

Since simeprevir as well as RBV resulted in hepatic cell necrosis accompanied by increases in ALT or AST in the non-clinical toxicity studies, it cannot be ruled out that triple therapy with simeprevir, Peg-IFN, and RBV may enhance effects on the liver. However, it is unlikely that triple therapy causes pharmacodynamic drug interactions in humans. In the Japanese clinical studies (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3004, HPC3008, and HPC3010), blood bilirubin increased transiently, but the change did not accompanied by increases in ALT or AST, and the effects on the liver were not of not major concern in the triple therapy group. In addition, based on the results of non-clinical studies, it is inferred that the transient increase in blood bilirubin is related to the inhibition of the major transporters involved in bilirubin uptake into the liver and bile acid excretion. Therefore, regular liver function tests that are routinely conducted in patients with chronic hepatitis C virus infection are sufficient for clinical monitoring of hepatic function.

PMDA accepted the applicant's explanation, but the effects of triple therapy on the liver when simeprevir is used in clinical practice will be discussed in "4.(iii).B.(2) Safety."

3.(iii).B.(2) Effects on pancreas observed in mice and rats

Given that repeated dose toxicity studies detected effects on the pancreas in mice and rats (increased pancreas weight, morphological changes [acinar cell vacuolization, decreased zymogen granules or basophilic changes, and apoptosis], and increased amylase/lipase), but not in dogs and monkeys, PMDA

66) Copegus Tablet 200 mg (ribavirin) Review report (dated on December 7, 2006)

asked the applicant to explain the factors to cause species differences and the extrapolation of the effects on the pancreas to humans.

The applicant explained as follows:
The differences among species are attributable to the difference in the dose given by oral gavage and species differences in the sensitivity to trypsin inhibitors. The doses given by oral gavage ranged from 5 to 10 mL/kg in rodents while being 1 to 2 mL/kg in dogs and monkeys. Simeprevir was in contact with the small intestine for a longer time in rodents, resulting in higher exposure levels in the intestinal tract. Since simeprevir shows the inhibitory activity against pancreatic protease (4.2.1.1.2), local activity of simeprevir as a protease inhibitor may have tended to be enhancedin the intestinal tract. Moreover, it has been reported that there are species differences in sensitivity to trypsin inhibitors. After dietary administration of raw soybean powder (a known trypsin inhibitor), swelling of the pancreas occurs in rats, but not in pigs and monkeys.[67] In addition, it has been reported that trypsin inhibitors are more likely to cause the enlarged pancreas in rats and mice because the relative weight of the pancreas in rodents (pancreas weight, >0.3% of body weight) is greater than that in dogs, pigs, and humans (pancreas weight, <0.3% of body weight).[68]

In the toxicity studies in rodents, a highly viscous formulation was administered at a high dose and volume when given by oral gavage, and animals continuously consumed feed admixture of simeprevir when a dietary dose was given. Thus, the duration of local exposure in the gastrointestinal tract was longer in both studies than in clinical studies in humans. Taking the above into account, it is considered that the local inhibitory activity of pancreatic proteases by simeprevir was more potent and longer in rodents than in humans.

Based on the above reports, it is unlikely that simeprevir will have any effect on the pancreas in humans. Moreover, the incidence of gastrointestinal disorder related events was lower in the simeprevir combination therapy group than in the control group (Peg-IFN and RBV combination therapy group) in the Japanese clinical studies. Lipase and amylase levels showed no clinically significant changes over time.

PMDA accepted the applicant's explanation that it is unlikely that simeprevir will have any effect on the pancreas in humans.

3.(iii).B.(3) Phototoxicity

PMDA asked the applicant to explain the clinical phototoxicity risk of simeprevir and the necessity of including the results of phototoxicity studies in the package insert, based on the facts that positive results were obtained in an *in vitro* phototoxicity study, and that photosensitivity related events were observed only in the simeprevir group in Japanese clinical studies, albeit with a low incidence.

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67) Struthers BJ, et al. *J Nutr.* 1983;113:86-97
68) Liener I, et al. *J Am Oil Chem Soc.* 1979;56:121-129

The applicant explained as follows:

A photosafety study of simeprevir in foreign healthy adult subjects (Study C125) indicated that there was no clinically significant skin photosensitivity. However, positive results were obtained in *in vitro* phototoxicity studies, and photosensitivity related events were observed only in the subjects treated with simeprevir in Japanese clinical studies (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3004, HPC3008, and HPC3010),[69)] albeit with a low incidence. In addition, the incidence of photosensitivity related events was higher in the simeprevir group than in the placebo group in the pooled analysis of foreign phase III studies (Studies C208, C216, and HPC3007), although the incidence was low.[70)] In particular, 2 cases of photosensitivity reaction in subjects who received simeprevir 150 mg for 12 weeks were considered to be serious adverse events.

Based on the above reports, the applicant will provide a caution by including the results of phototoxicity studies in the package insert.

PMDA accepted the applicant's explanation.

4. Clinical data

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

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

Results submitted as biopharmaceutic studies included those from a relative bioavailability (BA) study and a food effect study in Japanese healthy adult subjects, as well as 5 clinical studies (4 relative BA studies and 1 food effect study) in foreign healthy adult subjects. This section mainly describes the biopharmaceutic studies in Japanese subjects.

The simeprevir concentration in human plasma was measured by liquid chromatography/tandem mass spectrometry (LC/MS/MS; lower limit of quantification, 2.00 mg/mL).

Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or mean ± standard deviation.

4.(i).A.(1) Relative BA studies

4.(i).A.(1).1) Relative BA study in Japanese healthy adult subjects (5.3.1.2.1, Study HPC1003 [April 2012 to June 2012])

A single oral 100-mg dose, either F020 formulation ([redacted] mg/capsule) used in Japanese phase II studies or G008 formulation ([redacted] mg/capsule) used in Japanese phase III studies, was administered to 69 Japanese healthy adult male subjects (36 subjects in panel 1, 33 subjects in panel 2 [number of subjects

69) The incidence was 1.1% (5 of 436 subjects) in the simeprevir group and 0% (0 of 73 subjects) in the control group in the pooled analysis of 5 Japanese clinical studies.

70) The incidence was 3.3% (26 of 781 subjects) in the simeprevir group and 0.5% (2 of 397 subjects) in the control group in the pooled analysis of foreign phase III clinical studies.

for pharmacodynamic analysis][71]) in the fasted state[72] or after a meal[73] to study BA in a 2-period crossover comparative study[74].

Following administration in the fasted state, the ratio of least squares mean [90% confidence interval (CI)] of maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve from time zero to the last quantifiable time point (AUC_{last}) for F020 and G008 formulations was 1.10 [0.99, 1.22] and 1.09 [0.99, 1.19], respectively.

Following administration after a meal, the ratio of least squares mean [90% CI] of C_{max} and AUC_{last} for F020 and G008 formulations was 0.99 [0.93, 1.06] and 0.98 [0.93, 1.02], respectively.

4.(i).A.(2) Food effect studies

4.(i).A.(2).1) Food effect study in Japanese healthy adult subjects (5.3.1.2.5, Study HPC1007 [June 2012 to July 2012])

A 2-period crossover comparative study was conducted in 23 Japanese healthy adult male subjects (number of subjects for pharmacodynamicevaluation) to study the effect of food following a single oral 100-mg dose of G008 formulation ([redacted] mg/capsule, prepared for Japanese phase III studies). A single capsule was administered after ≥10 hours of fasting or within 10 to 15 minutes after consumption of a standard Japanese-style breakfast (approximately 450 kcal in total).[75]

The fed/fasted ratios of least squares mean [90% CI] for C_{max} and AUC_{∞} were 1.02 [0.87, 1.19] and 0.97 [0.84, 1.12], respectively.

4.(i).A.(2).2) Food effect study in foreign healthy adult subjecs (reference 5.3.1.2.6, Study C116 [March 2011 to June 2011])

A 3-period crossover comparative study was conducted in 24 foreign healthy adult subjects (number of subjects for pharmacodynamic evaluation) to study the effect of food following a single oral 150-mg dose of G007 formulation ([redacted] mg/capsule, prepared for foreign phase III studies). A single capsule was administered after ≥10 hours of fasting or 30 minutes after consumption of a standard breakfast (533 kcal in total) or high-fat breakfast (928 kcal in total) was started.[76]

The fed (standard breakfast)/fasted ratios of least squares mean [90% CI] for C_{max} and AUC_{∞} were 1.60 [1.30, 1.96] and 1.69 [1.36, 2.08], respectively. The fed (high-fat breakfast)/fasted ratio of least squares mean [90% CI] for C_{max} and AUC_{∞} were 1.49 [1.22, 1.82] and 1.61 [1.33, 1.93], respectively.

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

71) A single dose was given under fasting condition in panel 1, and after a meal in panel 2.
72) Each formulation was given after ≥10 hours of fasting.
73) Each formulation was given within 10 to 15 minutes after consumption of a Japanese-style breakfast (approximately 700 kcal in tota, low-fat meal)
74) A 9-day washout period was set between each treatment/observation period.
75) A 9-day washout period was set between each treatment/observation period.
76) A 7-day washout period was set between each treatment/observation period.

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

Although little effect of food on the pharmacokinetic parameters was found in Japanese subjects following administration of simeprevir, the C_{max} and AUC_{∞} were approximately 1.6-fold higher in the fed state than in the fasted state in foreign subjects. Consequently, PMDA asked the applicant to explain why food effect on the exposure to simeprevir differed between Japanese and foreign subjects.

The applicant explained as follows:

Because the dissolution of simeprevir decreases with decrease in pH (comparisons under the conditions of 0.1 mol/L hydrochloric acid, pH4.5 phosphate buffer, and pH6.8 phosphate buffer), and because gastrointestinal pH is lower in the fasted state than in the fed state,[77)] dissolution in the gastrointestinal tract may be lower when simeprevir is administered orally in the fasted state, as compared with in the fed state. In addition, the [redacted] mg formulation may be more sensitive to the change in dissolution than the [redacted] mg formulation because of its higher simeprevir content.

In a food effect study (Study HPC1007) in Japanese subjects, the dose was administered after consumption of the Japanese-style breakfast (approximately 450 kcal) with 200 mL of water, but in Study C116 in foreign subjects, the dose was administered after consumption of the Western-style breakfast (standard meal [533 kcal] or high-fat meal [928 kcal]) with 240 mL of water, indicating a difference between the Japanese and foreign studies. However, a foreign food effect study (Study C116) suggested that the food type does not affect the degree of increase in the exposure level. On the other hand, if the dose in the Japanese and foreign food effect studies (Japanese study, Study HPC1007; foreign study, Study C116) is taken into consideration, based on the difference in the amount of water consumed when taking simprevir, the theoretical highest simeprevir concentration in the gastrointestinal tract after administration is 0.5 mg/mL (100 mg/200 mL) in Japanese subjects and 0.625 mg/mL (150 mg/240 mL) in foreign subjects. Therefore, the amount of water relative to the amount of drug in the gastrointestinal tract was lower in Study C116 conducted in foreign subjects than in Study HPC1007 conducted in Japanese subjects. This difference may have affected the dissolution of simeprevir administered under fasting conditions.

Although little change in the exposure level of simeprevir by food was observed in Japanese subjects, there was an approximately 1.6-fold increase in C_{max} and AUC_{∞} in foreign subjects due to food. This may be because the differences in the dose of simeprevir and the amount of water consumed when taking simeprevir affected the dissolution of simeprevir.

PMDA considered as follows:

It is not rule out that the absorption of simeprevir may have been affected by the differences in the dose and the amount of water consumed when taking the drug, which were as contributing factors mentioned in the applicant's discussion, but it is difficult to conclude that there was no food effect because factors for different results obtained from the Japanese and foreign studies has not been clarified. However,

77) Asahi H, et al. Japanese Journal of Gastroenterological Surgery. 1984;17(10):1803-1807

there is no high necessity to provide a caution about food including the amount of water consumed in the clinical use of simeprevir, for the following reasons:

- Although C_{max} and AUC_{∞} increased approximately 1.6-fold under fed conditions in foreign healthy adult subjects in the food effect study (Study C116), the incidence of adverse events was comparable irrespective of whether simeprevir was taken with or without food,[78)] and the tolerability was favorable. The exposure level was comparable between 150 mg simeprevir administered to foreign patients with chronic hepatitis C virus infection and 100 mg simeprevir administered to Japanese patients with chronic hepatitis C virus infection [see "4.(ii).B.(1) Pharmacokinetics of simeprevir"].
- Although the exposure level was higher in Japanese patientss with chronic hepatitis C virus infection than in Japanese healthy adult subjects [see "4.(ii).B.(2) Pharmacokinetics in patients"], there would appear to be no specific safety concern based on the safety data [see "4.(iii).B.(2) Safety"] from the Japanese clinical studies[79)] in patients with chronic hepatitis C virus infection (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3004, HPC3008, and HPC3010).

4.(ii) Summary of clinical pharmacology studies

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

As studies to evaluate simeprevir pharmacokinetics, a phase I study in Japanese healthy adult male subjects, a QT/QTc study in foreign healthy adult subjects, a Japanese phase II study in Japanese patients, and 4 Japanese phase III studies were submitted as evaluation data for this application. As reference data, the results of 2 phase I studies in foreign healthy adult subjects, 2 pharmacokinetic studies in foreign patients with hepatic or renal impairment, 12 drug interaction studies in foreign healthy adult subjects and foreign subjects receiving a methadone maintenance therapy, a photosafety study, 3 foreign phase II studies in foreign patients, and 3 foreign phase III studies were submitted. In this section, mainly the clinical pharmacological studies in Japanese subjects will be described.

Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or mean ± standard deviation.

4.(ii).A.(1) Studies using human biomaterials

The following was investigated: cell membrane permeability of simeprevir using Caco-2 cell monolayer; plasma protein binding using human plasma, HSA, and AGP; various transporters; metabolism using human hepatic microsome; effect on CYP using human hepatocytes [see "3.(ii).A.(2) Distribution, (3) Metabolism, (5) Pharmacokinetic drug interactions, and (6) Other pharmacokinetic studies"].

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78) The incidences of adverse events reported following administration of simeprevir in the fasted state, after a standard meal, and after a high-fat meal were 37.5% (9 of 24 subjects), 29.2% (7 of 24 subjects), and 25.0% (6 of 24 subjects), respectively.

79) Food is not specified in relation to simeprevir administration.

4.(ii).A.(2) Studies in healthy adult subjects

4.(ii).A.(2).1) Phase I study in Japanese healthy adult male subjects (5.3.3.1.1, Study C109 [August 2008 to November 2008])

Pharmacokinetics was investigated in 24 Japanese healthy adult male subjects (subjects for pharmacokinetic evaluation, 8 subjects in each group), who received simeprevir (F002 solution) 100, 200, or 400 mg as a single oral dose and multiple oral doses[80] once daily (QD) for 5 days.

The pharmacokinetic parameters following a single dose are shown in the following table. The C_{max} and AUC increased more than dose-proportionally, but the time to maximum plasma concentration (t_{max}) (median) and elimination half-life ($t_{1/2}$) in the final phase were comparabl0e at all doses.

Table. Pharmacokinetic parameters following a single dose of simeprevir (solution) 100 to 400 mg

	Dose		
	100mg	200mg	400mg
	8 subjects	8 subjects	8 subjects
C_{max} (ng/mL)	926.9 ± 456.9	3036 ± 942.1	12340 ± 3961
t_{max} (h)[a)]	6.0 (4.0-16.0)	7.0 (4.0-8.0)	6.0 (4.0-8.0)
AUC_{24h} (ng·h/mL)	9653 ± 3831	31480 ± 12980	119800 ± 35020
AUC_{∞} (ng·h/mL)	12120 ± 4823	39530 ± 17800	161600 ± 66170
$t_{1/2}$ (h)	9.7 ± 1.7	10.8 ± 1.2	11.4 ± 3.3

a) Median (range)
AUC_{24h}: AUC from time zero to 24 hours

The pharmacokinetic parameters following multiple doses are shown in the following table. The minimum plasma concentration (C_{min}), C_{max}, and AUC_{24h} after multiple oral doses of simeprevir QD for 5 days increased a more than dose-proportional manner. Plasma concentration of simeprevir reached a steady state on Day 5 in the 100 mg group but not in the 200 and 400 mg groups.

Table. Pharmacokinetic parameters following multiple oral doses of simeprevir (solution) 100 to 400 mg for 5 days

	Dose		
	100mg	200mg	400mg
	7 subjects	8 subjects	6 subjects
C_{0h} (ng/mL)	307.6 ± 221.1	2214 ± 1371	18030 ± 2686
C_{min} (ng/mL)	261.0 ± 194.9	1984 ± 1224	15320 ± 3188
C_{max} (ng/mL)	1655 ± 652.6	6889 ± 3585	31300 ± 5789
t_{max} (h)[a)]	6.0 (4.0-6.0)	6.0 (4.0-8.0)	5.0 (4.0-6.0)
AUC_{24h} (ng·h/mL)	17260 ± 8417	89930 ± 45380	536800 ± 85600
$t_{1/2}$ (h)	10.0 ± 1.8	14.2 ± 3.8	38.5 ± 19.9
Cumulative rate (%)[b)]	193.9 ± 67.6	285.2 ± 106.9	448.9 ± 85.6

a) Median (range), b) AUC_{24h} after multiple doses/AUC_{24h} after a single dose
C_{0h}: plasma concentration before administration

4.(ii).A.(2).2) Phase I studies in foreign healthy adult subjects

(a) Phase I single-dose study in foreign healthy adult subjects (reference 5.3.3.1.3, Study C103 [February 2008 to April 2008])

Mass balance and metabolic profile were investigated by giving a single dose of ^{14}C-simeprevir (FK6555 solution) 200 mg to 6 foreign healthy adult male subjects.

80) Subjects received a single dose of simeprevir at the assigned dose level, followed by a 72-hour washout period, and then, followed by 5-day multiple oral doses at the same dose level.

The C_{max}, AUC_{last}, and AUC_{∞} of unchanged simeprevir in plasma accounted for 87.3%, 82.9%, and 84.2%, respectively, of those of total radioactivity in plasma, indicating that the majority of radioactivity in plasma was unchanged simeprevir. A small amount of M21 (oxidized form) was detected as a metabolite in plasma (8.0% of AUC_{24h} of unchanged simeprevir). The t_{max} (median) and $t_{1/2}$ of total plasma radioactivity were comparable to those of unchanged simeprevir. The ratio of blood radioactivity concentration to plasma radioactivity concentration (blood/plasma ratio) was 61.2% to 69.1% irrespective of the time after administration. By 8 days post-dose, 91.2% of the dose was recovered in urine and feces. Most of the radioactivity (58.9%-101.0% of the dose) was recovered in feces, and the recovery rate of radioactivity in urine was as small as 0.009% to 0.138% of the dose.[81)] Radioactivity excreted in feces as unchanged simeprevir was 31.0% of the dose. The amount of M21 (oxidized form) and M22 (oxidized form) excreted in feces was 25.9% of the dose in total (M21/M22 ratio of 60/40), indicating that M21 and M22 were the major metabolites in feces. The metabolites whose excretion rate in feces was >1% of the dose were M11, M16, M18, and M27. Other minor metabolites included M5, M14, M23, M24, M25, and M26.

(b) Phase I repeat-dose study in foreign healthy adult subjects (reference 5.3.3.1.2, Study C101 [January 2007 to September 2007])

Pharmacokinetics was investigated in 33 foreign healthy adult subjects (the number of subjects for pharmacokinetic evaluation: Part I, 6 subjects each in Panel 1 and Panel 2; Part II,[82)] 4 subjects in Panel 3, 5 subjects in Panel 4, 6 subjects each in Panel 5 and Panel 6), who received a single oral dose or multiple oral doses of simeprevir. In addition, pharmacokinetics of simeprevir following multiple oral doses was also investigated as Part III in 6 foreign male patients with chronic hepatitis C virus infection (genotype 1) who had failed to respond to or had relapsed after prior treatment with either IFN and RBV or Peg-IFN and RBV.

In Part I, a single dose of placebo (vehicle, PEG400) or simeprevir (F002 solution) 50, 100, 200, 300, 450, and 600 mg[83)] was given after a meal.[84)] In Part II, multiple oral doses of simeprevir (F002 solution) 100, 200, and 400 mg QD or simeprevir (F002 solution) 200 mg twice daily (BID) were given in the fed state for 5 days. In Part III, multiple oral doses of simeprevir (F002 solution) 200 mg QD were given in the fed state for 5 days.

The pharmacokinetic parameters following a single dose of simeprevir are shown in the following table. The C_{max} and AUC of plasma simeprevir increased with dose. There were more than dose-proportional increases between the 100 and 200 mg groups as well as between the 300 and 450 mg groups. The excretion rate of unchanged simeprevir in urine was approximately ≤0.006% in all treatment groups.

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81) A subject whose recovery rate in feces was 58.9% showed a total recovery rate of 59.1%. Apart from this subject, the recovery rate in feces was 93.0% to 101.0% of the administered radioactivity.

82) Simeprevir 100, 200, and 400 mg was administered once daily for 5 days in Panel 3, 4, and 6, respectively. In Panel 5, simeprevir 200 mg was administered in the fed state twice daily for 5 days.

83) Simeprevir was administered at 50, 200, and 450 mg in Panel 1, and at 100, 300, and 600 mg in Panel 2. A ≥10-day washout period was established between each treatment period.

84) In Panel 1, an additional single oral dose of simeprevir 200 mg was administered in the fasted state.

Table. Pharmacokinetic parameters following a single oral dose of simeprevir (solution) 50 to 600 mg

	In the fed state						In the fasted state
	50mg	100mg	200mg	300mg	450mg	600mg	200mg
	6 subjects	6 subjects	6 subjects	6 subjects	6 subjects	6 subjects	5 subjects
t_{max} (h)	5.0 (3.0-6.0)	5.0 (4.0-6.0)	6.0 (4.0-6.0)	6.0 (4.0-6.0)	6.0 (4.0-6.0)	6.0 (4.0-6.0)	4.0 (3.0-6.0)
C_{max} (ng/mL)	293.5 ± 96.1	582.0 ± 86.2	2957 ± 1022	5092 ± 786.1	10460 ± 2458	13550 ± 1787	2944 ± 1767
AUC_{last} (ng·h/mL)	4209 ± 2139	7550 ± 1630	37550 ± 14820	54720 ± 15890	175500 ± 69210	225000 ± 42670	35400 ± 19970
AUC_{∞} (ng·h/mL)	4283 ± 2218	7621 ± 1630	38150 ± 15500	55060 ± 16180	182400 ± 78910	229100 ± 46350	35740 ± 20090
$t_{1/2}$ (h)	9.8 ± 2.7	9.5 ± 1.3	10.9 ± 2.8	9.8 ± 1.4	13.3 ± 4.1	11.7 ±2.0	10.5 ± 2.4

t_{max}: Median (range)

The geometric mean ratio [90% CI] of C_{max}, AUC_{last}, and AUC_{∞} after administration of 200 mg of simeprevir in the fed state to those in the fasted state was 1.18 [0.62, 2.23], 1.19 [0.68, 2.08], and 1.20 [0.68, 2.09], respectively.

The pharmacokinetic parameters following multiple doses of simeprevir in the fed state are shown in the following table. The C_{min}, C_{max}, and AUC_{24h} of plasma simeprevir increased more than dose-proportionally, and the AUC_{24h} after the first dose and the multiple doses increased 3.9- and 10.5-fold, respectively, between the 100 and the 200 mg groups. A steady state was achieved on Day 5 in the 100 mg group, but not by Day 5 in other treatment groups. The excretion rate of unchanged simeprevir in urine was approximately ≤0.021% in all treatment groups.

Table. Pharmacokinetic parameters following multiple oral doses of simeprevir (solution) 100 to 400 mg in the fed state for 5 days

		Dosage regimen			
		100 mg QD	200 mg QD	200 mg BID	400 mg QD
		4 subjects	5 subjects	6 subjects	6 subjects
Day 1	C_{max} (ng/mL)	679.8 ± 174.3	2304 ± 917.8	2790 ± 622.0	7088 ± 1350
	AUC_{24h} (ng·h/mL)	6353 ± 1605	24630 ± 7331	20230 ± 4377[a)]	75700 ± 15510
Day 3	C_{0h} (ng/mL)	81.7 ± 30.7	749.0 ± 373.7	7663 ± 3696	3073 ± 1497
Day 4	C_{0h} (ng/mL)	77.6 ± 30.9	1005 ± 560.0	11280 ± 4672	6342 ± 3282
Day 5	C_{0h} (ng/mL)	97.1 ± 38.9	1482 ± 791.3	15590 ± 5326	8560 ± 4301
	t_{max} (h)	4.0 (4.0-6.0)	4.0 (3.93-8.0)	4.0 (3.0-6.0)	4.0 (3.0-6.0)
	C_{min} (ng/mL)	88.3 ± 32.2	1445 ± 767.3	13460 ± 4725	7795 ± 4015
	C_{max} (ng/mL)	758.3 ± 208.2	6172 ± 2859	21830 ± 5339	19380 ± 6251
	AUC_{24h} (ng·h/mL)	7620 ± 1912	79710 ± 37230	216800 ± 62690	332100 ± 120300
	$t_{1/2}$ (h)	7.7 ± 0.73	16.0 ± 5.1	37.6 ± 27.7	21.5 ± 11.9
	Cumulative rate (%)[b)]	120.1 ± 5.3	316.0 ± 101.2	1073 ± 196.4	431.8 ± 82.6

t_{max}: Median (range)
a) AUC_{12h}, b) AUC_{24h} after multiple doses/AUC_{24h} after the first dose

Following multiple oral doses of simeprevir 200 mg QD in the fed state for 5 days in patients with chronic hepatitis C virus infection, the C_{max} and AUC_{24h} of plasma simeprevir after the first dose were 4067 ± 1479 ng/mL and 56,430 ± 22,470 ng·h/mL, respectively. The C_{0h}, C_{min}, C_{max}, and AUC_{24h} of plasma simeprevir after multiple oral doses were 6057 ± 4213 ng/mL, 5743 ± 4089 ng/mL, 11,470 ± 5337 ng/mL, and 206,000 ± 113,600 ng·h/mL, respectively. Following multiple oral doses, the t_{max} (median), $t_{1/2}$, and cumulative rate were 4.0 hours, 41.3 hours, and 344.8%, respectively. The excretion rate of unchanged simeprevir in urine was approximately ≤0.016%.

4.(ii).A.(3) Studies in patients

4.(ii).A.(3).1) Late phase II study in Japanese subjects with chronic hepatitis C virus infection (5.3.5.1.2, Study C215 [July 2009 to April 2011])

Pharmacokinetics was investigated in 26 treatment-naïve[85)] Japanese patients with chronic hepatitis C virus infection (genotype 1)[86)] (number of subjects for pharmacokinetic evaluation who underwent frequent blood sampling), who received multiple oral doses of simeprevir 50 mg ([redacted] mg/capsule) or 100 mg ([redacted] mg/capsule) QD in combination with Peg-IFNα-2a and RBV (hereinafter referred to as PR[87)]) for 12 or 24 weeks.

The C_{max} and AUC_{24h} of plasma simeprevir increased more than dose-proportionally (C_{max} and AUC_{24h} were 1011 ± 725 ng/mL and 11182 ± 7763 ng•h/mL, respectively, in the 50 mg group and 4072 ± 3446 ng/mL and 60197 ± 65364 ng•h/mL, respectively, in the 100 mg group). Irrespective of doses, the t_{max} (median) was 5.97 to 6.00 hours. Since there was no marked difference in the C_{0h} of plasma simeprevir at Weeks 4, 12, and 24 among the dosage-regimen groups, the plasma simeprevir concentration may have reached a steady state by Week 4 during the multiple oral administration of simeprevir QD. The C_{0h} of serum Peg-IFNα-2a and plasma RBV at Weeks 4, 12, and 24 was comparable in all groups irrespective of simeprevir administration.

4.(ii).A.(3).2) Phase III studies in Japanese patients with chronic hepatitis C virus infection (5.3.5.1.5, Study HPC3003 [January 2011 to October 2012]; 5.3.5.2.1, Study HPC3008 [December 2010 to August 2012]; 5.3.5.2.2, Study HPC3004 [January 2011 to September 2012]; 5.3.5.2.3, Study HPC3010 [April 2011 to November 2012])

As part of the Japanese phase III studies (Studies HPC3003, HPC3004, HPC3008, and HPC3010[88)]), pharmacokinetics of simeprevir was investigated by population pharmacokinetic (PPK) analysis in Japanese patients with chronic hepatitis C virus infection (genotype 1) who were treatment-naïve, had relapsed after prior treatment,[89)] or had failed to respond to prior treatment[90)] using the plasma simeprevir concentrations (375 subjects, 2938 sampling points) obtained by multiple oral doses of simeprevir 100 mg QD for 12 or 24 weeks in combination with PR.

The pharmacokinetic parameters based on the PPK analysis are shown in the following table. The C_{0h}, C_{max}, and AUC_{24h} of plasma simeprevir in patients who had relapsed after prior treatment were comparable to or higher than those in treatment-naïve patient and patients who had failed to respond to

85) Patients who had never received treatment with any IFN or Peg-IFN product.
86) Plasma HCV RNA level was ≥5.0 Log IU/mL.
87) Hereinafter, the dosages of Peg-IFNα-2a and RBV are as follows unless otherwise specified.
Peg-IFNα-2a 180 μg was administered subcutaneously once weekly. RBV was administered orally at 600 mg/day (body weight, ≤60 kg), 800 mg/day (body weight, >60 kg and ≤80 kg), or 1000 mg (body weight, >80 kg).
88) In this study, Peg-IFNα-2b and RBV were used as PR. Peg-IFNα-2b 1.5 μg/kg was administered subcutaneously once weekly. RBV was administered orally at 600 mg/day (body weight, ≤60 kg), 800 mg/day (body weight, >60 kg and ≤80 kg), or 1000 mg (body weight, >80 kg).
89) Patients who became negative by ≥24 weeks of IFN treatments (combination therapy of Peg-IFN+RBV or IFN+RBV, and monotherapy of IFN or Peg-IFN), but relapsed within 1 year after the last treatment.
90) Patients whose plasma HCV RNA had never become negative despite ≥24 weeks of IFN treatment (combination therapy of Peg-IFN+RBV or IFN+RBV, and monotherapy of IFN or Peg-IFN) or patients whose IFN treatment was <24 weeks because plasma HCV RNA decreased by <2 Log IU/ml at Week 12 from the baseline.

prior treatment. Interindividual variability of C_{0h}, C_{max}, and AUC_{24h} of plasma simeprevir was large in all clinical studies. Following administration of simeprevir in combination with Peg-IFNα-2a and RBV (Studies HPC3003, HPC3004, and HPC3008) or with Peg-IFNα-2b and RBV (Study HPC3010), the C_{0h}, C_{max}, and AUC_{24h} of plasma simeprevir did not differ significantly between the two Peg-IFN products used in the combined treatment. The applicant explained that pharmacokinetic interaction is unlikely to occur between simeprevir and Peg-IFNα-2b or Peg-IFNα-2a because neither of the Peg-IFN products affected CYP3A, the major metabolizing enzyme for simeprevir, in a study[91] in which the effect on CYP isoenzymes was investigated by administrating Peg-IFNα-2b or Peg-IFNα-2a to patients with chronic hepatitis C virus infection and healthy adults.

Table. Pharmacokinetic parameters following multiple oral doses of simeprevir 100 mg (QD) in combination with PR in patients with chronic hepatitis C virus infection

Study	Study HPC3003[a]	Study HPC3004[a]		Study HPC3008[a]	Study HPC3010[b]		
Target patients	Treatment-naïve patients	Patients who had failed to respond to prior treatment		Relapsed patients	Treatment-naïve patients	Patients who failed to respond to prior treatment	Relapsed patients
Duration of treatment	12 weeks	12 weeks	24 weeks	12 weeks	12 weeks	12 weeks	12 weeks
Number of subjects	123	53	53	49	24	26	29
C_{0h} (ng/mL)	1581 ± 1719 (64-8543)	2264 ± 1985 (194-8461)	1787 ± 2297 (142-10209)	2668 ± 2447 (145-10693)	1028 ± 780 (171-2842)	1749 ± 2141 (184-9167)	2746 ± 2591 (287-9520)
C_{max} (ng/mL)	3145 ± 1762 (1317-10161)	3855 ± 2013 (1631-10074)	3361 ± 2341 (1536-11882)	4257 ± 2475 (1545-12273)	2593 ± 817 (1593-4450)	3330 ± 2165 (1616-10776)	4343 ± 2608 (1780-11117)
AUC_{24h} (ng·h/mL)	55775 ± 42790 (11569-225205)	73058 ± 48813 (18612-223155)	60887 ± 56605 (16296-266070)	82764 ± 59912 (16480-276230)	42402 ± 20081 (17659-87904)	60227 ± 52444 (18222-240055)	84868 ± 63074 (22208-248340)
CL/F (L/h)	2.74 ± 1.68	2.05 ± 1.25	2.67 ± 1.50	1.98 ± 1.44	2.83 ± 1.16	2.46 ± 1.23	1.83 ± 1.17

Mean ± standard deviation (range)
a) Study of combination therapy with Peg-IFNα-2a and RBV, b) Study of combination therapy with Peg-IFNα-2b and RBV
CL/F: Apparent total body clearance after extravascular administration

A PPK analysis was conducted using the plasma simeprevir concentrations (436 subjects, 3790 sampling points) obtained from Japanese clinical studies in patients with chronic hepatitis C virus infection (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3004, HPC3008, and HPC3010). Body weight and age were used as covariates for apparent volume of distribution (V_c/F) in the central compartment after extravascular administration; body weight was used as a covariate for apparent maximal elimination velocity (V_{max}/F) in the Michaelis-Menten equation. Based on the age and body weight data of Japanese patients with chronic hepatitis C virus infection used in the PPK analysis, plasma simeprevir concentrations in a young adult subject with high body weght (34 years, 78.68 kg) and an elderly subject with low body weight (68 years, 44.18 kg) were simulated. The results indicated that the C_{0h} and AUC_{24h} of plasma simeprevir in the young adult subject with high body weight were 71% and 60%, respectively, to the population values (58.5 years, 57.25 kg) and that those in the elderly subject with low body weight were 120% and 125%, respectively.

91) Gupta SK, et al. *Eur J Clin Pharmacol*. 2011;67:591-599, Brennan BJ, et al. *Br J Clin Pharmacol*. 2012;75(2):497-506

4.(ii).A.(4) Assessment of intrinsic factors

4.(ii).A.(4).1) Pharmacokinetic study in patients with hepatic impairment (reference 5.3.3.3.1, Study C113 [February 2010 to July 2011])

Pharmacokinetics was investigated in 8 foreign healthy adult subjects and 16 foreign patients with hepatic impairment (8 patients each with moderate [Child-Pugh classification B] and severe [Child-Pugh classification C] hepatic impairment), who received multiple oral doses of simeprevir ([redacted] mg/capsule) 150 mg QD for 7 days. The pharmacokinetic parameters in the healthy adults and patients with hepatic impairment are shown in the following table. The ratios [90% CI] of least squares mean of the pharmacokinetic parameters in patients with moderate and severe hepatic impairment to healthy adults were 1.71 [1.02, 2.88] and 3.13 [1.87, 5.26], respectively, for C_{max} and 2.44 [1.36, 4.38] and 5.22 [3.10, 8.79], respectively, for AUC_{24h}, indicating that both parameters were higher in patients with hepatic impairment.

Table. Pharmacokinetic parameters following multiple oral doses of simeprevir 150 mg QD in healthy adults or patients with hepatic impairment

	Healthy adults	Patients with moderate hepatic impairment	Patients with severe hepatic impairment
	8 subjects	8 subjects[a)]	8 subjects
t_{max} (h)	6.0 (4.0-9.0)	6.0 (6.0-9.0)	6.0 (3.0-12.0)
C_{0h} (ng/mL)	454.8 ± 337.1	1637 ± 1191	5568 ± 3519
C_{max} (ng/mL)	2096 ± 958.5	3780 ± 1980	7184 ± 4272
C_{min} (ng/mL)	378.1 ± 266.1	1517 ± 1092	4414 ± 2923
AUC_{24h} (ng·h/mL)	23740 ± 10920	65140 ± 38130	138000 ± 89890

t_{max}: median (range)
a) 6 subjects for C_{max}, AUC_{24h}, and t_{max}

4.(ii).A.(4).2) Pharmacokinetic study in patients with renal impairment (reference 5.3.3.3.2, Study C126 [August 2011 to January 2012])

Pharmacokinetics was investigated in 8 foreign healthy adult subjects and 8 foreign patients with severe renal impairment (eGFR ≤ 29 mL/min/1.73 m^2), who received multiple oral doses of simeprevir ([redacted]mg/capsule) 150 mg QD for 7 days. The pharmacokinetic parameters in the healthy adults and patients with renal impairment are shown in the following table. The ratios [90% CI] of least squares mean of C_{max} and AUC_{24h} of the patients with severe renal impairment to those of healthy adults was 1.34 [0.66, 2.72] and 1.62 [0.73, 3.59], respectively, indicating that both parameters were higher in patients with severe renal impairment.

Table. Pharmacokinetic parameters following multiple oral doses of simeprevir 150 mg QD to healthy adults or patients with renal impairment

	Healthy adults	Patients with severe renal impairment
	8 subjects	8 subjects
t_{max} (h)	6.0 (4.0-9.0)	6.0 (4.0-9.0)
C_{0h} (ng/mL)	1112 ± 1480	2220 ± 2696
C_{max} (ng/mL)	3378 ± 2636	4671 ± 3823
C_{min} (ng/mL)	961.3 ± 1191	1707 ± 1741
$t_{1/2}$ (h)	16.66 ± 10.2	24.00 ± 18.8
AUC_{24h} (ng·h/mL)	44380 ± 39920	76690 ± 71740

t_{max}: Median (range)

4.(ii).A.(5) Assessment of drug interactions (reference 5.3.3.4.1, Study C104 [November 2007 to January 2008]; reference 5.3.3.4.2, Study C105 [June 2008 to December 2008]; reference 5.3.3.4.3, Study C107 [March 2009 to July 2009]; reference 5.3.3.4.4, Study C108 [February 2011 to May 2011]; reference 5.3.3.4.5, Study C114 [November 2010 to March 2011]; reference 5.3.3.4.6, Study C110 [September 2009 to January 2010]; reference 5.3.3.4.7, Study C112 [May 2010 to September 2010]; reference 5.3.3.4.8, Study C115 [March 2011 to August 2011]; reference 5.3.3.4.9, Study C120 [November 2011 to December 2011]; reference 5.3.3.4.10, Study C123 [November 2010 to April 2011]; reference 5.3.3.4.11, Study C124 [November 2011 to February 2012]; reference 5.3.3.4.12, Study HPC1006 [July 2012 to August 2012])

Twelve foreign clinical studies were conducted to investigate drug interactions with simeprevir.

The table below lists the results in which the upper or lower limit of the 90% CI for the ratio (combination therapy/monotherapy) of pharmacokinetic parameters (least squares mean of C_{max}, AUC, and C_{min}) for simeprevir or the co-administered drug was outside of the range of 0.80 to 1.25.[92)]

Table. Effect of co-administered drugs on the pharmacokinetic parameters of simeprevir

	Dosage regimen		Number of subjects	Pharmacokinetic parameters of simeprevir		
Co-administered drug	Co-administered drug	Simeprevir		C_{max}	AUC	C_{min}
Ritonavir	100 mg BID	200 mg Single dose	12	1.30 [1.08, 1.56]	1.83 [1.64, 2.05]	NA
	100 mg BID 15 days	200 mg QD 7 days	12	4.70 [3.84, 5.76]	7.18 [5.63, 9.15]	14.35 [10.29, 20.01]
DRV/r	800/100 mg QD 7 days	50 mg QD 7 days	21	1.79 [1.55, 2.06]	2.59 [2.15, 3.11]	4.58 [3.54, 5.92]
Rilpivirine	25 mg QD 11 days	150 mg QD 11 days	21	1.10 [0.97, 1.26]	1.06 [0.94, 1.19]	0.96 [0.83, 1.11]
TDF	300 mg QD 7 days	150 mg QD 7 days	24	0.85 [0.73, 0.99]	0.86 [0.76, 0.98]	0.93 [0.78, 1.11]
Efavirenz	600 mg QD 14 days	150 mg QD 14 days	23	0.49 [0.44, 0.54]	0.29 [0.26, 0.33]	0.09 [0.08, 0.12]
Raltegravir	400 mg BID 7 days	150 mg QD 7 days	23	0.93 [0.85, 1.02]	0.89 [0.81, 0.98]	0.86 [0.75, 0.98]
Erythromycin	500 mg TID 7 days	150 mg QD 7 days	24	4.53 [3.91, 5.25]	7.47 [6.41, 8.70]	12.74 [10.19, 15.93]
Rifampicin	600 mg QD 7 days	200 mg QD 7 days	17	1.31 [1.03, 1.66]	0.52 [0.41, 0.67]	0.08 [0.06, 0.11]
Escitalopram	10 mg QD 7 days	150 mg QD 7 days	17	0.80 [0.74, 0.89]	0.75 [0.68, 0.83]	0.68 [0.59, 0.79]

Ratio of least squares mean [90% CI]
TID, three times daily; DRV/r, darunavir/ritonavir; TDF, tenofovir disoproxil fumarate; NA, not applicable

92) Apart from the drugs listed in the table, the 90% CI for the ratio (combination therapy/monotherapy) of the pharmacokinetic parameters (least squares mean) of co-administered drugs, efavirenz, S-warfarin, rifampicin, escitalopram, and methadone, was in the range of 0.80 to 1.25.

Table. Effect of simeprevir on the pharmacokinetic parameters of co-administered drugs

Co-administered drug	Dosage regimen		Number of subjects	Pharmacokinetic parameters of co-administered drugs		
	Co-administered drug	Simeprevir		C_{max}	AUC	C_{min}
DRV/r (Darunavir concentration)	800/100 mg QD 7 days	50 mg QD 7 days	23	1.04 [0.99, 1.10]	1.18 [1.11, 1.25]	1.31 [1.13, 1.52]
DRV/r (Ritonavir concentration)	800/100 mg QD 7 days	50 mg QD 7 days	23	1.23 [1.14, 1.32]	1.32 [1.25, 1.40]	1.44 [1.30, 1.61]
Rilpivirine	25 mg QD 11 days	150 mg QD 11 days	21	1.04 [0.95, 1.13]	1.12 [1.05, 1.19]	1.25 [1.16, 1.35]
TDF	300 mg QD 7 days	150 mg QD 7 days	24	1.19 [1.10, 1.30]	1.18 [1.13, 1.24]	1.24 [1.15, 1.33]
Raltegravir	400 mg BID 7 days	150 mg QD 7 days	23	1.03 [0.78, 1.36]	1.08 [0.85, 1.38]	1.14 [0.97, 1.36]
Midazolam [Oral administration]	0.075 mg/kg Single dose	150 mg QD 10 days	16	1.31 [1.19, 1.45]	1.45 [1.35, 1.57]	NA
Midazolam [Intravenous administration]	0.025 mg/kg Single dose	150 mg QD 11 days	16	0.78 [0.52, 1.17]	1.10 [0.95, 1.26]	NA
Caffeine	150 mg Single dose	150 mg QD 11 days	16	1.12 [1.06, 1.19]	1.26 [1.21, 1.32]	NA
Omeprazole	40 mg Single dose	150 mg QD 11 days	16	1.14 [0.93, 1.39]	1.21 [1.00, 1.46]	NA
Dextromethorphan	30 mg Single dose	150 mg QD 11 days	16	1.21 [0.93, 1.57]	1.08 [0.87, 1.35]	NA
Erythromycin	500 mg TID 7 days	150 mg QD 7 days	24	1.59 [1.23, 2.05]	1.90 [1.53, 2.36]	3.08 [2.54, 3.73]
Ethinyl estradiol	35 µg QD 21 days	150 mg QD 10 days	17	1.18 [1.09, 1.27]	1.12 [1.05, 1.20]	1.00 [0.89, 1.13]
Norethisterone	1.0 mg QD 21 days	150 mg QD 10 days	17	1.06 [0.99, 1.14]	1.15 [1.08, 1.22]	1.24 [1.13, 1.35]
Tacrolimus	2 mg Single dose	150 mg QD 7 days	14	0.76 [0.65, 0.90]	0.83 [0.59, 1.16]	NA
Cyclosporine	100 mg Single dose	150 mg QD 10 days	14	1.16 [1.07, 1.26]	1.19 [1.13, 1.26]	NA
Digoxin	0.25 mg Single dose	150 mg QD 7 days	15	1.31 [1.14, 1.51]	1.39 [1.16, 1.67]	NA
Rosuvastatin	10 mg Single dose	150 mg QD 7 days	16	3.17 [2.57, 3.91]	2.81 [2.34, 3.37]	NA
Atorvastatin	40 mg Single dose	150 mg QD 12 days	13	1.70 [1.42, 2.04]	2.12 [1.72, 2.62]	NA
Simvastatin	40 mg Single dose	150 mg QD 12 days	18	1.46 [1.17, 1.82]	1.51 [1.32, 1.73]	NA

Ratio of least squares mean [90% CI]
NA: not applicable

4.(ii).A.(6) QT/QTc study (5.3.4.1.1, Study C117 [January 2011 to July 2011])

The effect on QT/QTc interval was investigated in a 4-period crossover, double-blind comparative study with 4 arms in 60 foreign healthy adult subjects to whom multiple oral doses of placebo or simeprevir ([redacted] mg capsule and [redacted] mg capsule) 150 and 350 mg QD were given for 7 days. A single oral dose of moxifloxacin (MFLX) 400 mg was used as a positive control.

The differences between simeprevir and placebo in the change in corrected QT interval (QTcF) from baseline to Day 7 were 0.8 ms [90% CI; -1.26, 2.79] in the simeprevir 150 mg group (3 hours post-dose) and 1.2 ms [-0.95, 3.32] in the simeprevir 350 mg group (1 hour post-dose), which was the largest value. Because both values were within the criterion (10 ms) defined in the ICH E14 Guidelines, simeprevir ≤350 mg is unlikely to prolong QTcF interval. The difference between MFLX and placebo in the change from baseline at 4 hours post-dose was 11.3 ms [97.5% CI; 8.09, 14.49].

4.(ii).A.(7) Photosafety studies (reference 5.3.4.1.2, Study C125 [August 2010 to April 2011])

Photosafety was investigated in 36 foreign healthy adult subjects (12 subjects in each group) to whom

multiple oral doses of simeprevir 150 mg QD ([redacted] mg capsule) were given for 9 days. Multiple oral doses of simeprevir 150 mg QD, positive control (ciprofloxacin 500 mg BID), and the placebo were given for 9 days.

In the ciprofloxacin group, 91.7% of subjects (11 of 12 subjects) were considered to have photosensitivity to at least one wavelength range. In the placebo group, 33.3% of subjects (4 of 12 subjects) were considered to have at least mild photosensitivity to any wavelength range. In the simeprevir group, no subjects were considered to have photosensitivity except for a subject who showed mild phototoxicity (phototoxicity index, 1.67-3.0) in the wavelength ranges of 335 ± 30 nm and 365 ± 30 nm. Immediate type photosensitivity reaction (erythema with sign of pruritic edema in 2 subjects) occurred in 33.3% of subjects (4 of 12 subjects), but no abnormality was detected in a test at physiological irradiance (1/2 and 1/10 monochromator output).

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

4.(ii).B.(1) Pharmacokinetics of simeprevir

PMDA asked the applicant to explain the factors that caused the more than dose-proportional increase in some of the pharmacokinetic parameters of simeprevir and the pharmacokinetic differences between Japanese and foreign subjects.

The applicant explained as follows:

Following a single oral dose of simeprevir (F002 solution) in Japanese healthy adult subjects (Study C109) and foreign healthy adult subjects (Study C101), the C_{max} and AUC of plasma simeprevir increased more than dose-proportionally at doses of ≥100 mg. However, the $t_{1/2}$ stayed nearly constant, ranging from 9.54 to 13.31 hours at any dose in Japanese and foreign subjects, and did not increase with increase in dose. Therefore, increased BA in the gastrointestinal tract was considered to be one of the factors for nonlinearity of C_{max} and AUC of plasma simeprevir. Because total body clearance (CL) was as low as 4.75 to 6.23 L/h in Study C118,[93)] in which absolute BA was assessed in foreign healthy adult subjects, the hepatic first-pass effect was considered to be small. Nevertheless, absolute BA was higher in subjects who received simeprevir 150 mg than in those who received 50 mg (absolute BA following administration of simeprevir 50 and 150 mg was 45.98% and 62.12%, respectively), supporting the above-mentioned discussion based on the results of a single dose in Japanese healthy and foreign healthy adult subjects.

In the drug interaction study (Study C107), in which simeprevir and midazolam (orally or intravenously) were given to foreign healthy adult subjects, C_{max} and AUC of plasma midazolam increased after its oral administration but not after its intravenous administration. Therefore, the drug interaction between simeprevir and midazolam may have occured mainly due to CYP3A4 in the small intestine. In addition, an *in vitro* study showed that simeprevir is a substrate and inhibitor of CYP3A4 and P-gp: Michaelis

93) ^{3}H-simeprevir 100 μg (microdose) was administered intravenously 5 hours (near t_{max}) after oral administration of simeprevir 50 mg or 150 mg to investigate the nonlinearity of plasma pharmacokinetics. Plasma ^{3}H-simeprevir concentration was measured to obtain the pharmacokinetic parameters after intravenous administration in the presence of orally administered simeprevir.

constant (Km) calculated from the metabolic rate of simeprevir was 25.0 to 39.3 μmol/L (18.75-29.47μg/mL); IC_{50} for CYP3A4 and P-gp was calculated to be 84.5 to 155 μmol/L (63.37-116.24 μg/mL) and 85.9 μmol/L (64.42 μg/mL), respectively. Taking the above into consideration, it is likely that CYP3A4 and P-gp in the small intestine saturate when an oral dose of simeprevir ≥150 mg is given. Simeprevir concentration in the small intestine (estimated liquid volume of small intestine, 1.92 L[94]) following a single oral dose of simeprevir 50, 100, and 150 mg was estimated to be 26, 52, and 78 μg/mL, respectively, suggesting the possibility of saturation of CYP3A4 in the small intestine at doses of simeprevir ≥100 mg.

Moreover, in Study C118, in which absolute BA was investigated in foreign healthy adult subjects, the increase in C_{max} and AUC_{∞} following oral administration of simeprevir 50 mg and 150 mg cannot be explained by the increase in BA alone. Following intravenous administration of ^{3}H-simeprevir 100 μg after oral administration of simeprevir 50 mg and 150 mg, the decrease in CL and Vd was similar between the two oral dose levels (following administration of simeprevir 50 and 150 mg, CL was 6.23 ± 1.77 L/h and 4.75 ± 1.56 L/h, respectively, and Vd was 94.4 ± 15.4 L and 75.3 ± 15.9 L, respectively). Therefore, possible casues include a decrease in the liver distribution of simeprevir due to saturation of OATP1B1 accompanied by decreases in metabolism and biliary excretion.

On the other hand, following multiple oral doses of simeprevir in Japanese healthy and foreign healthy adult subjects, the $t_{1/2}$ increased at ≥200 mg, suggesting non-linear elimination due to saturation of liver CYP3A4.

Although the AUC_{24h} of plasma simeprevir was predicted to be 1.5- to 2-fold higher in Japanese patients than in foreign patients when an identical dose of simeprevir was given to Japanese and foreign patients with chronic hepatitis C virus infection, the difference in pharmacokinetics in Japanese and foreign patients cannot be explained by body weight etc., and was possibly affected by racial differences as was reported in terms of OATP1B.[95]

Based on the above reports, it was suggested that CYP3A4 and P-gp in the small intestine as well as OATP1B1 and CYP3A4 in the liver may be related to the nonlinear pharmacokinetics of simeprevir. Moreover, the involvement of racial differences with respect to OATP1B1, in addition to physical differences, was suggested to be one possible cause of the pharmacokinetic differences between Japanese and foreign patients. At present, however, it is difficult to evaluate the functions of these drug metabolizing enzymes and transporters separately, and to clarify the individual mechanisms involved.

Based on the PPK analysis of plasma simeprevir concentrations obtained in the foreign early phase II study (Study C201), AUC_{24h} values of plasma simeprevir following administration of simeprevir 50 to 200 mg to foreign patients with chronic hepatitis C virus infection were estimated. Based on the AUC_{24h}

94) Tachibana T, et al. *Xenobiotica.* 2009;39:430-443

95) Based on the assessment of pharmacokinetic data of pravastatin, a substrate of OATP1B1, in Japanese and Caucasian subjects, the OATP1B1 activity in Japanese subjects was calculated to be 0.584-fold that in Caucasian subjects.

ratio for the different dose levels, a dose that provided an AUC_{24h} ratio similar to those obtained in the Japanese and foreign phase I studies (1.5- to 2-fold; Japanese study, Study C109; foreign study, Study C101) in Japanese and foreign healthy adult subjects was chosen as the dose for the phase II study (Study C215) in Japanese patients with chronic hepatitis C virus infection. Based on AUC_{24h} at 150 mg QD which was the maximum dose of simeprevir established for clinical studies in foreign subjects, the maximum dose for clinical studies in Japanese subjects was set at 100 mg QD. The plasma simeprevir concentrations following administration of simeprevir 50 and 100 mg QD (Study C215) or 75 and 150 mg QD (Study C205) to Japanese (Study C215) and foreign (Study C205) patients with chronic hepatitis C virus infection are provided in the following table, which shows that C_{max} and AUC were comparable.

Table. Plasma simeprevir concentrations following multiple oral doses of simeprevir QD

	Dosage regimen			
	Study C215, 50 mg	Study C205, 75 mg	Study C215, 100 mg	Study C205, 150 mg
	14 subects	21 subjects[a)]	12 subjects	23 subjects[b)]
AUC_{24h} (ng·h/mL)	11182 ± 7763	13200 ± 6772	60197 ± 65364	70090 ± 93390
C_{0h} (ng/mL)	192 ± 134	213 ± 176.5	1732 ± 2669	1796 ± 3116
C_{max} (ng/mL)	1011 ± 725	1035 ± 522.4	4072 ± 3446	4394 ± 4330

a) 20 subjects for AUC_{24h}, b) 22 subjects for AUC_{24h}

PMDA considers that the applicant's explanation that the saturation of CYP3A4 and P-gp in the small intestine as well as OATP1B1 and CYP3A4 in the liver is involved in the nonlinearity of the pharmacokinetics of simeprevir is acceptable. The appropriateness of the dosage and administration of simeprevir established based on the pharmacokinetic differences between Japanese and foreign subjects will be discussed in "4.(iii).B.(5).1) Dosage and administration of simeprevir."

4.(ii).B.(2) Pharmacokinetics in patients

PMDA asked the applicant to explain the factors that caused the increase in the exposure and interindividual variability of simeprevir in patients as compared with healthy adults.

The applicant explained as follows:

Urinary excretion makes only a small contribution to the elimination of simeprevir, and the majority of simeprevir is probably eliminated through metabolism and excretion via non-renal route (i.e., the liver). Because CL following intravenous administration of simeprevir was 4.75 to 6.23 L/h, the hepatic clearance of simeprevir is estimated to be lower than hepatic blood flow (87 L/h[96)]), indicating that the clearance of simeprevir is limited by the intrinsic clearance. In addition, absolute BA following oral administration of simeprevir 50 and 150 mg was 46% to 62% in Study C118, in which absolute BA was investigated in foreign healthy adult subjects. Therefore, the variability in exposure after oral administration of simeprevir may be attributed to the variability in hepatic intrinsic clearance and absorption in the gastrointentional tract.

The following have been reported as factors for variation in hepatic intrinsic clearance: pathology, body

96) Davies B, et al. *Pharm Res.* 1993;10(7):1093-1095

weight, and age act in a integrated manner[97]; mRNA expression level of CYP3A4 and OATP1B1 decreases significantly with the progression of hepatic fibrosis in the hepatocytes collected from patients with chronic hepatitis C virus infection; and expression level of mRNA is higher in hepatocytes uninfected with HCV than in hepatocytes from patients with chronic hepatitis C infection.[98] In addition, it has also been reported that the activity of CYP3A tends to be lower in chronic hepatitis patients including patients with chronic hepatitis C virus infection than in healthy subjects, that mRNA expression level of OATP1B1 and OATP1B3 tends to be lower in hepatocytes collected from patients with chronic hepatitis C virus infection than in hepatocytes uninfected with HCV, and that liver volume is decreased in patients with chronic hepatitis C virus infection as compared with patients without hepatic disorder.[99]

As judged from patient background (age and body weight) in the Japanese clinical studies in patients with chronic hepatitis C virus infection (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3004, HPC3008, and HPC3010) and a study in Japanese healthy adult subjects (Study HPC1003), patients with chronic hepatitis C virus infection tended to have low body weight and advanced age, and their body weight and age tended to be distributed more broadly than those of healthy adults.

Based on the above reports, the increase in exposure to simeprevir in patients with chronic hepatitis C virus infection compared with healthy adults may be due to the following factors: the elimination of simeprevir is limited by hepatic intrinsic clearance, and patients with chronic hepatitis C virus infection may have reduced expression levels of metabolizing enzymes and transporters involved in the elimination of simeprevir; patients with chronic hepatitis C virus infection tended to be older and to have lower body weigh than healthy adults. The increase in the inter-individual variability of hepatic intrinsic clearance of simeprevir may have increased the inter-individual variability in exposure because body weight and age tended to be distributed more broadly in patients with chronic hepatitis C virus infection than in healthy adults, and because the expression level of CYP3A4 and OATP1B1 and liver volume changed in association with pathology.

PMDA accepted the applicant's explanation that: the pathology and the severity of chronic hepatitis C virus infection affected the metabolizing enzymes and transporters involved in the elimination of simeprevir, and this may be one of the factors for the increase in exposure to simeprevir in patients with chronic hepatitis C virus infection as compared with healthy adults; the variability in the patient background such as age is also a factor for the large inter-individual variability in the exposure level.

4.(ii).B.(3) Use in patients with hepatic impairment

The applicant explained the pharmacokinetics and safety of simeprevir in patients with hepatic impairment as follows:

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97) Rostami-Hodjegan A, et al. *Nat Rev Drug Discov.* 2007;6:140-148
98) Nakai K, et al. *Drug Metab Dispos.* 2008;36(9):1786-1793
99) Onishi A, et al. *J Clin Pharmacol*. 2005;45:1221-1229, Ogasawara K, et al. *Drug Metab. Pharmacokinet.* 2010;25(2):190-199, Lin X, et al. *Hepato-Gastroenterology*. 1998;45:1069-1074

Multiple oral doses of simeprevir 150 mg QD were administered for 7 days in patients with moderate and severe hepatic impairment (Child-Pugh classification B and C, respectively) in a pharmacokinetic study (Study C113) in foreign patients with hepatic impairment. Their C_{max} and AUC_{24h} of plasma simeprevir were higher than those in healthy adults [see "4.(ii).A.(4).1) Pharmacokinetic study in patients with hepatic impairment"]. The incidence of adverse events (including laboratory abnormalities) in this study was 25.0% (2 of 8 subjects) in healthy adults, 62.5% (5 of 8 subjects) in patients with moderate hepatic impairment, and 12.5% (1 of 8 subjects) in patients with severe hepatic impairment. The adverse event that occurred in ≥2 subjects was headache (2 subjects with moderate hepatic impairment). There were no deaths or adverse events leading to treatment discontinuation. Serious adverse events included pneumonia, which occurred in a patient with moderate hepatic impairment, but a causal relationship to the investigational drug was ruled out.

Based on the above reports, simeprevir was well tolerated in patients with moderate or severe hepatic impairment.

PMDA asked the applicant to explain the necessity to provide a caution on administration to patients with hepatic impairment, taking into account the fact that exposure to simeprevir is higher in patients with hepatic impairment than in healthy adults.

The applicant explained as follows:
The Guidelines for the Management of Hepatitis C Virus Infection[1)] define compensated cirrhosis as a condition where hepatic reserve is preserved and symptoms of hepatic failure such as jaundice, ascites, hepatic encephalopathy, and esophageal varices are absent (Child-Pugh class A), and decompensated cirrhosis as a condition where symptoms of hepatic failure are present (Child-Pugh classes B and C). Because hepatic cirrhosis is not included in the proposed indications for simeprevir, and because simeprevir will not be administered to patients with hepatic impairment classified as Child-Pugh class A, B, or C, it is not necessary to provide a caution for patients with hepatic impairment.

PMDA considers as follows:
In some cases, it is difficult to discriminate chronic hepatitis accompanied by severe fibrosis from hepatic cirrhosis in clinical practice, and thus simeprevir may be administered to patients in whom hepatic cirrhosis cannot be ruled out clearly. Because only a limited number of patients were investigated in Study C113, in which simeprevir was administered to patients with moderate or severe hepatic impairment, and because the plasma concentration of simeprevir clearly increases in patients with hepatic impairment, it is necessary to provide this information and provide a caution on the use of simeprevir in patients with hepatic impairment in the package insert.

The above conclusion will be finalized, taking account of comments from the expert advisors.

4.(ii).B.(4) Drug interactions involving transporters

PMDA asked the applicant to provide an explanation on drug interactions involving the transporters of simeprevir.

The applicant explained as follows:
Rosuvastatin, atorvastatin, and simvastatin were used as the substrates of OATP1B1, and increase in AUC for each substrate and its metabolites due to combined use with simeprevir was investigated in clinical studies (Studies C108 and HPC1006). The results were compared with the results reported in the literature for typical OATP1B1 inhibitors (rifampicin, cyclosporine, gemfibrozil, and eltrombopag). The results are shown in the following table. Although an *in vitro* study showed that simeprevir inhibits OATP1B1 slightly more potently than ritonavir, rifampicin, and cyclosporine [see "3.(ii).A.(6).2) Investigation of liver uptake and drug excretion transporters"], the clinical study results indicated that in terms of inhibitory activity, simeprevir is weaker than rifampicin and cyclosporine, and is comparable to or slightly more potent than gemfibrozil and eltrombopag.

Table. Effect of simeprevir and OATP1B1 inhibitors on *in vivo* exposure of OATP1B1 substrates

	Ratio of AUC when simeprevir or OATP1B1 inhibitor was not combined to AUC when combined				
	Simeprevir[a)]	Rifampicin[b)]	Cyclosporine[c)]	Gemfibrozil[d)]	Eltrombopag[e)]
Rosuvastatin	2.81	−	7.1	1.9	1.6
Atorvastatin	2.12 to 2.33	4.3 to 9.3	7.4 to 15.3[f)]	1.2	−
2-Hydroxy atorvastatin	2.29	−	−	1.5	−
Simvastatin	1.51 to 1.54	−	2.6 to 8[f)]	1.4	−
Simvastatin acid	1.88 to 2.40	−	−	2.9	−

a) Oral dose of 150 mg QD, b) single oral dose of 600 mg, c) oral dose of 75 to 200 mg BID, d) oral dose of 600 mg BID,
e) oral dose of 75 mg QD, f) CYP3A4 inhibition is also involved
−: not reported

HIV protease inhibitors inhibit OATP1B1. However, when comparison was made between the Ki value of HIV protease inhibitors against OATP1B1 and the maximum plasma concentration of their unbound form at the clinical dose, in the drugs other than atazanavir and lopinavir, for which the maximum plasma concentration of unbound form was comparable to their Ki value against OATP1B1, the Ki value against OATP1B1 was higher than the maximum plasma concentration of unbound form.[100)] Thus, the inhibitory activity against OATP1B1 would be limited in clinical use.

Following multiple oral doses of simeprevir in combination with rifampicin, C_{0h} of plasma simeprevir increased 1.81-fold after the first dose compared with the data for simeprevir alone. However, following multiple oral doses of simeprevir in combination with ritonavir or DRV/r, the C_{0h} or C_{min} of plasma simeprevir was 13.74- to 14.78-fold compared with the data for simeprevir alone. Therefore, the effect on the pharmacokinetics following administration of simeprevir in combination with atazanavir/ritonavir or lopinavir/ritonavir was considered to be mainly attributable to CYP3A.

When simeprevir was used in combination with itraconazole plus pravastatin, a substrate of OATP1B1, the pharmacokinetics of pravastatin was not affected.[101)] Therefore, the drug interaction between itraconazole and simeprevir was considered to be due primarily to CYP3A.

100) Annaert P, et al. *Xenobiotica.* 2010;40:163-176
101) Jacobson TA, et al. *Am J Cardiol*. 2004;94:1140-1146

When simeprevir was used in combination with efavirenz, which is known to induce CYP3A,[102] AUC_{24h} of plasma simeprevir decreased 0.29-fold compared with the data for simeprevir alone, and the elimination half-life decreased [see "4.(ii).A.(5) Assessment of drug interactions"]. Therefore, it was inferred that the mechanism of drug interaction with efavirenz resulted from induction of CYP3A.

Although simeprevir is a substrate of P-gp, given that the fecal excretion rate of unchanged simeprevir was 31.0% in humans [see "4.(ii).A.(2).2).(a) Phase I single-dose study in foreign healthy adult subjects"], and that the gastrointestinal absorption of simeprevir is relatively high, the effect of P-gp inhibition by possible concomitant drugs such as ritonavir, a protease inhibitor/ritonavir, and itraconazole on the pharmacokinetics of simeprevir was not considered to be greater than the effect of CYP3A inhibition.

PMDA considers as follows:
In vitro studies on transporters-mediated drug interactions indicated that simeprevir inhibits the uptake of the substrates of P-gp, NTCP, OATP1B1, BSEP, and MRP2, and that simeprevir is also a substrate of P-gp, BCRP1, and MRP2. However, taking into account the results of clinical studies and a comparison with drugs reported to inhibit OATP1B1, PMDA understands the applicant's explanation that among the drug interactions that may occur in clinical practice, the effect of CYP3A inhibition is greater than that of OATP1B1 and P-gp inhibition. It is necessary to continue to collect post-marketing information on the possibility of drug interactions between simeprevir and co-administered drugs, and to appropriately provide information on the results obtained to the clinical practice.

4.(iii) Summary of clinical efficacy and safety

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

As the efficacy and safety evaluation data, the results from a total of 9 studies (2 Japanese phase I studies, 1 Japanese phase II study, 4 Japanese phase III studies, and 2 foreign phase I studies) were submitted. The results from a total of 28 studies (22 foreign phase I studies, 3 foreign phase II studies, and 3 foreign phase III studies) were submitted as reference data. The clinical studies submitted as evaluation data are shown in the following table.

[102] Stocrin Tablets 200 mg/600 mg package insert (10th edition, January 2013)

Table. Clinical studies (evaluation data)

	Phase	Study number	Target	Major objectives	Number of subjects[a)]	Dosage regimen of simeprevir
Japanese	I	HPC1003	Healthy adult male subjects	Pharmacokinetics (relative bioavailability), safety	72	Single dose of 100 mg
		HPC1007	Healthy adult male subjects	Pharmacokinetics (food effect), safety	24	Single dose of 100 mg
	II	C215	Genotype 1 patients with chronic hepatitis C virus infection (treatment-naïve)	Efficacy, safety	93	50 or 100 mg QD for 12 or 24 weeks
	III	HPC3003	Genotype 1 patients with chronic hepatitis C virus infection (treatment-naïve)	Efficacy, safety	188	100 mg QD for 12 weeks
		HPC3008	Genotype 1 patients with chronic hepatitis C virus infection (had relapsed after prior treatment)	Efficacy, safety	49	100 mg QD for 12 weeks
		HPC3004	Genotype 1 patients with chronic hepatitis C virus infection (had failed to respond to prior treatment)	Efficacy, safety	108	100 mg QD for 12 or 24 weeks
		HPC3010	Genotype 1 patients with chronic hepatitis C virus infection (treatment-naïve, had relapsed after prior treatment, had failed to respond to prior treatment)	Efficacy, safety	79	100 mg QD for 12 weeks
Foreign	I	C109	Healthy adult male subjects (Japanese)	Pharmacokinetics, safety	30	100, 200, or 400 mg as a single dose or once daily for 5 days
		C117	Healthy adults	Effect on QT/QTc interval, pharmacokinetics, safety	60	150 or 350 mg QD for 7 days

a) Number of randomized subjects or number of enrolled subjects

In the Japanese phase II study (Study C215) and phase III studies (Studies HPC3003, HPC3004, HPC3008, and HPC3010), plasma HCV RNA levels below the quantification limit (1.2 Log IU/mL) were reported as "<1.2 Log IU/mL" or "undetectable." Of these cases, "undetectable" was defined as "plasma HCV RNA undetectable" or "virus undetectable." The efficacy endpoints, the SVR12 and SVR24 rates, were defined as follows:

SVR12 rate: proportion of subjects whose plasma HCV RNA was undetectable at the end of treatment (ETO) and at 12 weeks after ETO (sustained virologic response at ETO and at 12 weeks after ETO)

SVR24 rate: proportion of subjects whose plasma HCV RNA was undetectableat ETO and at 24 weeks after ETO (sustained virologic response at ETOand at 24 weeks after ETO)

4.(iii).A.(1) Clinical pharmacology studies

4.(iii).A.(1).1) Japanese phase I study in Japanese healthy adult male subjects (5.3.1.2.1, Study HPC1003 [April 2012 to June 2012])

In order to investigate the safety and pharmacokinetics of simeprevir in Japanese healthy adult male subjects (target sample size of 72; 36 subjects in panel 1 [fasted administration], 36 subjects in panel 2 [fed administration]), a 2-period, randomized, open-label, crossover comparative study was conducted

in 1 institution in Japan [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" for pharmacokinetics].

Period 1 and Period 2 were established for each panel.[71)] Subjects received a single oral dose of [redacted] capsules of either the G008 formulation (prepared for phase III studies) or the F020 formulation (prepared for phase II studies) in Period 1, and then in Period 2, subjects received a single oral dose of [redacted] capsules of the other formulation.[74)] Each capsule contained [redacted] mg of simeprevir.

All of the 72 treated subjects (36 subjects in each panel [18 subjects in each group]) were included in the safety analysis set.

The incidence of adverse events was 2.8% in the G008/fasted administration group (1 of 36 subjects, headache in 1 subject), 5.6% in the F020/fasted administration group (2 of 36 subjects; headache, ALT increased, AST increased in 1 subject each [including duplicates]), 0% in the G008/fed administration group (0 of 34 subjects), and 11.4% in the F020/fed administration group (4 of 35 subjects; headache, vomiting, discomfort, blood bilirubin increased, blood creatine phosphokinase [CPK] increased, and white blood cell count increased in 1 subject each [including duplicates]). A causal relationship to the investigational drug could not be ruled out for any of these adverse events except for discomfort, blood bilirubin increased, and blood CPK increased. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(iii).A.(1).2) Japanese phase I study in Japanese healthy adult male subjects (5.3.1.2.5, Study HPC1007 [June 2012 to July 2012])

In order to investigate the safety and pharmacokinetics of simeprevir in Japanese healthy adult male subjects (target sample size of 24), a 2-period, randomized, open-label crossover comparative study was conducted in 1 institution in Japan [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" for pharmacokinetics].

Subjects received [redacted] capsules of G008 formulation (prepared for phase III studies) containing [redacted] mg of simeprevir was orally administered in the fasted or fed state in Periods 1 and 2 in a cross-over fashion.[74)]

All of the 24 treated subjects were included in the safety analysis set.

The incidence of adverse events was 0% (0 of 24 subjects) after fasted administration and 4.3% (1 of 23 subjects, proteinuria in 1 subject) after fed administration. A causal relationship to the investigatioal drug could not be ruled out. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(iii).A.(1).3) Foreign phase I study in Japanese healthy adult male subjects (5.3.3.1.1, Study C109 [August 2008 to November 2008])

In order to investigate the safety and pharmacokinetics of simeprevir in Japanese healthy adult male subjects (target sample size of 30 subjects, 10 for each dose [8 subjects in the simeprevir group and 2 subjects in the placebo group]), a placebo-controlled, randomized, double-blind comparative study was conducted in 1 institution in the US [see "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetics].

A single oral dose of simeprevir 100 mg, 200 mg, or 400 mg was given to subjects in the simeprevir groups, and a single oral dose of vehicle (PEG400 solution) was given to subjects in the placebo group. At approximately 72 hours after the single dose, simeprevir or placebo was given orally once daily for 5 days.

All of the 30 treated subjects (8 subjects for each dose in the simeprevir group and 6 subjects in the placebo group) were included in the safety analysis set.

The incidence of adverse events was 12.5% (1 of 8 subjects) in the 100 mg group, 50.0% (4 of 8 subjects) in the 200 mg group, and 50.0% (4 of 8 subjects) in the 400 mg group after a single dose of simeprevir, and was 0% (0 of 6 subjects) in the placebo group. After multiple doses, the incidence of adverse events was 14.3% (1 of 7 subjects) in the 100 mg group, 37.5% (3 of 8 subjects) in the 200 mg group, 16.7% (1 of 6 subjects) in the 400 mg group, and 33.3% (2 of 6 subjects) in the placebo group.

The incidence of adverse events for which a causal relationship could not be ruled out (adverse drug reactions) was 12.5% (1 of 8 subjects) in the 100 mg group, 25.0% (2 of 8 subjects) in the 200 mg group, 37.5% (3 of 8 subjects) in the 400 mg group, and 0% (0 of 6 subjects) in the placebo group after a single dose; 0% (0 of 7 subjects) in the 100 mg group, 12.5% (1 of 8 subjects) in the 200 mg group, 0% (0 of 6 subjects) in the 400 mg group, and 0% (0 of 6 subjects) in the placebo group after multiple doses. The adverse event reported by ≥2 subjects in any group was diarrhoea, which occurred in 2 subjects in the 400 mg group after a single dose.

There were no deaths or serious adverse events. Adverse events leading to treatment discontinuation occurred in 3 subjects in the simeprevir group (1 subject in the 100 mg group [rash macular] and 2 subjects in the 400 mg group [diarrhoea and platelet aggregation in 1 subject each] after a single dose). A causal relationship to the investigational drug could not be ruled out for rash macular and diarrhoea, but their outcome was reported as "resolved." A causal relationship to the investigational drug was ruled out for platelet aggregation, but the outcome was reported as "not resolved."

4.(iii).A.(2) Phase II studies

4.(iii).A.(2).1) Japanese late phase II study in Japanese patients with chronic hepatitis C virus infection (5.3.5.1.2, Study C215 [July 2009 to April 2011])

In order to investigate the efficacy, safety, and pharmacokinetics of simeprevir in treatment-naïve[85)] patients with chronic hepatitis C virus infection (genotype 1)[103)] (target sample size of 84; 24 subjects in the 12-week simeprevir 50 mg group, 24 subjects in the 12-week simeprevir 100 mg group, 12 subjects in the 24-week simeprevir 50 mg group, 12 subjects in the 24-week simeprevir 100 mg group, and 12 subjects in the Peg-IFNα-2a/RBV group), a randomized, open-label, parallel-group comparative study[104)] was conducted with Peg-IFNα-2a/RBV as a control in 25 institutions in Japan [see "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetics].

Simeprevir was orally administered QD at 50 mg and 100 mg to the 12-week 50 mg simeprevir group and the 12-week 100 mg simeprevir group, respectively, for 12 weeks in combination with Peg-IFNα-2a/RBV (PR[105)]), followed by continued PR administration. Simeprevir was orally administered QD at 50 mg and 100 mg to the 24-week 50 mg simeprevir group and the 24-week 100 mg simeprevir group, respectively, for 24 weeks in combination with PR. The duration of PR administration in the simeprevir groups was 24 and 48 weeks in accordance with response-guided therapy criteria[106)] (RGT criteria). In the PR group, PR was administered for 48 weeks.

All of the 92 treated subjects (27 subjects in the 12-week 50 mg group, 26 subjects in the 12-week 100 mg group, 13 subjects in the 24-week 50 mg group, 13 subjects in the 24-week 100 mg group, and 13 subjects in the PR group) were included in the full analysis set (FAS) and safety analysis set. The per protocol set (PPS), defined as the efficacy analysis set, included 88 subjects (27 subjects in the 12-week 50 mg group, 24 subjects in the 12-week 100 mg group, 13 subjects in the 24-week 50 mg group, 13 subjects in the 24-week 100 mg group, and 11 subjects in the PR group), but excluded 4 subjects because of major protocol deviations[107)] identified before database lock. The proportion of subjects in the simeprevir group who terminated PR administration at Week 24 based on the RGT criteria were 92.6% (25 of 27 subjects) in the 12-week 50 mg group, 84.6% (22 of 26 subjects) in the 12-week 100 mg group, 76.9% (10 of 13 subjects) in the 24-week 50 mg group, and 92.3% (12 of 13 subjects) in the 24-week 100 mg group.

The SVR12 and SVR24 rates (efficacy measures) in each treatment group are shown in the following table.

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103) Patients who had a plasma HCV RNA level of ≥5.0 Log IU/mL, who had no diagnosis of hepatic cirrhosis, and who had no superinfection with HIV or HBV.

104) The subjects were proportionally allocated in order to minimize bias in the distribution of body weights among groups (allocation ratio was 2:2:1:1:1).

105) Hereinafter, the dosage regimens of Peg-IFNα-2a and RBV are as follows unless otherwise specified.
Peg-IFNα-2a 180 μg was administered subcutaneously once weekly. RBV was administered orally at 600 mg/day (body weight, ≤60 kg), 800 mg/day (body weight, >60 kg and ≤ 80 kg), or 1000 mg (body weight, >80 kg).

106) When a plasma HCV RNA level was <1.4 Log IU/mL or undetectable at Week 4 and remained undetectable at Weeks 12, 16, and 20, PR treatment was terminated at Week 24 in the simeprevir groups. PR treatment was continued up to Week 48 in other subjects in the simeprevir groups.

107) Two subjects whose total dose of Peg-IFNα-2a was <80%, and 1 subject each whose total dose of simeprevir was <80% and whose total dose of Peg-IFNα-2a/RBV was <80%.

Table. SVR12 rate and SVR24 rate (PPS)

	12-week 50 mg group	12-week 100 mg group	24-week 50 mg group	24-week 100 mg group	PR group
SVR12 rate	85.2 (23/27)	79.2 (19/24)	84.6 (11/13)	92.3 (12/13)	45.5 (5/11)
Differences between groups [95% CI]	39.7 [5.32, 69.53]	33.7 [-2.86, 65.20]	39.2 [-2.53, 71.46]	46.9 [5.91, 77.14]	
SVR24 rate	77.8 (21/27)	79.2 (19/24)	76.9 (10/13)	92.3 (12/13)	45.5 (5/11)
Differences between groups [95% CI]	32.3 [-2.60, 63.24]	33.7 [-2.86, 65.20]	31.5 [-10.52, 65.74]	46.9 [5.91, 77.14]	

% (number of subjects)

Adverse events (including laboratory abnormalities) occurred in all subjects to whom the investigational drugs were administered. In the simeprevir group, the incidence of adverse events (including laboratory abnormalities) for which a causal relationship to simeprevir could not be ruled out (adverse drug reactions) was 100% (27 of 27 subjects) in the 12-week 50 mg group, 96.2% (25 of 26 subjects) in the 12-week 100 mg group, 100% (13 of 13 subjects) in the 24-week 50 mg group, and 100% (13 of 13 subjects) in the 24-week 100 mg group. Adverse events reported by ≥10% of subjects in any group are shown in the following table.

Table. Adverse events reported by ≥10% of subjects in any group

Event	12-week 50 mg group	12-week 100 mg group	24-week 50 mg group	24-week 100 mg group	PR group
Number of subjects	27 subjects	26 subjects	13 subjects	13 subjects	13 subjects
Any adverse event	27 (100)	26 (100)	13 (100)	13 (100)	13 (100)
Any adverse drug reaction	27 (100)	25 (96.2)	13 (100)	13 (100)	
Anaemia	8 (29.6)	6 (23.1)	5 (38.5)	5 (38.5)	5 (38.5)
Palpitations	1 (3.7)	1 (3.8)	0	0	2 (15.4)
Retinal exudates	1 (3.7)	2 (7.7)	1 (7.7)	2 (15.4)	0
Retinopathy	0	2 (7.7)	0	1 (7.7)	3 (23.1)
Abdominal discomfort	6 (22.2)	3 (11.5)	3 (23.1)	1 (7.7)	2 (15.4)
Abdominal pain upper	1 (3.7)	4 (15.4)	1 (7.7)	0	0
Constipation	4 (14.8)	1 (3.8)	1 (7.7)	2 (15.4)	2 (15.4)
Diarrhoea	4 (14.8)	6 (23.1)	3 (23.1)	0	5 (38.5)
Nausea	5 (18.5)	5 (19.2)	2 (15.4)	1 (7.7)	0
Periodontitis	1 (3.7)	3 (11.5)	0	1 (7.7)	0
Stomatitis	7 (25.9)	5 (19.2)	5 (38.5)	2 (15.4)	2 (15.4)
Vomiting	1 (3.7)	1 (3.8)	2 (15.4)	2 (15.4)	2 (15.4)
Chest discomfort	0	0	2 (15.4)	0	0
Fatigue	0	0	2 (15.4)	0	0
Injection site erythema	3 (11.1)	2 (7.7)	1 (7.7)	2 (15.4)	1 (7.7)
Injection site reaction	7 (25.9)	2 (7.7)	6 (46.2)	5 (38.5)	3 (23.1)
Malaise	17 (63.0)	16 (61.5)	8 (61.5)	7 (53.8)	8 (61.5)
Pyrexia	18 (66.7)	10 (38.5)	7 (53.8)	7 (53.8)	7 (53.8)
Hyperbilirubinaemia	0	5 (19.2)	2 (15.4)	3 (23.1)	0
Influenza	0	0	0	2 (15.4)	0
Nasopharyngitis	9 (33.3)	4 (15.4)	4 (30.8)	2 (15.4)	3 (23.1)
Pharyngitis	3 (11.1)	1 (3.8)	0	0	0
Blood Amylase increased	0	0	0	2 (15.4)	0
Blood bilirubin increased	3 (11.1)	6 (23.1)	1 (7.7)	3 (23.1)	0
Blood calcium decreased	1 (3.7)	0	2 (15.4)	1 (7.7)	1 (7.7)
Blood lactate dehydrogenase increased	1 (3.7)	2 (7.7)	2 (15.4)	0	2 (15.4)
Blood triglycerides increased	1 (3.7)	1 (3.8)	2 (15.4)	2 (15.4)	3 (23.1)
Blood uric acid increased	4 (14.8)	2 (7.7)	1 (7.7)	0	0
Haematocrit decreased	4 (14.8)	6 (23.1)	4 (30.8)	3 (23.1)	4 (30.8)
Haemoglobin decreased	8 (29.6)	12 (46.2)	7 (53.8)	7 (53.8)	6 (46.2)

Event	12-week 50 mg group	12-week 100 mg group	24-week 50 mg group	24-week 100 mg group	PR group
Number of subjects	27 subjects	26 subjects	13 subjects	13 subjects	13 subjects
Any adverse event	27 (100)	26 (100)	13 (100)	13 (100)	13 (100)
Any adverse drug reaction	27 (100)	25 (96.2)	13 (100)	13 (100)	
Lipase increased	0	2 (7.7)	0	3 (23.1)	1 (7.7)
Neutrophil count decreased	12 (44.4)	14 (53.8)	10 (76.9)	12 (92.3)	9 (69.2)
Platelet count decreased	5 (18.5)	4 (15.4)	4 (30.8)	6 (46.2)	6 (46.2)
Red blood cell count decreased	4 (14.8)	6 (23.1)	5 (38.5)	3 (23.1)	4 (30.8)
Weight decreased	1 (3.7)	3 (11.5)	2 (15.4)	0	2 (15.4)
White blood cell count decreased	16 (59.3)	15 (57.7)	10 (76.9)	12 (92.3)	10 (76.9)
Blood phosphorus decreased	2 (7.4)	0	1 (7.7)	2 (15.4)	0
α1 acid glycoprotein increased	5 (18.5)	1 (3.8)	2 (15.4)	0	2 (15.4)
Protein urine presnt	0	0	1 (7.7)	0	2 (15.4)
Hypokalaemia	0	0	2 (15.4)	0	1 (7.7)
Decreased appetite	4 (14.8)	6 (23.1)	4 (30.8)	1 (7.7)	3 (23.1)
Arthralgia	9 (33.3)	7 (26.9)	6 (46.2)	5 (38.5)	2 (15.4)
Back pain	4 (14.8)	1 (3.8)	1 (7.7)	2 (15.4)	1 (7.7)
Myalgia	4 (14.8)	6 (23.1)	4 (30.8)	1 (7.7)	2 (15.4)
Dysgeusia	3 (11.1)	1 (3.8)	1 (7.7)	1 (7.7)	0
Headache	14 (51.9)	13 (50.0)	8 (61.5)	6 (46.2)	8 (61.5)
Insomnia	10 (37.0)	5 (19.2)	5 (38.5)	3 (23.1)	2 (15.4)
Cough	4 (14.8)	3 (11.5)	0	1 (7.7)	2 (15.4)
Rhinorrhoea	1 (3.7)	3 (11.5)	0	0	0
Oropharyngeal discomfort	1 (3.7)	3 (11.5)	0	0	0
Oropharyngeal pain	3 (11.1)	3 (11.5)	0	1 (7.7)	1 (7.7)
Alopecia	11 (40.7)	6 (23.1)	5 (38.5)	3 (23.1)	6 (46.2)
Dry skin	1 (3.7)	2 (7.7)	0	2 (15.4)	0
Pruritus	5 (18.5)	4 (15.4)	0	6 (46.2)	0
Rash	17 (63.0)	15 (57.7)	8 (61.5)	8 (61.5)	6 (46.2)
Seborrhoeic dermatitis	0	0	0	0	2 (15.4)
Urticaria	4 (14.8)	0	0	0	0
Asteatosis	0	0	0	0	2 (15.4)
Hypertension	3 (11.1)	0	0	0	1 (7.7)

Number of subjects (%)

One death due to cerebral infarction occurred in the 12-week 100 mg group, but a causal relationship to the investigational drug was ruled out. Other serious adverse events occurred in 2 subjects in the 12-week 100 mg group (malaise/subarachnoid haemorrhage and vulvar erosion in 1 subject each), 1 subject in the 24-week 50 mg group (rash), 1 subject in the 24-week 100 mg group (incorrect dose administered), and 1 subject in the PR group (fall/spinal compression fracture in 1 subject). A causal relationship to the investigational drug could not be ruled out for vulvar erosion in the subject in the 12-week 100 mg group and rash in the subject in the 24-week 50 mg group, but the outcomes were reported as “resolved” for both events. A causal relationship to the investigational drug was ruled out for malaise and subarachnoid haemorrhage in the subject in the 12-week 100 mg group, incorrect dose administered to the subject in the 24-week 100 mg group, and fall/spinal compression fracture in the subject in the PR group, for all of which the outcomes were reported as “resolved” except for spinal compression fracture.

Adverse events leading to discontinuation of all investigational drugs[108] included: anaemia and taste disturbance (1 subject each) in the 12-week 100 mg group; anaemia, rash, and hyperthyroidism (1 subject each) in the 24-week 50 mg group; bronchitis (1 subject) in the 24-week 100 mg group. A causal relationship to the investigational drug could not be ruled out for any of these events, and the outcomes were reported as "resolved" for all events except for hyperthyroidism.

4.(iii).A.(3) Phase III studies

4.(iii).A.(3).1) Japanese phase III study in Japanese chronic hepatitis C patients (5.3.5.1.5: HPC3003 Study [January 2011 to October 2012])

For the purpose of investigating the efficacy and safety of simeprevir in untreated[85] Japanese chronic hepatitis C (genotype 1) patients[86] (target sample size of 183; 122 subjects in simeprevir group, 61 subjects in placebo group), a placebo-controlled, randomized, double-blind, parallel-group, comparative study[109] was conducted in 37 institutions in Japan. Simeprevir was administered as a 100 mg oral dose QD for 12 weeks in combination with PR, followed by administration of PR for 12 or 36 weeks based on the RGT criteria.[110] The placebo group received placebo QD for 12 weeks in combination with PR, followed by 36-week administration of PR.[111]

All of a total of 183 treated subjects (123 subjects in the simeprevir group and 60 subjects in the placebo group) were included in the FAS and the safety analysis set, and were evaluated for efficacy. The subjects in whom PR administration was terminated at Week 24 based on the RGT criteria were 91.9% (113 of 123 subjects) in the simeprevir group.

The primary endpoint, SVR12 rate,[112] and the secondary endpoint, SVR24 rate, are shown in the table below. A statistically significant difference was found between the simeprevir group and the placebo group, demonstrating the superiority of the 12-week administration of 100 mg of simeprevir and the 48-week PR administration, which is the concomitant therapy with PR (24- or 48-week administration) based on the RGT criteria.

Table. SVR12 rate and SVR24 rate (FAS, NRI [a])

	Simeprevir group	Placebo group	Differences between groups [95% CI][b]	P value [c]
SVR12 rate	88.6 (109/123)	61.7 (37/60)	27.5 [14.38, 40.56]	$P < 0.0001$
SVR24 rate	88.6 (109/123)	56.7 (34/60)	32.6 [19.75, 45.40]	

% (number of subjects)

a) The missing data on the viral load 12 or 24 weeks after the actual completion of treatment were completed by non-SVR.

b) The rate difference adjusted by age and polymorphism of *IL28B* gene (TT, TG, and GG) and the 95% CI based on normal approximation

c) Cochran-Mantel-Haenszel test

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108) The criteria for discontinuation of drug treatment had been specified with respect to serious adverse events and adverse events/laboratory values classified as Grade ≥3. The criteria for reduction, withdrawal, and discontinuation of PR were the same as the corresponding criteria in the package insert. Dose reduction of simeprevir was not permitted, and discontinuation of PR occurred as simultaneous discontinuation of both drugs. When PR was withheld or discontinued, simeprevir was also withheld or discontinued. The following were specified as the discontinuation criteria for simeprevir (continuation of PR was permitted).
- AST or ALT increase to Grade 4, exceeding 2-fold the level specified in the criteria
- Pancreatic amylase level of Grade 4 or lipase level of Grade ≥3
- Total bilirubin level of Grade ≥3

109) In this study, subjects were randomized to the simeprevir group or the placebo group (allocation ratio, 2:1) using age (<65 years or ≥65 years) and *IL28B* polymorphism (TT, TG, and GG) as stratification factors.

110) When plasma HCV RNA was <1.2 Log IU/mL or undetectable at Week 4 and then undetectable at Week 12, the duration of PR treatment was 24 weeks. Otherwise, the duration of PR treatment was 48 weeks.

111) When plasma HCV RNA was >3.0 Log IU/mL at Week 4, the administration of this drug product or placebo was discontinued. When plasma HCV RNA was detected at Week 36 (≥ 1.2 Log IU/mL), the administration of PR was discontinued.

112) The SVR24 rate was selected as the primary endpoint at the start of the study, but it was changed to the SVR12 rate [see "4.(iii).B.(1).1) Efficacy evaluation" for the details].

Adverse events (including laboratory abnormalities) occurred in all subjects to whom the investigational drugs were administered. The adverse events (adverse drug reactions) (including laboratory abnormalities) for which a causal relationship to this drug product or placebo could not be denied occurred in 95.1% (117 of 123 subjects) in the simeprevir group and 96.7% (58 of 60 subjects) in the placebo group. Adverse events reported by ≥10% of subjects in any group are shown in the following table.

Table. Adverse events reported by ≥10% of subjects in any group

Adverse event	Simeprevir group	Placebo group
Number of subjects	123	60
Any adverse event	123 (100)	60 (100)
Any dverse drug reaction	117 (95.1)	58 (96.7)
Nasopharyngitis	21 (17.1)	17 (28.3)
Anaemia	70 (56.9)	36 (60.0)
Decreased appetite	28 (22.8)	20 (33.3)
Insomnia	27 (22.0)	25 (41.7)
Headache	54 (43.9)	27 (45.0)
Dysgeusia	20 (16.3)	8 (13.3)
Cough	11 (8.9)	8 (13.3)
Stomatitis	28 (22.8)	12 (20.0)
Diarrhoea	20 (16.3)	17 (28.3)
Abdominal discomfort	16 (13.0)	5 (8.3)
Nausea	16 (13.0)	12 (20.0)
Upper abdominal pain	5 (4.1)	6 (10.0)
Rash	57 (46.3)	37 (61.7)
Alopecia	44 (35.8)	28 (46.7)
Pruritus	35 (28.5)	18 (30.0)
Erythema	17 (13.8)	4 (6.7)
Dry skin	8 (6.5)	9 (15.0)
Arthralgia	30 (24.4)	14 (23.3)
Back pain	9 (7.3)	9 (15.0)
Myalgia	9 (7.3)	11 (18.3)
Pyrexia	75 (61.0)	31 (51.7)
Malaise	52 (42.3)	28 (46.7)
Injection site reaction	22 (17.9)	9 (15.0)
Fatigue	13 (10.6)	7 (11.7)
Injection site erythema	4 (3.3)	6 (10.0)
White blood cell count decreased	78 (63.4)	41 (68.3)
Neutrophil count decreased	69 (56.1)	37 (61.7)
Platelet count decreased	60 (48.8)	23 (38.3)
Haemoglobin decreased	27 (22.0)	9 (15.0)
Blood bilirubin increased	20 (16.3)	4 (6.7)
Blood triglycerides increased	17 (13.8)	5 (8.3)
Haematocrit decreased	16 (13.0)	8 (13.3)
Red blood cell count decreased	13 (10.6)	6 (10.0)
Weight decreased	9 (7.3)	8 (13.3)

Number of subjects (%)

No deaths occurred. Serious adverse events were reported in 4 subjects in the simeprevir group (erythema in 2 subjects; peritonitis/cardiac failure and glomerulonephritis membranous in 1 subject each) and 6 subjects in the placebo group (dizziness, headache, vertigo positional, malaise, hepatic mass, inclusion body myositis, and intervertebral disc protrusion in 1 subject each [including duplicates]). A causal relationship to the study drug could not be ruled out in the simeprevir group except for cardiac failure and glomerulonephritis membranous, and the outcomes were reported as “resolved” except for hepatic mass and inclusion body myositis.

Adverse events leading to discontinuation of administration of all investigational drugs[113)] were retinopathy in 2 subjects and peritonitis, rash/retinal exudates, and haemoglobin decreased in 1 subject each in the simeprevir group; and in the placebo group, they were rash, erythema multiforme, intervertebral disc protrusion, malaise, and platelet count decreased in 1 subject each. A causal relationship to the investigational drug could not be ruled out for all events in the simeprevir group, and the outcomes were reported as "resolved" except for rash.

4.(iii).A.(3).2) Phase III study in Japanese patients with chronic hepatitis C virus infection (5.3.5.2.1, Study HPC3008 [December 2010 to August 2012])

In order to investigate the efficacy and safety of simeprevir in Japanese patients with chronic hepatitis C infection (genotype 1)[86)] (target sample size of 47) who had relapsed[89)] within 1 year after prior treatment with interferon (≥ 24 weeks), an open-label uncontrolled study was conducted in 12 institutions in Japan.

Simeprevir 100 mg was orally administered QD for 12 weeks in combination with PR, followed by 12- or 36-week administration of PR[114)] based on the RGT criteria.[110)]

A total of 49 treated subjects were included in the FAS and the safety analysis set, and were evaluated for efficacy. PR administration was terminated in 95.9% (47 of 49 subjects) of subjects at Week 24 based on the RGT criteria.

The primary endpoint, SVR12 rate[112)] [95% CI], was 95.9% [86.02, 99.50], which was higher than the predefined threshold of 50%[115)] ($P < 0.0001$[116)]). The secondary endpoint, SVR24 rate, is shown in the following table.

Table. SVR12 rate and SVR24 rate (FAS, NRI[a)])

SVR12 rate	95.9 (47/49) [86.02, 99.50]	$P < 0.0001$[b)]
SVR24 rate	89.8 (44/49) [77.77, 96.60]	

% (number of subjects) [95%CI]

a) The missing data on the viral load 12 or 24 weeks after the actual completion of treatment were completeed by non-SVR.

b) Test for threshold, 50%, (null hypothesis) was performed using binomial distribution

Adverse events occurred in all subjects to whom the investigational drugs were administered. The incidence of adverse events (including laboratory abnormalities) for which a causal relationship to

113) The criteria for discontinuation of drug treatment had been specified with respect to serious adverse events and adverse events/laboratory values classified as Grade ≥3. The criteria for reduction, withdrawal, and discontinuation of PR were the same as the corresponding criteria in the package insert. Dose reduction of simeprevir was not permitted, and discontinuation of PR occurred as simultaneous discontinuation of both drugs. When PR was withheld or discontinued, simeprevir was also withheld or discontinued. The following were specified as the discontinuation criteria for simeprevir (continuation of PR was permitted).
• AST or ALT increase to Grade 4, exceeding the level specified in the criteria
• Bilirubin increase to Grade 4, with the same or higher level on retest

114) When plasma HCV RNA was >3.0 Log IU/mL at Week 4, simeprevir treatment was discontinued. When the decrease from the baseline was <2.0 Log IU/mL at Week 12 or plasma HCV RNA was detected at Week 24 or 36 (≥1.2 Log IU/mL), PR treatment was discontinued.

115) Established based on the clinical results (Jacobson IM, et al. *Am J Gastroenterol*. 2005;100(11):2453-2462) that the SVR24 rate was 50% (15 of 30 patients) when Peg-IFNα-2b 1.5 μg/kg was administered subcutaneously once weekly and RBV 800 mg/day was administered orally for 48 weeks to patients who had relapsed after prior treatment.

116) A null hypothesis that the SVR12 rate is "below the threshold (50%) to determine lack of efficacy" was planned to be tested using binominal distribution.

simeprevir could not be ruled out (adverse drug reactions) was 98.0% (48 of 49 subjects). Adverse events reported by ≥10% of subjects were pyrexia (73.5%, 36 subjects), neutrophil count decreased, white blood cell count decreased (61.2%, 30 subjects each), headache (51.0%, 25 subjects), malaise (46.9%, 23 subjects), anaemia, platelet count decreased (44.9%, 22 subjects each), arthralgia, haemoglobin decreased (40.8%, 20 subjects each), pruritus (38.8%, 19 subjects), alopecia (34.7%, 17 subjects), rash (32.7%, 16 subjects), decreased appetite (28.6%, 14 subjects), myalgia, haematocrit decreased (26.5%, 13 subjects each), injection site reaction, nausea, red blood cell count decreased (22.4%, 11 subjects each), white blood cell count decreased, stomatitis (20.4%, 10 subjects each), diarrhoea, blood triglycerides increased (18.4%, 9 subjects each), dry skin, back pain (16.3%, 8 subjects each), constipation, blood bilirubin increased, weight decreased (14.3%, 7 subjects each), cough, blood potassium decreased (12.2%, 6 subjects each), nasopharyngitis, insomnia, dysgeusia, retinal exudates, hepatic function abnormal, eczema, AST increased, and ALP increased (10.2%, 5 subjects each).

No deaths occurred. Serious adverse events included herpes zoster, malaise/nausea, appendicitis, breast cancer female, pneumonia, and cerebral haemorrhage (1 subject each). A causal relationship could not be ruled out for any of these events except for herpes zoster and breast cancer female, and the outcome of all events was reported as "relieved" or "resolved." All investigational drugs were discontinued[113] in the subject with malaise/nausea and the subject with female breast cancer.

4.(iii).A.(3).3) Phase III study in Japanese patients with chronic hepatitis C virus infection (5.3.5.2.2, Study HPC3004 [January 2011 to September 2012])

In order to investigate the efficacy and safety of simeprevir in Japanese patients with chronic hepatitis C virus infection (genotype 1)[86] (target sample size of 90 subjects, 45 in each group) who had failed to respond[90] to prior treatment with interferon (≥ 24 weeks), a randomized, open-label, parallel-group comparative study[117] was conducted in 23 institutions in Japan.

Simeprevir 100 mg was orally administered QD for 12 weeks (12-week group) or 24 weeks (24-week group) in combination with 24-week administration of PR, followed by discontinuation of PR administration or 24-week administration of PR[118] in accordance with the RGT criteria.[110]

A total of 106 treated subjects (53 subjects each in the 12-week group and the 24-week group) were included in the FAS and the safety analysis set, and were evaluable for efficacy. The percentage of subjects who terminated PR administration at Week 24 based on the RGT criteria was 81.1% (43 of 53 subjects) in the 12-week group and 73.6% (39 of 53 subjects) in the 24-week group.

The primary endpoint, SVR12 rate[112] [95% CI] , was 52.8% [38.64, 66.70] in the 12-week group and 35.8% [23.14, 50.20] and in the 24-week group ($P < 0.0001$ and $P = 0.0001$[119]). The secondary endpoint,

[117] In this study, the subjects were randomly allocated to the 12-week group or the 24-week group taking account of stratification factors includingage (<65 years or ≥65 years) and *IL28B* polymorphism (TT, TG, and GG) .

[118] When plasma HCV RNA was >3.0 Log IU/mL at Week 4, simeprevir treatment was discontinued. When plasma HCV RNA was >2.0 Log IU/mL at Week 12, treatment with simeprevir and PR was discontinued. When plasma HCV RNA was detected at Week 24 or 36 (≥1.2 Log IU/mL), PR treatment was discontinued.

[119] A test for null hypothesis that the SVR12 rate is "below the threshold (14%) to determine lack of efficacy" was planned to be performed using binominal distribution.

SVR24 rate, is shown in the following table.

Table. SVR12 rate and SVR24 rate (FAS, NRI[a])

	12-week group		24-week group	
SVR12 rate	52.8 (28/53) [38.64, 66.70]	$P < 0.0001$[b]	35.8 (19/53) [23.14, 50.20]	$P = 0.0001$[b]
SVR24 rate	50.9 (27/53) [36.84, 64.94]		35.8 (19/53) [23.14, 50.20]	

% (number of subjects) [95%CI]

a) The missing data on the viral load 12 or 24 weeks after the actual completion of treatment were completed by non-SVR.

b) Test for threshold, 14%*, (null hypothesis) was performed using binomial distribution

*: Established based on the clinical results (Jensen DM et al. *Ann Intern Med*. 2009;150(8):528-540) that SVR24 rate was 14% (22 of 156 subjects) when Peg-IFNα-2a 180 μg was administered subcutaneously once weekly and RBV 1000 mg/day (body weight, <75 kg) or 1200 mg/day (body weight, ≥75 kg) was administered orally for 72 weeks to patients who had failed to respond to prior treatment.

The incidence of adverse events (including laboratory abnormalities) was 100% (53 of 53 subjects) in the 12-week group and 98.1% (52 of 53 subjects) in the 24-week group. The incidence of adverse events (including laboratory abnormalities) for which a causal relationship to simeprevir could not be ruled out (adverse drug reactions) was 100% (53 of 53 subjects) in the 12-week group and 96.2% (51 of 53 subjects) in the 24-week group. Adverse events reported by ≥10% of subjects in any group are shown in the following table.

Table. Adverse events reported by ≥10% of subjects in any group

Event	12-week group	24-week group
Number of subjects	53	53
Any adverse event	53 (100)	52 (98.1)
Any adverse drug reaction	53 (100)	51 (96.2)
Nasopharyngitis	10 (18.9)	16 (30.2)
Anaemia	28 (52.8)	31 (58.5)
Leukopenia	2 (3.8)	8 (15.1)
Thrombocytopenia	2 (3.8)	6 (11.3)
Decreased appetite	12 (22.6)	15 (28.3)
Insomnia	5 (9.4)	10 (18.9)
Headache	23 (43.4)	23 (43.4)
Dysgeusia	4 (7.5)	6 (11.3)
Cough	11 (20.8)	4 (7.5)
Stomatitis	11 (20.8)	10 (18.9)
Nausea	6 (11.3)	9 (17.0)
Abdominal discomfort	5 (9.4)	9 (17.0)
Diarrhoea	6 (11.3)	7 (13.2)
Rash	20 (37.7)	23 (43.4)
Alopecia	21 (39.6)	15 (28.3)
Pruritus	16 (30.2)	12 (22.6)
Dry skin	6 (11.3)	4 (7.5)
Arthralgia	13 (24.5)	13 (24.5)
Myalgia	7 (13.2)	6 (11.3)
Back pain	2 (3.8)	6 (11.3)
Pyrexia	33 (62.3)	31 (58.5)
Malaise	30 (56.6)	24 (45.3)
Fatigue	9 (17.0)	11 (20.8)
Injection site reaction	6 (11.3)	12 (22.6)
White blood cell count decreased	33 (62.3)	31 (58.5)
Neutrophil count decreased	28 (52.8)	28 (52.8)
Platelet count decreased	27 (50.9)	21 (39.6)
Haemoglobin decreased	13 (24.5)	12 (22.6)
Blood bilirubin increased	9 (17.0)	11 (20.8)
Haematocrit decreased	8 (15.1)	8 (15.1)
Blood triglycerides increased	7 (13.2)	7 (13.2)
Red blood cell count decreased	8 (15.1)	5 (9.4)

Event	12-week group	24-week group
Number of subjects	53	53
Any adverse event	53 (100)	52 (98.1)
Any adverse drug reaction	53 (100)	51 (96.2)
Blood cholesterol decreased	7 (13.2)	5 (9.4)
Blood calcium decreased	6 (11.3)	4 (7.5)
High density lipoprotein decreased	7 (13.2)	1 (1.9)
ALT increased	6 (11.3)	1 (1.9)
AST increased	6 (11.3)	1 (1.9)

Number of subjects (%)

No deaths occurred. Serious adverse events included erythema multiforme, laceration (1 subject each) in the 12-week group, anaemia, pyelonephritis acute/calculus ureteric, and hypoaesthesia (1 subject each) in the 24-week group. A causal relationship to the study drug could not be ruled out for anaemia, pyelonephritis acute, hypoaesthesia, and erythema multiforme; however, the outcome of all events was reported as "resolved."

Adverse events leading to discontinuation of all investigational drugs[113)] were anaemia and erythema multiforme (1 subject each) in the 12-week group, interstitial lung disease and erythema multiforme (1 subject each) in the 24-week group. A causal relationship to the investigational drug could not be ruled out for any of these events; however, the outcome of all events was reported as "resolved."

4.(iii).A.(3).4) Phase III study in Japanese patients with chronic hepatitis C virus infection (5.3.5.2.3, Study HPC3010 [April 2011 to November 2012])

In order to investigate the efficacy and safety of simeprevir in Japanese patients with chronic hepatitis C virus infection (genotype 1)[86)] who were treatment-naïve,[85)] had relapsed after prior treatment[89)], or had failed to respond to prior treatment[90)] (target sample size of 70 subjects; ≥20 each for respective groups of patients who were treatment-naïve, those who had relapsed after prior treatment, and those who had failed to respond to prior treatment), an open-label uncontrolled study was conducted in 14 Japanese institutions.

Treatment-naïve patients or patients who had relapsed after prior treatment received oral doses of simeprevir 100 mg QD for 12 weeks in combination with Peg-IFNα-2b and RBV,[120)] followed by 12- or 36-week administration of Peg-IFNα-2b and RBV based on the RGT criteria.[110)] Patients who had failed to respond to prior treatment received oral doses of simeprevir 100 mg QD for 12 weeks in combination with Peg-IFNα-2b and RBV, followed by 36-week administration of Peg-IFNα-2b and RBV.

Seventy-nine patients to whom the investigational drug was administered (24 treatment-naïve patients, 29 patients who had relapsed after prior treatment, 26 patients who had not responded to prior treatment) were included in the FAS and the safety analysis set, and were evaluated for efficacy. PR administration was terminated in 91.7% (22 of 24 patients) of treatment-naïve patients and 96.6% (28 of 29 patients) of patients who had relapsed after prior treatment at Week 24 based on the RGT criteria.

[120)] Peg-IFNα-2b 1.5μg/kg was administered subcutaneously once weekly. RBV 600 mg/day (body weight, ≤60 kg), 800 mg/day (body weight, >60 kg and ≤80kg), or 1000 mg/day (body weight, >80 kg) was administered orally.

SVR12 and SVR24 rates in the treatment-naïve patients and patients who had relapsed after or had failed to respond to prior treatment are shown in the following table.

Table. SVR12 rate and SVR24 rate (FAS)

	Treatment-naïve patients	Patients who had relapsed after prior treatment	Patients who had failed to respond to prior treatment
SVR12 rate	91.7 (22/24) [73.00, 98.97]	100 (29/29) [88.06, 100.00]	38.5 (10/26) [20.23, 59.43]
SVR24 rate	91.7 (22/24) [73.00, 98.97]	96.6 (28/29) [82.24, 99.91]	38.5 (10/26) [20.23, 59.43]

% (number of subjects) [95%CI]

Adverse events and adverse events (including laboratory abnormalities) for which a causal relationship to the investigational drugs could not be ruled out (adverse drug reactions) occurred in all subjects. Adverse events reported by ≥10% of subjects are shown in the following table.

Table. Adverse events reported by ≥10% of subjects in any group

Event	Treatment-naïve patients	Patients who had relapsed after prior treatment	Patients who had not responded to prior treatment	Total
Number of subjects	24	29	26	79
Any adverse event	24 (100)	29 (100)	26 (100)	79 (100)
Any dverse drug reaction	24 (100)	29 (100)	26 (100)	79 (100)
Nasopharyngitis	3 (12.5)	7 (24.1)	6 (23.1)	16 (20.3)
Anaemia	11 (45.8)	21 (72.4)	8 (30.8)	40 (50.6)
Neutropenia	6 (25.0)	2 (6.9)	5 (19.2)	13 (16.5)
Leukopenia	4 (16.7)	2 (6.9)	1 (3.8)	7 (8.9)
Decreased appetite	12 (50.0)	12 (41.4)	7 (26.9)	31 (39.2)
Hypocalcaemia	4 (16.7)	0	1 (3.8)	5 (6.3)
Insomnia	4 (16.7)	4 (13.8)	7 (26.9)	15 (19.0)
Headache	11 (45.8)	12 (41.4)	13 (50.0)	36 (45.6)
Dysgeusia	4 (16.7)	3 (10.3)	1 (3.8)	8 (10.1)
Cough	4 (16.7)	4 (13.8)	2 (7.7)	10 (12.7)
Productive cough	4 (16.7)	1 (3.4)	1 (3.8)	6 (7.6)
Stomatitis	6 (25.0)	6 (20.7)	9 (34.6)	21 (26.6)
Diarrhoea	6 (25.0)	0	6 (23.1)	12 (15.2)
Nausea	4 (16.7)	5 (17.2)	2 (7.7)	11 (13.9)
Abdominal discomfort	3 (12.5)	2 (6.9)	4 (15.4)	9 (11.4)
Cheilitis	2 (8.3)	1 (3.4)	3 (11.5)	6 (7.6)
Constipation	3 (12.5)	1 (3.4)	0	4 (5.1)
Dental caries	0	1 (3.4)	3 (11.5)	4 (5.1)
Hyperbilirubinaemia	3 (12.5)	4 (13.8)	3 (11.5)	10 (12.7)
Rash	12 (50.0)	8 (27.6)	10 (38.5)	30 (38.0)
Alopecia	14 (58.3)	9 (31.0)	5 (19.2)	28 (35.4)
Pruritus	7 (29.2)	7 (24.1)	6 (23.1)	20 (25.3)
Erythema	3 (12.5)	2 (6.9)	1 (3.8)	6 (7.6)
Arthralgia	11 (45.8)	10 (34.5)	6 (23.1)	27 (34.2)
Myalgia	8 (33.3)	3 (10.3)	10 (38.5)	21 (26.6)
Back pain	6 (25.0)	5 (17.2)	3 (11.5)	14 (17.7)
Pyrexia	18 (75.0)	27 (93.1)	22 (84.6)	67 (84.8)
Malaise	12 (50.0)	12 (41.4)	14 (53.8)	38 (48.1)
Injection site reaction	11 (45.8)	8 (27.6)	12 (46.2)	31 (39.2)
Fatigue	6 (25.0)	7 (24.1)	1 (3.8)	14 (17.7)
Injection site erythema	5 (20.8)	2 (6.9)	1 (3.8)	8 (10.1)
White blood cell count decreased	17 (70.8)	16 (55.2)	13 (50.0)	46 (58.2)
Neutrophil count decreased	11 (45.8)	8 (27.6)	7 (26.9)	26 (32.9)
Platelet count decreased	11 (45.8)	6 (20.7)	8 (30.8)	25 (31.6)

Event	Treatment-naïve patients	Patients who had relapsed after prior treatment	Patients who had not responded to prior treatment	Total
Number of subjects	24	29	26	79
Any adverse event	24 (100)	29 (100)	26 (100)	79 (100)
Any dverse drug reaction	24 (100)	29 (100)	26 (100)	79 (100)
Blood bilirubin increased	5 (20.8)	12 (41.4)	6 (23.1)	23 (29.1)
Haemoglobin decreased	10 (41.7)	2 (6.9)	5 (19.2)	17 (21.5)
Haematocrit decreased	8 (33.3)	2 (6.9)	1 (3.8)	11 (13.9)
Red blood cell count decreased	7 (29.2)	2 (6.9)	1 (3.8)	10 (12.7)
Weight decreased	4 (16.7)	3 (10.3)	3 (11.5)	10 (12.7)
Blood calcium decreased	5 (20.8)	1 (3.4)	1 (3.8)	7 (8.9)
Lipase increased	3 (12.5)	4 (13.8)	0	7 (8.9)
Blood albumin decreased	5 (20.8)	1 (3.4)	0	6 (7.6)
Blood cholesterol decreased	5 (20.8)	0	1 (3.8)	6 (7.6)
Lymphocyte percentage increased	5 (20.8)	0	0	5 (6.3)
Bilirubin conjugated increased	4 (16.7)	0	0	4 (5.1)
Blood bilirubin unconjugated increased	4 (16.7)	0	0	4 (5.1)
High density lipoprotein decreased	3 (12.5)	0	0	3 (3.8)
Eosinophil percentage increased	3 (12.5)	0	0	3 (3.8)

Number of subjects (%)

No deaths occurred. Serious adverse events included hyperbilirubinaemia in 1 treatment-naïve patient, and peripheral T-cell lymphoma and thyroid cancer in 1 patient each among those who had failed to respond to prior treatment. A causal relationship to the investigational drugs could not be ruled out for hyperbilirubinaemia and thyroid cancer. The outcomes were reported as "resolved" for all events except for peripheral T-cell lymphoma.

Adverse events leading to discontinuation of all investigational drugs[113)] were dermatitis allergic in 1 treatment-naïve patient, anaemia in 1 patient who had relapsed after prior treatment, and depression in 1 patient who had failed to respond to prior treatment. A causal relationship to the study drugs could not be ruled out for any of these events, and the outcomes of all events were reported as "resolved."

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

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

As a result of the following reviews on the efficacy of simeprevir, PMDA concluded that the efficacy of triple therapy with simeprevir and PR (hereinafter, referred to as "triple therapy") in the treatment of chronic hepatitis C has been demonstrated.

The above conclusion by PMDA will be finalized taking account of comments from the expert advisors.

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

The primary endpoint for Japanese phase III studies (Studies HPC3003, HPC3004, and HPC3008) of simeprevir was the SVR24 rate, which had been selected at the start of the studies, but was changed to the SVR12 rate midway through.

The applicant commented on the rationale and justification for the change and explained that it is possible to change the primary endpoint for Japanese phase III studies (Studies HPC3003, HPC3004,

and HPC3008) from the SVR24 rate to the SVR12 rate during the stadies, for the following reasons:

- It has been reported that, when a combination of Peg-IFN and RBV was given, SVR24 was achieved in 99.7% of subjects (408 of 409 subjects) who achieved SVR12.[121] Similar results have been obtained in Japanese phase III studies in which a combination of Peg-IFNα-2a and RBV was given.[122]
- Japanese phase III studies of telaprevir, a drug of the same class, also showed that the SVR12 rate was similar to the SVR24 rate when a combination of telaprevir, Peg-IFN, and RBV or a combination of Peg-IFN and RBV was given.[123]
- In the Japanese late phase II study (Study C215) of simeprevir, most patients relapsed by the 12 weeks after the end of treatment, and the SVR12 rate equaled the SVR24 rate in the simeprevir 100 mg group and the PR group. Also in the foreign phase II studies (Studies C205 and C206), the SVR12 rate was the same as the SVR24 rate in the simeprevir 150 mg group.
- The results of foreign clinical studies of boceprevir and telaprevir showed that the SVR12 rate was consistent with the SVR24 rate.[124),125]
- In the Japanese phase III study (Study HPC3003), the risk of a potential bias in the study conduct in terms of the SVR24 rate due to unblinding at the time of the database lock for the SVR12 rate was considered to be avoidable given the evaluation criteria of this study.[126]
- Taking into consideration the seriousness of the disease, it is important to shorten the development period.

An agreement has been reached with foreign regulatory authorities on setting the SVR12 rate as the primary endpoint in foreign clinical studies that are ongoing or planned in the future. The US FDA recommends the use of the SVR12 rate as the primary endpoint in clinical studies in view of accelerating the development of drugs for treatment of chronic hepatitis C, which requires a long period of time, and speeding up the availability of clinical data for useful drugs.[127),128]

PMDA considers as follows:

It is understandable that the SVR12 and SVR24 rates are related, taking into account the results of the Japanese and foreign phase II studies of simeprevir and clinical studies of other drugs of the same class. Although unblinding occurred 12 weeks after the end of treatment in the Japanese phase III study (Study HPC3003), the risk of biases in the evaluation of efficacy and safety is avoidable given that: (1) HCV RNA viral load was selected as the efficacy endpoint; (2) in terms of safety, the evaluation of adverse events based on the data up to 4 weeks after the end of treatment was planned and implemented; (3)

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121) Martinot-Peignoux M, et al. *Hepatology.* 2010;51:1122-1126
122) Copegus Tablets 200 mg Application Form. 2.7.6. Available from: http://www.info.pmda.go.jp/shinyaku/P200700005/index.html, June 2013
123) Hayashi N, et al. *J Viral Hepat*. 2012;19(2):e134-e142
124) Victrelis (Boceprevir). Statistics Filing Checklist for a New NDA/BLA. Center for Drug Evaluation and Research. Application number: 202258Orig1s000. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202258Orig1s000StatR.pdf, June 2013
125) Incivek (Telaprevir). Statistics Filing Checklist for a New NDA/BLA. Center for Drug Evaluation and Research. Application number: 201917Orig1s000. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201917Orig1s000StatR.pdf, June 2013
126) The indexes for the efficacy endpoints were exclusively HCV RNA viral load and ALT level; in terms of safety, the evaluation of adverse events was to be conducted based on the data up to 4 weeks after the end of treatment; allocation information and the SVR12 results were not disclosed to the study monitors and study institutions until the database was locked.
127) Florian J, et al. *Hepatol*. 2011;54(S1):1444A
128) Chen J, et al. *Gastroenterology*. 2013;144:1450-1455

allocation information and SVR12 results were not disclosed to the study monitors and study institutions until the database was locked. Then, taking into account the facts that chronic hepatitis C is a serious disease that can progress to hepatocellular carcinoma, and that it is important to shorten the development period of the study drug, PMDA has concluded that changing the primary endpoint from the SVR24 rate to the SVR12 rate in the Japanese phase III studies (Studies HPC3003, HPC3004, and HPC3008) after their start is acceptable. However, it is necessary to confirm the consistency between the SVR24 rate as the secondary endpoint and the SVR12 rate. The review of the SVR12 and SVR24 rates in 4 Japanese phase III studies (Studies HPC3003, HPC3004, HPC3008, and HPC3010) demonstrated that there was no significant difference between the SVR12 and SVR24 rates. The results are shown in the following table.

Table. SVR12 and SVR24 rates in 4 Japanese phase III studies

	Target patients	Treatment group (treatment duration)	Number of patients	SVR12 rate	SVR24 rate
HPC3003	Treatment-naïve patients	Simeprevir group (12 weeks)	123	88.6 (109)	88.6 (109)
		Placebo group (PR 48 weeks)	60	61.7 (37)	56.7 (34)
HPC3008	Patients who had relapsed after prior treatment	Simeprevir group (12 weeks)	49	95.9 (47)	89.8 (44)
HPC3004	Patients who had failed to respond to prior treatment	Simeprevir group (12 weeks)	53	52.8 (28)	50.9 (27)
		Simeprevir group (24 weeks)	53	35.8 (19)	35.8 (19)
HPC3010	Treatment-naïve patients	Simeprevir group (12 weeks)	24	91.7 (22)	91.7 (22)
	Patients who had relapsed after prior treatment	Simeprevir group (12 weeks)	29	100.0 (29)	96.6 (28)
	Patients who had failed to respond to prior treatment	Simeprevir group (12 weeks)	26	38.5 (10)	38.5 (10)

% (Number of patients)

4.(iii).B.(1).2) Efficacy in Japanese phase III studies

The SVR12 rates in 4 Japanese phase III studies (Studies HPC3003, HPC3004, HPC3008, and HPC3010) are shown in the following table.

Table. SVR12 rate in 4 Japanese phase III studies

	Target patients	Treatment group (treatment duration)	Number of patients	SVR12 rate	95% CI	Differences between groups [95% CI]
HPC3003	Treatment-naïve patients	Simeprevir group (12 weeks)	123	88.6 (109)	[83.63, 94.39]	27.5
		Placebo group (PR 48 weeks)	60	61.7 (37)	[49.61, 73.47]	[14.38, 40.56]
HPC3008	Patients who had relapsed after prior treatment	Simeprevir group (12 weeks)	49	95.9 (47)	[86.02, 99.50]	
HPC3004	Patients who had failed to respond to prior treatment	Simeprevir group (12 weeks)	53	52.8 (28)	[38.64, 66.70]	
		Simeprevir group (24 weeks)	53	35.8 (19)	[23.14, 50.20]	
HPC3010	Treatment-naïve patients	Simeprevir group (12 weeks)	24	91.7 (22)	[73.00, 98.97]	
	Patients who had relapsed after prior treatment	Simeprevir group (12 weeks)	29	100.0 (29)	[88.06, 100.00]	
	Patients who had failed to respond to prior treatment	Simeprevir group (12 weeks)	26	38.5 (10)	[20.23, 59.43]	

% (Number of patients)

(a) Efficacy in treatment-naïve patients

PMDA concluded that the efficacy of triple therapy in treatment-naïve patients has been demonstrated

since the superiority of triple therapy with simeprevir and PR over PR therapy alone was verified in the Japanese phase III study (Study HPC3003) in treatment-naïve[85)] patients with chronic hepatitis C virus (genotype 1) infection [see "4.(iii).A.(3).1) Japanese phase III study in Japanese patients with chronic hepatitis C virus infection"].

(b) Efficacy in patients who had relapsed after prior treatment and patients who had failed to respond to prior treatment

Open-label uncontrolled studies (Studies HPC3008 and HPC3004) were conducted to investigate the efficacy and safety of triple therapy with simeprevir and PR in patients with chronic hepatitis C virus (genotype 1) infection who had relapsed[89)] after prior treatment, IFN therapy (≥ 24 weeks), and those who had failed to respond[90)] to prior treatment.

PMDA asked the applicant to explain the efficacy of triple therapy in patients who had failed to respond to prior treatment, taking into account the fact that the SVR12 rates in the 12-week and 24-week simeprevir groups were 52.8% (28 of 53 patients) and 35.8% (19 of 53 patients), respectively, in the Japanese phase III study (Study HPC3004) in patients who had failed to respond to prior treatment.

The applicant explained as follows:

There are overseas reports that the SVR24 rate was 4% (19 of 431 patients) following administration of Peg-IFN and RBV for 48 weeks to patients with chronic hepatitis C virus (genotype 1) infection who had failed to respond to the combination therapy with Peg-IFN and RBV.[129)] However, other oversea reports stated that the SVR24 rate was 14% following administration of Peg-IFNα-2a and RBV for 72 weeks to patients with chronic hepatitis C virus infection who had failed to respond to the combination therapy with Peg-IFNα-2b and RBV.[130)] In Japan, it was reported that the SVR24 rate was 13% (3 of 24 patients) when retreatment with the same therapy was provided to patients with chronic hepatitis C virus infection who had faild respond to the combination therapy with Peg-IFN and RBV. It also stated that none of the 16 patients who had failed to respond to prior treatment[131)] achieved SVR24.[132)]

Based on the above reports, the applicant considered that the SVR12 rate after triple therapy with simeprevir in the Japanese phase III study (Study HPC3004) demonstrated a high therapeutic effect in patients who had failed respond to prior treatment.

PMDA's view on the efficacy in patients who had relapsed after prior treatment and patients who had failed to respond to prior treatment is as follows:

Strict evaluation of efficacy and safety is difficult because the open-label uncontrolled design was used in the Japanese phase III studies (Studies HPC3008 and HPC3004). However, efficacy evaluation based on the results of open-label uncontrolled studies is unavoidable because when simeprevir was developed,

129) Poynard T, et al. *Gastroenterology*. 2009;136:1618-1628
130) Jensen DM, et al. *Ann Intern Med*. 2009;150(8):528-540
131) Patients whose treatment period was <24 weeks because the HCV RNA level did not decrease by ≥2 log at Week 12 of the combination therapy with Peg-IFN and RBV.
132) Oze T, et al. *J Gastroenterol*. 2011;46:1031-1037

appropriate therapeutic methods had not been established for patients who had relapsed after prior treatment and patients who had failed to respond to prior treatment.

On that basis, a certain level of efficacy can be expected with triple therapy including simeprevir in patients who had relapsed after prior treatment and patients who had failed to respond to prior treatment for the following reasons:

- The SVR12 rate was as high as 95.9% in the Japanese phase III study (Study HPC 3008) in patients who had relapsed after prior treatment, demonstrating the superiority over the previously established threshold (50%).[115)]
- The SVR12 rate was 52.8% in the 12-week simeprevir group and 35.8% in the 24-week simeprevir group in the Japanese phase III study (Study HPC 3004) in patients who had failed to respond to prior treatment, and exceeded the previously established threshold (14%).

(c) Interferon products for combination therapy

PMDA asked the applicant to explain the efficacy of combination therapy using simeprevir in conjunction with Peg-IFNα-2b and RBV, because a Japanese phase III study (Study HPC3010) was conducted to investigate the efficacy and safety of simeprevir in combination with Peg-IFNα-2b and RBV, whereas the efficacy and safety of simeprevir in combination with Peg-IFNα-2a and RBV was investigated in other Japanese phase III studies (Studies HPC3003, HPC3008, and HPC3004).

The applicant explained as follows:

Following administration of simeprevir in combination with Peg-IFNα-2b and RBV in the Japanese phase III study (Study HPC3010), the SVR12 rate in treatment-naïve patients, patients who had relapsed after prior treatment, and patients who had failed to respond to prior treatment was 91.7% (22 of 24 patients), 100% (29 of 29 patients), and 38.5% (10 of 26 patients), respectively, and the SVR24 rate was 91.7% (22 of 24 patients), 96.6% (28 of 29 patients), and 38.5% (10 of 26 patients), respectively. The rates did not differ significantly from those in the Japanese phase III studies (Studies HPC3003, HPC3008, and HPC3004), and were high, when compared with the clinical results[130)] of 72-week retreatment with co-administration of PR in patients who had failed to respond to prior treatment. Taking the above into account, triple therapy with simeprevir can be expected to be effective irrespective of the types of Peg-IFN used in the combination (i.e., Peg-IFNα-2a or Peg-IFNα-2b).

PMDA considers as follows:

The efficacy of simeprevir can be expected in patients with chronic hepatitis C virus (genotype 1) infection when simeprevir is administered in combination with Peg-IFNα-2b and RBV because the Japanese phase III study (Study HPC3010) on the efficacy of triple therapy with simeprevir, Peg-IFNα-2b, and RBV demonstrated that the SVR12 rate and SVR24 rate did not differ significantly from those in the Japanese phase III studies (Studies HPC3003, HPC3004, and HPC3008), which investigated the efficacy of triple therapy with simeprevir, Peg-IFNα-2a, and RBV. However, since the number of patients who received simeprevir in combination with Peg-IFNα-2b and RBV was limited, it is necessary

to continue to collect post-marketing information on the efficacy and safety of simeprevir in combination with Peg-IFNα-2b and RBV [see "4.(iii).B.(2).7) Effect of co-administration of different Peg-IFN on safety" for safety].

(d) Efficacy against chronic hepatitis C (genotype 1a)

PMDA asked the applicant to explain the efficacy of simeprevir against HCV genotype 1a because most patients with chronic hepatitis C virus (genotype 1) infection enrolled in the Japanese phase III studies (Studies HPC3003, HPC3004, HPC3008, and HPC3010) were infected with HCV genotype 1b.

The applicant explained as follows:

Most patients with chronic hepatitis C virus (genotype 1) infection enrolled in the Japanese phase III studies (Studies HPC3003, HPC3004, HPC3008, and HPC3010) were infected with HCV genotype 1b. The number of patients with HCVgenotype 1a infection who achieved SVR12 was 2 of 2 patients in the simeprevir group in Study HPC3003 conducted in treatment-naïve patients, 1 of 1 patient in Study HPC3008 conducted in patients who had relapsed after prior treatment, and 1 of 3 patients in Study HPC3004 conducted in patients who had failed to respond to prior treatment; SVR12 was not achieved in one patient who had failed to respond to prior treatment in Study HPC3010.

In the foreign phase II study (Study C205) conducted in treatment-naïve patients with chronic hepatitis C virus infection, the SVR24 rate in the simeprevir 150 mg group[133)] was 82.4% (61 of 74 patients) in patients infected with HCV genotype 1a and 83.8% (67 of 80 patients) in patients infected with HCV genotype 1b. The SVR 24 rates were higher than those in the placebo group[134)] (66.7% [20 of 30 patients] in patients infected with HCV genotype 1a; 63.8% [30 of 47 patients] in patients infected with HCV genotype 1b).

The following table shows the SVR24 rates for genotype 1a and genotype 1b in the simeprevir 150 mg group and the placebo group in the foreign phase II study (Study C206)[135)] conducted in patients with chronic hepatitis C virus infection who had relapsed after prior treatment, patients who had partially responded to prior treatment, and patients who had failed to respond to prior treatment. The SVR24 rates against both HCV genotypes were higher in the simeprevir 150 mg group than in the placebo group.

133) Combination of a group in which simeprevir 150 mg QD was administered for 12 weeks in combination with PR, followed by 12-week administration of placebo in combination with PR and a group in which simeprevir 150 mg QD was administered for 24 weeks in combination with PR. The dosage regimen in foreign phase III studies was 150 mg QD, at which exposure is comparable to 100 mg QD, the dosage and administration in Japan [see "4.(ii).B.(1) Pharmacokinetics of simeprevir"].

134) PR was administered for 48 weeks. Placebo was co-administered for the first 24 weeks.

135) The simeprevir 150 mg group is a combination of a group in which simeprevir 150 mg QD was administered for 12 weeks in combination with PR, followed by 36-week administration of placebo in combination with PR; a group in which simeprevir 150 mg QD was administered for 24 weeks in combination with PR, followed by 24-week administration of placebo in combination with PR; and a group in which simeprevir 150 mg QD was administered for 48 weeks in combination with PR. In the placebo group, placebo was administered for 48 weeks in combination with PR.

Table. SVR24 rate by HCV genotype (Study C206)

	Patients who had relapsed after prior treatment		Patients who had partially responded to prior treatment		Patients who had failed to respond to prior treatment	
	Simeprevir 150 mg group	Placebo group	Simeprevir 150 mg group	Placebo group	Simeprevir 150 mg group	Placebo group
Genotype 1a	84.8 (28/33 patients)	33.3 (4/12 patients)	56.0 (14/25 patients)	12.5 (1/8 patients)	42.3 (11/26 patients)	0 (0/7 patients)
Genotype 1b	84.4 (38/45 patients)	40.0 (6/15 patients)	88.4 (38/43 patients)	6.7 (1/15 patients)	58.3 (14/24 patients)	33.3 (3/9 patients)

SVR rate (%) (Number of patients who achieved SVR/Number of evaluated patients)

The SVR12 rates in the simeprevir 150 mg group and the placebo group in the foreign phase III study (pooled Studies C208/C216)[136] conducted in treatment-naïve patients with chronic hepatitis C virus infection, and in the foreign phase III study (Study HPC3007)[137] conducted in patients who had relapsed after prior treatment, are shown in the following table. The SVR12 rates against both genotypes were higher in the simeprevir 150 mg group than in the placebo group.

Table. SVR12 rate by HCV genotype (Studies C208/C216, Study HPC3007)

	Studies C208/C216		Study HPC3007	
	Simeprevir 150 mg group	Placebo group	Simeprevir 150 mg group	Placebo group
Genotype 1a/other	75.2 (191/254 patients)	47.3 (62/131 patients)	70.3 (78/111 patients)	27.8 (15/54 patients)
Genotype 1b	85.4 (228/267 patients)	52.6 (70/133 patients)	85.9 (128/149 patients)	43.0 (34/79 patients)

SVR rate (%) (Number of patients who achieved SVR/Number of evaluated patients)

Based on the above reports, since the efficacy of simeprevir in patients infected with HCV genotype 1a was comparable to that in patients infected with HCV genotype 1b in the foreign clinical studies, the applicant considered that the efficacy of simeprevir in patients infected with HCV genotype 1a has been demonstrated, although the efficacy data for patients infected with HCV genotype 1a in Japanese clinical studies are limited.

Since the SVR24 rate and the SVR12 rate in patients who received triple therapy including simeprevir were comparable for both genotype 1a and genotype 1b in foreign clinical studies, PMDA considers that the efficacy of simeprevir in patients infected with HCV genotype 1a can be expected, even though there has been scant investigation in Japanese clinical studies on the efficacy of triple therapy including simeprevir in patients infected with HCV genotype 1a. The inclusion of genotypes in the indication of simeprevir will be discussed in "4.(iii).B.(4) Indication."

(e) Effect of polymorphism of *IL28B*

The polymorphism of *IL28B* (single nucleotide polymorphism, SNP) is an important factor that affects the therapeutic effect of Peg-IFN and RBV, and the expected efficacy rate is known to be high for the major alleles (TT in SNP rs8099917, CC in SNP rs12979860) but low for the minor alleles (TG and GG

136) The simeprevir group is a combination of a study (Study C208) in which simeprevir 150 mg QD was administered for 12 weeks in combination with PR (PR was administered for 24 or 48 weeks in accordance with the RGT criteria) and a study (Study C216) in which simeprevir 150 mg was administered for 12 weeks in combination with PR or Peg-IFNα-2b/RBV (Peg-IFN/RBV was administered for 24 or 48 weeks in accordance with the RGT criteria). In the placebo group, placebo was administered for 12 weeks in combination with PR, followed by 36-week administration of PR (PR or Peg-IFNα-2b/RBV in Study C216).

137) In the simeprevir group, a combination therapy of simeprevir 150 mg and PR was conducted for 12 weeks (PR was administered for 24 or 48 weeks in accordance with the RGT criteria). In the placebo group, placebo was administered for 12 weeks in combination with PR, followed by 36-week administration of PR.

in SNP rs8099917, CT and TT in SNP rs12979860).[138)]

PMDA asked the applicant to explain the effect of *IL28B* polymorphism on the efficacy of simeprevir.

The applicant explained as follows:
The SVR12 rates for each *IL28B* polymorphism in Japanese phase III studies (Studies HPC3003, HPC3004, and HPC3008) are shown in the following table.

Table. SVR12 rate for each *IL28B* polymorphism (Studies HPC3003, HPC3008, and HPC3004)

	HPC3003		HPC3008	HPC3004	
	Treatment-naïve patients		Patients who had relapsed after prior treatment	Patients who had failed to respond to prior treatment	
	Simeprevir (12 weeks)	Placebo group	Simeprevir (12 weeks)	Simeprevir (12 weeks)	Simeprevir (24 weeks)
	123 patients	60 patients	49 patients	53 patients	53 patients
SNP rs8099917					
TT	77/82 (93.9)	31/42 (73.8)	34/35 (97.1)	3/8 (37.5)	4/6 (66.7)
TG	30/39 (76.9)	6/17 (35.3)	13/14 (92.9)	24/44 (54.5)	14/46 (30.4)
GG	2/2 (100.0)	0/1 (0.0)	–	1/1 (100.0)	1/1 (100.0)
SNP rs12979860					
CC	76/79 (96.2)	31/42 (73.8)	34/35 (97.1)	3/8 (37.5)	4/6 (66.7)
CT	31/42 (73.8)	6/17 (35.3)	13/14 (92.9)	34/43 (55.8)	14/45 (31.1)
TT	2/2 (100.0)	0/1 (0.0)	–	1/2 (50.0)	1/2 (50.0)

Number of patients (%)

In the treatment-naïve patients, the difference in the SVR12 rate between the major alleles and minor alleles was smaller (approximately 20%) in the simeprevir group than the placebo group (approximately 40%) for all SNPs, with a tendency to reduce the effect of *IL28B* polymorphism. In patients who had relapsed after prior treatment, the effect of *IL28B* polymorphism was limited. In patients who had failed to respond to prior treatment, SNPs showed no consistent trend: the SVR12 rate in the 12-week simeprevir group was lower for the major alleles than for the minor alleles; the SVR12 rate in the 24-week simeprevir group was higher for the major alleles than for the minor alleles. The reason for this inconsistency was unclear because of the small number of examined patients.

It has been reported that the effect of SNP rs12979860 on the SVR24 rate was investigated in a foreign clinical study of triple therapy including telaprevir. The results showed that the SVR24 rate for CC, CT, and TT genotypes was 88% (51 of 58 patients), 85% (100 of 117 patients), and 85% (29 of 34 patients), respectively, in the patients who had relapsed after prior treatment, 63% (5 of 8 patients), 58% (33 of 57 patients), and 71% (10 of 14 patients), respectively, in the patients who had partially responded to prior treatment, and 40% (4 of 10 patients), 29% (27 of 92 patients), and 31% (10 of 32 patients), respectively, in the patients who had failed to respond to prior treatment. The report has concluded that *IL28B* polymorphism had limited effect on therapeutic efficacy in patients who had relapsed after prior treatment and patients who had failed to respond to prior treatment.[139)]

138) Tanaka Y, et al. *Nat Genet.* 2009;41(10):1105-1109
139) Pol S, et al. *J Hepatol.* 2013;58:883-889

PMDA accepted the above explanation from the applicant. It is necessary to continue to investigate the factors that affect the efficacy of triple therapy including simeprevir in patients who had failed to respond to prior treatment and to appropriately provide the information on the results obtained to the clinical practice.

4.(iii).B.(1).3) Viral mutants

The applicant explained the development of simeprevir-resistant viruses as follows:

The simeprevir-resistant mutations of genotype 1b detected in Japanese patients were similar to those in foreign patients [see "3.(i).B.(2) Resistance to simeprevir"].

In addition, in terms of the persistence of resistance mutations, a certain proportion of amino acid mutations detected at the time of "failure"[140] became below the quantification limit at the end of the study. The proportions of patients with undetectable amino acid mutations were as follows: 25.0% (3 of 12 patients) in treatment-naïve patients (follow-up time [median, range], 12.00 weeks, 0.00-28.86 weeks), 33.3% (1 of 3 patients) in patients who had relapsed after prior treatment (12.00 weeks, 0.00-12.00 weeks), and 55.4% (36 of 65 patients) in patients who had failed to respond to prior treatment (20.00 weeks, 0.00-34.29 weeks).

The observation that the mutations detected in the "subjects with treatment failure" at the time of "failure" were below the quantification limit at the end of study can be interpreted in several ways: the amino acid mutations that expressed disappeared and returned to the baseline sequence; alternatively, the mutations decreased below the detection sensitivity of the analysis methods employed (population sequencing, approximately 25%-30%; deep sequencing, < 1%). However, the possibility that viruses with resistance mutations remained *in vivo* cannot be completely ruled out.

PMDA considers as follows:

The applicant explained that, although no genetic mutations were detected in "subjects with failure" in Japanese clinical studies, the possibility of resistant viruses remaining *in vivo* could not be completely ruled out, which is understandable. Since the information on the resistance mutations obtained to date is very limited, the applicant should collect post-marketing information on the mutations in "subjects with failure" of triple therapy with simeprevir, including post-treatment follow-up, and should appropriately provide the obtained information to the clinical practice.

4.(iii).B.(2) Safety

PMDA reviewed the safety of simeprevir mainly based on the results of Japanese phase III studies (Studies HPC3003, HPC3004, HPC3008, and HPC3010) shown below, and concluded that the applicant

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[140] In the Japanese phase III study, the following subjects were defined as "subjects with failure," and the amino acid sequence in the NS3 protease region was analyzed and evaluated. To a subject who met multiple failure criteria, the failure criterion with smaller number (see below) was applied. In a subject who met the criterion, "4) Relapse," priority was given to the analysis of the data during relapse.
1) Subjects who experienced breakthrough during the treatment period
2) Subjects who met the virological discontinuation criteria established for each study during the treatment period
3) Subjects whose plasma HCV RNA was detectable at the end of treatment
4) Subjects who relapsed after the end of treatment

should provide caution about increases in blood bilirubin levels that may be caused by triple therapy including simeprevir in comparison with PR therapy. It is necessary to provide sufficient information on these events and to continue to collect post-marketing information. In addition, caution should also be advised regarding adverse events that occur frequently in PR therapy, such as pyrexia, malaise, headache, alopecia, insomnia, white blood cell count decreased, and neutrophil count decreased.

Since there is a paucity of information on the safety of Peg-IFNα-2b/RBV from Japanese clinical studies, it is necessary to collect post-marketing information on the safety of simeprevir co-administered with Peg-IFNα-2b/RBV as well.

The above conclusion by PMDA will be finalized, taking account of comments from the expert advisors.

4.(iii).B.(2).1) Comparison of the safety of triple therapy and PR

The applicant explained the safety of triple therapy including simeprevir in comparison with PR therapy as follows:

Adverse events occurred in practically all subjects during the entire treatment period[141)] in the Japanese clinical studies (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3008, HPC3004, and HPC3010).

The adverse events (including laboratory abnormalities) reported by ≥10% of subjects in any of the following simeprevir groups are shown in the table below: the group to which simeprevir 100 mg was administered for 12 weeks (12-week simeprevir 100 mg group),[142)] the group to which simeprevir 100 mg was administered for the entire treatment period (simeprevir 100 mg group [entire treatment period]),[143)] the total simeprevir group,[144)] and the placebo group.[145)]

Adverse events reported by ≥10% of subjects in any of the simeprevir groups (pooled data of 5 Japanese studies)

Event	12-week simeprevir 100 mg group	Simeprevir 100 mg group (entire treatment period)	Total simeprevir group	Placebo group
Number of subjects	330	396	436	73
Any adverse event	330 (100.0)	395 (99.7)	435 (99.8)	73 (100.0)
Nasopharyngitis	56 (17.0)	74 (18.7)	87 (20.0)	20 (27.4)
Anaemia	166 (50.3)	202 (51.0)	215 (49.3)	41 (56.2)
Decreased appetite	91 (27.6)	107 (27.0)	115 (26.4)	23 (31.5)
Insomnia	57 (17.3)	70 (17.7)	85 (19.5)	27 (37.0)
Headache	151 (45.8)	180 (45.5)	202 (46.3)	35 (47.9)
Dysgeusia	38 (11.5)	45 (11.4)	49 (11.2)	8 (11.0)
Cough	41 (12.4)	46 (11.6)	50 (11.5)	10 (13.7)
Stomatitis	75 (22.7)	87 (22.0)	99 (22.7)	14 (19.2)
Diarrhoea	53 (16.1)	60 (15.2)	67 (15.4)	22 (30.1)

141) From the start of administration of simeprevir/placebo or PR to 28 days after the end of administration of all drugs.
142) The 12-week simeprevir 100 mg group in Study C215, the 12-week simeprevir group in Study HPC3003, the subjects who received simeprevir for 12 weeks in Study HPC3004, and all subjects in Studies HPC3008 and HPC3010
143) The 12- and 24-week simeprevir 100 mg group in Study C215, the 12-week simeprevir group in Study HPC3003, and all subjects in Studies HPC3004, HPC3008, and HPC3010
144) Subjects in treatement groups other than the PR group in Study C215 (12-week simeprevir 50 mg group, 12-week simeprevir 100 mg group, 24-week simeprevir 50 mg group, and 24-week simeprevir 100 mg group), subjects in the 12-week simeprevir group in Study HPC3003, and all subjects in Studies HPC3004, HPC3008, and HPC3010
145) "Placebo group" in this section refers to the subjects in the PR group in Study C215 and in the placebo group in Study HPC3003.

Event	12-week simeprevir 100 mg group	Simeprevir 100 mg group (entire treatment period)	Total simeprevir group	Placebo group
Number of subjects	330	396	436	73
Any adverse event	330 (100.0)	395 (99.7)	435 (99.8)	73 (100.0)
Nausea	49 (14.8)	59 (14.9)	66 (15.1)	12 (16.4)
Abdominal discomfort	37 (11.2)	47 (11.9)	56 (12.8)	7 (9.6)
Rash	138 (41.8)	169 (42.7)	194 (44.5)	43 (58.9)
Alopecia	116 (35.2)	134 (33.8)	150 (34.4)	34 (46.6)
Pruritus	94 (28.5)	112 (28.3)	117 (26.8)	18 (24.7)
Arthralgia	96 (29.1)	114 (28.8)	129 (29.6)	16 (21.9)
Myalgia	56 (17.0)	63 (15.9)	71 (16.3)	13 (17.8)
Back pain	34 (10.3)	42 (10.6)	47 (10.8)	10 (13.7)
Pyrexia	221 (67.0)	259 (65.4)	284 (65.1)	38 (52.1)
Malaise	159 (48.2)	190 (48.0)	215 (49.3)	36 (49.3)
Injection site reaction	72 (21.8)	89 (22.5)	102 (23.4)	12 (16.4)
Fatigue	40 (12.1)	51 (12.9)	53 (12.2)	7 (9.6)
White blood cell count decreased	202 (61.2)	245 (61.9)	271 (62.2)	51 (69.9)
Neutrophil count decreased	167 (50.6)	207 (52.3)	229 (52.5)	46 (63.0)
Platelet count decreased	138 (41.8)	165 (41.7)	174 (39.9)	29 (39.7)
Haemoglobin decreased	89 (27.0)	108 (27.3)	123 (28.2)	15 (20.5)
Blood bilirubin increased	65 (19.7)	79 (19.9)	83 (19.0)	4 (5.5)
Haematocrit decreased	54 (16.4)	65 (16.4)	73 (16.7)	12 (16.4)
Red blood cell count decreased	48 (14.5)	56 (14.1)	65 (14.9)	10 (13.7)
Blood triglycerides increased	36 (10.9)	45 (11.4)	47 (10.8)	8 (11.0)

Number of subjects (%)

Among adverse events that occurred in the entire treatment period, the following events were ≥10% more frequently reported by subjects in the 12-week simeprevir 100 mg group than in the placebo group: pyrexia (67.0% in the 12-week simeprevir 100 mg group and 52.1% in the placebo group) and blood bilirubin increased (19.7% and 5.5%, respectively). One subject in the 12-week simeprevir 100 mg group died of cerebral infarction, but a causal relationship to the study drug was ruled out. The incidence of serious adverse events was 5.2% (17 of 330 subjects) in the 12-week simeprevir 100 mg group and 8.2% (6 of 73 subjects) in the placebo group.

Since the simeprevir group showed an increasing tendency in incidence of blood bilirubin increased as compared with the placebo group, PMDA reviewed the details, taking into account the assessments in the sections below. In addition, the following was also reviewed, taking into account the assessments in the sections below: the incidence of adverse events of which serious cases have been reported for other drugs of the same class as simeprevir, including rash-related events, nephrotoxicity, and blood disorders such as granulocytosis; safety in the elderly; the safety of simeprevir in combination with Peg-IFNα-2b and RBV used in Study HPC3010.

4.(iii).B.(2).2) Increases in blood bilirubin levels

The applicant explained the increases in blood bilirubin levels as follows:

The events related to increased bilirubin[146)] were tallied from the pooled data of the Japanese clinical studies (phase II study, Study C215; phase III studies, Study HPC3003, HPC3008, HPC3004, and

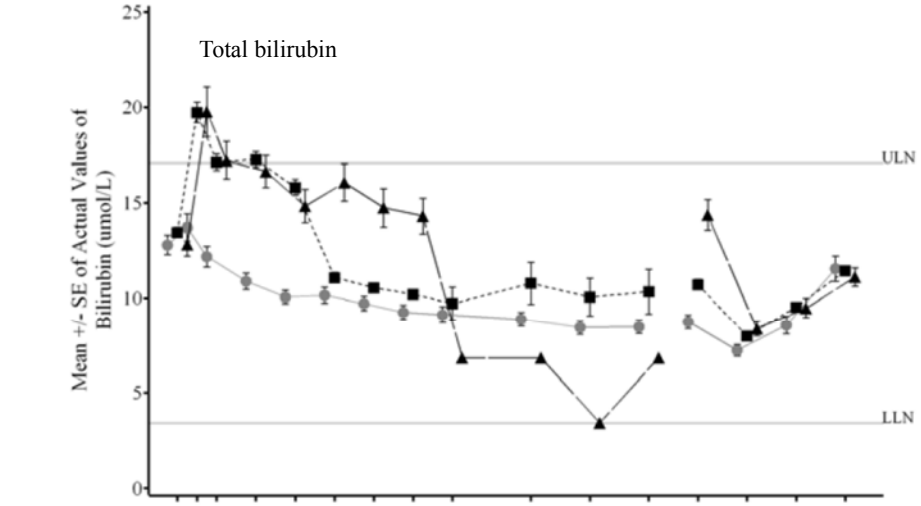
146) Adverse events coded according to MedDRA PT were "bilirubin conjugated abnormal," "bilirubin conjugated increased," "bilirubin excretion disorder," "bilirubinuria," "blood bilirubin abnormal," "blood bilirubin increased," "blood bilirubin unconjugated increased," "hyperbilirubinaemia," "jaundice," "jaundice cholestatic," "jaundice extrahepatic obstructive," "jaundice hepatocellular," "urine bilirubin increased," and "yellow skin."

HPC3010).

The incidence of events related to increased bilirubin that occurred during the entire treatment period was 31.5% (104 of 330 subjects) in the 12-week simeprevir 100 mg group and 8.2% (6 of 73 subjects) in the placebo group. Events related to increased bilirubin occurred during the first 12 weeks of treatment.

Serious adverse events related to increased bilirubin included hyperbilirubinaemia[147)] in 1 subject in the 12-week simeprevir 100 mg group in a Japanese phase III study (Study HPC3010). The event was considered probably related to simeprevir, but considered unlikely related to Peg-IFNα-2b and RBV. The incidence of Grade ≥3 events related to increased bilirubin was 1.8% (6 of 330 subjects) in the 12-week simeprevir 100 mg group and 1.4% (1 of 73 subjects) in the placebo group. Grade ≥4 events related to increased bilirubin did not occur in any group.

The time course of total bilirubin, direct bilirubin, and indirect bilirubin was studied. The following figures shows that total bilirubin, direct bilirubin, and indirect bilirubin increased after the start of simeprevir administration. Peak bilirubin levels were reached at Week 2 in all simeprevir groups, and bilirubin levels returned close to baseline 4 weeks after the end of the simeprevir treatment period (at Week 16 in the 12-week treatment group and at Week 28 in the 24-week treatment group). There was no tendency for AST or ALT to increase with the increase in total bilirubin.



147) A 61-year-old treatment naïve woman participated in Study HPC3010. A high level of total bilirubin (4.2 mg/dL, Grade 3) was detected on Day 7, and only simeprevir was withheld. Total bilirubin decreased to 3.2 mg/dL on Day 9, and simeprevir treatment was restarted. Total bilirubin at Week 2 was 3.5 mg/dL. Jaundice symptoms were present, and the hospital stay period was extended to allow the patient's condition to be monitored closely (the planned hospital stay was for a 2-week period from the start of treatment). The subject was discharged from the hospital3 days after the end of Week 2, and hyperbilirubinaemia was considered "resolved" at Week 14. The subject completed administration of simeprevir for 12 weeks and PR for 24 weeks.

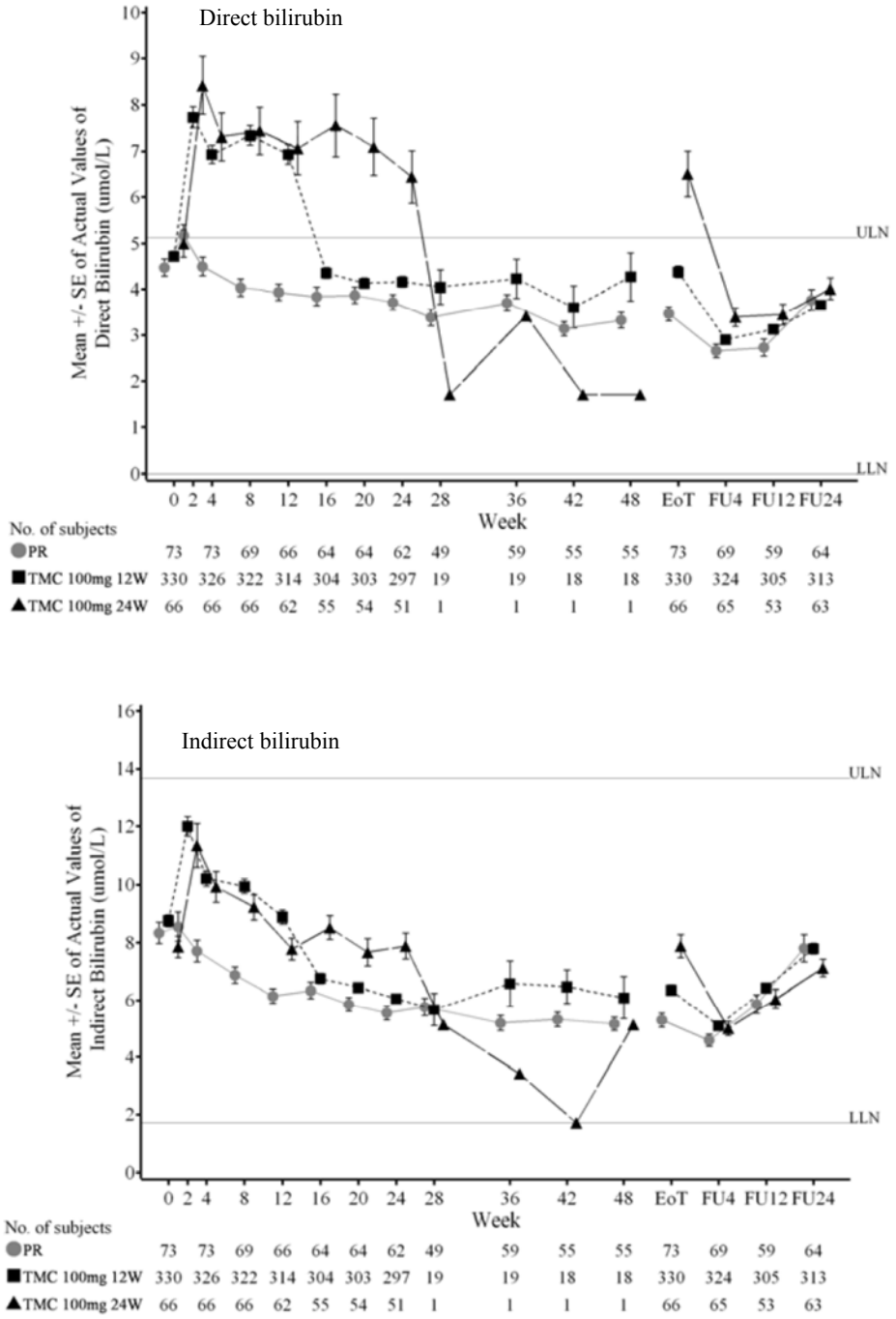


Figure. Course of total bilirubin, direct bilirubin, and indirect bilirubin over time (mean ± standard error)
ULN, upper limit of normal; LLN, lower limit of normal (pooled data of 5 Japanese studies)

Based on the above reports, the incidence of events related to increased bilirubin was higher in the 12-week simeprevir 100 mg group than in the placebo group. However, many of the events were of Grade 1 or 2 and simeprevir was considered to be well tolerated. Increases in total bilirubin, direct bilirubin, and indirect bilirubin were noted, but the increases were transient and the bilirubin levels declined rapidly after the end of the simeprevir treatment period.

PMDA considers as follows:

Administration of simeprevir resulted in a high incidence of events related to increased bilirubin as

compared to the placebo group. However, most events were mild and tended to resolve after the end or discontinuation of simeprevir administration. There were no associated increases in ALT or AST. Although the evaluation of nonclinical study results [see "3.(ii).B.(1) Mechanism for the increases in bilirubin levels"] suggests that inhibition of OATP1B1 and MRP2 is primarily involved in the increase in plasma bilirubin levels, administration of triple therapy including simeprevir is feasible if bilirubin levels during simeprevir treatment are closely monitored. It is necessary to continue to investigate the incidence of events related to increased bilirubin via post-marketing surveillance.

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

The applicant explained rash-related events as follows:

Rash-related events[148)] were tallied from the pooled data of the Japanese clinical studies (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3008, HPC3004, and HPC3010).

The incidence of rash-related events that occurred during the entire treatment period was 50.9% (168 or 330 subjects) in the 12-week simeprevir 100 mg group and 65.8% (48 of 73 subjects) in the placebo group. The incidence was lower in the 12-week simeprevir 100 mg group than in the placebo group, but the incidences in both groups were comparable up to Week 12 (45.8% [151 of 330 subjects] in the 12-week simeprevir 100 mg group and 45.2% [33 of 73 subjects] in the placebo group).

Serious rash-related events occurred in 4 subjects (2 subjects in the 12-week group in Study HPC3003, and 1 subject each in the 24-week 50 mg group in Study C215 and the 12-week group in Study HPC3004) who received simeprevir, and one of them was treated with intravenous administration of steroids. A causal relationship to the investigational drug could not be ruled out in any of the 4 subjects, but the outcomes were "resolved."

Although there was no rash-related events which resulted in discontinuation of either simeprevir or placebo alone, the rash-related events which resulted in discontinuation of all drugs were reported by 0.6% (2 of 330 subjects) in the 12-week simeprevir 100 mg group and 2.7% (2 of 73 subjects) in the placebo group.

In the pooled data of foreign phase III studies (Studies C208, C216, and HPC3007), the incidence of rash-related events was, for the entire treatment period, 27.9% (218 of 781 subjects) in the 12-week simeprevir 150 mg group and 24.9% (99 of 397 subjects) in the placebo group. For the first 12 weeks, they were 23.2% (181 of 781 subjects) in the 12-week simeprevir 150 mg group and 16.9% (67 of 397 subjects) in the placebo group, thus resulting in the high incidence in the 12-week simeprevir 150 mg group. The incidence of serious rash-related events was 0.3% (2 of 781 subjects) in the 12-week

148) Tallied rash-related events included the following: adverse events coded according to MedDRA HLT as erythemas, papulosquamous conditions,rashes, eruptions and exanthems NEC, or photosensitivity conditions; adverse events included in the narrow terms (PT) from the Standardised MedDRA Queries for "Severe cutaneous adverse reaction"; adverse events included in the following broad terms (PT). Broad terms (PT): acquired epidermolysis bullosa, blister, bullous impetigo, drug eruption, drug rash with eosinophilia and systemic symptoms, epidermolysis, epidermolysis bullosa, mucocutaneous ulceration, nikolsky's sign, pemphigoid, pemphigus, skin erosion, and skin exfoliation.

simeprevir 150 mg group (both subjects were admitted to hospital because of a photosensitivity reaction [1 each for Grade 2 and Grade 3]), and the events were considered related to simeprevir (serious rash-related events did not occur in the placebo group).

Administration of simeprevir or placebo alone was discontinued due to rash-related events in 2 subjects (0.3%) in the 12-week simeprevir 150 mg group and 1 subject (0.3%) in the placebo group. All drugs were discontinued due to rash-related events in 0.5% (4 of 781 subjects) in the 12-week simeprevir 150 mg group.

PMDA considers as follows:
Rash-related events are also known to occur in patients receiving PR therapy. There is no concern that the risk of rash-related events increases greatly in combination therapy with simeprevir plus PR versus PR therapy alone, taking into account the incidence reported in clinical studies and the information on the severity of these events. Given that the risk of exacerbation of skin eruptions has been pointed out for other drugs of the same class, it is necessary to collect post-marketing information on the incidence of skin eruption-related events and, if new information becomes available, to appropriately provide the information to the clinical practice.

4.(iii).B.(2).4) Hematotoxicity

(a) Anemia-related events

The applicant explained anemia-related events as follows:
Anemia-related events[149)] were tallied from the pooled data of Japanese clinical studies (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3008, HPC3004, and HPC3010).

The incidence of anemia-related events that occurred during the entire treatment period was 77.6% (256 of 330 subjects) in the 12-week simeprevir 100 mg group, which was comparable to 76.7% (56 of 73 subjects) in the placebo group, but the incidence during the first 12 weeks of administration was 63.3% (209 of 330 subjects) in the 12-week simeprevir 100 mg group, which was higher than 46.6% (34 of 73 subjects) in the placebo group. Serious anemia-related events did not occur in the 12-week simeprevir 100 mg group, but occurred in 1 subject[150)] (anaemia) in the 24-week treatment group in the Japanese phase III study (Study HPC3004) conducted in patients who had failed to respond to prior treatment. The event was considered unlikely related to simeprevir, while it was considered less likely related to Peg-IFN and highly likely related to RBV. Anemia-related events led to discontinuation of either simeprevir or placebo alone in 1 subject (1.7%) in the placebo group, but not in the 12-week simeprevir 100 mg group. Anemia-related events led to discontinuation of all study drugs in 4 subjects (1.2%) in the 12-week simeprevir 100 mg group, but not in the placebo group.

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149) Adverse events coded according to MedDRA PT as anaemia, haemoglobin decreased, or haemolytic anaemia were tallied as anemia-related events.

150) A 63-year-old woman participated in Study HPC3004. She had developed Grade 2 anaemia at Week 3 and fell off a chair during an examination at Week 8 as a result of losing consciousness. She suffered bleeding of the left hand and lower lip as well as a contusion in the left temporal region. As a consequence, administration of simeprevir and PR was discontinued. She was discharged from the hospital at Week 9, and her anaemia resolved at Week 14.

In the 12-week simeprevir 100 mg group and in the placebo group, dose reduction of RBV was caused by anaemia in 29.1% (96 of 330 subjects) and 37.0% (27 of 73 subjects) of subjects, respectively, and by haemoglobin decreased in 16.7% (55 of 330 subjects) and 9.6% (7 of 73 subjects) of subjects, respectively. Anemia-related events led to dose reduction of Peg-IFN in only 1 subject (anaemia) in the 12-week simeprevir 100 mg group.

In addition, the hemoglobin level decreased in all groups during the first 8 weeks after the start of administration of simeprevir or placebo in combination with PR, and remained at low levels. However, it increased rapidly after the end of the treatment period (end of administration of all drugs), and returned close to the baseline level at Week 12 in the follow-up observation period.

Based on the above, since a serious event occurred in only 1 subject until Week 12 of simeprevir administration, the combination therapy with simeprevir and PR is considered to have little effect on the continuation of and adherence to PR therapy, despite the high incidence of anemia-related events in the 12-week simeprevir 100 mg group. The hemoglobin level decreased in all treatment groups after the start of simeprevir administration, which is not considered to be a major problem since the hemoglobin level recovered rapidly after the end of the triple therapy.

(b) Events related to decreased neutrophil count

The applicant explained events related to decreased neutrophil count as follows:

Events related to decreased neutrophil count[151)] were tallied from the pooled data of the Japanese clinical studies (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3008, HPC3004, and HPC3010).

The incidence of events related to decreased neutrophil count during the entire treatment period was 58.5% (193 of 330 subjects) in the 12-week simeprevir 100 mg group and 64.4% (47 of 73 subjects) in the placebo group, and the incidence during the first 12 weeks of administration was 53.0% (175 of 330 subjects) in the 12-week simeprevir 100 mg group and 43.8% (32 of 73 subjects) in the placebo group.

None of the events related to decreased neutrophil count was considered serious adverse events. Events related to decreased neutrophil count led to discontinuation of either simeprevir or placebo alone in only 1 subject (0.3%) in the 12-week simeprevir 100 mg group. There was no case that led to discontinuation of all study drugs.

The neutrophil count decreased in both simeprevir and placebo groups during the first 4 weeks after the start of administration of simeprevir or placebo in combination with PR, and remained at low levels, but increased rapidly after the end of the treatment period (end of administration of all drugs) until returning

151) Adverse events coded according to MedDRA PT as “neutropenia” or “neutrophil count decreased” were tallied as events related to decreased neutrophil count.

close to the baseline level at Week 12 in the follow-up observation period.

Based on the above reports, events related to decreased neutrophil count is not considered to be a clinically significant problem since these events occurred to a similar extent in the simeprevir group and placebo group, and no serious cases were observed.

(c) Events related to decreased platelet count

The applicant explained events related to decreased platelet count as follows:

Events related to decreased platelet count[152)] were tallied from the pooled data of the Japanese clinical studies (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3008, HPC3004, and HPC3010).

The incidence of events related to decreased platelet count during the entire treatment period was 45.2% (149 of 330 subjects) in the 12-week simeprevir 100 mg group and 43.8% (32 of 73 subjects) in the placebo group, and the incidence during the first 12 weeks of administration was 41.8% (138 of 330 subjects) in the 12-week simeprevir 100 mg group and 32.9% (24 of 73 subjects) in the placebo group. None of the events related to decreased platelet count was considered serious adverse events, and there was no case that led to drug discontinuation.

The platelet count decreased in both simeprevir and placebo groups after the start of administration of simeprevir or placebo in combination with PR, and remained at low levels, but recovered rapidly after the end of administration of all drugs.

Based on the above reports, events related to decreased platelet count is considered not to be a clinically significant problem since these events occurred to a similar extent in the simeprevir group and placebo group; no serious events were observed; and the platelet count recovered rapidly after the end of triple therapy.

PMDA considers as follows:

Although anaemia, platelet count decreased, white blood cell count decreased, and neutrophil count decreased also occur in the PR therapy, they are not considered to be significant problems if appropriate measures are taken in accordance with the criteria for dose reduction and discontinuation of PR therapy because no tendency toward exacerbation was observed when PR was used in combination with simeprevir. It is necessary to continue to collect post-marketing information on events related hematotoxicity.

4.(iii).B.(2).5) Events related to renal impairment

Since renal impairment has been reported for other drugs of the same class, PMDA asked the applicant

152) Adverse events coded according to MedDRA PT as “thrombocytopenia” or “platelet count decreased” were tallied as events related to decreased platelet count

to explain whether renal impairment had been observed following administration of simeprevir.

The applicant explained as follows:

Events related to renal impairment[153)] were tallied from the pooled data of the Japanese clinical studies (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3008, HPC3004, and HPC3010). The incidence of renal and urinary disorders during the entire treatment period was 4.8% (16 of 330 subjects) in the 12-week simeprevir 100 mg group and 5.5% (4 of 73 subjects) in the placebo group. In addition, the incidence during the first 12 weeks of administration was 3.0% (10 of 330 subjects) in the 12-week simeprevir 100 mg group and 2.7% (2 of 73 subjects) in the placebo group, which showed the similar results to each other. Renal and urinary disorders have been reported as serious adverse events in 2 subjects (calculus ureteric and glomerulonephritis membranous in 1 subject each) treated with simeprevir, but a causal relationship to simeprevir was ruled out in both subjects. Blood creatinine increased also occurred in 2 subjects (1 subject each in the 12-week simeprevir 100 mg group and the 24-week simeprevir 100 mg group), but both were Grade 1 events. The time course of serum creatinine level (mean) showed practically no change as seen in the following figure. No high creatinine level of Grade ≥2 was observed. None of renal or urinary disorders or blood creatinine increased resulted in treatment discontinuation.

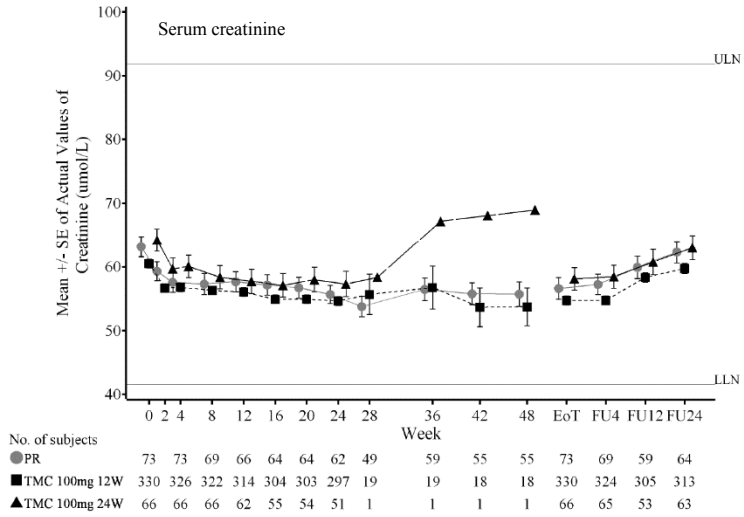

Figure. Time course of serum creatinine level (mean ± standard deviation); ULN, upper limit of normal; LLN, lower limit of normal (pooled data of 5 Japanese studies)

In the pooled data of the foreign phase III studies (Studies C208, C216, and HPC3007), the incidence of renal and urinary disorders during the entire treatment period was 4.9% (38 of 781 subjects) in the 12-week simeprevir 150 mg group and 5.0% (20 of 397 subjects) in the placebo group. The incidence during the first 12 weeks of administration was 3.6% (28 of 781 subjects) in the 12-week simeprevir 150 mg group, which was comparable to 3.0% (12 of 397 subjects) in the placebo group. Serious renal or urinary disorder occurred in 1 subject in the 12-week simeprevir 150 mg group (acute prerenal failure), but a causal relationship to simeprevir was ruled out. The incidence of blood creatinine increased during the entire treatment period was 0.4% (3 of 781 subjects) in the 12-week simeprevir 150 mg group and

153) Renal and urinary disorders (SOC) and blood creatinine increased (PT) were tallied as events related to renal impairment.

0.5% (2 of 397 subjects) in the placebo group, and no serious events were observed. None of renal or urinary disorders or blood creatinine increased resulted in treatment discontinuation.

Based on the above, no particular clinical problem is considered in association with events related to renal impairment.

PMDA considers as follows:
Since triple therapy including simeprevir did not lead to an increase in the incidence of renal impairment, currently, there is no significant problem. However, given that caution on renal impairment has been provided for other drugs of the same class after their market launch, it is necessary to continue to collect post-marketing information.

4.(iii).B.(2).6) Elderly

The Japanese phase III studies (Studies HPC3003, HPC3008, HPC3004, and HPC3010) were conducted in subjects aged ≥20 years and ≤70 years. The SVR12 rates for triple therapy including simeprevir by age (≤45 years, >45 and <65 years, ≥65 years) are shown in the following table.

Table. SVR12 rate by age (Studies HPC3003, HPC3008, HPC3004, and HPC3010)

	Target patients	Treatment group (duration of treatment)	Number of patients	≤45 years	<45 and <65 years	≥65 years
HPC3003	Treatment-naïve patients	Simeprevir group (12 weeks)	123	87.0 (20/23)	89.7 (70/78)	86.4 (19/22)
		Placebo group (PR48 weeks)	60	63.6 (7/11)	59.0 (23/39)	70.0 (7/10)
HPC3008	Patients who had relapsed after prior treatment	Simeprevir group (12 weeks)	49	94.6 (35/37)[a)]		100 (12/12)
HPC3004	Patients who had failed to respond to prior treatment	Simeprevir group (12 weeks)	53	40.0 (2/5)	55.9 (19/34)	50.0 (7/14)
		Simeprevir group (24 weeks)	53	42.9 (3/7)	47.1 (16/34)	0 (0/12)
HPC3010	Treatment-naïve patients	Simeprevir group (12 weeks)	24	100 (19/19)[a)]		60.0 (3/5)
	Patients who had relapsed after prior treatment	Simeprevir group (12 weeks)	29	100 (20/20)[a)]		100 (9/9)
	Patients who had not failed to respond to prior treatment	Simeprevir group (12 weeks)	26	31.8 (7/22)[a)]		75.0 (3/4)

SVR rate (%) (Number of patients who achieved SVR/Number of evaluated patients)
a) Includes patients aged ≤45 years

In addition, the applicant explained the safety of simeprevir in the elderly as follows:
The adverse events that occurred during the entire treatment period based on the pooled data of the Japanese clinical studies (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3008, HPC3004, and HPC3010) are tallied for age groups of <65 years and ≥65 years as shown in the following table. Although comparison is difficult because of the small number of patients aged ≥65 years, the incidence of adverse events, serious adverse events, Grade ≥3 adverse events, and adverse events that led to study discontinuation did not differ significantly by age.

Table. Incidence of adverse events by age (events reported by ≥10% of patients aged ≥65 years in the 12-week simeprevir 100 mg group)

Event	Placebo group		12-week simeprevir 100 mg group	
	<65 years	≥65 years	<65 years	≥65 years
Number of subjects	61	12	261	69
Any adverse event	61 (100.0)	12 (100.0)	261 (100.0)	69 (100.0)
Serious adverse events	6 (9.8)	0	16 (6.1)	1 (1.4)
Adverse events of Grade ≥3	16 (26.2)	4 (33.3)	70 (26.8)	16 (23.2)
Adverse events that led to study discontinuation	6 (9.8)	2 (16.7)	13 (5.0)	5 (7.2)
Nasopharyngitis	26 (42.6)	5 (41.7)	41 (15.7)	15 (21.7)
Anaemia	34 (55.7)	7 (58.3)	126 (48.3)	40 (58.0)
Decreased appetite	21 (34.4)	2 (16.7)	68 (26.1)	23 (33.3)
Insomnia	21 (34.4)	6 (50.0)	46 (17.6)	11 (15.9)
Headache	30 (49.2)	5 (41.7)	125 (47.9)	26 (37.7)
Dysgeusia	5 (8.2)	3 (25.0)	29 (11.1)	9 (13.0)
Stomatitis	12 (19.7)	2 (16.7)	65 (24.9)	10 (14.5)
Nausea	10 (16.4)	2 (16.7)	40 (15.3)	9 (13.0)
Abdominal discomfort	5 (8.2)	2 (16.7)	25 (9.6)	12 (17.4)
Constipation	7 (11.5)	0	16 (6.1)	9 (13.0)
Hyperbilirubinaemia	2 (3.3)	0	21 (8.0)	8 (11.6)
Rash	38 (62.3)	5 (41.7)	113 (43.3)	25 (36.2)
Alopecia	30 (49.2)	4 (33.3)	96 (36.8)	20 (29.0)
Pruritus	16 (26.2)	2 (16.7)	72 (27.6)	22 (31.9)
Erythema	4 (6.6)	1 (8.3)	20 (7.7)	8 (11.6)
Arthralgia	13 (21.3)	3 (25.0)	84 (32.2)	12 (17.4)
Myalgia	11 (18.0)	2 (16.7)	43 (16.5)	13 (18.8)
Pyrexia	32 (52.5)	6 (50.0)	178 (68.2)	43 (62.3)
Malaise	32 (52.5)	4 (33.3)	121 (46.4)	38 (55.1)
Injection site reaction	9 (14.8)	3 (25.0)	56 (21.5)	16 (23.2)
Injection site erythema	5 (8.2)	2 (16.7)	13 (5.0)	7 (10.1)
White blood cell count decreased	46 (75.4)	5 (41.7)	163 (62.5)	39 (56.5)
Neutrophil count decreased	40 (65.6)	6 (50.0)	130 (49.8)	37 (53.6)
Platelet count decreased	25 (41.0)	4 (33.3)	113 (43.3)	25 (36.2)
Haemoglobin decreased	11 (18.0)	4 (33.3)	71 (27.2)	18 (26.1)
Blood bilirubin increased	4 (6.6)	0	48 (18.4)	17 (24.6)
Haematocrit decreased	9 (14.8)	3 (25.0)	42 (16.1)	12 (17.4)
Red blood cell count decreased	8 (13.1)	2 (16.7)	36 (13.8)	12 (17.4)
Weight decreased	9 (14.8)	1 (8.3)	23 (8.8)	9 (13.0)

Number of subjects (%)

Adverse events frequently occurring (≥ 40%) in patients aged ≥65 years in the 12-week simeprevir 100 mg group were pyrexia (62.3%), anaemia (58.0%), white blood cell count decreased (56.5%), malaise (55.1%), and neutrophil count decreased (53.6%). The incidence of each event was comparable to that in patients aged <65 years except for anaemia (≥ 65 years, 58.0%; < 65 years, 48.3%). The incidence of anaemia in patients aged ≥65 years was comparable between the 12-week simeprevir 100 mg group and the placebo group. These results indicate that anaemia was not due to co-administration of simeprevir, and the same caution as for combination therapy with Peg-IFN and RBV is considered to be sufficient.

PMDA considers as follows:

Although it is difficult to draw any conclusion about the efficacy of simeprevir in elderly Japanese patients because of the small number of evaluated patients, the SVR12 rate after 12-week simeprevir treatment does not differ markedly between patients aged ≥65 years and those aged <65 years. Based on the information to date on the safety of simeprevir in elderly Japanese patients, there are no events

that raise any particular concern about the drug's safety.

However, given that the number of evaluated elderly patients was limited, and that, in general, physiological function decreases in the elderly, a possible increase in the incidence of adverse events in this population cannot be ruled out. For these reasons, the collection of the post-marketing information on the efficacy and safety in the elderly should be continued.

4.(iii).B.(2).7) Effect of safety by difference in co-administered Peg-IFN

The applicant explained the safety of the use of simeprevir in combination with Peg-IFNα-2b and RBV as follows:

Taking into consideration that the type and incidence of adverse events reported in the Japanese phase III study (Study HPC3010), in which simeprevir was administered in combination with Peg-IFNα-2b and RBV [see 4.(iii).A.(3).4) Phase III study in Japanese patients with chronic hepatitis C virus infection"] are similar to those in other Japanese phase III studies (Studies HPC3003, HPC3004, and HPC3008), no adverse events are considered to be characteristic of the use of simeprevir in combination with Peg-IFNα-2b and RBV.

Based on the above reports, the safety profile of triple therapy with simeprevir, Peg-IFNα-2b and RBV is not considered to differ significantly from that of triple therapy with simeprevir, Peg-IFNα-2a, and RBV.

PMDA considers as follows:

PMDA considers that triple therapy with simeprevir, Peg-IFNα-2b, and RBV does not raise significant safety concerns at present in comparison with triple therapy with simeprevir, Peg-IFNα-2a, and RBV. However, since the number of subjects included in the investigation of triple therapy with simeprevir, Peg-IFNα-2b, and RBV was limited, the collection of post-marketing information on the safety should be continued.

4.(iii).B.(3) Clinical positioning

The applicant explained the clinical positioning of this drug product as follows:

IFN, Peg-IFN, PBV, and telaprevir, a HCV NS3/4A serine protease inhibitor, are currently approved in Japan as drugs for treatment of chronic hepatitis C virus infection aiming at eradication of HCV. Dual therapy with Peg-IFN and RBV is one of the treatment options for treatment-refractory HCV genotype 1-infected patients with high viral load, but the treatment period is as long as 48 weeks (72 weeks if the effect is insufficient) and the SVR24 rate is approximately 50%.[5)] The total treatment period for triple therapy with telaprevir, Peg-IFN, and RBV is 24 weeks, and therefore the treatment is possible within a shorter period than with dual therapy with PegIFN and RBV. The triple therapy shows an improvement in the therapeutic effect,[6)] while producing new issues such as restriction of prescription due to safety concerns and the response to adverse drug reactions.[7),8),9)] Therefore, there is a high medical need for a novel therapeutic drug.

Given that co-administration of simeprevir with Peg-IFN and RBV to treatment-naïve patients showed a higher therapeutic effect than that of dual therapy with PEG-IFN and RBV [see "4.(iii).B.(1).2).(a) Efficacy in treatment-naïve patients"], that a favorable therapeutic effect was also obtained in patients who had failed to respond to or had relapsed after prior treatment [see "4.(iii).B.(1).2).(b) Efficacy in patients who had failed to respond to or had relapsed after prior treatment"], and that there were no clinically evident safety problems [see "4.(iii).B.(2) Safety"], the clinical benefits expected from the co-administration of simeprevir with Peg-INF and RBV outweigh the predicted risks.

Based on the above reports, the triple therapy with simeprevir, Peg-INF, and RBV can be a new first-line therapy that meets the medical needs that have not been met by dual therapy with Peg-IFN and RBV or triple therapy with telaprevir, Peg-INF, and RBV.

PMDA considers as follows:
Although the study results of a direct comparison of triple therapy including simeprevir and that including telaprevir have not yet been obtained, a higher SVR rate was obtained using triple therapy including simeprevir than with dual therapy using Peg-IFN and RBV in the Japanese phase III study as well as telaprevir. Therefore, this indicates that clinically significant efficacy can be expected with triple therapy including simeprevir. Moreover, the Japanese phase III study results did not show any evident problems that raise a concern about combined administration in clinical practice, though attention should be paid to the safety of simeprevir in combination with Peg-IFN and RBV.

Based on the above reports, triple therapy withsimeprevir, Peg-INF, and RBV has the potential to become a novel therapeutic option for Japanese chronic hepatitis C patients. However, given that the assessment in patients infected with HCV genotype 1a is limited, information on the efficacy and safety that have been obtained thus far needs to be provided toclinical practice.

The above conclusion by PMDA will be finalized, taking into account the comments from the expert advisors.

4.(iii).B.(4) Indication

Taking into account the review in "4.(iii).B.(1) Efficacy," "4.(iii).B.(2) Safety," and "4.(iii).B.(3) Clinical positioning" as well as the review in the following sections, PMDA concluded that the indication should be as follows.

Improvement of viraemia in any of the following patients with serogroup 1 (genotype I [1a] or II [1b]) chronic hepatitis C virus infection:
1) Treatment-naïve patients with high blood HCV RNA load
2) Patients who has failed to respond to or has relapsed after interferon therapy

The above conclusion by PMDA will be finalized, taking account of comments from the expert advisors.

4.(iii).B.(4).1) Serogroup 1 (genotype I [1a] or II [1b]) as the intended population

Although the Japanese clinical studies were conducted mainly in HCV genotype 1b patients, no problem is found in defining serogroup 1 (genotype I [1a] or II [1b]) as the intended population for triple therapy including simeprevir, based on the discussion on the efficacy against genotype 1a in the foreign phase III studies [see 4.(iii).B.(1).2).(d) Efficacy against chronic hepatitis C (genotype 1a)"].

4.(iii).B.(4).2) Simeprevir use in patients with low viral load

Since the Japanese clinical studies on simeprevir were conducted in patients with high viral load,[86)] PMDA asked the applicant to explain the efficacy of triple therapy with simeprevir, Peg-IFN, and RBV in patients with low viral load (< 5.0 Log IU/mL) who had relapsed after or had failed respond to prior treatment.

The applicant explained as follows:

Subjects who had plasma HCV RNA levels of >4.0 Log IU/mL were enrolled in the foreign late phase II study (Study C206) and foreign phase III studies (Studies C208, C216, and HPC3007). The following patients with low viral load achieved SVR12: 1 of 1 patient who had relapsed after prior treatment and 3 of 4 patients who had partially responded to prior treatment in Study C206; 3 of 4 patients in Study C208 (treatment-naïve patients); 7 of 8 patients in Study C216 (treatment-naïve patients); 3 of 3 patients in Study HPC3007 (patients who had relapsed after prior treatment).

Based on the above reports, triple therapy including simeprevir is expected to produce a similar SVR rate in patients with low viral load as in those with high viral load.

However, since PR therapy is not indicated in treatment-naïve patients with low viral load in Japan, the applicant considers that the triple therapy should not be recommended in treatment-naïve patients with low viral load even though favorable efficacy can be expected.

PMDA considers as follows:

Although patients with low viral load were not enrolled in the Japanese clinical studies, SVR12 was achieved in patients with low viral load who had relapsed after prior treatment or had failed to respond to prior treatment in the foreign clinical studies, albeit a limited number of patients examined.

The Japanese guidelines[1)] recommend PR therapy for the retreatment of HCV genotype 1 patients with low viral load if the prior treatment was IFN or Peg-IFN monotherapy, and moreover, triple therapy with telaprevir (if tolerated) if the prior treatment was PR therapy. If the prior treatment is IFN or Peg-IFN monotherapy, high efficacy is expected for simeprevir triple therapy in comparison with PR therapy recommended in the guidelines, and the addition of simeprevir to PR therapy would yield no particular safety problems. Moreover, if the prior treatment was PR therapy, the level of efficacy of simeprevir

triple therapy can be expected to be similar to that achieved with telaprevir triple therapy, with no particular safety problems envisaged.

Based on the above reports, it is acceptable to use triple therapy including simeprevir in patients with low viral load who had relapsed after prior treatment or had failed to respond to prior treatment. However, since no results have been obtained from patients with low viral load in Japanese clinical studies, it is necessary to continue to collect post-marketing information.

Concerning treatment-naïve patients with low viral load, PR therapy is not indicated in interferon treatment-naïve patients in Japan, and the Japanese guidelines[1)] also recommend the use of monotherapy with an IFN or Peg-IFN product in this population. Therefore, although favorable efficacy can be expected, it is not appropriate to recommend the use of triple therapy in treatment-naïve patients with low viral load, because in view of safety and tolerability, the clinical significance is low in selecting a combination therapy including RBV.

4.(iii).B.(4).3) Simeprevir use in patients whose prior treatment was triple therapy including telaprevir

PMDA asked the applicant to explain the efficacy of triple therapy including simeprevir in patients whose response to previous triple therapy including telaprevir was insufficient.

The applicant explained as follows:

The following patients can be assumed to be "patients who have already received triple therapy including telaprevir without achieving SVR."

- Patients who have not gained adequate virologic response to treatment, even though triple therapy including telaprevir was conducted in accordance with a specified dosage regimen.
- Patients who have experienced viral breakthrough during the treatment
- Patients who have relapsed after the treatment

Since it is likely that resistance mutations against telaprevir have detected in the above patient populations,[154)] the effect of telaprevir-resistant mutations on the susceptibility to simeprevir was investigated.

Major mutations detected in the Japanese phase III studies of triple therapy including telaprevir were V36A/C/M, T54A, R155K, A156S, and T54S+A156S.[155)] Of these mutations, R155K shows resistance to simeprevir in non-clinical studies, but the other mutations did not affect the activity of simeprevir. According to the foreign phase III study cited in the package insert[156)] for telaprevir in the US, the resistance mutations detected in patients who did not achieve SVR included R155G/K/T, A156F/N/T/V, and D168N, which were identified as resistance mutations of genotype 1b virus against simeprevir [see

154) Meyer D et.al. *Hepatology*. 2012;56:2106-2115
155) Telavic tablets 250 mg (telaprevir) Application dossier for marketing authorization, CTD2.7.3
156) INCIVEK™ (telaprevir) USPI. Revised Apr 2013. Vertex Pharmaceuticals Inc. http://pi.vrtx.com/files/uspi_telaprevir.pdf [June 2013]

"3.(i).A.(1).5).(a) Influence of site-dependent mutations (SDMs) on antiviral activity of simeprevir" for the susceptibility of each mutant virus to simeprevir].

Although these resistance mutations have been reported to become undetectable with the passage of time after treatment,[154),157),158)] complete elimination of mutant strains is difficult to prove because of the assay sensitivity of sequence analysis. Mutants that have fallen below the detection limit may proliferate again due to simeprevir administration. In addition, there are the potential risk of cross-resistance and the lack of efficacy data on retreatment with triple therapy including simeprevir in patients that have already received triple therapy including telaprevir without achieving SVR. Therefore, the retreatment with triple therapy including simeprevir cannot be recommended in the patient population at present. The treatment guidelines[159)] issued by the American Association for the Study of Liver Diseases also do not recommend retreatment with other protease inhibitors for patients who experienced treatment failure with a protease inhibitor. Overseas clinical evidence is also scanty at present.

On the other hand, some patients have to discontinue telaprevir treatment because of serious skin manifestations or severe anaemia, both of which are adverse events characteristic of telaprevir.[1)] Taking this and the safety data on triple therapy including simeprevir into consideration, the possibility of retreatment with simeprevir triple therapy should be considered after screening for resistance mutations in patients who discontinued telaprevir immediately after the initiation of the treatment because of adverse events characteristic of telaprevir.

PMDA considers as follows:
Efficacy data have not been obtained in patients who had received prior treatment with telaprevir triple therapy, and who were retreated with simeprevir triple therapy. Taking this into account, it is understandable that some of the resistance mutations that emerged during triple therapy including telaprevir show cross-resistance to simeprevir. However, the efficacy of the simeprevir triple therapy can be expected in some cases even in patients pretreated with telaprevir triple therapy for the following reasons.

- It has been confirmed that the susceptibility to simeprevir does not decrease for some types of telaprevir resistance mutations.
- Mutations with cross-resistance to simeprevir, such as R155K, detected mainly in treatment failure patients with HCV genotype 1a in foreign clinical studies. The mutations were detected at a low incidence in treatment failure patients with HCV genotype 1b in and outside Japan.[160)] In addition, HCV serogroup 1 patients in Japan, most of who have genotype 1b, are considered to possibly remain responsive to simeprevir.

Retreatment with simeprevir triple therapy should be considered after screening for resistance mutations

157) Sarrazin C et.al. *Gastroenterology*. 2007;132:1767-1777
158) Yamada I et.al. *J Viral Hepat*. 2012;19:e112-e119
159) Ghany MG et.al. *Hepatology*. 2011;54:1433-1444
160) Telavic tablets 250 mg (telaprevir) Review report (August 10, 2011)

in patients who discontinued triple therapy including telaprevir for safety reasons.

Based on the above reports, the description of the "INDICATIONS" section is changed to exclude the combined use of protease inhibitors with interferon in the prior treatment and to include "interferon therapy" for types of prior treatment in previously-treated patients. Furthermore, clinicians should be made aware of the existence of cross-resistance to other drugs of the same class, and of the unavailability of efficacy data in patients previously treated with protease inhibitor-containing regimens. In addition, physicians with adequate knowledge of treating chronic hepatitis C and of HCV resistance should decide the appropriateness of treatment with simeprevir triple therapy in patients who have failed existing therapies. In the post-marketing surveillance, it is necessary to collect as much information on patient background, efficacy, and safety from the use of simeprevir in patients previously treated with triple therapy including telaprevir as possible, and to provide the obtained information to the clinical practice.

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

Based on the review below, PMDA has concluded that the dosage and administration section should state that "The usual adult dosage is 100 mg of simeprevir given orally once daily. The duration of treatment is 12 weeks. Simeprevir must be used in combination with either Peg-interferon α-2a (genetical recombination) and ribavirin or Peg-interferon α-2b (genetical recombination) and ribavirin." The information on the duration of treatment, discontinuation criteria of simeprevir, dose reduction/discontinuation of concomitant drugs should be provided in the package insert and other informational materials.

The above conclusion by PMDA will be finalized, taking account of comments from the expert advisors.

4.(iii).B.(5).1) Dosage and administration of simeprevir

The applicant explained the rationale for the dosage and administration of simeprevir as follows:

Based on the following results from the foreign phase II study (Study C201), it was decided that simeprevir be administered in combination with PR, and the highest dose of simeprevir that had been investigated in foreign countries (150 mg QD) was employed.

- Following 4-weeks administration of simeprevir 75 mg QD in combination with PR to treatment-naïve patients with chronic hepatitis C virus (genotype 1) infection, the antiviral effect (RVR rate)[161)] was higher than that after 4-weeks administration of simeprevir 25 mg QD in combination with PR. The antiviral effect of simeprevir 75mg QD was comparable to that after 4-weeks administration of simeprevir 200 mg QD in combination with PR (33.3% [3 of 9 subjects] in the simeprevir 25 mg group, 88.9% [8 of 9 subjects] in the simeprevir 75 mg group, and 66.7% [6 of 9 subjects] in the simeprevir 200 mg group).
- Simeprevir 75 to 200mg QD in combination with RP was administered to patients with chronic hepatitis C virus (genotype 1) infection who had relapsed after or had failed to respond to prior treatment. As a result, the antiviral effect (RVR rate) was higher for the simeprevir 150 and 200 mg

161) Negative conversion rate of plasma HCV RNA at Week 4

QD than for 75 mg QD (22.2% [2 of 9 subjects] in the simeprevir 75 mg group, 55.6% [5 of 9 subjects] in the simeprevir 150 mg group, and 30.0% [3 of 10 subjects] in the simeprevir 200 mg group).

- Administration of simeprevir up to 200 mg QD for 4 weeks to treatment-naïve patients and previously-treated patients was well tolerated, but blood bilirubin levels increased in a dose- and exposure-dependent manner. The maximum increase was recorded in the 200 mg group.

In addition, in the foreign phase II study (Study C205) in treatment-naïve patients with chronic hepatitis C virus (genotype 1) infection and the foreign phase II study (Study C206) in patients with chronic hepatitis C virus (genotype 1) infection who had relapsed after or had failed to respond to prior treatment, the dose of simeprevir (Study C205, 75 mg or 150mg; Study C206, 100 mg or 150 mg), duration of simeprevir treatment, and SVR rate were as shown in the following table. Although there was no consistent trend, 150 mg QD for 12 weeks was selected as the dosage regimen for simeprevir in the foreign phase III studies. This is because simeprevir 150 mg demonstrated a favorable antiviral effect in the sub-group analysis, tolerability was favorable, and the occurrence of relapse and breakthrough did not change when administered for >12 weeks.

Table. SVR24 rate of simeprevir (by dose and duration of treatment) (Studies C205 and C206)

	Simeprevir 75/100 mg 12 weeks[a)]	Simeprevir 75/100 mg 24 weeks[a)]	Simeprevir 150 mg 12 weeks	Simeprevir 150 mg 24 weeks	Placebo group
Study C205	82.1 (64/78)	74.7 (56/75)	80.5 (62/77)	86.1 (68/79)	64.9 (50/77)
Study C206	69.7 (46/66)	66.2 (43/65)	66.7 (44/66)	72.1 (49/68)	22.7 (15/66)

SVR rate (%) (Number of patients who achieved SVR/Number of evaluated patients)
a) 75 mg was administered in Study C205, and 100 mg was administered in Study C206.

Based on the exposure level in the Japanese and foreign phase I studies (Japanese study, Study C109; foreign study, Study C101) and foreign phase II study (Study C201), simeprevir 50 and 100 mg were selected as the doses used in the Japanese phase II study (Study C215) in Japanese patients with chronic hepatitis C virus (genotype 1) infection [see "4.(ii).B.(1) Pharmacokinetics of simeprevir"]. Although the SVR rate did not show a consistent dose-dependent trend (50 or 100 mg of simeprevir) or a clear relationship with the duration of simeprevir treatment (12 or 24 weeks) [see "4.(iii).A.(2).1) Late phase II study in Japanese patients with chronic hepatitis C virus infection"], the early antiviral effect (virus negative conversion rate at Week 2) was slightly higher in the simeprevir 100 mg group (28.2% [11 of 39 subjects] in the simeprevir 50 mg group, 43.2% [16 of 37 subjects] in the simeprevir 100 mg group), and the tolerability was favorable. Therefore, the dosage regimen of simeprevir was set at 100 mg QD for 12 weeks in the Japanese phase III studies (Studies HPC3003 and HPC3008) in treatment-naïve patients and patients who had relapsed after prior treatment. However, the response to IFN therapy was reduced[130),162)] in the Japanese phase III study (Study HPC3004) in patients who had failed to respond to prior treatment Taking this into consideration, the duration of simeprevir treatment was set at 12 or 24 weeks, and the duration of simeprevir treatment in patients who had failed to respond to prior treatment was investigated on an exploratory basis. The results suggest that an improvement in the SVR rate cannot be expected even if the duration of simeprevir treatment was extended to 24 weeks [see

[162)] Jacobson IM, et al. *Am J Gastroenterol*. 2005;100(11):2453-2462

"4.(iii).A.(3).3) Phase III study in Japanese patients with chronic hepatitis C virus infection"]. Thus, the applicant considered 100 mg QD for 12 weeks was appropriate as the recommended dosage and administration in Japan in any of the patients with chronic hepatitis C virus infection who were treatment-naïve, had relapsed after prior treatment, or had failed to respond to prior treatment.

The Japanese phase III study demonstrated the efficacy of administration of simeprevir 100 mg for 12 weeks. Moreover, there were no significant safety problems in patients with chronic hepatitis C virus (genotype 1) infection who were treatment-naïve, had relapsed after prior treatment, or had failed to respond to prior treatment. On the basis of the reports, PMDA accepted the above explanation by the applicant.

4.(iii).B.(5).2) Dosage and administration of PR

The applicant explained the rationale for the dosage and administration of PR used in combination with simeprevir as follows:

Following administration of simeprevir in combination with PR for 4 weeks to treatment-naïve patients, patients who had relapsed after prior treatment, and patients who had failed to respond to prior treatment in the foreign phase II study (Study C201). Consequently, the plasma HCV RNA level decreased 3 to 7 days after administration, and plasma HCV RNA was <25 IU/mL or undetectable at Week 4 in 44.4% to 100% of subjects in the simeprevir 75 to 150 mg groups. This result suggested that the standard duration of PR therapy, 48 weeks, could be shortened by combining PR with simeprevir. Therefore, the RGT criteria[106),110)] of 24 or 48 weeks as the duration of PR treatment depending on the response of subjects were established for treatment-naïve patients, patients who had relapsed after prior treatment, and patients who had failed to respond to prior treatment in the Japanese clinical studies (phase II study, Study C215; phase III studies, Studies HPC3003, HPC3008, HPC3004, and HPC3010), and were applied to the simeprevir group.[163)] In addition, it was decided that the dosage regimens of both Peg-IFN and RBV and their dose reduction/discontinuation criteria associated with the safety should conform to what is recommended in each package insert already approved for dual therapy.

As decribed in the above paragraph, the Japanese phase III studies (Studies HPC3003, HPC3008, HPC3004) were conducted in treatment-naïve patients, patients who had relapsed after prior treatment, and patients who had failed to respond to prior treatment. The proportion of subjects and the SVR12 rate by RGT criteria were as shown in the following table. The SVR12 rate in subjects who met the RGT criteria and terminated PR treatment at Week 24 was high in the treatment-naïve patients and patients who had relapsed after prior treatment. Even in patients who had failed to respond to prior treatment, the SVR12 rate was 60.5% in the 12-week simeprevir group and 48.7% in the 24-week simeprevir group. Hence, it was suggested that the duration of PR treatment can be shortened to 24 weeks by using triple therapy with simeprevir and PR in any patient population.

[163)] In Study HPC3010, PR was administered for 48 weeks without applying the RGT criteria to the patients who had failed to respond to prior treatment.

Table. SVR12 rate by RGT criteria (Studies HPC3003, HPC3008, and HPC3004)

	Study HPC3003	Study HPC3008	Study HPC3004	
	Simeprevir group (12 weeks)	Simeprevir group (12 weeks)	Simeprevir group (12 weeks)	Simeprevir group (24 weeks)
Met RGT criteria (termination of PR treatment at Week 24)				
Proportion of subjects	113/123 (91.9)	47/49 (95.9)	43/53 (81.1)	39/53 (73.6)
SVR12 rate	104/113 (92.0)	45/47 (95.7)	26/43 (60.5)	19/39 (48.7)
Did not meet RGT criteria (PR treatment for 48 weeks)				
Proportion of subjects	1/123 (0.8)	0/49	2/53 (3.8)	1/53 (1.9)
SVR12 rate	0/1	0	1/2 (50.0)	0/1
Discontinuation of triple therapy before Week 24				
Proportion of subjects	9/123 (7.3)	2/49 (4.1)	8/53 (15.1)	13/53 (24.5)
SVR12 rate	5/9 (55.6)	2/2 (100.0)	1/8 (12.5)	0/13

Number of patients (%)

Also in Study HPC3010, in which simeprevir was administered in combination with Peg-IFNα-2b and RBV, 91.7% (22 of 24 subjects) of treatment-naïve patients and 96.6% (28 of 29 subjects) of patients who had relapsed after prior treatment met the RGT criteria and terminated the PR treatment at Week 24. The SVR12 rates of these patients were 90.9% (20 of 22 subjects) and 100% (28 of 28 subjects),[163] respectively.

The relapse rate[164] and breakthrough rate[165] in Japanese phase III studies (Studies HPC3003, HPC3008, HPC3004, and HPC3010) are shown in the following table.

Table. Relapse rate and breakthrough rate (Japanese phase III studies)

	Target patients	Treatment group (duration of treatment)	SVR12 rate	Relapse rate	Breakthrough rate
HPC3003	Treatment-naïve patients	Simeprevir group (12 weeks)	109/123 (88.6)	9/118 (7.6)	1/123 (0.8)
		Placebo group (PR48 weeks)	37/60 (61.7)	15/49 (30.6)	2/60 (3.3)
HPC3008	Patients who had relapsed after prior treatment	Simeprevir group (12 weeks)	47/49 (95.9)	4/49 (8.2)	0/49 (0.0)
HPC3004	Patients who had failed to respond to prior treatment	Simeprevir group (12 weeks)	28/53 (52.8)	17/44 (38.6)	7/53 (13.2)
		Simeprevir group (24 weeks)	19/53 (35.8)	23/45 (51.1)	6/53 (11.3)
HPC3010	Treatment-naïve patients	Simeprevir group (12 weeks)	22/24 (91.7)	2/24 (8.3)	0/24 (0.0)
	Patients who had relapsed after prior treatment	Simeprevir group (12 weeks)	29/29 (100.0)	1/29 (3.4)	0/29 (0.0)
	Patients who had failed respond to prior treatment	Simeprevir group (12 weeks)	10/26 (38.5)	4/15 (26.7)	6/26 (23.1)

Number of patients (%)

In Study HPC3004 conducted in patients who had failed to respond to prior treatment, the relapse rate by the PR treatment period in subjects who received simeprevir for 12 weeks and the RGT criteria were not estabilised. The relapse rates in the Japanese and foreign clinical studies (Japanese study, Study HPC3010; foreign study, Study C206), in which all subjects received PR for 48 weeks without applying RGT criteria, are shown in the following table. Although the number of patients is limited, the relapse rates in the Japanese and foreign clinical studies, in which all subjects received PR for 48 weeks, tended to be lower than that in Study HPC3004.

164) Proportion of subjects whose plasma HCV RNA was undetectable at the end of treatment but detected in the follow-up observation period
165) Proportion of subjects whose plasma HCV RNA increased by >1.0 Log IU/mL compared with the minimum level during the treatment period or patients whose plasma HCV RNA became <1.2 Log IU/mL or undetectable but later exceeded 2.0 Log IU/mL.

Table. Relapse rate at Week 12 of simeprevir treatment in subjects who had failed to respond to prior treatment

	Target patients	Dose of simeprevir	Duration of PR treatment	Relapse rate
HPC3004	Patients who had failed to respond to prior treatment	100mg	24 weeks	17/43 (39.5)
			48 weeks	0/1 (0)
HPC3010	Patients who had failed to respond to prior treatment	100mg	48 weeks	4/15 (26.7)
C206	Patients who had partially responded to prior treatment	150mg	48 weeks	1/17 (5.9)
	Patients who had failed to respond to prior treatment	150mg	48 weeks	2/11 (18.2)

Number of patients (%)

Based on the above reports, the co-administration of PR at the dose approved in Japan and simeprevir resulted in high therapeutic effect in all patient populations (treatment-naïve patients, patients who had relapsed after prior treatment, and patients who had failed to respond to prior treatment). Therefore, it was considered appropriate that Peg-IFN and RBV should be administered at the dose recommended in each package insert when used in combination with simeprevir in Japanese patients with chronic hepatitis C virus (genotype 1) infection. A duration of 24 weeks of PR treatment in combination with simeprevir was considered possible in all patient populations (treatment-naïve patients, patients who had relapsed after prior treatment, and patients who had failed to respond to prior treatment), because a high therapeutic effect was obtained in many patients following 24-week combination therapy. However, continuous treatment with PR after Week 24 needs to be considered depending on the treatment history since 48-week PR treatment may suppress the relapse rate in patients who had failed to respond to prior treatment. This discussion is based on the observation that the relapse rate tended to be lower in the Japanese and foreign clinical studies (Japanese study, Study HPC3010; foreign study, Study C206), in which all patients who had failed to respond to prior treatment received PR for 48 weeks without applying the RGT criteria, than in the Japanese phase III study (Study HPC3004). The study HPC3004 was conducted in patients who had failed to respond to prior treatment, and most patients terminated the PR treatment at Week 24 because their response met the RGT criteria.

PMDA considers as follows:

Taking into account the results of the Japanese phase III studies (Studies HPC3003, HPC3008, HPC3004, and HPC3010), there is no particular problem with the dosage regimens of Peg-IFN and RBV and their dose reduction/discontinuation criteria associated with the safety since no significant problems have occurred by conforming to what is recommended in each package insert. It is acceptable to select a duration of 24 weeks of PR treatment, taking into account the fact that a high SVR12 rate was achieved by triple therapy with simeprevir and PR in all of the treatment-naïve patients, patients who had relapsed after prior treatment, and patients who had failed to respond to prior treatment. However, the relapse rate tended to be lower in the Japanese and foreign clinical studies (Japanese study, Study HPC3010; foreign study, Study C206), in which PR was given for 48 weeks without applying the RGT criteria, than in the patients who received PR for 24 weeks in the Japanese phase III study (Study HPC3004), in which the RGT criteria were applied. Thus, this information should be appropriately provided to the clinical practice, and it should be cautioned that the continuation of PR administration after Week 24 needs to be considered depending on treatment history and tolerability. It is necessary to continue investigating the RGT criteria after the market launch, and to appropriately provide newly obtained

information to the clinical practice.

4.(iii).B.(6) Post-marketing investigations

A plan of post-marketing drug use-results survey proposed by the applicant in this application is as follows:

- Objectives of survey: to investigate the safety and efficacy of simeprevir under routine use in patients with chronic hepatitis C virus infection
- Number of patients surveyed: [redacted] patients (target number of enrolled patients)
  [Rationale] The lowest incidence of adverse drug reactions was 0.23% (1 of 436 patients) in the pooled analysis of 5 Japanese clinical studies. Thus, this survey requires [redacted] patients to detect, at least, [redacted] cases of adverse drug reactions with an incidence of [redacted]%, at a probability of ≥95%.
  The target number of enrolled patients is [redacted] assuming that the loss to follow-up rate is approximately 10% in this survey.
- Observation period: for safety, until the completion (or discontinuation) of treatment; for efficacy, until 24 weeks after the completion (or discontinuation) of treatment.
- Survey items: patient background, prior treatment history (antiviral therapy), administration record of triple therapy, concomitant drugs, safety analysis (including clinical laboratory tests related to adverse events), blood HCV RNA levels during treatment period, efficacy evaluation, patient status, follow-up monitoring (blood HCV RNA measurement)
- Planned survey period:
  Planned enrollment period: for 2 years and 1 month after market release
  Planned survey period: for 4 years and 1 month after market release

It is planned to continuously collect information on resistance mutations against simeprevir by conducting an information search of conference presentations and academic papers from Japan and other countries. It is also planned to continuously analyze and evaluate virological data on simeprevir in terms of genetic polymorphism and resistance mutations obtained from foreign clinical studies currently underway and clinical studies that are planned to be conducted in Japan and overseas in future. In addition, it is also planned to regularly analyze and evaluate information on resistance mutations in individual cases collected overseas, including information on those collected from clinical studies. The applicant plans to provide information on how resistance mutations against simeprevir and cross-resistance with other antiviral drugs will affect future treatment of chronic hepatitis C in collaboration with specialists so that more effective drugs can be selected for use in clinical practice.

PMDA considers that following information should be collected in addition to what is proposed by the applicant:

- Efficacy and safety in the elderly
- Efficacy and safety when simeprevir is used in combination with Peg-IFNα-2b and RBV
- Efficacy and safety in HCV genotype 1a patients
- Efficacy in low viral load patients who has relapsed after or has failed to respond to prior treatment

- A relationship between the duration of PR treatment and the efficacy of triple therapy
- Appropriateness of the RGT criteria
- Efficacy and safety in patients previously treated with triple therapy including telaprevir

The above conclusion will be finalized, taking account of comments from the expert advisors.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.2, 5.3.5.1.5-1, 5.3.5.1.5-2, 5.3.5.2.1, 5.3.5.2.2-1, 5.3.5.2.2-2, 5.3.5.2.3-1, and 5.3.5.2.3-2). As a result, the following findings were noted at some trial sites: (1) non-compliance with procedures for the control of investigational drugs (supply of an incorrect investigational drug and its administration to subjects); (2) failure of medical institutions to store a part of the source documents to be stored there; (3) collection of blood samples for genetic analysis from subjects who had not provided consent to participate in pharmacogenomic research. Despite the above findings that required improvement, PMDA acknowledged overall GCP compliance in the conduct of clinical studies because the cases in question were handled appropriately, and concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of simeprevir in patients with chronic hepatitis C virus infection has been demonstrated and the safety of simeprevir is acceptable in view of its observed benefits.

Simeprevir selectively inhibits HCV protease, and it demonstrated a superior therapeutic effect when used in combination with PR while showing no apparent problems of concern for clinical use. Therefore, simeprevir has clinical significance as a new therapeutic option for Japanese patients with chronic hepatitis C virus infection.

The indication of simeprevir based on the clinical positioning of triple therapy including simeprevir will be finalized, taking account of comments from the Expert Discussion.

PMDA considers that simeprevir may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

September 3, 2013

I. Product Submitted for Registration

[Brand name]	Sovriad Capsules 100mg
[Non-proprietary name]	Simeprevir Sodium
[Applicant]	Janssen Pharmaceutical K.K.
[Date of application]	February 22, 2013

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

The conclusion of PMDA described in Review Report (1) was largely supported at the Expert Discussion, and PMDA conducted an additional review of the following points and took necessary actions.

(1) Indication

The following comments were raised from the expert advisors concerning the PMDA's conclusion about the indication [see "Review Report (1), 4.(iii).B.(4) Indication"]:

- Although prior treatment is defined as "interferon therapy" in the indication to include interferon therapy in combination with protease inhibitors, it is appropriate to define the prior treatment as "therapy including interferon" because "interferon therapy" may be misunderstood as therapy with interferon alone in clinical practice.
- Although there is no objection to the use of simeprevir in patients whose prior treatment was triple therapy including telaprevir, it is necessary to provide an adequate caution to the clinical practice because, as PMDA considers, the appropriateness of the use of simeprevir should be carefully determined.

Taking into account the comments from the expert advisors, PMDA instructed the applicant to include the following as the indication for simeprevir, and the applicant accepted the instruction.

The expert advisors supported PMDA's view that, if simeprevir is administered to patients whose prior treatment had been triple therapy including telaprevir, the appropriateness of the use of simeprevir should be carefully determined after screening resistance mutations etc. Based on the above, PMDA instructed the applicant to provide a caution in the Precautions for Indications section of the package

insert that simeprevir should be administered to patients under supervision of a physician with adequate knowledge and experience in the treatment of viral liver diseases. The applicant accepted this instruction.

[Indication] Improvement of viraemia in any of the following patients with serogroup 1 (genotype I [1a] or II [1b]) chronic hepatitis C virus infection: 1) Treatment-naïve patients with high blood HCV RNA load 2) Patients who has failed to respond to or has relapsed after therapies containing interferon

(2) Increases in blood bilirubin levels

The following comments were raised from the expert advisors regarding the conclusion of PMDA on the increases in blood bilirubin levels among the issues related to the safety of simeprevir [see "Review Report (1), 4.(iii).B.(2).2) Increases in blood bilirubin levels"].

- Given that increases in blood bilirubin levels were not associated with other abnormalities in liver function tests, and that the blood bilirubin level recovered after the completion of treatment, there is no particular concern about the increases in blood bilirubin levels due to simeprevir treatment. Thus, simeprevir treatment should not be prematurely suspended or discontinued solely because of increases in blood bilirubin levels. However, all patients with increased blood bilirubin levels do not necessarily have a benign course. Therefore, monitoring is indispensable for other abnormalities in liver function tests, and the information needs to be disseminated among physicians through instruction materials to ensure awareness of the characteristics of this event.

Taking account of comments from the expert advisors, PMDA instructed the applicant to prepare instruction materials on the increase in blood bilirubin levels, which occurred during triple therapy with simeprevir, so that physicians and other healthcare professionals will be appropriately informed of the characteristics of the increases in blood bilirubin due to simeprevir administration, including the time course of blood bilirubin level and the information on other liver function tests.

(3) Post-marketing surveillance

The conclusion of PMDA about the post-marketing investigations for simeprevir [see "Review Report (1), 4.(iii).B.(6) Post-marketing investigations"] was supported by the expert advisors. Accordingly, PMDA instructed the applicant to collect information on the following points in addition to the survey items proposed by the applicant. The applicant explained that the survey would be conducted on issues other than the appropriateness of the RGT criteria. The applicant explained in regard to the RGT criteria that, given that the necessity for PR treatment after Week 24 will be decided by the physician, the relationship between the duration of PR treatment and the efficacy will be assessed by collecting information on the reasons for continuation of PR treatment after Week 24 in the post-marketing surveillance.

- Efficacy and safety in the elderly
- Efficacy and safety when simeprevir is used in combination with Peg-IFNα-2b and RBV

- Efficacy and safety in HCV genotype 1a patients
- Efficacy in low viral load patients who has relapsed after or has failed to respond to prior treatment
- A relationship between the duration of PR treatment and the efficacy of triple therapy with simeprevir
- Appropriateness of the RGT criteria
- Efficacy and safety in patients previously treated with triple therapy with protease inhibitors other than simeprevir

PMDA concluded that the applicant's explanation is acceptable.

III. Overall evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the indication and dosage and administration statements as shown below. The re-examination period is 8 years, the drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indication]	Improvement of viraemia in any of the following serogroup 1 (genotype I [1a] or II [1b]) patients with chronic hepatitis C virus infection: 1) Treatment-naïve patients with high blood HCV RNA load 2) Patients who has failed to respond to or has relapsed after therapies containing interferon
[Dosage and administration]	The usual adult dosage is 100 mg of simeprevir given orally once daily. The duration of treatment is 12 weeks. The drug product should be used in combination with either Peg-interferon α-2a (genetical recombination) and ribavirin or Peg-interferon α-2b (genetical recombination) and ribavirin.