Report on the Deliberation Results

March 10, 2015

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

[Brand name]	Sovaldi Tablets 400 mg
[Non-proprietary name]	Sofosbuvir (JAN*)
[Name of applicant]	Gilead Sciences K.K.
[Date of application]	June 27, 2014

[Results of deliberation]
In the meeting held on March 5, 2015, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years and neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug and the product is not classified as a biological product or a specified biological product.

[Condition for approval]
The applicant is required to develop a risk management plan for the product and implement it appropriately.

**Japanese Accepted Name (modified INN)*

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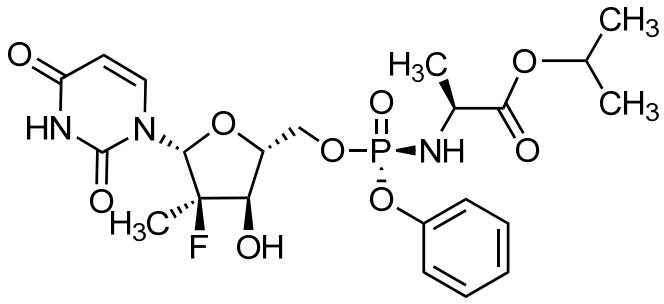
Review Report

February 23, 2015
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	(a) Sovaldi Tablets 400 mg
	(b) Copegus Tablets 200 mg
[Non-proprietary name]	(a) Sofosbuvir
	(b) Ribavirin
[Applicant]	(a) Gilead Sciences K.K.
	(b) Chugai Pharmaceutical Co., Ltd.
[Date of application]	(a) June 27, 2014
	(b) September 18, 2014
[Dosage form/Strength]	(a) Tablets: Each tablet contains 400 mg of Sofosbuvir.
	(b) Tablets: Each tablet contains 200 mg of Ribavirin.
[Application classification]	(a) Prescription drug (1) Drug with a new active ingredient
	(b) Prescription drug (4) Drug with a new indication, (6) Drug with a new dosage
[Chemical structure]	(a) Sofosbuvir



Molecular formula: $C_{22}H_{29}FN_3O_9P$
Molecular weight: 529.45

Chemical name:
1-Methylethyl *N*-[(*S*)-{[(2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl]methoxy}phenoxyphosphoryl]-L-alaninate

[Items warranting special mention]	(a) Priority Review (Notification No. 0715-1 of Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated July 15, 2014)

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(b) Expedited Review (Notification No. 0114-1 of Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated January 14, 2015)

[Reviewing office] Office of New Drug IV

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Review Results

February 23, 2015

[Brand name]	(a) Sovaldi Tablets 400 mg
	(b) Copegus Tablets 200 mg
[Non-proprietary name]	(a) Sofosbuvir
	(b) Ribavirin
[Applicant]	(a) Gilead Sciences K.K.
	(b) Chugai Pharmaceutical Co., Ltd.
[Date of application]	(a) June 27, 2014
	(b) September 18, 2014

[Results of review]

Based on the submitted data, the efficacy of Sovaldi Tablets 400 mg and Copegus Tablets 200 mg in serogroup 2 (genotype 2) chronic hepatitis C patients with or without compensated cirrhosis has been demonstrated and their safety is acceptable in view of their observed benefits.

As a result of its review, the Pharmaceuticals and Medical Devices Agency concluded that the products may be approved for "Indications" and "Dosage and administration" as shown below, with the following conditions.

[Indications]

(a) Sovaldi Tablets 400 mg

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

(b) Copegus Tablets 200 mg (Underline denotes added text.)

1. Suppression of viremia in either of the following patients with chronic hepatitis C in combination with Peginterferon Alfa-2a (Genetical Recombination):
   (1) patients with serogroup 1 (genotype I [1a] or II [1b]) and high levels of HCV-RNA, or
   (2) patients who have failed to respond to or relapsed following interferon monotherapy
2. Suppression of viremia in patients with chronic hepatitis C and compensated cirrhosis in combination with Peginterferon Alfa-2a (Genetical Recombination).
3. <u>Suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients with or without compensated cirrhosis in combination with Sofosbuvir.</u>

[Dosage and administration] (a) Sovaldi Tablets 400 mg

The usual adult dosage is 400 mg of Sofosbuvir, administered orally once daily in combination with Ribavirin for 12 weeks.

(b) Copegus Tablets 200 mg (Underline denotes added text.)

Ribavirin should be used in combination with Peginterferon Alfa-2a (Genetical Recombination) or Sofosbuvir.

The usual adult oral dosage of Ribavirin is provided in the following table. The dose should be reduced or discontinued, or other appropriate measures should be taken, depending on the patient's condition.

Body weight	Ribavirin daily dose	After breakfast	After evening meal
≤60 kg	600 mg	200 mg	400 mg
>60 kg and ≤80 kg	800 mg	400 mg	400 mg
>80 kg	1000 mg	400 mg	600 mg

[Condition for approval] (a) and (b)

The applicant (of each product) is required to develop a risk management plan for the product (Sovaldi or Copegus) and implement it appropriately.

Review Report (1)

December 22, 2014

I. Products Submitted for Registration

[Brand name] (a) Sovaldi Tablets 400 mg
(b) Copegus Tablets 200 mg

[Non-proprietary name] (a) Sofosbuvir
(b) Ribavirin

[Name of applicant] (a) Gilead Sciences K.K.
(b) Chugai Pharmaceutical Co., Ltd.

[Date of application] (a) June 27, 2014
(b) September 18, 2014

[Dosage form/Strength] (a) Tablets: Each tablet contains 400 mg of Sofosbuvir.
(b) Tablets: Each tablet contains 200 mg of Ribavirin.

[Proposed indications]

(a) Sovaldi Tablets 400 mg

Serogroup 2 (genotype 2) chronic hepatitis C virus (HCV) infection with or without compensated cirrhosis

(b) Copegus Tablets 200 mg (Underline denotes added text.)

1. Suppression of viremia in either of the following patients with chronic hepatitis C in combination with Peginterferon Alfa-2a (Genetical Recombination):
   (1) patients with serogroup 1 (genotype I [1a] or II [1b]) and high levels of HCV-RNA, or
   (2) patients who have failed to respond to or relapsed following interferon monotherapy
2. Suppression of viremia in patients with chronic hepatitis C and compensated cirrhosis in combination with Peginterferon Alfa-2a (Genetical Recombination).
3. <u>Suppression of viremia in chronic hepatitis C patients with or without compensated cirrhosis in combination with anti-HCV agents (excluding interferon).</u>

[Proposed dosage and administration]

(a) Sovaldi Tablets 400 mg

The usual adult dosage is 400 mg of Sofosbuvir, administered orally once daily. The recommended duration of treatment is 12 weeks. Sofosbuvir should be used in combination with Ribavirin.

(b) Copegus Tablet 200 mg (Strike-through denotes deleted text.)

~~Copegus should be used in combination with Peginterferon Alfa-2a (Genetical Recombination).~~

The usual adult oral dosage of Rivavirin is provided in the following table. The dose should be reduced or discontinued, or other appropriate measures should be taken, depending on the patient's condition.

Body weight	Ribavirin daily dose	After breakfast	After evening meal
≤60 kg	600 mg	200 mg	400 mg
>60 kg and ≤80kg	800 mg	400 mg	400 mg
>80 kg	1000 mg	400 mg	600 mg

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

The data submitted by Gilead Sciences K.K., the application for Sovaldi Tablets 400 mg, and the outline of a review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below. The partial change application for approval of a new indication and a new dosage of Copegus Tablet 200 mg was submitted by Chugai Pharmaceutical Co., Ltd., and its supporting data included some of the clinical study data submitted by Gilead Sciences K.K. but did not include new quality or non-clinical data.

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

Sofosbuvir (SOF) is a nucleotide analog discovered by Pharmasset Inc. (the US) and the active metabolite of SOF, the uridine triphosphate form, suppresses viral proliferation by inhibiting the NS5B polymerase, which is essential for hepatitis C virus (HCV) replication. Outside Japan, the clinical development of SOF was conducted by Gilead Sciences, Inc. (the US) and as of December 2014, SOF has been approved for the treatment of HCV infection in 38 countries including the US and the EU. Ribavirin (RBV), which is used in combination with SOF, is a nucleoside analog that shows activity against some DNA and RNA viruses, which was discovered by ICN Pharmaceuticals, Inc. (the US) in 1970. RBV for inhalation and oral RBV have been approved overseas. In Japan, multiple oral RBV products have been approved for use in combination with interferon for the treatment of HCV infection.

The number of people infected with HCV is estimated to be approximately 180 million globally[1)] and 1.3 to 2.4 million in Japan. Approximately 30% of infections in Japan are associated with genotype 2.[2)] Currently in Japan, peginterferon α/RBV combination therapy or interferon β/RBV combination therapy, etc., are recommended for the treatment of patients with chronic hepatitis C (genotype 2)[3),4)] and the sustained virologic response (SVR) rates with these therapies have been reported to be 70% to 90%[5),6),7),8),9)] in treatment-naïve patients and approximately 50%[9),10)] in treatment-experienced patients who failed to achieve SVR with initial therapy.

1) Ghany MG, et al. *Hepatology*. 2009;49(4):1335-1374.
2) Sievert W, et al. *Liver Int*. 2011;31 Suppl 2:61-80.
3) 2013 Health and Labour Sciences Research Grant for Research on Hepatitis etc., (Hepatitis), *2014 Guidelines for the Management of Chronic Hepatitis B/C and cirrhosis*
4) Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology ed. *Guidelines for the Management of Hepatitis C Virus Infection (3.1th edition)*, 2014
5) Feron, 6 million for injection/Rebetol Capsules 200 mg Review Report (August 20, 2009)
6) Irishio K, et al. *Kanzo.* 2011;52:236-243.
7) Iwasaki Y, et al. *Hepatol Int*. 2009;3:468-479.
8) Inoue Y, et al. *J Viral Hepat*. 2010;17(5):336-344.
9) Kanda T, et al. *Dig Dis Sci.* 2011;56(11):3335-3342.
10) Oze T, et al. *J Gastroenterol.* 2011;46:1031-1037.

Since a Japanese clinical study showed favorable results for Sovaldi Tablets 400 mg (containing SOF as the active substance) in combination with Copegus Tablet 200 mg (oral RBV) in chronic hepatitis C patients with or without compensated cirrhosis (genotype 2), a marketing application for Sovaldi Tablets 400 mg and a partial change application for Copegus Tablet 200 mg have been filed.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The Sofosbuvir (SOF) drug substance is a white to off-white powder and has been characterized by solubility, melting point, hygroscopicity, dissociation constant (pKa), partition coefficient, polymorphism, and stereochemistry. [redacted] [11)] [redacted] [12)] [redacted]

The chemical structure of the drug substance has been elucidated by elemental analysis, ultraviolet spectroscopy, infrared spectroscopy (IR), nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, ^{19}F-NMR), mass spectrometry, and single-crystal X-ray diffraction.[13)]

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

[redacted]

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

The proposed drug substance specifications include content, appearance, identification (IR and liquid chromatography [HPLC] or ultra high performance liquid chromatography [UHPLC]), melting point, purity (clarity of solution, elemental impurities [inductively coupled plasma-optical emission spectroscopy], related

11) Controlled by the specification (melting point).
12) Form [redacted] of the drug substance was chosen for the to-be-marketed formulation.
13) Monocrystal of Form [redacted] was used.

substances [HPLC or UHPLC], residual solvents, organic volatile impurities), particle size, and assay (HPLC or UHPLC).

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

Stability studies on the drug substance are as shown in Table 1. The photostability results indicate that the drug substance is photostable.

Table 1. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage period	Storage package
Long-term	4 pilot-scale batches[a)]	25°C	60%RH	12 months	in double polyethylene bags inside a polyethylene container
Accelerated	3 commercial-scale batches	40°C	75%RH	6 months	

a) Data up to 24 months for 1 batch have been obtained.

Based on the above, in accordance with "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003), a re-test period of [redacted] months has been proposed for the drug substance when stored in double polyethylene bags within a polyethylene container at room temperature. The long-term testing will be continued up to [redacted] months.

2.A.(2) Drug product

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

The proposed drug product is a film-coated tablet containing 400 mg SOF and the excipients D-mannitol, microcrystalline cellulose, croscarmellose sodium, light anhydrous silicic acid, magnesium stearate, and Opadry II Yellow.

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

[redacted]

Quality by Design (QbD) approaches were utilized and the following studies were mainly performed.[14)]

● [redacted]

● Identification of critical process parameters (CPPs) through design of experiments

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

The proposed drug product specifications include strength, appearance, identification (ultraviolet-visible spectroscopy and HPLC or UHPLC), purity (related substances [HPLC or UHPLC]), water content, uniformity of dosage units (mass variation test), dissolution, and assay (HPLC or UHPLC).

[14)] Since the applicant intends to operate within the normal operating ranges during production, the applicant states that this is not a QbD application.

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

Stability studies on the drug product were as shown in Table 2. The photostability results indicated that the drug product is photostable.

Table 2. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage period	Storage package
Long-term	3 pilot-scale batches	25°C	60%RH	12 months	High-density polyethylene container (with a silica gel desiccant)
Accelerated	3 pilot-scale batches	40°C	75%RH	6 months	

Based on the above, in accordance with "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003), a shelf-life of 24 months has been proposed for the drug product when stored in a high-density polyethylene container (with a silica gel desiccant) at room temperature. The long-term testing will be continued up to [redacted] months.

2.B Outline of the review

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

2.B.(1) Polymorphic forms of drug substance

The applicant explained polymorphism in the drug substance and its control as follows:

[redacted]

PMDA asked the applicant to explain the control of polymorphic forms in the drug substance manufacturing process.

The applicant explained as follows:

Process parameters of the manufacturing process steps from SOF intermediates through SOF isolation were examined in order to identify the process conditions that have an influence on the formation of Form [redacted] during the development of the drug substance manufacturing process. [redacted]

Based on the above explanation, PMDA concluded that the polymorphic forms of SOF are adequately controlled.

2.B.(2) Drug product package

Twenty-eight SOF tablets are packaged in a high density polyethylene bottle. Since SOF tablets may be

repackaged into smaller quantities and then dispensed to patients in the Japanese medical practice, PMDA asked the applicant to explain the stability of the repackaged tablets.

The applicant explained as follows:
One batch of the to-be-marketed tablet formulation was stored in open glass dishes, outside of the bottles at 25°C/60%RH and 30°C/75%RH (45 days) and 40°C/75%RH (6 months) to evaluate the stability of the drug product. As a result, a slight increase in water content was noted at all storage conditions, but the level remained within the specification. There were no out-of-specification results for other attributes tested. These results indicate that the tablets are stable for at least 45 days even when they are repackaged and dispensed.

Stability studies on the SOF tablets in blister packs are ongoing.

PMDA considers that the applicant's explanation (the repackaged tablets are stable for at least 45 days) is acceptable.

2.B.(3) Specifications for impurities (related substances) in drug substance or drug product

The impurities or degradantion products (related substances) listed in the specifications for the drug substance and the drug product include Related Substance A, Related Substance B, Related Substance C, and Related Substance D. The proposed specification limits for Related Substance A, Related Substance B, Related Substance C, and Related Substance D are higher than the qualification threshold according to "Revision of the Guideline on Impurities in New Drug Substances" (PMSB/ELD Notification No.1216001 dated December 16, 2002) or "Revision of the Guideline on Impurities in New Drug Products" (PMSB/ELD Notification No. 0624001 dated June 24, 2003). However, none of the related substances were subjected to *in vitro* genotoxicity testing (Ames test and chromosomal aberration test).

PMDA asked the applicant to explain the safety of the related substances present in the drug substance and the drug product.

The applicant explained as follows:
The specification limits for the related substances in the drug substance will be tightened to ≤0.15% according to "Revision of the Guideline on Impurities in New Drug Substances" and the specification limits for the related substances in the drug product will be tightened to ≤0.20% according to "Revision of the Guideline on Impurities in New Drug Products".

PMDA considered that the following applicant's proposed action is acceptable and agreed with it: the specification limits for the related substances will be lowered to match the qualification threshold.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

The study results were submitted based on primary pharmacodynamic studies of Sofosbuvir (SOF) to determine inhibition of hepatitis C virus (HCV) NS5B polymerase, inhibition of HCV replicon replication, pharmacodynamic interactions with other anti-HCV agents, and the resistance profile. Secondary pharmacodynamic studies were performed to determine the activity against other non-HCV viruses, cytotoxicity, and the effects on mitochondria, human polymerases, and a panel of receptors, enzymes, and ion channels. Safety pharmacology studies were performed to assess the effects on the function of the central nervous, cardiovascular, and respiratory systems.

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

3.(i).A.(1).1) *In vitro* antiviral activity (4.2.1.1.2, 4.2.1.1.3, 4.2.1.1.4.1, 4.2.1.1.4.2)

GS-461203,[15] the active metabolite of SOF, was tested for the inhibition of the NS5B polymerase from HCV strains Con-1 (genotype 1b), JFH-1 (genotype 2a), S52 (genotype 3a), and ED43 (genotype 4a). The 50% inhibitory concentration (IC_{50}) values of GS-461203 were 3.3, 0.36, 1.4, and 2.7 μmol/L for the respective strains above.

In HCV replicon assays (a luciferase reporter gene assay),[16] the antiviral activity (50% effective concentration [EC_{50}]) of SOF against different genotypes was determined by quantifying HCV replicon replication (Table 3).

Table 3. Antiviral activity of SOF against HCV replicon cell lines

HCV genotype (strain)	EC_{50} (nmol/L)
1a (H77)	40
1b (Con-1)	110
2a (JFH-1)	50
2b [a)]	15
3a (S52)	50
4a (ED43)	40
5a [a)]	15
6a [a)]	14

Mean

a) The chimeric genotype 1b (Con-1) replicons encoding NS5B from HCV genotype 2b, 5a, or 6a were used.

The antiviral activity of SOF against chimeric replicons encoding NS5B sequences from HCV isolates obtained from 217 patients enrolled into foreign phase II and III studies of SOF[17] was determined. The EC_{50} value was 67.8 nmol/L for genotype 1a (N = 67), 105.3 nmol/L for genotype 1b (N = 29), 35.0 nmol/L for genotype 2 (N = 15), and 84.6 nmol/L for genotype 3a (N = 106).

The antiviral activity of GS-331007, the predominant metabolite of SOF in plasma, against HCV replicon cell lines (genotype 1a [H77], 1b [Con-1], 2a [JFH-1], 3a [S52], 4a [ED43]) was determined. As a result, GS-331007 showed no antiviral activity against any genotypes even at the highest concentration tested (89 μmol/L).

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15) SOF is converted to the active uridine triphosphate form (GS-461203) in hepatoma cell lines (Clone A cells) and human primary hepatocytes (CTD 4.2.1.1.1).

16) Lohmann V, et al. *Science*. 1999;285(5424):110-113.

17) Studies P7977-0523, P7977-0724, P7977-0221, P2938-0721, P7977-1231, GS-US-334-0107, and GS-US-257-0102

3.(i).A.(1).2) *In vitro* resistance selection (4.2.1.1.2, 4.2.1.1.5, 5.3.5.4.1)

HCV replicon cells (genotypes 1b, 2a, 2b, 3a, 4a, 5a, 6a) were cultured in the presence of SOF to determine their SOF resistance profiles (Table 4). S282T has been reported to represent the primary mutation conferring resistance to SOF[18] and the S282T substitution was observed in all replicon genotypes examined and the susceptibility to SOF (fold change) was reduced with increasing frequency of S282T substitution.

Table 4. Changes in SOF susceptibility for HCV replicons (genotype 1-6) and NS5B substitutions selected

HCV genotype (strain)	Days of selection	SOF concentration [a] (nmol/L)	Fold change in SOF EC_{50} [b]	NS5B substitutions (Deep Sequencing)	
				S282T (%)	Others (≥15%)
1b (Con-1)	82	2000	2.0	15.4	T344A, C445F
	98	2000	3.4	53.6	T344A, C445F, S549N
	109	4000	4.1	98.4	T344A, S549N
2a (JFH-1)	6	200	1.7	<1.0	I178V
	56	1200	11.0	32.1	T286P, M289L, V421A, S549N
	66	1200	21.5	52.1	K100Q, T286P, M289L, T483M
	79	2000	24.3	98.5	K51R, T286P, M289L
2b [c]	25	500	3.5	18.3	None
	39	500	6.6	90.8	R498K
	81	1000	99.5	99.8	R498K
3a (S52)	6	200	0.7	<1.0	None
	72	2000	6.7	57.4	None
	94	3000	21.2	99.6	None
4a (ED43)	6	200	1.0	<1.0	K531R, K544N
	85	3000	40.0	50.9	V67A, E237G, R304K, K544N
	108	3000	24.2	99.6	V67A, E237G, R304K, A324V, K544N, C575G
5a [c]	25	500	2.4	<1.0	None
	56	1000	14.3	77.9	None
	70	1000	60.4	98.1	None
6a [c]	25	500	1.9	<1.0	E375D
	64	1000	5.5	53.4	E375D
	89	1000	32.7	99.1	N237S, E375D, T580I

a) Concentrations of SOF at which the mutation(s) were identified while replicon cells were proliferated.
b) EC_{50} for mutant replicon/EC_{50} for wild-type replicon
c) The chimeric genotype 1b replicons encoding NS5B from HCV genotype 2b, 5a, or 6a were used.

Using S282T mutant replicon cells, the antiviral activities of SOF and ribavirin (RBV) were determined (Table 5).

Table 5. Antiviral activities of SOF and RBV against wild-type and S282T mutant replicons

HCV genotype	SOF			RBV		
	EC_{50} (nmol/L)		Fold change [a]	EC_{50} (μmol/L)		Fold change [a]
	Wild-type	S282T		Wild-type	S282T	
1a	30.2	253.5	8.4	26.1	3.8	0.1
1b	21.5	189.2	8.8	6.6	1.6	0.2
2a	146.8	346.1	2.4	8.3	0.6	0.1
2b [b]	13.3	215.6	16.2	2.6	0.6	0.2

Mean

a) EC_{50} for mutant replicon/EC_{50} for wild-type replicon
b) The chimeric genotype 1b replicon carrying NS5B coding sequence from HCV genotype 2b was used.

NS5B substitutions (except S282T) detected in *in vitro* resistance selection were introduced individually or in combination with S282T into HCV replicons. Using these replicon cells, the changes in susceptibility to SOF (fold change) was evaluated (Table 6).

[18] Lam AM, et al. *Antimicrob Agents Chemother*. 2012;56(2):3359-3368.

Table 6. Changes in SOF susceptibility for mutant replicons

HCV genotype	Mutations	Fold change in SOF EC_{50} [c)]
Genotype 2a [a)]	K51R	0.88
	K100Q	1.00
	T286P	1.27
	M289L	1.94
	T483M	0.89
	S549N	0.78
	S282T	2.40
	M289L + S282T	3.35
Genotype 2b [b)]	R498K	1.34
	S282T	10.04
	R498K + S282T	12.30

a) EC_{50} for wild-type replicon, 55.8 nmol/L
b) EC_{50} for wild-type replicon, 28.1 nmol/L
c) EC_{50} for mutant replicon/EC_{50} for wild-type replicon

The IC_{50} values of GS-461203 against recombinant NS5B polymerase from HCV genotypes 1b and 2a encoding the S282T substitution were 24.0- and 22.7-fold higher, respectively, than those against their respective wild-types (3.3 and 0.36 μmol/L, respectively).

The effect of the S282T substitution on HCV RNA replication capacity was evaluated in HCV genotypes 1a, 1b, 2a, and 2b replicon cells. The replication capacities of S282T mutant replicons from genotypes 1a, 1b, 2a, and 2b were reduced to 1.3%, 8.4%, 11.2%, and 11.3%, respectively, of those of the corresponding wild-type replicons.

3.(i).A.(1).3) Cross-resistance with other anti-HCV agents (4.2.1.1.5, 4.2.1.1.6, 4.2.1.1.7)

The effects of non-nucleoside NS5B polymerase inhibitor resistance-associated NS5B substitutions[19)] or the NS5B substitutions (T390I and F415Y) identified in HCV patients experiencing virologic failure following treatment with RBV-containing regimens[20)] on the antiviral activities of SOF, GS-9669 (a non-nucleoside NS5B polymerase inhibitor), and RBV were evaluated using HCV genotypes 1a and 1b NS5B mutant replicons (Table 7).

Table 7. Effects of NS5B substitutions on the antiviral activities of non-nucleoside NS5B polymerase inhibitor or RBV

HCV genotype	Mutation	Fold change in EC_{50} [c)]		
		SOF	GS-9669	RBV
Genotype 1a [a)]	T390I	0.9	NT	1.2
	F415Y	1.0	NT	1.2
	L419M	0.9	87.3	0.9
	L419S	0.5	197.1	0.2
	R422K	0.7	144.7	0.3
	M423I	0.9	10.6	0.8
	M423T	0.8	15.9	0.6
	M423V	0.8	8.5	0.7
	I482L	0.9	26.1	0.7
	A486V	0.9	39.6	0.7
	V494A	0.6	17.4	0.5
	P495L	0.9	1.7	1.1
Genotype 1b [b)]	C316Y	1.2	0.9	0.9
	M414T	1.0	1.0	1.1
	L419M	0.9	123.4	0.9
	L419S	0.9	789.8	0.6
	R422K	0.8	814.6	0.9

19) Kukolj G, et al. *J Biol Chem*. 2005;280(47):39260-39267, Andersson T, et al. *Clin Pharmacokinet*. 2001;40(6):411-426, Le Pogam S, et al. Phase I study with GS-9669 (PC-257-2028). *J Virol*. 2006;80(12):6146-6154, Shih I-h, et al. *Antimicrob Agents Chemother*. 2011;55(9):4196-4203.
20) Bartels DF, et al. *6th International Workshop on Hepatitis C- Resistance & New Compounds*. 2011 June, 23-24. Boston, MA.

	M423I	0.8	4.6	0.7
	M423T	1.0	19.3	0.7
	M423V	0.8	7.0	1.0
	Y448H	0.8	0.6	0.7
	I482L	1.0	51.4	1.1
	A486I	0.8	48.7	0.8
	A486T	0.8	31.1	0.9
	A486V	0.8	49.8	0.9
	V494A	1.0	18.1.	1.1
	P495A	1.1	0.9	0.9
	P495L	0.9	1.7	1.1

Mean
a) EC_{50} for wild-type replicon: 142.3 nmol/L for SOF; 10.1 nmol/L for GS-9669; 36,000 nmol/L for RBV
b) EC_{50} for wild-type replicon: 132.5 nmol/L for SOF; 3.4 nmol/L for GS-9669; 15,500 nmol/L for RBV
c) EC_{50} for mutant replicon/EC_{50} for wild-type replicon

The effects of NS3 protease inhibitor resistance-associated substitutions[21] on the antiviral activities of SOF and NS3 protease inhibitors (telaprevir, boceprevir [unapproved in Japan], simeprevir sodium [simeprevir]) were evaluated using HCV genotypes 1a and 1b NS3 mutant replicon cells (Table 8).

Table 8. Effects of NS3 substitutions on the antiviral activities of SOF and NS3 protease inhibitors

HCV genotype	Mutation	Fold change in EC_{50} [c]			
		SOF	Telaprevir	Boceprevir	Simeprevir
Genotype 1a [a]	V36M	1.0	NT	NT	NT
	R155K	2.5	9.5	2.7	30.0
	R155T	1.4	> 55.0	> 27.0	17.0
	R155W	0.8	1.2	1.1	23.0
	D168A	1.9	0.9	1.4	> 50.0
	D168E	2.6	0.5	0.4	36.1
	D168G	0.8	0.9	0.7	8.1
	D168H	2.2	0.8	0.4	> 50.0
	D168N	1.1	0.9	1.1	> 43.0
	D168V	2.2	1.0	1.5	> 59.0
	D168Y	1.7	0.9	1.7	> 50.0
Genotype 1b [b]	V36A	1.5	4.3	NT	2.9
	V36M	1.0	10.1	2.6	2.8
	Q41R	1.7	2.5	NT	NT
	F43S	1.3	2.8	NT	NT
	T54A	0.8	9.1	4.6	2.5
	T54S	NT	12.6	6.9	1.9
	R155C	0.7	7.2	4.5	0.8
	R155K	1.4	16.1	5.9	18.8
	R155Q	0.3	2.1	1.2	1.2
	R155W	0.8	2.0	1.3	33.7
	A156D	2.6	> 13.0	3.1	14.6
	A156G	1.7	0.9	2.3	21.6
	A156S	1.0	NT	> 11.8	0.5
	A156T	1.2	> 542.0	> 68.0	31.5
	A156V	1.0	24.4	54.0	112.4
	D168A	1.8	0.6	1.0	> 249.0
	D168E	1.7	1.3	0.9	54.2
	D168G	1.4	0.9	1.0	8.4
	D168H	2.0	2.1	0.9	191.0
	D168N	1.6	1.2	1.3	13.0
	D168V	0.9	0.5	0.7	> 296.0
	D168Y	0.4	0.7	0.8	> 140.0

Mean
NT: Not tested.
a) EC_{50} for wild-type replicon: 142.3 nmol/L for SOF; 942.6 nmol/L for telaprevir; 906.4 nmol/L for boceprevir; 18.8 nmol/L for simeprevir
b) EC_{50} for wild-type replicon: 132.5 nmol/L for SOF; 414.3 nmol/L for telaprevir; 264.1 nmol/L for boceprevir; 16.6 nmol/L for simeprevir
c) EC_{50} for mutant replicon/EC_{50} for wild-type replicon

SOF was tested against HCV replicons expressing nucleoside NS5B polymerase inhibitor resistance-associated

21) He Y, et al. *Antimicrob Agents Chemother*. 2008;52(3):1101-1110, Summa V, et al. *Antimicrob Agents Chemother*. 2012;56(8):4161-4167.

NS5B substitutions (L159F and L320F).[22] The EC_{50} values of SOF against genotype 1a replicons encoding NS5B L159F, L320F, or L159 + L320F substitutions (48, 86, and 92 nmol/L, respectively) were 1.2-, 1.8-, and 2.3-fold higher than the wild-type EC_{50} value (40 nmol/L), respectively, and the EC_{50} value of SOF against a genotype 1b replicon encoding NS5B L159F (143 nmol/L) was 1.3-fold higher than the wild-type EC_{50} value (110 nmol/L).

The EC_{50} values of SOF and RBV against HCV genotype 1a NS5A mutant replicons[23] were all ≤2-fold compared to those against the wild-type replicon.

3.(i).A.(1).4) Antiviral activity in combination with other anti-HCV agents (4.2.1.4.1, 4.2.1.4.2)

The antiviral effects of SOF in combination with other anti-HCV agents (ledipasvir [a NS5A inhibitor, unapproved in Japan], GS-5816 [a NS5A inhibitor], GS-9190 [a non-nucleoside NS5B polymerase inhibitor], GS-9669 [a non-nucleoside NS5B polymerase inhibitor], GS-9451 [a NS3 protease inhibitor], telaprevir, boceprevir [unapproved in Japan], RBV, interferon [IFN] α) were evaluated in HCV genotypes 1a and 2a replicon cells. The results were as shown in Table 9.

Table 9. Antiviral activity of SOF in combination with other anti-HCV agents

HCV genotype	Compound	Volume [(μmol/L)²%] [a]	Interaction [b]
Genotype 1a	SOF + ledipasvir	3.3	Additive
	SOF + GS-5816	0	Additive
	SOF+ GS-9190	4.7	Additive
	SOF+ GS-9669	1.3	Additive
	SOF + GS-9451	1.0	Additive
	SOF + telaprevir	4.7	Additive
	SOF + boceprevir	1.7	Additive
	SOF + RBV	35.3	Weak synergistic
	SOF + IFNα	12.0	Additive
Genotype 2a	SOF + ledipasvir	33.25	Weak synergistic
	SOF + GS-5816	36.75	Weak synergistic

Mean

a) Calculated using MacSynergy II program, based on Prichard MN et al.'s report (*Antivir Ther*. 1996;1(1): 9-20).

b) Volume [(μmol/L)²%]: ≤-25, antagonism; >-25 and ≤25, additive interaction; >25 and ≤50, weak synergistic interaction; >50 and ≤100, moderate synergistic interaction; and >100, strong synergistic interaction

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

3.(i).A.(2).1) Antiviral activity against other non-HCV viruses (4.2.1.2.1)

The antiviral activity of SOF was tested against human immunodeficiency virus type 1, human rhinovirus types 10 and 14, RS virus, and influenza virus A. As a result, the EC_{50} value of SOF was >100 μmol/L for all of these viruses.

3.(i).A.(2).2) *In vitro* cytotoxicity (4.2.1.2.3)

The cytotoxicity of SOF was determined in human cell lines (human hepatocarcinoma cell lines [Huh-7 and HepG2], human prostate carcinoma cell line [PC-3], human lung fibroblast cell line [MRC-5], human T cell leukemia cell line [MT-4]) and human primary cells (primary hepatocytes, peripheral blood mononuclear cells [quiescent and activated]). The 50% cytotoxic concentration (CC_{50}) of SOF was 66 μmol/L in Huh-7 cells and either >89 or >100 μmol/L in the other cell lines tested.

22) Levin J, et al. *AASLD 2012*. 2012. Boston.

23) Replicons carrying K24E, K24N, K24R, M28T, Q30H, Q30R, Q30E, L31M, Y93C, Y93H, or Y93N mutation in NS5A

3.(i).A.(2).3) Effect on mitochondria (4.2.1.2.8, 4.2.1.2.10)

The effect of SOF on mitochondrial DNA levels was assessed in HepG2 cells. SOF did not affect mitochondrial DNA synthesis in HepG2 cells at the highest concentration tested (20 μmol/L). The effect of SOF on mitochondrial cytochrome c oxidase biogenesis was teste d in PC-3 cells. As a result, SOF showed no inhibition of cytochrome c oxidase expression in PC-3 cells at the highest concentration tested (100 μmol/L). On the other hand, BMS-986094, which is also a NS5B polymerase inhibitor like SOF, showed inhibition of cytochrome c oxidase expression (IC_{50}, 0.82 μmol/L).

3.(i).A.(2).4) Effect on human polymerases (4.2.1.2.11)

GS-461203 was tested for the inhibition of human DNA and RNA polymerases. The IC_{50} values of GS-461203 for human DNA polymerases α, β, and γ and human RNA polymerase II were >200 μmol/L. The IC_{50} value of GS-461203 for mitochondrial RNA polymerase was >500 μmol/L.

3.(i).A.(2).5) Effects on receptors, enzymes, and ion channels (4.2.1.2.12)

GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241)[24)] was evaluated *in vitro* for possible interactions with a panel of 171 receptors, enzymes, and ion channels. As a result, GS-9851 (10 μmol/L) did not show >50% inhibition or induction of any enzymatic activity or ligand binding.

3.(i).A.(3) Safety pharmacology (4.2.1.3.1, 4.2.1.3.2, 4.2.1.3.4; Reference data 4.2.1.3.6, 4.2.1.3.7)

Safety pharmacology studies were performed to assess the effects of GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241)[24)] or its metabolites on the central nervous, cardiovascular, and respiratory systems (Table 10).

Table 10. Summary of safety pharmacology studies

Organ systems evaluated	Animal species/ Cell species	Method of administration	Doses or concentrations	Gender and No. per group	Noteworthy findings
Central nervous system (Irwin test)	Rat (SD)	Oral	0, 100, 300, 1000 mg/kg	5M, 5F	None.
Cardiovascular system	HEK-293 cells (hERG assay)	*In vitro*	10, 300 μmol/L	–	hERG current: 0.6% inhibition at 10 μmol/L, 12.7% inhibition at 300 μmol/L
			GS-331007: 10, 100 μmol/L	–	hERG current: 0.8% inhibition at 10 μmol/L, 0.6% inhibition at 100 μmol/L
	Beagle dog (telemetry)	Oral	0, 100, 300, 1000 mg/kg	3M, 3F	None.
Respiratory system	Rat (SD)	Oral	0, 100, 300, 1000 mg/kg	5M, 5F	None.

GS-9851 inhibited hERG current by 12.7% at 300 μmol/L (159 μg/mL), which was approximately 300-fold higher than the clinical exposure (the maximum plasma concentration of SOF [C_{max}], 0.511 μg/mL).[25)] The

[24)] The applicant explained that the data from studies using GS-9851 can be used for SOF efficacy and safety evaluation because the metabolites formed when administrating SOF and GS-9851 are the same [see "3.(ii).A.(3).3) *In vitro* metabolism"] and oral doses of SOF or GS-9851 yield similar plasma GS-566500 and GS-331007 exposures [see "3.(ii).A.(1).3) Multiple-dose studies (Toxicokinetics)"].

[25)] Steady-state GS-331007 and SOF pharmacokinetic parameters after once daily administration of SOF 400 mg in patients with chronic hepatitis C were calculated from the population pharmacokinetic analysis using the data from foreign phase II and III studies (P2938-0721, P7977-0221, P7977-0422, P7977-0523, P7977-0724, P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110) [see "4.(ii).A.(2).2) PPK analysis in foreign healthy adult subjects and patients with chronic hepatitis C"].

highest concentration of GS-331007, the predominant metabolite in plasma, was (100 μmol/L [26 μg/mL]), which was approximately 45-fold higher than the clinical exposure (C_{max} of GS-331007, 0.582 μg/mL).[25)]

3.(i).B Outline of the review

3.(i).B.(1) Antiviral activity of SOF

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

SOF undergoes intracellular metabolism to form the active uridine analog triphosphate (GS-461203), which selectively inhibits the HCV NS5B polymerase. When the antiviral activity of SOF was tested using HCV replicon cells, SOF inhibited HCV replicon replication. Taking account of these findings, the antiviral activity of SOF against HCV can be expected [see "3.(i).A.(1).1) *In vitro* antiviral activity", "3.(i).A.(2).1) Antiviral activity against other non-HCV viruses," and "3.(i).A.(2).5) Effects on receptors, enzymes, and ion channels"]. The efficacy of SOF in chronic hepatitis C patients with or without compensated cirrhosis is discussed in "4.(iii).B.(2) Efficacy".

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

The applicant explained the resistance profile of SOF against HCV as follows:

The NS5B substitution S282T was identified as the substitution associated with resistance to SOF in *in vitro* studies. Reduced susceptibility to SOF was observed in the NS5B S282T mutant replicons compared to the corresponding wild-type replicons. On the other hand, no reduction in the antiviral activity of SOF was observed for replicons with non-nucleoside NS5B polymerase inhibitor, NS3 protease inhibitor, or NS5A inhibitor resistant variants.

PMDA considers as follows:

SOF-resistant replicons were selected in *in vitro* resistance selection experiments [see "3.(i).A.(1).2) *In vitro* resistance selection"] and it was confirmed that the NS5B S282T substitution confers decreased susceptibility to SOF. The correlation between the emergence of resistance mutations and the efficacy of the SOF+RBV regimen in clinical studies is discussed in "4.(iii).B.(2) Efficacy". As the presence or absence of resistance mutations gives important information regarding the efficacy of SOF, it is important to continue to collect information on SOF resistance also after the market launch and to promptly provide the information to healthcare providers in clinical settings if new findings are obtained.

3.(i).B.(3) Cardiac toxicity

BMS-986094, which is also a NS5B polymerase inhibitor like SOF, has been associated with adverse reactions such as cardiac toxicity (cardiac dysfunction and others) in patients with chronic hepatitis C, which led to discontinuation of clinical development.[26)]

PMDA asked the applicant to explain the risk of cardiac toxicity associated with SOF from a pharmacological point of view.

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26) Ahmad T, et al. *Hepatology*. 2014;doi:10.1002/hep.27488.

The applicant explained as follows:
The mechanism of cardiac events associated with BMS-986094 is unknown. However, cardiac dysfunction and other clinical findings[26)] were reported and BMS-986094 also showed evidence of mitochondrial toxicity in *in vitro* studies [see "3.(i).A.(2).3) Effect on mitochondria"]. Moreover, a relationship between mitochondrial toxicity and adverse events including cardiac events has been suggested for other antivirals (fialuridine and zalcitabine).[27)] Therefore, cardiac events reported with BMS-986094 were considered related to mitochondrial effects.

Although SOF or GS-461203 showed no evidence of mitochondrial toxicity in *in vitro* studies, BMS-986094 inhibited mitochondrial cytochrome c oxidase biogenesis [see "3.(i).A.(2).3) Effect on mitochondria"]. It has been suggested that GS-461203 is not a substrate for mitochondrial RNA polymerase[28)] and that the triphosphorylated metabolite of BMS-986094 is a substrate for mitochondrial RNA polymerase.[29)] These differences in mitochondrial effects are considered attributable to differences in the chemical structure between SOF and BMS-986094.

Based on the above, SOF showed no evidence of mitochondrial toxicity in *in vitro* studies and SOF is unlikely to induce cardiac toxicity.

Taking account of the results from *in vitro* studies, and from a pharmacological point of view, PMDA confirmed that SOF or GS-461203 showed no evidence of mitochondrial toxicity and that GS-461203 was suggested to be not a substrate for mitochondrial RNA polymerase. The cardiac effects of SOF based on toxicity studies etc., are described in "3.(iii).B.(1) Cardiac effects".

3.(ii) Summary of pharmacokinetic studies

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

The pharmacokinetics of SOF after intravenous or oral administration of ^{14}C-labeled or unlabeled SOF and GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241) were studied in mice, rats, rabbits, and dogs. Liquid chromatography/tandem mass spectrometry was utilized for determining concentrations of SOF and its metabolites in biomaterials (lower limit of quantitation [LLOQ]: 5 ng/mL for SOF; 10 ng/mL for GS-566500 [a metabolite of SOF] in mice, rats, and rabbits and 9.322 or 10 ng/mL for GS-566500 in dog samples; 20 ng/mL for GS-331007 [a metabolite of SOF] in mouse, rat, dog, and rabbit samples; and 50 ng/mL for GS-606965 [a metabolite of SOF] in rat and dog samples). Radioactivity levels in biomaterials were determined using liquid scintillation counting and tissue radioactivity levels were determined using quantitative whole-body autoradiography (LLOQ, 0.073 or 0.04 μg eq./g in rats).

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27) Lewis W, et al. *Biochemistry*. 1994;33(48):14620-14624, Lewis W, et al. *Lab Invest*. 1997;76(1):77-87, Lewis W, et al. *Nat Rev Drug Discov*. 2003;2(10): 812-822, Lee H, et al. *Biochemistry*. 2003;42(50):14711-14719.

28) The incorporation rate of GS-461203 into RNA by mitochondrial RNA polymerase was ≤0.45% that of UTP (CTD4.2.1.2.11).

29) The incorporation rate of the triphosphorylated metabolite of BMS-986094 into RNA by mitochondrial RNA polymerase was 75% that of GTP (Arnold JJ, et al. *PLoS Pathog*. 2012;8(11): e1003030).

Unless otherwise specified, pharmacokinetic parameters are expressed as mean.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) *In vitro* study (4.2.2.2.1)

The apparent permeability of SOF through Caco-2 cell monolayers was determined. The efflux ratio of SOF (the ratio of the apparent permeability coefficient determined in the basolateral to apical direction to that determined in the apical to basolateral direction) was 49.7, 35.4, and 7.3 at 10, 700, and 2800 µmol/L, respectively.

3.(ii).A.(1).2) Single-dose studies (4.2.2.2.6, 4.2.2.2.7)

The plasma pharmacokinetics of SOF and its metabolites (GS-566500, GS-331007) and liver concentrations of metabolites (GS-331007, GS-566500, GS-606965, GS-607596, GS-461203) following a single 5 mg/kg oral dose of SOF in dogs (2 males/timepoint) were determined. SOF, GS-566500, and GS-331007 plasma concentrations reached C_{max} (519, 181, and 827 ng/mL, respectively) at 0.38, 0.75, and 5.00 hours post-dose, respectively, and the area under the plasma concentration-time curve extrapolated to infinite time (AUC_{inf}) was 418, 563, and 7025 ng·h/mL, respectively. The active metabolite GS-461203 was present in the highest concentrations in the liver (GS-461203 was shown to inhibit the HCV NS5B polymerase in "3.(i).A.(1).1) *In vitro* antiviral activity") (C_{max} [at 8 hours post-dose], 23,760 ng/mL; AUC from time 0 to the last quantifiable concentration [AUC_{0-t}], 416,767 ng·h/mL).

The absolute bioavailability calculated from the AUC_{0-t} of plasma SOF following administration of a single intravenous dose of SOF 0.5 mg/kg or a single oral dose of SOF 5 mg/kg to dogs (3 males/group) was 9.89%.

3.(ii).A.(1).3) Repeated-dose studies (Toxicokinetics) (4.2.3.2.2, 4.2.3.2.6, 4.2.3.2.10.2, 4.2.3.5.2.4, 4.2.3.7.7.1, 4.2.3.7.7.2)

The AUCs from time 0 to 12 or 24 hours[30] (AUC_{0-12} or AUC_{0-24}) of SOF and its metabolites after repeated oral administration of SOF to mice, rats, dogs, and pregnant rabbits were as shown in Table 11. The AUC_{0-24} value of GS-331007 in female rats and the AUC_{0-24} values of SOF and GS-331007 in pregnant rabbits were higher after repeated doses than on Day 1 and no accumulation appeared to take place in male and female mice, male rats, and male and female dogs. In mice, the AUC_{0-24} values of GS-331007 on Day 1 and after repeated doses were higher in females than in males and no differences in the AUC_{0-12} or AUC_{0-24} of GS-566500 between males and females were observed on Day 1 but the AUC_{0-12} or AUC_{0-24} of GS-566500 was higher in females than in males after repeated doses. In rats, although the AUC_{0-24} of GS-331007 was higher in males than in females on Day 1, no gender differences were observed after repeated doses.

[30] Up to the last timepoint.

Table 11. AUC_{0-24} on Day 1 and after repeated doses

Animal species Duration of dosing	SOF or metabolite	Dose (mg/kg/day)	Number of animals	Day 1 AUC_{0-24} (ng·h/mL)		After the last dose AUC_{0-24} (ng·h/mL)	
				Male	Female	Male	Female
Mouse [a] 3 months	GS-566500	100	3/sex/timepoint	8549 [b]	6274 [b]	4349 [b]	6838 [b]
		300	3/sex/timepoint	24600	20385 [b]	11916 [b]	20984 [b]
		1000	3/sex/timepoint	66611	65363	48065	67068
	GS-331007	100	3/sex/timepoint	24740	64558	23706	84918
		300	3/sex/timepoint	71264	145456	81530	161118
		1000	3/sex/timepoint	136064	249880	224314	361242
Rat 6 months	GS-331007	20	3/sex/timepoint	3661	1920	3944	3503
		100	3/sex/timepoint	15382	7407	18704	13128
		500	3/sex/timepoint	58922	37211	66460	65508
Dog 9 months	GS-331007	20	6/sex/timepoint	26860	23028	26623	26954
		100	6/sex/timepoint	98169	103916	76284	103675
		500	6/sex/timepoint	322892	188362	175387 [c]	215155
Pregnant rabbit 14 days [d]	SOF	30	2 females	—	97.4	—	506
		90	2 females	—	451	—	1417
		300	3 females	—	1694	—	7258 [e]
	GS-566500	30	2 females	—	4661	—	4200
		90	2 females	—	14919	—	11199
		300	3 females	—	45375	—	45559 [e]
	GS-331007	30	2 females	—	6649	—	8717
		90	2 females	—	21891	—	47434
		300	3 females	—	85933	—	119964 [e]

Mean
a) SOF plasma concentrations were also determined, which were below the LLOQ at all timepoints.
b) AUC_{0-12}
c) n = 5/timepoint
d) Dosed from gestation day 6 to gestation day 19.
e) n = 2

Rats (n = 3/sex/timepoint) and dogs (n = 2/sex/timepoint) orally received 500 mg/kg/day of SOF or GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241) for 14 days. The pharmacokinetic parameters (AUC_{0-12} or AUC_{0-24}, time to reach the maximum plasma concentration [T_{max}], half-life [$t_{1/2}$]) of their metabolites (GS-566500, GS-331007) were similar for SOF and GS-9851.

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

3.(ii).A.(2).1) Protein binding (4.2.2.3.2)

SOF (dog, 1-100 µg/mL; human, 0.1-20 µg/mL) was 35% to 60% plasma protein bound in dogs and 61% to 65% in humans. Plasma protein binding of GS-331007 (mice, rats, rabbits, and dogs, 1-100 µg/mL; humans, 0.1-20 µg/mL) was <11% in all of these species.

3.(ii).A.(2).2) Tissue distribution (4.2.2.3.1)

Tissue distribution of radioactivity was examined in albino and pigmented rats (1 male/timepoint) following a single 20 mg/kg oral dose of ^{14}C-SOF. Highest levels of radioactivity were determined in tissues of albino rats at 1 or 2 hours post-dose and radioactivity levels were below the LLOQ in most tissues by 48 hours post-dose. Tissues with highest radioactivity included the small intestine (396 µg eq./g), the large intestine (158 µg eq./g), the stomach (78 µg eq./g), and the liver (24 µg eq./g) and radioactivity concentrations of ≥10 µg eq./g were found in the spleen, thymus, and lymph node. The blood/plasma radioactivity concentration ratios ranged from 0.69 to 1.28 for up to 24 hours post-dose. Tissue distribution of radioactivity in pigmented rats was similar to

that in albino rats.

3.(ii).A.(2).3) Placental transfer (4.2.2.3.3)

Rats on gestation day 13 (n = 1/timepoint) received a single 20 mg/kg oral dose of ^{14}C-SOF. The maximal radioactivity levels in fetal blood and brain were higher than those observed in dams (fetal blood, 2.03 µg eq./g [at 4 hours post-dose]; fetal brain, 3.27 µg eq./g [at 4 hours post-dose]; maternal blood, 0.992 µg eq./g [at 1 hour post-dose]; maternal cerebrum, cerebellum, and medulla oblongata, 0.214, 0.184, and 0.151 µg eq./g, respectively [all at 4 hours post-dose]).

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) Possible metabolic pathway

Based on the study results in "3.(ii).A.(3).2) *In vivo* metabolism" and "3.(ii).A.(3).3) *In vitro* metabolism", the possible metabolic pathway of SOF are as shown in Figure 1.

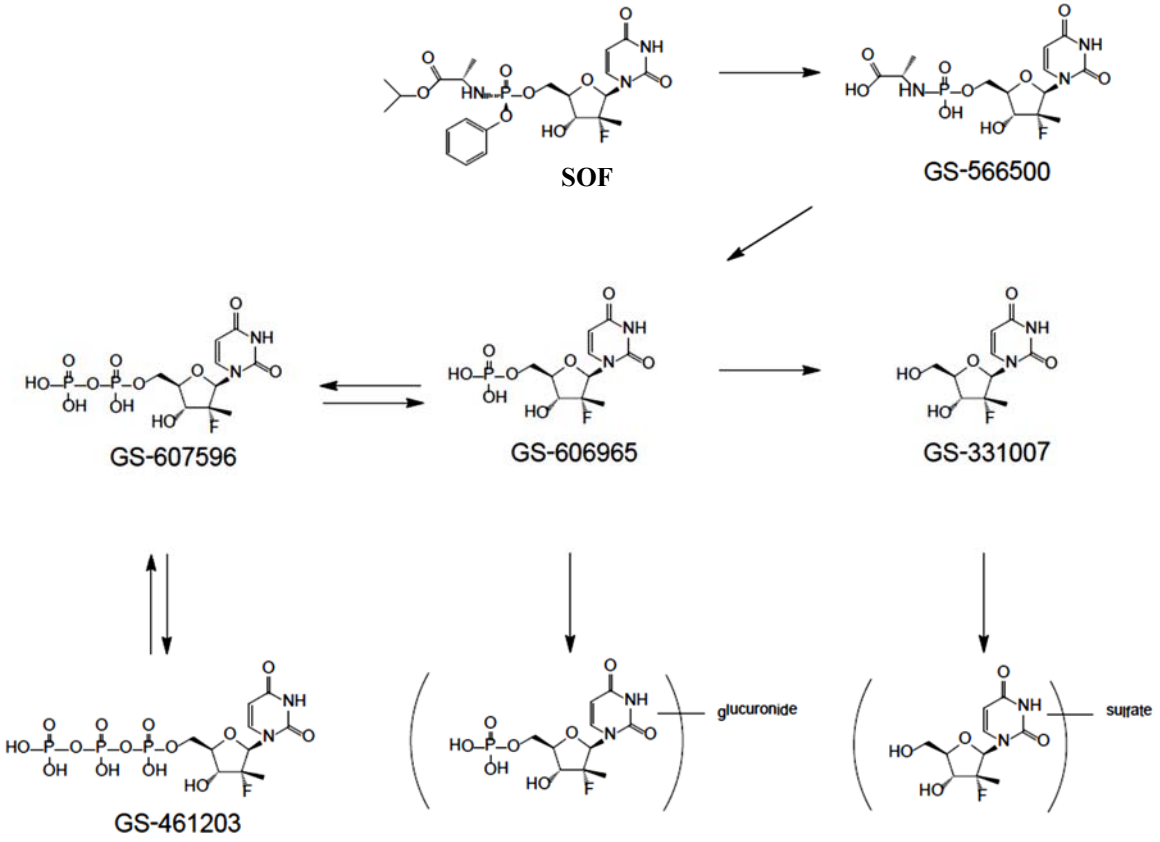

Figure 1. Possible metabolic pathway of SOF

3.(ii).A.(3).2) *In vivo* metabolism (4.2.2.4.1 to 4.2.2.4.4)

The metabolism of SOF was studied in mice (plasma sampling, 8 males/timepoint; urine and feces sampling, 3 males/timepoint), rats (3 males and 1 female/timepoint), and dogs (3 males/timepoint) following a single 20 mg/kg oral dose of ^{14}C-SOF. GS-331007 and GS-566500 were detected in mouse plasma, urine, and feces. In male rats, GS-331007 and GS-566500 were found in plasma and urine and GS-331007 was detected in feces. In male rat liver, GS-331007, GS-566500, and GS-606965 were observed. GS-331007, GS-566500, and sulfate

conjugates of GS-331007 were found in plasma and milk of female rats. In dogs, GS-331007, GS-566500, and a glucuronide conjugate of GS-606965 were observed in plasma and GS-331007 and GS-566500 were detected in urine and feces. The primary metabolite detected was GS-331007 in all species.

In a mass balance study in humans, SOF, GS-331007, and GS-566500 were detected in human plasma and urine [see "4.(ii).A.(1).2) Mass balance study in foreign healthy adult subjects"].

3.(ii).A.(3).3) *In vitro* metabolism (4.2.2.4.6, 4.2.2.4.11 to 4.2.2.4.13; Reference data 4.2.2.4.14, 4.2.2.4.19, 4.2.2.4.20)

The elimination half-lives of SOF in human liver S9 fraction and plasma were 0.23 hours and ≥24 hours, respectively.

The metabolism of ^{14}C-SOF was studied in human primary hepatocytes and human peripheral blood mononuclear cells. In primary hepatocytes, GS-331007, GS-566500, GS-606965, GS-607596, and GS-461203 were found at 48 hours after the addition of ^{14}C-SOF and the major metabolite was GS-461203.[31)] In peripheral blood mononuclear cells, GS-566500 and GS-461203 were detected at 48 hours after the addition of ^{14}C-SOF. The level of GS-461203 was ≥10-fold higher in primary hepatocytes than in peripheral blood mononuclear cells.

The metabolism of GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241) to GS-461203 was studied in rat, dog, monkey, and human primary hepatocytes. GS-461203 reached its maximum level in rat primary hepatocytes at 4 to 8 hours, in dog and human primary hepatocytes at 24 hours, and in monkey primary hepatocytes at 48 hours after the addition of GS-9851.

The metabolism of SOF, GS-566500, GS-606965, and GS-331007 was studied in human liver microsomes. While there was no decrease in the concentration of GS-566500 or GS-331007 in human liver microsomal incubations, approximately 70% of GS-606965 remained in the presence of uridine diphosphate glucuronic acid, suggesting that the metabolism of GS-606965 involved uridine diphosphate-glucuronyltransferase (UGT).

Using human cytochrome P450 (CYP) expression system (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4), the metabolism of SOF and GS-331007 was studied. Neither SOF nor GS-331007 was a substrate of the CYP enzymes tested.

Using human cathepsin A (CatA) expression system, carboxylesterase (CES) 1, and histidine triad nucleotide binding protein 1 (Hint1) expression system, the metabolism of SOF and GS-566500 was studied. The results indicated that CatA and CES1 are responsible for the conversion of SOF to GS-566500 and that Hint1 is responsible for the conversion of GS-566500 to GS-606965.

The phosphorylation of GS-606965 and GS-607596 by human uridine monophosphate-cytidine monophosphate

31) The metabolism of ^{3}H-GS-9851 was also studied in human primary hepatocytes. GS-331007, GS-566500, GS-606965, GS-607596, and GS-461203 were found at 24 hours after the addition of ^{3}H-GS-9851, and the major metabolite was GS-461203 (CTD4.2.2.4.15).

kinase and nucleoside diphosphate kinase was investigated, which indicated the involvement of these enzymes in the phosphorylation of GS-606965 and GS-607596.

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

3.(ii).A.(4).1) Urinary and fecal excretion and biliary excretion (4.2.2.5.1 to 4.2.2.5.3)

Following a single oral dose of ^{14}C-SOF in mice (20 mg/kg), rats (20 mg/kg), and dogs (22.01 mg/kg) for 3 males/timepoint, the radioactivity excreted in the urine and feces accounted for 65.6% and 14.2% of the administered doce, respectively, in mice; 72.2% and 18.4%, respectively, in rats; and 80.7% and 1.8%, respectively, in dogs. In bile duct cannulated rats (3 males/timepoint) given a single 20 mg/kg oral dose of ^{14}C-SOF, the radioactivity excreted in the urine, feces, and bile accounted for 63.3%, 18.1%, and 5.6% of the administered dose, respectively.

3.(ii).A.(4).2) Excretion in milk (4.2.2.3.3)

Following a single 20 mg/kg oral dose of ^{14}C-SOF in rats on post-partum Day 2 (3 females/timepoint), the radioactivity concentrations in milk were 0.514 and 0.030 µg eq./g at 1 and 24 hours post-dose, respectively, and the milk to plasma ratios for SOF-related material collected from the dam were 0.1 and 0.8, respectively.

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

3.(ii).A.(5).1) Enzyme inhibition or induction (*in vitro*) (4.2.2.6.1, 4.2.2.6.3, 4.2.2.6.6, 4.2.2.6.7, 4.2.2.6.8)

The potential of SOF and its metabolites to inhibit the activities of CYP isozymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A) and UGT1A1 was evaluated using CYP expression system, UGT1A1 expression system, and human liver microsomes. SOF hardly inhibited CYP enzymes (IC_{50}, 53.1 and >100 µmol/L for CYP3A[32]; IC_{50}, >100 µmol/L for other CYP isozymes). The metabolites (GS-607596, GS-606965, GS-566500, GS-461203, GS-331007) did not inhibit any of the CYP isozymes (IC_{50} >100 µmol/L). None of SOF, GS-331007, or GS-606965 inhibited UGT1A1 (IC_{50} >50 µmol/L).

The inductive effects of SOF on CYP izozymes (CYP1A2, 2B6, 3A) were investigated in human primary hepatocytes. The results indicated that SOF does not induce the CYP isoforms.[33]

3.(ii).A.(5).2) Drug transporter substrate assays (4.2.2.6.9, 4.2.2.6.11, 4.2.2.6.13, 4.2.2.6.16)

In the presence of human P-glycoprotein (P-gp) inhibitors verapamil or cyclosporine A, the efflux ratio of ^{14}C-SOF (12.4) was reduced to 3.66 or 4.66, respectively, in Caco-2 cell monolayers. In the presence of a P-gp inhibitor, the efflux ratio of ^{14}C-GS-331007 was not altered. These results indicated that SOF is a substrate of P-gp but GS-331007 is not a substrate of P-gp.

The efflux ratios of ^{14}C-SOF and ^{14}C-GS-331007 were 3.33 and 1.74, respectively, on breast cancer resistance protein (BCRP) transfected MDCKII cells, and the efflux ratios were 0.96 and 0.30, respectively, on parental

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32) As CYP3A substrates, midazolam and testosterone were used.

33) SOF (1-100 µmol/L) increased the activities and mRNA expression levels as follows: of CYP1A2, by 1.0- to 1.1-fold and 1.3- to 1.4-fold, respectively; of CYP2B6, by 1.1- to 2.7-fold and 1.5- to 2.0-fold, respectively; and of CYP3A, by 1.0- to 1.2-fold and 1.2- to 2.7-fold, respectively.

MDCKII cells. In the presence of Ko143 (a BCRP inhibitor), the efflux ratio of SOF was decreased in BCRP transfected MDCKII cells. These results suggested that SOF is a substrate of BCRP but GS-331007 is not a substrate of BCRP.

The accumulation of SOF in organic anion transporting polypeptide (OATP) 1B1 and 1B3 or organic cation transporter (OCT) 1 expressing cells was ≤2-fold that in control cells, indicating that SOF is not a substrate of OATP1B1, OATP1B3, or OCT1.

The accumulation of GS-331007 in cells expressing organic anion transporter (OAT) 1, OAT3, OCT1, OCT2, or multidrug and toxin extrusion (MATE) 1 was <2-fold that in control cells, indicating that GS-331007 is not a substrate of OAT1, OAT3, OCT1, OCT2, or MATE1.

3.(ii).A.(5).3) Drug transporter inhibition assays (4.2.2.6.9, 4.2.2.6.11 to 4.2.2.6.16)

SOF or GS-331007 was evaluated as inhibitors of P-gp, BCRP, multidrug resistance-associated protein (MRP) 2, bile salt export pump (BSEP), OATP1B1, OATP1B3, OCT1, OCT2, MATE1, and OAT1. The IC_{50} of SOF or GS-331007 was >100 μmol/L for all transporters.

3.(ii).B Outline of the review

PMDA concluded that there are no particular problems with the submitted non-clinical pharmacokinetic data.

3.(iii) Summary of toxicology studies

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

As SOF toxicity data, the results from single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies (local tolerance studies, a skin sensitization study, a study on impurities, comparison of the toxicity profiles of SOF and GS-9851) were submitted. The single-dose toxicity study, rat and dog repeat-dose toxicity studies (7 days, 28 days), and genotoxicity studies were performed with GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241).[34)] Unless otherwise specified, 95% polyethylene glycol 400/5% polysorbate 80 was used as the vehicle for the test articles.

3.(iii).A.(1) Single-dose toxicity (Reference data 4.2.3.1.1)

Rats (n = 3/sex/group) received single oral doses of 0 (vehicle[35)]), 50, 300, or 1800 mg/kg of GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241). GS-9851 did not produce mortality, clinical signs, body weight or organ weight changes, or macroscopic pathologic findings. Based on the above, the approximate lethal dose was determined to be >1800 mg/kg.

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34) The applicant explained that the data from studies using GS-9851 can be used for SOF toxicity evaluation because SOF and GS-9851 have the same metabolites [see "3.(ii).A.(3).3) *In vitro* metabolism"], oral doses of SOF or GS-9851 yield similar plasma GS-566500 and GS-331007 exposures [see "3.(ii).A.(1).3) Repeated-dose studies (Toxicokinetics)"], and there were no toxicological differences between SOF and GS-9851 [see "3.(iii).A.(6).3) Comparison of toxicity profiles of SOF and GS-9851"].

35) 30% polyethylene glycol 400/30% polysorbate 20/20% corn oil/20% purified water

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

Oral toxicity studies were conducted in mice, rats, and dogs. The primary target organs for the toxicity of SOF were the gastrointestinal tract and cardiovascular system in rats and the gastrointestinal tract, hepatobiliary system, and hematopoietic (red blood cells) system in dogs.

Exposures to the major metabolite GS-331007[36] in plasma (AUC) at the no-observed-adverse-effect levels (NOAELs) in mouse 13-week, rat 26-week, and dog 39-week toxicity studies (male mice, 100 mg/kg/day; female mice, 300 mg/kg/day; rats, 500 mg/kg/day; dogs, 100 mg/kg/day) were 3.3- and 23-fold (male mice and female mice), 9-fold (rats, males and females combined), and 13-fold (dogs, males and females combined) the human plasma exposure at the maximum recommended clinical dose (400 mg/day).[37]

3.(iii).A.(2).1) Mouse 14-day toxicity study (Reference data 4.2.3.2.1)

CD-1 mice (n = 5/sex/group) orally received 0 (vehicle), 50, 150, 500, or 1500 mg/kg/day of SOF for 14 days. One male in the 1500 mg/kg/day group was found dead. Reduced body weight was observed during the dosing period in males in the 1500 mg/kg/day group. Based on the above, the NOAELs were determined to be 500 mg/kg/day in males and 1500 mg/kg/day in females.

3.(iii).A.(2).2) Mouse 13-week toxicity study (4.2.3.2.2)

CD-1 mice (n = 20/sex/group) orally received 0 (vehicle), 100, 300, or 1000 mg/kg/day of SOF for 13 weeks. Mortality occurred during the dosing period in all groups (2 males in the vehicle group, 6 males and 5 females in the 100 mg/kg/day group, 6 males and 1 female in the 300 mg/kg/day group, 4 males and 3 females in the 1000 mg/kg/day group).[38] The applicant explained that 6 of the 27 deaths were due to gavage error (gavage error and aspiration) and that the cause of death in the remaining 21 animals was undetermined. Reduced body weight gain was observed in males in the 300 mg/kg/day group and males and females in the 1000 mg/kg/day group and decreased food consumption was noted in the 1000 mg/kg/day group. Based on the above, the NOAELs were determined to be 100 mg/kg/day in males and 300 mg/kg/day in females.

3.(iii).A.(2).3) Rat 7-day toxicity study with a 14-day recovery period (4.2.3.2.3)

SD rats (n = 13/sex/group) orally received 0 (vehicle[35]), 30, 250, or 2000 mg/kg/day (15, 125, or 1000 mg/kg, respectively, was given twice daily, 6 hours apart) of GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241) for 7 days and the reversibility of toxicity following a 14-day recovery period was evaluated in 3 males and 3 females from all groups. Rats receiving 2000 mg/kg/day were found dead (3 males and 6 females) and in addition, soft feces/watery diarrhea, body weight loss, and cardiac myofiber degeneration were observed. The histopathological finding in the heart was observed also following the recovery period. In 1 of the 9 cases, the cause of death was acute myocardial inflammation with myofiber mineralization. Although the cause of death in the remaining 8 animals was undetermined, 6 of the 8 rats had mild multiple cardiac myofiber degeneration.

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36) Since GS-9851 and SOF in mouse and rat plasma were below the LLOQ at most timepoints, exposure margins were calculated using the major metabolite GS-331007.

37) Compared with plasma exposure in patients with chronic hepatitis C (AUC_{tau}, 7.12 μg·h/mL [see "4.(ii).A.(2).2) PPK analysis in foreign healthy adult subjects and patients with chronic hepatitis C"]).

38) Including animals used for toxicokinetic analysis.

Dosing of 2000 mg/kg/day was discontinued after the first dose on Day 5. Based on the above, the NOAEL for both males and females was determined to be 250 mg/kg/day.

3.(iii).A.(2).4) Rat 28-day toxicity study with a 14-day recovery period (4.2.3.2.4)

SD rats (n = 15/sex/group) orally received 0 (vehicle), 20, 100, or 500 mg/kg/day of GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241) for 28 days and the reversibility of toxicity following a 14-day recovery period was evaluated in 5 males and 5 females from all groups. Mortality occurred in the vehicle group (2 females) and the 100 mg/kg/day group (1 male). The cause of death for the 1 rat in the vehicle group was gavage-related injury and the cause of death in the remaining 2 animals was undetermined. As there were no abnormal examination findings, the NOAEL for both males and females was determined to be 500 mg/kg/day.

3.(iii).A.(2).5) Rat 13-week toxicity study with a 4-week recovery period (4.2.3.2.5)

SD rats (n = 20/sex/group) orally received 0 (vehicle), 20, 100, or 500 mg/kg/day of SOF for 13 weeks and the reversibility of toxicity following a 4-week recovery period was evaluated in 5 males and 5 females from all groups. As there were no abnormal findings in any group, the NOAEL for both males and females was determined to be 500 mg/kg/day.

3.(iii).A.(2).6) Rat 26-week toxicity study with a 4-week recovery period (4.2.3.2.6)

SD rats (n = 20/sex/group) orally received 0 (vehicle), 20, 100, or 500 mg/kg/day of SOF for 26 weeks and the reversibility of toxicity following a 4-week recovery period was evaluated in 5 males and 5 females from all groups. As there were no abnormal findings in any group, the NOAEL for both males and females was determined to be 500 mg/kg/day.

3.(iii).A.(2).7) Dog 7-day toxicity study with a 14-day recovery period (4.2.3.2.7)

Beagle dogs (n = 4/sex/group) orally received 0 (empty gelatin capsules), 30, 150, or 1500 mg/kg/day (15, 75, or 750 mg/kg, respectively, was given twice daily, 6 hours apart) of GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241) for 7 days and the reversibility of toxicity following a 14-day recovery period was evaluated in 1 male and 1 female from all groups. Soft feces/watery diarrhea and emesis, body weight loss and reduced food consumption, increases in blood alanine aminotransferase, aspartate aminotransferase, and bilirubin, increased urine urobilinogen and bilirubin concentration, and hepatobiliary histopathological changes (hepatocyte hypertrophy, hepatocyte microvesicles and apoptosis, less hepatocyte glycogen, Kupffer cell pigmentation, mononuclear-cell infiltrates in the gallbladder) in males and females and depressed behavior and hypothermia, an increase in blood alkaline phosphatase, and prolonged QT/QTc interval in males in the 1500 mg/kg/day group were observed. Increased liver weight was noted at all dose levels of GS-9851 as compared to the control. All findings were reversible. Based on the above, the NOAEL for both males and females was determined to be 150 mg/kg/day.

3.(iii).A.(2).8) Dog 28-day toxicity study with a 14-day recovery period (4.2.3.2.8)

Beagle dogs (n = 5/sex/group [n = 3/sex in the 20 mg/kg/day group only]) orally received 0 (empty gelatin capsules), 20, 100, or 500 mg/kg/day of GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241) for 28 days and the reversibility of toxicity following a 14-day recovery period was evaluated in 2 males and 2 females from the 0, 100, and 500 mg/kg/day groups. Emesis, soft feces, and body weight loss in males and females and decreases in red blood cell parameters (red blood cell count, hematocrit, hemoglobin concentration) in males at 500 mg/kg/day were noted. All findings were reversible. Based on the above, the NOAEL for both males and females was determined to be 100 mg/kg/day.

3.(iii).A.(2).9) Dog 13-week toxicity study with a 4-week recovery period (4.2.3.2.9)

Beagle dogs (n = 6/sex/group [n = 4/sex/group for the 20 mg/kg/day group only]) orally received 0 (empty gelatin capsules), 20, 100, or 500 mg/kg/day of SOF for 13 weeks and the reversibility of toxicity following a 4-week recovery period was evaluated in 2 males and 2 females from the 0, 100, and 500 mg/kg/day groups. Black foci on stomach mucosa corresponding to hemorrhage in the pyloric stomach were noted in one male at 500 mg/kg/day. Based on the above, the NOAEL for both males and females was determined to be 100 mg/kg/day.

3.(iii).A.(2).10) Dog 39-week toxicity study with a 4-week recovery period (4.2.3.2.10.1, 4.2.3.2.10.2)

Beagle dogs (n = 6/sex/group [n = 4/sex in the 100 mg/kg/day group for 26-week dosing]) orally received 0 (empty gelatin capsules), 20, 100, or 500 mg/kg/day of SOF for 39 weeks or 0, 100, or 500 mg/kg/day of SOF for 26 weeks[39)] and the reversibility of toxicity following a 4-week recovery period was evaluated in 2 males and 2 females from the 0, 20, 100, and 500 mg/kg/day groups for 39-week dosing and 2 males and 2 females from the 0 and 500 mg/kg/day groups for 26-week dosing. One male in the 500 mg/kg/day group was euthanized moribund. Necropsy of this animal revealed intestinal hemorrhage. Based on the above, the NOAEL for both males and females was determined to be 100 mg/kg/day.

3.(iii).A.(3) Genotoxicity (4.2.3.3.1.1, 4.2.3.3.1.2, 4.2.3.3.2.1)

GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241) was not genotoxic in the bacterial reverse mutation assay, the mammalian chromosome aberration assay, or the mouse bone marrow micronucleus assay.

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

Carcinogenicity studies in rats and mice were conducted with SOF, which indicated no carcinogenic potential of SOF. At the highest doses tested (male mice, 200 mg/kg/day; female mice, 600 mg/kg/day; rats, 750 mg/kg/day), plasma exposures to the predominant metabolite GS-331007 (AUC) were 7 (male mice), 30 (female mice) and 16 (rats, males and females combined) times higher than the AUC in humans at the maximum recommended clinical dose (400 mg/day).[37)]

[39)] Twenty-six week oral dosing was conducted for an interim analysis of a 39-week oral toxicity study.

3.(iii).A.(4).1) Mouse carcinogenicity study (4.2.3.4.1.1)

CD-1 mice (n = 60/sex/group) orally received 0 (vehicle), 0 (deionized water), 20, 60, or 200 mg/kg/day of SOF (males) or 0 (vehicle), 0 (deionized water), 60, 200, or 600 mg/kg/day of SOF (females) for 2 years. No increase in the incidence of SOF-related neoplastic lesions was observed, indicating no carcinogenic potential of SOF.

3.(iii).A.(4).2) Rat carcinogenicity study (4.2.3.4.1.2)

SD rats (n = 55/sex/group orally received 0 (vehicle), 0 (deionized water), 75, 250, or 750 mg/kg/day of SOF for 2 years. No increase in the incidence of SOF-related neoplastic lesions was observed, indicating no carcinogenic potential of SOF.

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

A fertility and early embryonic development to implantation study in rats, embryo-fetal development studies in rats and rabbits, and a study of effects on pre- and postnatal development, including maternal function, in rats were performed and there were no treatment-related abnormal findings in any of the studies. Plasma exposures to the predominant metabolite GS-331007 (AUC) at the NOAELs in the embryo-fetal development studies in rats (500 mg/kg/day) and rabbits (300 mg/kg/day) were 10- and 28-fold, respectively, the plasma exposure in humans at the maximum recommended clinical dose (400 mg/day)[37)] and plasma exposure to the predominant metabolite GS-331007 at the NOAEL in the rat study of effects on pre- and postnatal development, including maternal function (500 mg/kg/day), was 12-fold the clinical exposure.

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

SD rats (n = 22/sex/group) orally received 0 (vehicle), 0 (deionized water), 20, 100, or 500 mg/kg/day of SOF from 28 days prior to mating through day of necropsy for males and 14 days prior to mating through gestation day 7 for females. No treatment-related effects on parental general toxicity, fertility, or early embryonic development were observed. Based on the above, the NOAELs for parental general toxicity, fertility, and early embryonic development were determined to be 500 mg/kg/day.

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

3.(iii).A.(5).2).(a) Rat study (4.2.3.5.2.1)

Pregnant SD rats (n = 24/group) orally received 0 (vehicle), 0 (deionized water), 20, 100, or 500 mg/kg/day of SOF from gestation day 6 to gestation day 18. There were no treatment-related abnormal findings in maternal animals in any group and no treatment-related effects were seen on external, visceral, and skeletal fetal morphology. Based on the above, the NOAELs for maternal general toxicity and embryo-fetal development were determined to be 500 mg/kg/day.

3.(iii).A.(5).2).(b) Rabbit study (4.2.3.5.2.4)

Pregnant NZW rabbits (n = 20/group) orally received 0 (vehicle[40)]), 0 (deionized water), 30, 90, or 300

[40)] polyethylene glycol 400

mg/kg/day of SOF from gestation day 6 to gestation day 19. There were no treatment-related abnormal findings in maternal animals in any group and no treatment-related effects were seen on external, visceral, and skeletal fetal morphology. Based on the above, the NOAELs for maternal general toxicity and embryo-fetal development were determined to be 300 mg/kg/day.

3.(iii).A.(5).3) Study of effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1)

Pregnant SD rats (n = 25/group) orally received 0 (vehicle), 50, 250, or 500 mg/kg/day of SOF from gestation day 6 to lactation day 20. There were no treatment-related abnormalities in maternal animals in any group and no effects on the F1 pups were observed. The NOAELs for maternal general toxicity and the development and reproductive performance of the F1 generation were determined to be 500 mg/kg/day.

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

3.(iii).A.(6).1) Local tolerance studies and skin sensitization study (4.2.3.6.1, 4.2.3.6.2, 4.2.3.7.1.1)

An *in vitro* bovine corneal opacity and permeability assay was performed to assess the eye irritation potential of SOF, a dermal irritation study in NZW rabbits was performed to assess the dermal irritation potential of SOF, and a local lymph node assay in the mouse was performed to assess the skin sensitization potential of SOF. The results indicated that SOF has no irritant effects on the skin or eyes and is not a skin sensitizer.

3.(iii).A.(6).2) Study on impurities (4.2.3.7.6.1)

To assess the toxicity of manufacturing process-related impurities, the toxicity profile in SD rats (n = 10/sex/group) orally given 0 (vehicle), 100, or 500 mg/kg/day of SOF (Batch number, 5364-84-9; purity, 94.8%) for 28 days was compared to that when given the control lot (SOF [Batch number, 40411001; purity, 99.6%] 500 mg/kg/day). No treatment-related abnormalities were observed in any group.

3.(iii).A.(6).3) Comparison of toxicity profiles of SOF and GS-9851 (4.2.3.7.7.1, 4.2.3.7.7.2)

Since a single-dose toxicity study, rat repeat-dose toxicity studies (7 days, 28 days), dog repeat-dose toxicity studies (7 days, 28 days), and genotoxicity studies were conducted with GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241), with a view to applying these study data to SOF, 14-day oral bridging toxicity studies were conducted in rats and dogs to compare the toxicity profiles of SOF and GS-9851.

3.(iii).A.(6).3).(a) Rat 14-day oral briding toxicity study comparing SOF to GS-9851 (4.2.3.7.7.1)

SD rats (n = 10/sex/group) orally received vehicle or 500 mg/kg/day of SOF or GS-9851 for 14 days. One male in the GS-9851 group had minimal mononuclear cell infiltration in the heart and another male in the GS-9851 group had minimal myofiber degeneration located at the apex of the heart. No test article-related abnormal findings were observed in any group. Based on the above results, it was concluded that there are no toxicological differences between the two compounds.

3.(iii).A.(6).3).(b) Dog 14-day oral briding toxicity study comparing SOF to GS-9851 (4.2.3.7.7.2)

Beagle dogs (n = 2/sex/group) orally received empty gelatin capsules or 500 mg/kg/day of SOF or GS-9851 for 14 days. No test article-related abnormal findings were observed in any group. Based on the above results, it was concluded that there are no toxicological differences between the two compounds.

3.(iii).B Outline of the review

Based on the submitted data and the following considerations, PMDA concluded that there are no particular toxicological concerns about SOF.

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

Cardiac effects of GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241) were observed in its rat repeat-dose toxicity studies. PMDA asked the applicant to explain the cardiac effects of SOF in clinical use.

The applicant explained as follows:

Although 1 rat had acute myocardial inflammation and 6 rats had multiple cardiac myofiber degeneration in the GS-9851 2000 mg/kg/day group in a rat 7-day oral toxicity study, these findings occurred only at high systemic exposure (Exposure to GS-331007 was approximately 29-fold the clinical exposure[37)]) and were not observed in any other toxicity studies, including carcinogenicity studies.

In a 14-day oral bridging toxicity study comparing SOF to GS-9851 in rats, one male in the GS-9851 500 mg/kg/day group had minimal mononuclear cell infiltration in the heart and another male in the same group had minimal myofiber degeneration located at the apex of the heart. Mononuclear cell infiltration in the heart are considered an early manifestation of cardiomyopathy that occurs spontaneously at high prevalence in rats (especially in male rats).[41)] According to historical control data for the incidence of cardiomyopathy within the same rat strain from the contract laboratory where toxicity studies of SOF were conducted, the percentage of male control animals that had cardiomyopathy ranged from 0% to 33% per study. In the 14-day oral bridging toxicity study comparing SOF to GS-9851 in rats, only 1 of 10 male rats in the GS-9851 group had cardiac myofiber degeneration, which is within the historical control of the laboratory. Therefore, this finding in this study was considered unrelated to GS-9851.

In a dog 7-day oral toxicity study, 3 of 4 males in the GS-9851 1500 mg/kg/day group had prolonged QTc interval, but there were no abnormal ECG findings in females. The C_{max} of GS-331007 in the 1500 mg/kg/day group in this study (53.8 μg/mL in males, 51.1 μg/mL in females) was approximately 90-fold (males and females combined) higher than the C_{max} in humans at 400 mg (0.582 μg/mL) [see "4.(ii).A.(2).2) PPK analysis in foreign healthy adult subjects and patients with chronic hepatitis C"]. In other repeat-dose toxicity studies of SOF or GS-9851 in dogs, there were no ECG findings or abnormal cardiovascular findings at the highest dose tested (500 mg/kg/day). Also when dogs orally received 1000 mg/kg of GS-9851 in a safety pharmacology study to assess the effects on the cardiovascular system, no abnormal cardiovascular findings were observed [see

41) Ruben Z, et al. Non-proliferative Lesions of the Heart and Vasculature in Rats. In: *Guides for Toxicologic Pathology. 2000*.

"3.(i).A.(3) Safety pharmacology"].

In Japanese or foreign phase III studies, there were no Grade 3 or higher cardiac adverse events, serious cardiac adverse events, or cardiac adverse events leading to treatment discontinuation in the SOF group. In SOF clinical studies, no events suggestive of cardiomyopathy observed in the toxicity studies were reported.

Cardiac toxicity in patients with chronic hepatitis C, which is considered related to mitochondrial toxicity, has been reported with BMS-986094, a NS5B polymerase inhibitor as SOF, whereas SOF or GS-461203 showed no evidence of mitochondrial toxicity in *in vitro* studies [see 3.(i).B.(3) Cardiac toxicity"].

The above results indicate that the cardiac effects observed in the toxicity studies are unlikely to be of concern for human safety.

PMDA considers as follows:
The applicant's explanation about the cardiac effects of SOF-related material observed in the toxicity studies is acceptable. Taking also into account that no particular cardiac effects have been reported to date in clinical studies, there are no particular toxicological concerns about the cardiac effects of SOF.

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

Gastrointestinal effects (e.g., intestinal hemorrhage) were noted in repeat-dose toxicity studies of SOF or GS-9851 in dogs. PMDA asked the applicant to explain the gastrointestinal effects of SOF in clinical use.

The applicant explained as follows:

One dog in the SOF 500 mg/kg/day group had intestinal hemorrhage (Day 172) in a dog 39-week oral toxicity study. Clinical signs and necropsy and histopathological findings of this animal were consistent with idiopathic hemorrhagic gastroenteritis. Although a causal relationship of these findings to SOF could not be denied, as idiopathic hemorrhagic gastroenteritis is a spontaneous disease of unknown etiology occurring in young adult dogs[42)] and there was no similar finding in other animals, the observed finding was considered to be of spontaneous origin. In dog repeat-dose toxicity studies of SOF or GS-9851, increases in the frequency and incidence of soft feces/diarrhoea or emesis were observed, which were not associated with histopathological findings. Increased mucus secretion in the stomach (related to stress and emesis or debilitation) was observed in 2 males and 3 females in the 1500 mg/kg/day group in a dog 7-day oral toxicity study of GS-9851 and minimal petechial hemorrhage of the gastric mucosa (related to local irritancy) was noted in 1 male in the 500 mg/kg/day group in a dog 13-week toxicity study of SOF.

In repeat-dose toxicity studies of SOF or GS-9851 in rats, increases in the frequency and incidence of soft feces/diarrhoea were noted and similar gastrointestinal findings were observed also in the vehicle control group,

42) Hemorrhagic Gastroenteritis – *The Merck Veterinary Manual.* Whitehouse Station, NJ, USA Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc, 2011.

suggesting that the vehicle also may have contributed to the development of these symptoms. These gastrointestinal symptoms resolved in many rats with continued dosing and were not associated with histopathological findings.

In foreign phase III studies, adverse events of gastrointestinal disorders occurred in 42.8%[43)] of subjects in the SOF/RBV group, but this incidence was not so different from that in the placebo group (39.4%[44)]) and gastrointestinal symptoms are known adverse reactions to RBV.[45)] Thus, these events were considered unrelated to SOF.

The above results indicate that the gastrointestinal effects observed in the toxicity studies are unlikely to be of concern for human safety.

PMDA considers as follows:
The applicant's explanation about the gastrointestinal effects found in the toxicity studies is acceptable. Given that there have so far been no large differences in the incidence of adverse events of gastrointestinal disorders between the SOF/RBV and placebo groups in foreign phase III studies and that no serious or fatal adverse events of gastrointestinal disorders or those leading to study drug discontinuation were reported in a Japanese phase III study [see "4.(iii).A.(2).1) Japanese phase III study"], there are no particular toxicological concerns about the gastrointestinal effects of SOF.

4. Clinical data

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

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

In the clinical development of SOF, 4 different formulations (Formulations 1-4)[46)] were used. Since Formulation 3 and Formulation 4 were used in the main clinical studies[47)] and Formulation 4 is the to-be-marketed formulation, the results from biopharmaceutic studies with Formulation 3 or Formulation 4 (relative bioavailability and food effect studies) are described in this section. Liquid chromatography/tandem mass spectrometry was utilized to determine the concentrations of SOF and its metabolites in human plasma and urine (LLOQ: 5 ng/mL for SOF, 10 ng/mL for metabolites [GS-331007, GS-566500]).[48)]

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43) The incidence of adverse events classified under the system organ class "gastrointestinal disorders" in the SOF/RBV group (566 subjects) in foreign phase III studies (P7977-1231, GS-US-334-0107, GS-US-334-0108).

44) The incidence of adverse events classified under the system organ class "gastrointestinal disorders" in the placebo group (28 subjects) in a foreign phase III study (GS-US-334-0107).

45) Copegus Tablet 200 mg package insert (14th edition, November 2013)

46) Formulation 1, GS-9851 (a 1:1 mixture of SOF and its diastereomer GS-491241) capsules; Formulation 2, SOF (Form [redacted]) 100-mg tablets; Formulation 3, SOF (Form [redacted]) 200-mg and 400-mg tablets; Formulation 4, SOF (Form [redacted]) 400-mg tablets

47) Formulation 3 was used in the following main clinical studies: clinical pharmacology studies (P2938-0515, P7977-0613, P7977-0814, P7977-0915, P7977-1318, P7977-1819, P7977-1910, GS-US-334-0111); and foreign phase III studies (P7977-1231, GS-US-334-0107).
Formulation 4 was used in the following main clinical studies: a clinical pharmacology study (GS-US-334-0131); a Japanese phase III study (GS-US-334-0118); and a foreign phase III study (GS-US-334-0108).

48) The results from pharmacology and pharmacokinetic studies indicated that SOF is extensively metabolized to form the active GS-461203 within the hepatocyte, but GS-461203 was not detected in plasma [see "3.(i).A.(1).1) *In vitro* antiviral activity" and "3.(ii).A.(3) Metabolism"].

4.(i).A.(1) Relative bioavailability study (Reference data 5.3.3.4.1, Study GS-US-334-0131 [March 2012 to May 2012])

The relative bioavailability of Formulation 4 to Formulation 3 was evaluated in foreign healthy adult subjects (36 subjects in the Formulation 3 group and 16 subjects in the Formulation 4 group included in pharmacokinetic assessment). The geometric mean ratios of the C_{max} and AUC_{inf} (Formulation 4/Formulation 3) [90% CI] were 0.99 [0.76, 1.28] and 0.92 [0.75, 1.13], respectively, for SOF, 1.07 [0.89, 1.28] and 1.02 [0.87, 1.18], respectively, for GS-566500, and 1.00 [0.86, 1.17] and 1.03 [0.93, 1.14], respectively, for GS-331007, demonstrating the bioequivalence of the two formulations.

4.(i).A.(2) Food effect study (Reference data 5.3.1.2.2; Study P7977-1318 [August 2011 to September 2011])

A food effect study was conducted in foreign healthy adult subjects receiving a single oral dose of Formulation 3 (400-mg tablets)[49] (39 subjects included in pharmacokinetic assessment).[50] The geometric mean ratios of C_{max} and AUC_{inf} after administration of the 400-mg tablet with a high-fat meal (800-1000 kcal, 50% fat) vs. fasted [90% CI] were 0.84 [0.67, 1.06] and 1.80 [1.60, 2.02], respectively, for SOF, 1.14 [1.01, 1.29] and 1.57 [1.44, 1.71], respectively, for GS-566500, and 0.76 [0.70, 0.82] and 1.03 [0.99, 1.08], respectively, for GS-331007. Administration with a high-fat meal resulted in a 1-hour increase in the time to reach the maximum plasma concentration (T_{max}) of SOF and GS-331007.

4.(i).B Outline of the review

Food effect

PMDA asked the applicant to explain pharmacokinetic differences between the formulations administered under fasted conditions and with a high-fat meal in a food effect study.

The applicant explained as follows:

After administration of Formulation 3 (400-mg tablets)[49] under fed conditions, the rate of absorption slowed down and the C_{max} of GS-331007 was 24% lower than that under fasted conditions, but the AUC of GS-331007 was unchanged. These results indicate that the administration of SOF with food mainly affects the absorption rate, but not the extent of absorption and the food effect is not considered clinically significant. Since SOF was taken together with RBV, which has to be taken with food, SOF was also taken with food in the Japanese phase III study, and the efficacy and safety of SOF in combination with RBV when taken with food were confirmed. Taking account of the above, SOF can be administered without regard to food.

PMDA concluded that the applicant's explanation is acceptable and that SOF can be administered without regard to food.

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[49] Although the to-be-marketed formulation is Formulation 4, food effect was evaluated using Formulation 3. The applicant explained that biopharmaceutic profiles after fasted or fed administration should be similar between Formulation 3 and Formulation 4 because *in vitro* dissolution studies showed that both Formulation 3 and Formulation 4 are highly soluble and SOF is a weak acid (a pKa of 9.3) and exhibits pH-independent solubility over the physiological range.

[50] The relative bioavailability of the 200-mg and 400-mg tablets of Formulation 3 was also evaluated in this 3-period, crossover study. A washout period of at least 7 days was included between 2 adjacent periods.

4.(ii) Summary of clinical pharmacology studies

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

The results from 9 foreign phase I studies (including 1 study to compare pharmacokinetics between Japanese and Caucasian healthy adult subjects and 4 drug-drug interaction studies), 1 foreign phase II study, and 1 Japanese phase III study and the results of a population pharmacokinetic analysis using the data from foreign phase II and III studies were submitted in the application. *In vitro* studies using human biomaterials are described in "3.(ii).A.(2) Distribution, 3.(ii).A.(3) Metabolism, and 3.(ii).A.(5) Pharmacokinetic interactions".

Unless otherwise specified, pharmacokinetic parameters are expressed as mean.

4.(ii).A.(1) Healthy adult subject studies

4.(ii).A.(1).1) Foreign phase I single-dose study in Japanese and Caucasian healthy adult subjects (5.3.3.1.1, Study GS-US-334-0111 [April 2012 to November 2012])

The pharmacokinetics of SOF, GS-566500, and GS-331007 following administration of single oral doses of SOF 200 to 800 mg to healthy adult subjects in the fasted state (64 subjects included in pharmacokinetic assessment [32 Japanese subjects and 32 Caucasian subjects]) were investigated (Table 12). The geometric mean ratios of C_{max} and AUC_{inf} following administration of SOF 200 to 800 mg in Japanese subjects vs. Caucasian subjects were 0.96 to 1.07 and 0.97 to 1.22, respectively, for SOF; 1.18 to 1.54 and 1.24 to 1.54, respectively, for GS-566500; and 0.73 to 1.13 and 0.82 to 0.96, respectively, for GS-331007.

Table 12. Pharmacokinetic parameters of SOF and its metabolites following single oral doses of SOF in Japanese and Caucasian healthy adult subjects

Dose	N	C_{max} (ng/mL)		AUC_{inf} (ng·h/mL)		T_{max} [a)] (h)		$t_{1/2}$ (h)	
		Japanese	Caucasian	Japanese	Caucasian	Japanese	Caucasian	Japanese	Caucasian
SOF									
200 mg	8	349 (51.3)	319 (47.4)	297 (46.2)	300 (41.7)	0.5 [0.5, 1.0]	1.0 [0.5, 1.0]	0.4 (22.2)	0.4 (32.8)
400 mg	8	639 (28.6)	631 (39.1)	649 (46.5)	499 (16.8)	0.5 [0.5, 1.0]	0.5 [0.5, 1.0]	0.5 (22.6)	0.4 (42.5)
800 mg	8	1149 (45.3)	1219 (35.2)	1212 (27.1)	1147 (30.0)	0.6 [0.5, 1.0]	0.5 [0.5, 1.0]	0.4 (9.5)	0.4 (17.2)
GS-566500									
200 mg	8	243 (39.1)	153 (28.8)	768 (47.7)	477 (23.1)	1.0 [1.0, 1.5]	1.0 [1.0, 1.5]	1.8 (12.1)	1.9 (7.9)
400 mg	8	392 (22.5)	287 (28.7)	1471 (23.7)	1004 (27.0)	1.0 [0.5, 1.0]	1.0 [0.5, 1.5]	2.0 (8.3)	2.0 (11.7)
800 mg	8	647.3 (20.8)	547 (18.1)	2387 (20.4)	1931 (23.7)	1.0 [0.7, 2.0]	1.3 [0.5, 3.0]	2.0 (4.3)	2.0 (7.0)
GS-331007									
200 mg	8	736 (29.6)	988 (20.3)	6462 (26.0)	7720 (17.5)	2.0 [1.5, 3.0]	1.8 [1.0, 4.0]	26.6 (25.9)	23.2 (24.2)
400 mg	8	1438 (32.2)	1232 (17.8)	10989 (21.9)	11478 (23.3)	2.1 [1.5, 3.0]	2.0 [1.5, 3.0]	26.1 (15.7)	24.1 (20.3)
800 mg	8	1809 (34.1)	1748 (32.2)	17415 (14.6)	20751 (11.4)	2.5 [1.5, 4.0]	3.0 [1.5, 3.0]	30.0 (26.4)	25.9 (18.5)

Mean (CV%); $t_{1/2}$, half-life
a) Median [Range]

4.(ii).A.(1).2) Mass balance study in foreign healthy adult subjects (Reference data 5.3.3.1.2; Study P7977-0312 [June 2010 to July 2010])

A mass balance study was conducted in healthy adult subjects receiving a single oral dose of SOF 400 mg

containing a mixture of ^{12}C-SOF and ^{14}C-SOF in the fasted state (7 subjects included in pharmacokinetic assessment). The total recovery of the radioactive dose was 92.6% by 168 hours post-dose (76.1% in urine, 14.0% in feces, 2.5% in expired air). SOF, GS-331007, and GS-566500 were detected in plasma and urine and 77.7% of the administered dose was eliminated in urine as GS-331007.

4.(ii).A.(2) Studies in patients with chronic hepatitis C

4.(ii).A.(2).1) Foreign phase II study (Reference data 5.3.4.2.1; Study P7977-0221 [January 2010 to August 2011])

Patients with chronic hepatitis C (genotype 1) (48 subjects included in pharmacokinetic assessment) orally received 100, 200, or 400 mg of SOF once daily (QD) for 28 days, in combination with Peginterferon (PegIFN) α-2a (Genetical Recombination) and ribavirin (RBV). The pharmacokinetics of SOF, GS-566500, and GS-331007 were investigated. The results were as shown in Table 13.

Table 13. Pharmacokinetic parameters of SOF and its metabolites following multiple oral doses of SOF in patients with chronic hepatitis C (Day 1 and Day 28)

Dose	N	C_{max} (ng/mL)		AUC_{tau} (ng·h/mL)		T_{max} [a)] (h)		$t_{1/2}$ (h)	
		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
SOF									
100 mg	16	218 (83.3)	254 (67.5)	280 (71.2)	376 (54.1)	1.0 [0.5, 2.0]	0.5 [0.5, 3.0]	0.6 (44.7)	0.8 (57.6)
200 mg	17 [b)]	332 (64.9)	475 (75.5)	585 (58.5)	732 (40.6)	1.0 [0.5, 3.0]	1.0 [0.5, 3.0]	0.8 (52.6)	0.8 (44.2)
400 mg	15	1258 (58.6)	1356 (63.0)	1865 (51.4)	2011 (49.1)	1.0 [0.5, 3.0]	1.0 [0.5, 3.0]	0.8 (52.0)	0.9 (66.7)
GS-566500									
100 mg	16	70.0 (51.4)	64.8 (59.5)	270 (45.1)	262 (46.1)	1.7 [0.5, 3.0]	1.5 [0.5, 4.0]	2.0 (34.0)	2.2 (37.1)
200 mg	17 [b)]	146 (22.0)	133 (37.2)	645 (35.3)	572 (27.4)	1.5 [0.5, 4.0]	2.0 [1.0, 3.0]	2.1 (20.9)	2.1 (29.2)
400 mg	15	294 (31.6)	238 (21.8)	1313 (47.0)	1073 (30.5)	1.5 [1.0, 4.0]	2.0 [0.9, 4.0]	2.4 (21.5)	2.2 (21.9)
GS-331007									
100 mg	16	197 (44.9)	234 (44.9)	1767 (39.2)	2257 (43.5)	3.5 [1.5, 6.0]	3.0 [2.0, 6.0]	10.3 (49.1)	10.4 (27.8)
200 mg	17 [b)]	357 (28.0)	357 (30.8)	3339 (22.9)	3389 (24.6)	4.0 [2.0, 8.0]	4.0 [1.0, 6.0]	9.4 (43.5)	13.5 (32.4)
400 mg	15	662 (32.4)	717 (29.1)	6493 (39.4)	7399 (35.6)	4.0 [2.0, 8.0]	4.0 [1.5, 8.0]	8.1 (35.7)	13.5 (57.0)

Mean (CV%); AUC_{tau}, AUC over the dosing interval
a) Median [Range]
b) N = 16 on Day 28

4.(ii).A.(2).2) PPK analysis in foreign healthy adult subjects and patients with chronic hepatitis C (5.3.3.5.1, 5.3.3.5.2)

Using the pharmacokinetic data from foreign phase I, II, and III studies[51)] in healthy adult subjects or patients with chronic hepatitis C (genotypes 1-6) (SOF, n = 1374, 8295 sampling points; GS-331007, n = 2089, 24,889 sampling points), a population pharmacokinetic (PPK) analysis (NONMEM version 7.2) was performed. For

51) The data from a total of 1374 subjects (296 healthy adult subjects and 1078 patients with chronic hepatitis C) in the following studies were used in the SOF PPK analysis: 7 phase I studies (P7977-0111, GS-US-334-0131, P7977-0613, P7977-0814, P7977-0915, P7977-1318, P7977-1819); and 7 phase II and III studies (GS-US-334-0107, GS-US-334-0108, GS-US-334-0110, P2938-0212, P7977-0221, P2938-0515, P7977-1231).
The data from a total of 2089 subjects (294 healthy adult subjects and 1795 patients with chronic hepatitis C) in the following studies were used in the GS-331007 PPK analysis: 7 phase I studies (P7977-0111, GS-US-334-0131, P7977-0613, P7977-0814, P7977-0915, P7977-1318, P7977-1819); and 11 phase II and III studies (GS-US-334-0107, GS-US-334-0108, GS-US-334-0110, P2938-0212, P7977-0221, P7977-0422, P2938-0515, P7977-0523, P2938-0721, P7977-0724, P7977-1231).

the final model, the pharmacokinetics of SOF were described by a 1-compartment model with zero- and first-order absorption and absorption lag time and the pharmacokinetics of GS-331007 were described by a 2-compartment model with first-order absorption and absorption lag time. HCV infection status as a covariate of the oral clearance (CL/F) and absorption rate constant (KA) of SOF and HCV genotype and baseline creatinine clearance as covariates of GS-331007 CL/F were selected[52)] and these were identified as factors affecting the CL/F and KA of SOF or the CL/F of GS-331007. The C_{max} and AUC_{tau} of SOF in healthy adult subjects following oral administration of SOF 400 mg and those in patients with chronic hepatitis C following oral administration of SOF 400 mg (in combination with RBV or PegIFN/RBV) were estimated from the final population PK model. The estimates of SOF C_{max} and AUC_{tau} were 385 ng/mL and 642 ng·h/mL, respectively, in healthy adult subjects and 511 ng/mL and 1030 ng·h/mL, respectively, in patients with chronic hepatitis C and the C_{max} and AUC_{tau} of SOF were 39% and 60% higher, respectively, in patients with chronic hepatitis C than in healthy adult subjects. The C_{max} and AUC_{tau} of GS-331007 estimated from the final population PK model were 1110 ng/mL and 11,400 ng·h/mL, respectively, in healthy adult subjects and 582 ng/mL and 7120 ng·h/mL, respectively, in patients with chronic hepatitis C and the C_{max} and AUC_{tau} of GS-331007 were 50% and 39% lower, respectively, in patients with chronic hepatitis C than healthy adult subjects. The C_{max} and AUC_{tau} were comparable across HCV genotypes.

4.(ii).A.(2).3) Japanese phase III study (5.3.5.2.1, Study GS-US-334-0118 [June 2013 to March 2014])

Using SOF and GS-331007 pharmacokinetic data from patients with chronic hepatitis C (genotype 2) orally received SOF 400 mg QD in combination with RBV (SOF; n = 35, 79 sampling points: GS-331007; n = 140, 1331 sampling points), PPK analysis (NONMEM version 7.2) was performed. Previously built models as mentioned in "4.(ii).A.(2).2) PPK analysis in foreign healthy adult subjects and patients with chronic hepatitis C" were used as the final models and the PK of SOF were described by a 1-compartment model with zero- and first-order absorption and absorption lag time and the PK of GS-331007 were described by a 2-compartment model with first-order absorption and absorption lag time. Age, gender, BMI, baseline creatinine clearance, cirrhosis, and prior treatment were tested as covariates on the CL/F of SOF and GS-331007[53)] and baseline creatinine clearance was identified as a factor affecting the CL/F of GS-331007. The C_{max} and AUC_{tau} in patients with chronic hepatitis C following oral administration of SOF 400 mg in combination with RBV were estimated from the final population PK model and the estimates of C_{max} and AUC_{tau} were 529 ng/mL and 953 ng·h/mL, respectively, for SOF and 824 ng/mL and 10,491 ng·h/mL, respectively, for GS-331007.

4.(ii).A.(3) Intrinsic factor pharmacokinetic studies

4.(ii).A.(3).1) Pharmacokinetic study in subjects with hepatic impairment (Reference data 5.3.3.3.1; Study P2938-0515 [May 2011 to April 2012])

The pharmacokinetics of SOF, GS-566500, and GS-331007 were studied in foreign chronic hepatitis C patients

52) Age, gender, race, body weight, BMI, body surface area, formulation, combination therapy (PegIFN/RBV or RBV), treatment duration, creatinine clearance, eGFR, renal impairment, hepatic impairment, cirrhosis, HCV infection status, HCV genotype, IL28B, and concomitant medication were tested as covariates.

53) Based on the covariates tested in "4.(ii).A.(2).2) PPK analysis in foreign healthy adult subjects and patients with chronic hepatitis C", variables to be evaluated to determine pharmacokinetic variations in a specific population were selected.

with hepatic impairment[54] (8 subjects each in moderate and severe hepatic impairment groups included in pharmacokinetic assessment) following 7-day oral administration of SOF 400 mg QD.[55] The results were as shown in Table 14. Although the C_{max} and AUC_{tau} of SOF and GS-566500 were higher in subjects with hepatic impairment than in subjects with normal hepatic function, the C_{max} and AUC_{tau} of GS-331007 were comparable. As there were no particular tolerability issues in subjects with moderate or severe hepatic impairment,[56] the applicant explained that no dose adjustment for SOF is required for patients with hepatic impairment.

Table 14. Pharmacokinetic parameters of SOF and its metabolites following multiple oral doses of SOF in subjects with hepatic impairment

Degree of hepatic impairment	N	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	Geometric mean ratio [90% CI] (Hepatic impairment/Normal hepatic function)	
				C_{max}	AUC_{tau}
SOF					
Normal hepatic function	8	602 (47.2)	538 (39.0)	—	—
Moderate hepatic impairment	8	1127 (61.0)	1350 (58.1)	1.72 [1.07, 2.76]	2.26 [1.39, 3.67]
Severe hepatic impairment	8	1125 (49.4)	1379 (52.0)	1.85 [1.15, 2.96]	2.43 [1.50, 3.96]
GS-566500					
Normal hepatic function	8	235 (38.4)	853 (45.7)	—	—
Moderate hepatic impairment	8	349 (36.2)	1425 (43.7)	1.49 [1.06, 2.11]	1.66 [1.08, 2.53]
Severe hepatic impairment	8	379 (42.2)	1607 (42.2)	1.60 [1.13, 2.26]	1.87 [1.22, 2.86]
GS-331007					
Normal hepatic function	8	1378 (19.2)	9639 (18.7)	—	—
Moderate hepatic impairment	8	1441 (58.9)	12561 (57.0)	0.94 [0.63, 1.40]	1.18 [0.78, 1.76]
Severe hepatic impairment	8	1439 (59.5)	12206 (63.1)	0.91 [0.61, 1.36]	1.09 [0.73, 1.63]

Mean (CV%)

4.(ii).A.(3).2) Pharmacokinetic study in subjects with renal impairment (Reference data 5.3.3.3.2; Study P7977-0915 [March 2011 to August 2011])

The pharmacokinetics of SOF, GS-566500, and GS-331007 were studied in foreign subjects with renal impairment[57] (6 subjects each in the normal renal function, mild, moderate, and severe renal impairment, and end stage renal disease [ESRD] groups included in pharmacokinetic assessment) following a single oral dose of SOF 400 mg and the results were as shown in Table 15. The hemodialysis extraction ratios for SOF, GS-566500, and GS-331007 were 13%, 68%, and 53%, respectively.

54) Subjects were grouped according to Child-Pugh classification (Class A, mild; Class B, moderate; Class C, severe). Subjects with mild hepatic impairment were not enrolled into the study because it was concluded from the results from subjects with moderate hepatic impairment that no dose adjustment is needed.

55) Compared with the pharmacokinetic parameters in chronic hepatitis C patients with normal hepatic function (genotype 1) following 7-day oral administration of SOF 400 mg QD (Study P2938-0212).

56) Adverse events of diarrhoea (1 subject) and nausea (1 subject) occurred in the group of subjects with moderate hepatic impairment and adverse events of abdominal distension, asthenia, discomfort, oedema peripheral, hyperbilirubinaemia, fluid retention, and pruritus (1 subject each) occurred in the group of subjects with severe hepatic impairment. There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

57) Subjects were grouped according to the followingcriteria based on the estimated eGFR by MDRD formula: normal renal function group, subjects with an eGFR >80 mL/min/1.73cm^2; mild renal impairment group, subjects with an eGFR ≥50 and ≤80 mL/min/1.73cm^2; moderate renal impairment group, subjects with an eGFR ≥30 and <50 mL/min/1.73cm^2; severe renal impairment group, subjects with an eGFR<30 mL/min/1.73cm^2 and not on dialysis; ESRD group, subjects with ESRD requiring dialysis. Subjects with ESRD received 2 single oral doses of SOF 400 mg separated by at least 2 weeks. SOF was administered approximately 1 hour prior to the dialysis session during Period 1 and immediately following the dialysis session during Period 2.

Table 15. Pharmacokinetic parameters of SOF and its metabolites following a single oral dose of SOF in subjects with renal impairment

Degree of renal impairment	N	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	Geometric mean ratio [90% CI] (Renal impairment/Normal renal function)	
				C_{max}	AUC_{inf}
SOF					
Normal renal function	6	715 (37.5)	590 (29.9)	—	—
Mild renal impairment	6	896 (35.8)	964 (36.6)	1.28 [0.70, 2.34]	1.61 [1.09, 2.39]
Moderate renal impairment	6	1329 (84.0)	1305 (50.4)	1.54 [0.84, 2.81]	2.07 [1.39, 3.07]
Severe renal impairment	6	1305 (41.6)	1581 (28.1)	1.77 [0.97, 3.24]	2.71 [1.83, 4.02]
ESRD (prior to hemodialysis)	6	958 (60.6)	785 (42.7) [a)]	1.21 [0.66, 2.21]	1.28 [0.85, 1.93]
ESRD (after hemodialysis)	6	833 (74.3)	948 (32.9) [a)]	0.98 [0.53, 1.79]	1.60 [1.06, 2.42]
GS-566500					
Normal renal function	6	248 (25.4)	888 (22.6)	—	—
Mild renal impairment	6	370 (37.0)	1499 (32.1)	1.42 [0.95, 2.10]	1.61 [1.13, 2.28]
Moderate renal impairment	6	426 (36.6)	2136 (32.2)	1.66 [1.12, 2.46]	2.35 [1.66, 3.34]
Severe renal impairment	6	508 (40.5)	3218 (40.9)	1.96 [1.32, 2.91]	3.44 [2.42, 4.89]
ESRD (prior to hemodialysis)	6	380 (43.0)	1647 (18.4)	1.46 [0.99, 2.17]	1.87 [1.31, 2.65]
ESRD (after hemodialysis)	6	484 (38.0)	3301 (35.2)	1.88 [1.27, 2.79]	3.59 [2.53, 5.10]
GS-331007					
Normal renal function	6	1358 (42.3)	12744 (19.1)	—	—
Mild renal impairment	6	1644 (16.3)	19645 (14.3)	1.28 [0.94, 1.75]	1.55 [0.88, 2.73]
Moderate renal impairment	6	1464 (33.2)	24101 (23.3)	1.10 [0.81, 1.50]	1.88 [1.07, 3.31]
Severe renal impairment	6	1737 (23.0)	92564 (85.9)	1.34 [0.99, 1.83]	5.51 [3.13, 9.68]
ESRD (prior to hemodialysis)	6	1472 (39.5)	225947 (78.6) [b)]	1.10 [0.81, 1.50]	13.8 [6.93, 27.6]
ESRD (after hemodialysis)	6	2419 (35.0)	358352 (70.7) [b)]	1.80 [1.32, 2.46]	21.7 [10.9, 43.3]

Mean (CV%)
a) N = 5, b) N = 3

4.(ii).A.(4) Drug interaction studies (Reference data 5.3.3.4.1, Study GS-US-334-0131 [March 2012 to May 2012]; Reference data 5.3.3.4.2, Study P7977-0814 [December 2010 to May 2011]; Reference data 5.3.3.4.3, Study P7977-1819 [October 2011 to February 2012]; Reference data 5.3.3.4.6, Study GS-US-334-1344 [March 2014 to April 2014]; Reference data, 5.3.3.4.5, Study GS-US-334-0146 [November 2012 to March 2013])

Six drug-drug interaction studies were conducted to evaluate the effect of coadministered drugs on the PK of SOF and its metabolites or the effect of SOF on the PK of coadministered drugs. The geometric mean ratios of C_{max} and AUC_{tau} of SOF, GS-566500, and GS-331007 with coadministered drugs (coadministration/single-agent administration) [90% CI] were as shown in Table 16 and Table 17.

Table 16. Impact of coadministered drugs on pharmacokinetic parameters of SOF and its metabolites

Coadministered drug	Dosage regimen		N (with/without coadministered drug)	Geometric mean ratio [90% CI] (with/without coadministered drug)					
				SOF		GS-566500		GS-331007	
	Coadministered drug	SOF		C_{max}	AUC [a)]	C_{max}	AUC [a)]	C_{max}	AUC [a)]
EFV/3TC/TDF	600/200/300 mg QD	400 mg single dose	16/16	0.81 [0.60, 1.10]	0.94 [0.76, 1.16]	0.72 [0.62, 0.84]	0.79 [0.69, 0.90]	0.77 [0.70, 0.84]	0.84 [0.76, 0.92]
DRV/r	800/100 mg QD	400 mg single dose	18/18	1.45 [1.10, 1.92]	1.34 [1.12, 1.59]	1.80 [1.56, 2.08]	1.80 [1.64, 1.98]	0.97 [0.90, 1.05]	1.24 [1.18, 1.30]
RAL	400 mg BID	400 mg single dose	19/19	0.87 [0.71, 1.08]	0.95 [0.82, 1.09]	0.89 [0.79, 1.00]	0.94 [0.85, 1.04]	1.09 [0.99, 1.20]	1.03 [0.97, 1.08]
RPV	25 mg QD	400 mg single dose	17/17	1.21 [0.90, 1.62]	1.09 [0.94, 1.27]	1.03 [0.88, 1.21]	0.98 [0.88, 1.08]	1.06 [0.99, 1.14]	1.01 [0.97, 1.04]
Methadone	30-130 mg (Daily dose)	400 mg QD	14/14	0.95 [0.68, 1.33]	1.30 [1.00, 1.69]	1.02 [0.81, 1.28]	1.29 [0.98, 1.69]	0.73 [0.65, 0.83]	1.04 [0.89, 1.22]
Cyclosporine	600 mg single dose	400 mg single dose	19/18	2.54 [1.87, 3.45]	4.53 [3.26, 6.30]	2.54 [2.07, 3.13]	2.99 [2.45, 3.64]	0.60 [0.53, 0.69]	1.04 [0.90, 1.20]
Tacrolimus	5 mg single dose	400 mg single dose	16/15	0.97 [0.65, 1.43]	1.13 [0.81, 1.57]	0.95 [0.76, 1.17]	1.10 [0.89, 1.35]	0.97 [0.83, 1.14]	1.00 [0.87, 1.13]
Rifampicin	600 mg single dose	400 mg single dose	17/17	0.23 [0.19, 0.29]	0.28 [0.24, 0.32]	0.56 [0.50, 0.61]	0.55 [0.50, 0.61]	1.23 [1.14, 1.34]	0.95 [0.88, 1.03]

EFV, efavirenz; 3TC, emtricitabine; TDF, tenofovir disoproxil fumarate
DRV/r, darunavir/ritonavir; RAL, raltegravir; RPV, rilpivirine
a) AUC_{inf} for single dose; AUC_{tau} for multiple doses

Table 17. Impact of SOF on pharmacokinetic parameters of coadministered drugs

Coadministered drug (assessed for pharmacokinetics)	Dosage regimen		N (with/without SOF)	Geometric mean ratio [90% CI] (with/without SOF)	
	Coadministered drug	SOF		C_{max}	AUC [e]
3TC [a]	600 mg QD	400 mg single dose	16/16	0.97 [0.88, 1.07]	0.99 [0.94, 1.05]
EFV [a]	200 mg QD			0.95 [0.85, 1.06]	0.96 [0.91, 1.03]
TFV [a]	300 mg QD			1.25 [1.08, 1.45]	0.98 [0.91, 1.05]
DRV [b]	800/100 mg QD	400 mg single dose	18/18	0.97 [0.94, 1.01]	0.97 [0.94, 1.00]
RAL	400 mg BID	400 mg single dose	19/19	0.57 [0.44, 0.75] [f]	0.73 [0.59, 0.91]
RPV	25 mg QD	400 mg single dose	17/17	1.05 [0.97, 1.15]	1.06 [1.02, 1.09]
R-methadone	30-130 mg (Daily dose)	400 mg QD	14/14	0.99 [0.85, 1.16]	1.01 [0.85, 1.21]
S-methadone				0.95 [0.79, 1.13]	0.95 [0.77, 1.17]
Cyclosporine	600 mg single dose	400 mg single dose	19/19	1.06 [0.94, 1.18]	0.98 [0.85, 1.14]
Tacrolimus	5 mg single dose	400 mg single dose	16/16	0.73 [0.59, 0.90] [g]	1.09 [0.84, 1.40]
Norelgestromin [c]	0.180/0.215/0.250 mg [d] QD	400 mg single dose	16/16	1.07 [0.94, 1.22]	1.06 [0.92, 1.21]
Norgestrel [c]				1.18 [0.99, 1.41]	1.19 [0.98, 1.45]
Ethinyl estradiol [c]	0.025 mg QD			1.15 [0.97, 1.36]	1.09 [0.94, 1.26]

TFV, tenofovir; BID, twice daily
a) Administered as 3TC/EFV/TDF fixed dose tablet. b) DRV was taken with ritonavir.
c) Administered as norgestimate/ethinyl estradiol combination product. d) Norgestimate dose
e) AUC_{inf} for single dose; AUC_{tau} for multiple doses
f) The geometric mean ratio of trough concentrations (with/without SOF) [90% CI] was 0.95 [0.81, 1.12].
g) The geometric mean ratio of trough concentrations (with/without SOF) [90% CI] was 1.22 [1.02, 1.45].

4.(ii).A.(5) QT/QTc study (5.3.4.1.1, Study P7977-0613 [January 2011 to April 2011])

A 4-treatment, 4-period, crossover study was conducted to investigate the effect of a single oral dose of SOF 400 or 1200 mg, moxifloxacin 400 mg, or placebo on the QT/QTc interval in foreign healthy adult subjects (N = 60).[58] The upper bound of the two-sided 90% confidence interval for the largest mean difference in change from baseline in the QT interval corrected for heart rate using the Fridericia formula (QTcF) between SOF 400 mg and placebo or between 1200 mg and placebo was 4.34 msec, which was below 10 msec. Thus, it was concluded that SOF does not prolong the QTc interval. The lower bound of the 90% confidence interval for the largest mean difference in change from baseline in QTcF between moxifloxacin and placebo was above 5 msec. Following a single oral dose of SOF 1200 mg, the C_{max} and AUC_{inf} were 2252 ng/mL and 2482 ng·h/mL, respectively, for SOF, 747 ng/mL and 3092 ng·h/mL, respectively, for GS-566500, and 2099 ng/mL and 27,635 ng·h/mL, respectively, for GS-331007.

4.(ii).A.(6) Exposure-response analyses

Based on the data from foreign phase I and II studies in patients with chronic hepatitis C (genotype 1) (P7851-1102,[59] P2938-0212,[60] P7977-0221[61]), the relationship between AUC of SOF or GS-331007 and change from baseline in HCV RNA levels was evaluated using a sigmoid maximal effect (E_{max}) model.[62] As a result, a relationship between AUC_{tau} of GS-331007 and change from baseline in HCV RNA levels was observed and it

58) A washout period of at least 1 week was included between each dose.
59) Exposure and HCV RNA data from a total of 39 subjects following placebo or GS-9851 50, 100, 200, and 400 mg QD monotherapy at Day 3 of treatment (CTD5.3.3.2.1)
60) Exposure and HCV RNA data from 8 subjects following SOF 400 mg QD monotherapy at Day 3 of treatment (CTD5.3.4.2.3)
61) Exposure and HCV RNA data from a total of 61 subjects following placebo or SOF 100, 200, and 400 mg QD in combination with PegIFN and RBV at Day 3 of treatment (CTD5.3.4.2.1)
62) The applicant explained that the relationship between the active metabolite GS-461203 exposure and efficacy was not evaluated because *in vitro* metabolism studies [see "3.(ii).A.(3).3) *In vitro* metabolism"] indicated that GS-461203 is present in the liver, but it was not detected in human blood and it is difficult to evaluate the relationship between GS-461203 exposure and efficacy.

was predicted that approximately 90% of the maximal effect for change from baseline in HCV RNA levels is achieved at the mean AUC_{tau} of GS-331007 (7120 ng·h/mL) after administration of SOF 400 mg in foreign phase III studies. The change from baseline in HCV RNA levels was compared between patients with genotype 1 and genotype 2 chronic hepatitis C, which showed no differences between the genotypes.[63)] No particular relationship between the sustained virologic response rate at post-treatment Week 12 (SVR12) and AUC_{tau} was identified in patients with chronic hepatitis C (genotype 2) over the range of SOF and GS-331007 exposures achieved by administration of SOF 400 mg in combination with RBV or PegIFN/RBV (AUC_{tau} ranged from 247 to 3630 ng·h/mL and from 1780 to 17,400 ng·h/mL, respectively) in foreign phase III studies.[64)]

4.(ii).B Outline of the review

Use in patients with renal impairment

In a pharmacokinetic study in subjects with renal impairment (P7977-0915), the AUC of GS-331007 was approximately 5-fold higher in subjects with severe renal impairment and approximately 14-fold higher (SOF dosed prior to hemodialysis) or approximately 22-fold higher (SOF dosed after hemodialysis) in subjects with ESRD than in subjects with normal renal function [see "4.(ii).A.(3).2) Pharmacokinetic study in subjects with renal impairment"]. PMDA asked the applicant to explain the need for a precautionary statement regarding the use of SOF in patients with severe renal impairment or ESRD.

The applicant explained as follows:

While GS-331007 exposure increased in subjects with severe renal impairment or ESRD relative to subjects with normal renal function, there were no differences in the incidence of adverse events among the groups of subjects: 66.7% (4 of 6 subjects) in subjects with normal renal function, 66.7% (4 of 6 subjects) in subjects with mild renal impairment, 50.0% (3 of 6 subjects) in subjects with moderate renal impairment, 50.0% (3 of 6 subjects) in subjects with severe renal impairment, and 66.7% (4 of 6 subjects) in subjects with ESRD. Grade 3 or higher laboratory abnormalities occurred in 4 subjects (blood creatinine increased in 4 subjects [1 subject with normal renal function, 3 subjects with severe renal impairment], blood glucose increased in 1 subject with severe renal impairment, lipase increased in 1 subject with ESRD, including multiple events in the same subjects. In all 3 subjects with severe renal impairment who had blood creatinine increased, Grade 3 or 4 blood creatinine increased was detected at screening. The finding of blood glucose increased or lipase increased was not associated with clinical symptoms. No deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported in any subject group. Based on the above, there should be no differences in the safety and tolerability of a single 400 mg dose of SOF between the severities of renal impairment.

In post-marketing experience out of Japan (December 6, 2013 through December 10, 2014), 70 adverse events were reported in patients with severe renal impairment or ESRD treated with SOF 400 mg (including patients on the triple regimen of SOF, RBV, and PegIFN[65)]). Adverse events reported by ≥3 patients were anaemia (10

63) Treatment-naïve patients with chronic hepatitis C (genotypes 1, 2, or 3) received SOF 400 mg in combination with PegIFN/RBV and the change from baseline in HCV RNA by genotype was 3.64 Log_{10}IU/mL for genotype 1; 3.62 Log_{10}IU/mL for genotype 2; and 3.47 Log_{10}IU/mL for genotype 3 [Study P7977-0523 (CTD5.3.5.1.6) and Study P7977-0221 (CTD5.3.4.2.1)].

64) Studies P7977-1231, GS-US-334-0107, GS-US-334-0108, and GS-US-334-0110.

65) The triple regimen of SOF, RBV, and PegIFN has been approved overseas for patients with genotype 1 HCV infection.

patients), renal failure (7 patients), blood creatinine increased (6 patients), hepatic encephalopathy (6 patients), acute kidney injury (5 patients), encephalopathy (4 patients), sepsis (4 patients), pancytopenia (3 patients), pneumonia (3 patients), and renal impairment (3 patients each). Serious adverse events were reported by 65 patients and there were 12 deaths with the following events including multiple events in the same patients: sepsis (3 patients); renal failure, bacteraemia, acute kidney injury, and hepatic cirrhosis (2 patients each); hepatic failure, hepatitis C, cardiac arrest, acute myeloid leukaemia, multi-organ disorder, encephalopathy, asphyxia, vomiting, oedema, renal impairment, lactic acidosis, circulatory collapse, completed suicide, cardiac failure, and hepatic encephalopathy, (1 patient each). The reported events are considered to be events that may be related to the underlying renal impairment or complications or known adverse events associated with coadministered PegIFN or RBV. However, there has so far been little clinical experience with SOF in patients with severe renal impairment or ESRD and the use of SOF is not recommended in these patients.

On the other hand, hematotoxicity such as neutrophil count decreased may occur following interferon (IFN)-containing therapy in chronic hepatitis C patients with renal impairment due to decreased creatinine clearance and it is difficult to treat such patients with existing therapies. Thus, the SOF+RBV regimen may become necessary in some patients. Taking account of this point, SOF may be used in patients with severe renal impairment or ESRD, but a precautionary statement should be included in the package insert so that SOF is used with caution in these patients. A clinical study to evaluate the safety, efficacy, and pharmacokinetics of SOF in combination with RBV in chronic hepatitis C (genotype 1) patients with or without cirrhosis who have severe renal impairment or ESRD[66)] is currently ongoing and the need for a further precautionary statement and the recommended dosing regimen for these patients will be determined after the study results become available.

PMDA considers as follows:
According to the foreign post-marketing safety information, multiple cases of serious adverse events and deaths were reported in patients with severe renal impairment or ESRD on SOF-containing regimen. Although a causal relationship of the adverse events reported in these patients to coadministered PegIFN or RBV etc., can not be ruled out, administration of SOF to patients with severe renal impairment or ESRD results in increased GS-331007 exposure, which may affect safety. Given this point, the safety of SOF 400 mg in patients with severe renal impairment or ESRD can not be assured at present. Therefore, SOF should be contraindicated in these patients.

RBV, which is combined with SOF, is also contraindicated in patients with chronic renal failure or renal impairment with creatinine clearance ≤50 mL/minute.

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66) Subjects were enrolled into one of the following cohorts (Target sample size of 10 per cohort).
Cohort 1: Chronic hepatitis C patients with or without cirrhosis who have severe renal impairment not requiring hemodialysis (eGFR <30 mL/min) receive SOF 200 mg in combination with RBV 200 mg QD for 24 weeks.
Cohort 2: Chronic hepatitis C patients with or without cirrhosis who have severe renal impairment not requiring hemodialysis (eGFR <30 mL/min) receive SOF 400 mg in combination with RBV 200 mg QD for 24 weeks.
Cohort 3: Chronic hepatitis C patients with or without cirrhosis who have ESRD requiring hemodialysis receive SOF 200 mg in combination with RBV 200 mg QD for 24 weeks.
Cohort 4: Chronic hepatitis C patients with or without cirrhosis who have ESRD requiring hemodialysis receive SOF 400 mg in combination with RBV 200 mg QD for 24 weeks.

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

4.(iii) Summary of clinical efficacy and safety

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

The results from a total of 6 studies (2 foreign phase I studies, 1 Japanese phase III study, 3 foreign phase III studies) as the efficacy and safety evaluation data and the results from a total of 13 studies (6 foreign phase I studies, 5 foreign phase II studies, 2 foreign phase III studies) as the reference data were submitted in support of the application. A summary of clinical studies submitted as the evaluation data is as shown in Table 18.

Table 18. Clinical studies (Evaluation data)

	Phase	Study Number	Study Population	Primary objectives	Number of subjects	Dosing regimen
Overseas	I	GS-US-334-0111	Japanese and Caucasian healthy adult subjects	PK Safety Tolerability	64	Single dose of SOF 200, 400, or 800 mg
Overseas	I	P7977-0613	Healthy adult subjects	QT/QTc	60	Single dose of SOF 400 or 1200 mg
Japan	III	GS-US-334-0118	Genotype 2 chronic hepatitis C patients with or without compensated cirrhosis (Treatment-naïve or treatment-experienced patients)	Efficacy Safety	153	12 weeks of SOF 400 mg QD + RBV
Overseas	III	P7977-1231	Genotype 2 or 3 chronic hepatitis C patients with or without compensated cirrhosis (Treatment-naïve patients)	Efficacy Safety	499	12 weeks of SOF 400 mg QD + RBV
Overseas	III	GS-US-334-0107	Genotype 2 or 3 chronic hepatitis C patients with or without compensated cirrhosis (Patients intolerant of, ineligible for, or unwilling to receive IFN)	Efficacy Safety	278	12 weeks of SOF 400 mg QD + RBV
Overseas	III	GS-US-334-0108	Genotype 2 or 3 chronic hepatitis C patients with or without compensated cirrhosis (patients who failed prior treatment with an IFN-based regimen)	Efficacy Safety	201	12 or 16 weeks of SOF 400 mg QD + RBV

4.(iii).A.(1) Phase I study (5.3.3.1.1, Study GS-US-334-0111 [April 2012 to November 2012])

An open-label study was conducted at 1 site in the US to investigate the pharmacokinetics, safety, and tolerability of SOF or SOF/ledipasvir (NS5A inhibitor, unapproved in Japan) fixed-dose combination tablet (FDC tablet) in healthy adult subjects (Target sample size, 32 Japanese and 32 Caucasian subjects) [see "4.(ii).A.(1).1) Foreign phase I single-dose study in Japanese and Caucasian healthy adult subjects" for pharmacokinetic data].

Single oral doses of SOF 200, 400, or 800 mg or the FDC tablet of SOF 400 mg and ledipasvir 90 mg were to be administered in the fasted state.

All of 64 subjects who received study drug (8 Japanese and 8 Caucasian subjects per group) were included in the Safety Analysis Set.

Adverse events occurred in 2 subjects in the 200 mg group (0 Japanese subjects, 2 Caucasian subjects [muscle strain, headache, and premenstrual syndrome (1 subject each)] including multiple events in one subject), in 5 subjects in the 400 mg group (3 Japanese subjects [back pain, tendonitis, and erythema (1 subject each)], 2 Caucasian subjects [tooth infection and contusion (1 subject each)]), in 1 subject in the 800 mg group (0 Japanese subjects, 1 Caucasian subject [back pain]), and in 3 subjects in the FDC tablet group (2 Japanese subjects [presyncope and dysmenorrhoea (1 subject each)], 1 Caucasian subject [muscle spasms and headache (1 subject each)] including multiple events in one subject), of which tendonitis was assessed as causally related to study drug, and the outcome was reported as "resolving."

There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

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

4.(iii).A.(2).1) Japanese phase III study (5.3.5.2.1, Study GS-US-334-0118 [June 2013 to March 2014])

An open-label, uncontrolled study was conducted at 20 sites in Japan to investigate the efficacy and safety of the SOF+RBV regimen in chronic hepatitis C patients with or without compensated cirrhosis[67] (genotype 2) (Target sample size, 84 treatment-naïve patients[68] and 50 treatment-experienced patients[69]).

SOF 400 mg QD in combination with weight-based (600 mg/day [body weight ≤60 kg], 800 mg/day [body weight >60 kg and ≤80 kg], or 1000 mg/day [body weight >80 kg] in two divided doses) RBV (brand name, Copegus Tablet 200 mg) was to be administered orally after a meal for 12 weeks.

[redacted][70]

The primary endpoint of the SVR12[71] rate was 96.4% (135 of 140 subjects) in the overall population, 97.6% (81 of 83 subjects) in the treatment-naïve patients, and 94.7% (54 of 57 subjects) in the treatment-experienced patients. The SVR12 rate [95% CI] in the non-cirrhotic treatment-naïve patients with chronic hepatitis C was 97.3% (73 of 75 subjects) [90.7%, 99.7%] and the lower bound of the 95% confidence interval was greater than

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67) Diagnosed by either liver biopsy (a Metavir score of 4 or Ishak score ≥5, etc.) or Fibroscan (>12.5 kPa).

68) Patients naïve to IFN, RBV, and other anti-HCV agents.

69) Patients previously treated with IFN who met any of the following conditions.
(1) Patient received ≤12 weeks of treatment with IFN and then discontinued due to adverse drug reactions etc.
(2) Patient failed to achieve undetectable HCV RNA levels on treatment with IFN.
(3) Patient achieved undetectable HCV RNA levels during or within 4 weeks after treatment with IFN, but failed to achieve SVR.

70) Since submission of the investigator's brochure (revised version) and protocol (revised version) to the investigator and the head of medical institution was delayed at 2 trial sites, 13 subjects enrolled at these 2 sites were excluded from the analysis populations.

71) The proportion of subjects with HCV RNA < LLOQ at 12 weeks after the end of treatment.
Since a high concordance between SVR12 and SVR24 has been reported (Chen J, et al. *Gastroenterology*. 2013;144:1450-1455), SVR12 rate was chosen as the primary endpoint. The US FDA Guidance (draft), which was released after the initiation of the study, recommends that the primary endpoint should be SVR12 (FDA Guidance for industry, Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Drugs for Treatment, Draft Guidance, 2013).

the adjusted historical null rate (69%[72]), demonstrating the efficacy of SOF+RBV. In the full analysis set (FAS), the SVR12 rate was 96.7% (148 of 153 subjects) in the overall population, 97.8% (88 of 90 subjects) in the treatment-naïve patients, and 95.2% (60 of 63 subjects) in the treatment-experienced patients.

The incidence of adverse events (including abnormal changes in laboratory values) was 75.0% (105 of 140 subjects) and the incidence of adverse drug reactions[73] (including abnormal changes in laboratory values) was 43.6% (61 of 140 subjects). Adverse events (including abnormal changes in laboratoryvalues) reported in ≥5% of subjects were nasopharyngitis (43 subjects [30.7%]), anaemia (16 subjects [11.4%]), headache (14 subjects [10.0%]), malaise (11 subjects [7.9%]), pruritus (9 subjects [6.4%]), constipation (7 subjects [5.0%]), and nausea (7 subjects [5.0%]). Adverse drug reactions reported in ≥5% of subjects were anaemia (16 subjects [11.4%]) and headache (7 subjects [5.0%]).

No deaths were reported. Serious adverse events occurred in 2 subjects (allergy to arthropod sting, and anaemia [1 subject each]), of which anaemia was assessed as related to study drug, but the outcome was reported as resolved. No adverse events leading to study drug discontinuation were reported.

In the 13 subjects excluded from the Safety Analysis Set, the incidence of adverse events was 54% (7 of 13 subjects) and those reported by ≥2 subjects were nasopharyngitis, hyperuricaemia, and anaemia (2 subjects each). There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

4.(iii).A.(2).2) Foreign phase III study (5.3.5.1.1, Study P7977-1231 [December 2011 to April 2013])

A randomized, open-label, active-controlled, parallel-group study[74] was conducted at a total of 90 sites in 7 countries including the US, Australia, and New Zealand to investigate the efficacy and safety of the SOF+RBV regimen compared to PegIFNα-2a+RBV in treatment-naïve[75] chronic hepatitis C patients with or without compensated cirrhosis[76] (genotype 2 or 3) (Target sample size of 500, 250 subjects each in the SOF/RBV and PegIFN/RBV groups).

Subjects in the SOF/RBV group were to be orally treated with SOF 400 mg QD in combination with weight-based (1000 mg/day [body weight ≤75 kg] or 1200 mg/day [body weight >75 kg] in two divided doses) RBV (brand name, Ribasphere) for 12 weeks and subjects in the PegIFN/RBV group were to be orally treated with PegIFNα-2a[77] in combination with RBV 400 mg BID for 24 weeks.

Of 527 randomized subjects, 499 subjects received the study drug (256 subjects in the SOF/RBV group, 243

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72) The adjusted historical null rate was based on the expected historical SVR rate for noncirrhotic, treatment-naïve Japanese patients with chronic hepatitis C (genotype 2) receiving 24 weeks of PegIFN/RBV (Watanabe T, et al. *Hepatol Res*. 2011;41(8):722-730, Inoue Y, et al. *J Viral Hepat*. 2010;17(5):336-344, Kanda T, et al. *Dig Dis Sci*. 2011;56(11):3335-3342) and a discount in efficacy due to an expected improved safety profile and shorter treatment duration.

73) Adverse events assessed by the investigators (sub-investigators) as related to study drug.

74) The subjects were stratified by HCV genotype (2 vs. 3), HCV RNA level screening at screening (<6 $\log_{10}$ IU/mL vs. ≥6 $\log_{10}$ IU/mL), and compensated cirrhosis at screening (presence vs. absence) and randomized in a 1:1 ratio to the SOF/RBV or PegIFN/RBV group.

75) Patients naïve to all HCV antiviral therapies, including but not limited to immunomodulatory and nucleoside/tide therapies for chronic HCV infection.

76) Diagnosed by liver biopsy, transient elastography (>12.5 kPa), or Fibrosure score >0.75 with APRI score >2.

77) PegIFNα-2a (Genetical Recombination) 180 μg was to be subcutaneously administered once weekly.

subjects in the PegIFN/RBV group) and were included in the Safety Analysis Set and 496 subjects excluding 3 subjects who were found to have genotype 1 HCV infection at screening (253 subjects in the SOF/RBV group, 243 subjects in the PegIFN/RBV group) were included in the FAS and the FAS was used for efficacy analyses.

The primary endpoint of the SVR12 rate was as shown in Table 19. The difference in the SVR12 rate [95% CI] between the treatments was 0.3% [-7.5%, 8.0%] and the lower bound of the 95% confidence interval was greater than the pre-specified non-inferiority margin (-15%[78)]), therefore establishing the non-inferiority of the SOF+RBV regimen to the PegIFN+RBV regimen.

Table 19. SVR12 rate (FAS)

	SOF/RBV	PegIFN/RBV
SVR12 rate	67.2 (170/253) [b)]	66.7 (162/243) [c)]
Between-group difference [95% CI] [a)]	0.3 [-7.5, 8.0]	

% (n/N)

a) Cochran-Mantel-Haenszel test stratified by HCV genotype (2 vs. 3), screening HCV RNA levels (<6 $\log_{10}$ IU/mL vs. ≥6 $\log_{10}$ IU/mL), and compensated cirrhosis (presence vs. absence).

b) SVR12 rate by genotype: 97.1% (68 of 70 subjects) for genotype 2 and 55.7% (102 of 183 subjects) for genotype 3.

c) SVR12 rate by genotype: 77.6% (52 of 67 subjects) for genotype 2 and 62.5% (110 of 176 subjects) for genotype 3.

The incidences of adverse events (including abnormal changes in laboratory values) were 85.9% (220 of 256 subjects) in the SOF/RBV group and 95.9% (233 of 243 subjects) in the PegIFN/RBV group. The incidences of adverse drug reactions[73)] (including abnormal changes in laboratory values) were 71.5% (183 of 256 subjects) in the SOF/RBV group and 93.8% (228 of 243 subjects) in the PegIFN/RBV group. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in either group were as shown in Table 20.

Table 20. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in either group

Event term	Adverse events		Adverse drug reactions	
	SOF/RBV (N = 256)	PegIFN/RBV (N = 243)	SOF/RBV (N = 256)	PegIFN/RBV (N = 243)
Any event	220 (85.9)	233 (95.9)	183 (71.5)	228 (93.8)
Fatigue	92 (35.9)	134 (55.1)	86 (33.6)	131 (53.9)
Headache	64 (25.0)	108 (44.4)	54 (21.1)	102 (42.0)
Nausea	46 (18.0)	70 (28.8)	42 (16.4)	65 (26.7)
Insomnia	31 (12.1)	70 (28.8)	28 (10.9)	65 (26.7)
Rash	23 (9.0)	43 (17.7)	21 (8.2)	39 (16.0)
Diarrhoea	23 (9.0)	42 (17.3)	15 (5.9)	32 (13.2)
Irritability	25 (9.8)	40 (16.5)	20 (7.8)	39 (16.0)
Decreased appetite	17 (6.6)	44 (18.1)	16 (6.3)	40 (16.5)
Myalgia	21 (8.2)	40 (16.5)	14 (5.5)	36 (14.8)
Pruritus	19 (7.4)	42 (17.3)	18 (7.0)	40 (16.5)
Dizziness	27 (10.5)	33 (13.6)	25 (9.8)	29 (11.9)
Influenza like illness	7 (2.7)	44 (18.1)	5 (2.0)	44 (18.1)
Arthralgia	15 (5.9)	35 (14.4)	9 (3.5)	31 (12.8)
Chills	7 (2.7)	43 (17.7)	4 (1.6)	39 (16.0)
Anaemia	20 (7.8)	28 (11.5)	20 (7.8)	28 (11.5)
Depression	14 (5.5)	34 (14.0)	9 (3.5)	32 (13.2)
Cough	19 (7.4)	21 (8.6)	12 (4.7)	15 (6.2)
Vomiting	17 (6.6)	23 (9.5)	8 (3.1)	17 (7.0)
Pyrexia	6 (2.3)	33 (13.6)	1 (0.4)	30 (12.3)
Dyspnoea	18 (7.0)	20 (8.2)	17 (6.6)	18 (7.4)
Pain	5 (2.0)	30 (12.3)	5 (2.0)	28 (11.5)
Alopecia	12 (4.7)	21 (8.6)	8 (3.1)	21 (8.6)
Dry skin	11 (4.3)	22 (9.1)	11 (4.3)	21 (8.6)
Neutropenia	0	30 (12.3)	0	30 (12.3)
Back pain	9 (3.5)	20 (8.2)	4 (1.6)	10 (4.1)
Anxiety	11 (4.3)	16 (6.6)	9 (3.5)	13 (5.3)

78) The treatment benefit of PegIFN (M1, 70%) was estimated from the difference between the expected SVR rate with 24 weeks of PegIFN/RBV (Shiffman ML, et al. *N Eng J Med*. 2007;357(2):124-134, Lagging M, et al. *Hepatology*. 2008;47(6):1837-1845, Nelson DR, et al. *Gastroenterology*. 2010;139(4):1267-1276) and the expected SVR rate with RBV alone (Brok J, et al. *Am J Gastroenterol*. 2006;101(4):842-847) in patients with chronic hepatitis C (genotypes 2 or 3) and a non-inferiority margin of 15% was selected to preserve at least 50% of M1.

Event term	Adverse events		Adverse drug reactions	
	SOF/RBV (N = 256)	PegIFN/RBV (N = 243)	SOF/RBV (N = 256)	PegIFN/RBV (N = 243)
Any event	220 (85.9)	233 (95.9)	183 (71.5)	228 (93.8)
Dry mouth	10 (3.9)	14 (5.8)	10 (3.9)	13 (5.3)
Oropharyngeal pain	14 (5.5)	10 (4.1)	3 (1.2)	3 (1.2)
Thrombocytopenia	0	23 (9.5)	0	23 (9.5)
Nasopharyngitis	13 (5.1)	5 (2.1)	1 (0.4)	2 (0.8)
Injection site reaction	0	17 (7.0)	0	17 (7.0)
Injection site erythema	0	14 (5.8)	0	14 (5.8)

n (%)

One death occurred in the SOF/RBV group (toxicity to various agents [cocaine and heroin intoxication]), which was assessed as probably unrelated to study drug. Serious adverse events occurred in 7 subjects in the SOF/RBV group (allergy to arthropod sting; anaemia, cellulitis; chest pain, chronic obstructive pulmonary disease, osteomyelitis chronic, toxicity to various agents, and urinary tract infection [1 subject each] including multiple events in the same subjects) and 3 subjects in the PegIFN/RBV group (atrioventricular block, breast cancer in situ, clavicle fracture, infection, pneumothorax, and rib fracture [1 subject each] including multiple events in the same subjects), of which anaemia was assessed as related to study drug and the outcome was reported as resolved.

Adverse events leading to study drug discontinuation occurred in 3 subjects in the SOF/RBV group (depression, abnormal dreams, agitation, apathy, blood creatine phosphokinase increased, chest pain, decreased appetite, and weight decreased [1 subject each] including multiple events in the same subjects) and 29 subjects in the PegIFN/RBV group (fatigue [6 subjects]; depression, anaemia [4 subjects each]; insomnia, nausea [3 subjects each]; alanine aminotransferase [ALT] increased, anxiety, haemoglobin decreased, irritability, loss of consciousness, neutropenia, pain, platelet count decreased, [2 subjects each]; anger, arthralgia, arthropathy, aspartate aminotransferase [AST] increased, asthenia, blood alkaline phosphatase [ALP] increased, feeling abnormal, leukopenia, malaise, mood altered, mood swings, myalgia, neuropathy peripheral, neutrophil count decreased, oropharyngeal discomfort, pain of skin, palpitations, rash, retinal exudates, retinal haemorrhage, skin burning sensation, skin reaction, tachycardia, and white blood cell count decreased [1 subject each] including multiple events in the same subjects). All those events except for blood creatine phosphokinase increased (1 subject) and chest pain (1 subject) in the SOF/RBV group and insomnia (1 subject), arthropathy (1 subject) and AST increased (1 subject) in the PegIFN/RBV group were assessed as related to study drug and the outcome was reported as "resolved" except for decreased appetite (1 subject) and weight decreased (1 subject) in the SOF/RBV group and fatigue (2 subjects), depression (2 subjects), anxiety (1 subject), and neuropathy peripheral (1 subject) in the PegIFN/RBV group including multiple events in the same subjects.

4.(iii).A.(2).3) Foreign phase III study (5.3.5.1.2, Study GS-US-334-0107 [March 2012 to February 2013])

A placebo-controlled, randomized, double-blind, parallel-group study[79)] was conducted at a total of 54 sites in 4 countries including the US, Canada, and Australia to investigate the efficacy and safety of the SOF+RBV

79) The subjects were stratified by compensated cirrhosis at screening (presence vs. absence) and randomized in a 3:1 ratio to the SOF/RBV or placebo group.

regimen in chronic hepatitis C patients with or without compensated cirrhosis[76] (genotype 2 or 3) who were IFN-intolerant,[80] IFN-ineligible,[81] or unwilling to receive IFN[82] (Target sample size of 240, 180 subjects in the SOF/RBV group and 60 subjects in the placebo group).

Subjects in the SOF/RBV group were to be orally treated with SOF 400 mg QD in combination with weight-based (1000 mg/day [body weight ≤75 kg] or 1200 mg/day [body weight >75 kg] in two divided doses) RBV (brand name, Ribasphere) for 12 weeks and subjects in the placebo group were to be orally treated with SOF placebo in combination with RBV placebo for 12 weeks.

Of 280 randomized subjects, 278 subjects received study drug (207 subjects in the SOF/RBV group, 71 subjects in the placebo group) and were included in the FAS and in the Safety Analysis Set and the FAS was used for efficacy analyses.

The primary endpoint of the SVR12 rate was as shown in Table 21 and the difference [95% CI] between treatments was 77.3% [71.0%, 83.6%], therefore establishing the superiority of the SOF+RBV regimen over placebo ($P < 0.001$, Cochran-Mantel-Haenszel test stratified by compensated cirrhosis status).

Table 21. SVR12 rate (FAS)

	SOF/RBV	Placebo
SVR12 rate	77.8 (161/207) [b]	0 (0/71)
Between-group difference [95% CI] [a]	77.3 [71.0, 83.6]	
P-value [a]	<0.001	

% (n/N)
a) Cochran-Mantel-Haenszel test stratified by compensated cirrhosis status
b) SVR12 rate by genotype: 92.7% (101 of 109 subjects) for genotype 2 and 61.2% (60 of 98 subjects) for genotype 3.

The incidences of adverse events (including abnormal changes in laboratory values) were 89.4% (185 of 207 subjects) in the SOF/RBV group and 77.5% (55 of 71 subjects) in the placebo group. The incidences of adverse drug reactions[73] (including abnormal changes in laboratoryvalues) were 72.5% (150 of 207 subjects) in the SOF/RBV group and 56.3% (40 of 71 subjects) in the placebo group. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in either group were as shown in Table 22.

Table 22. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in either group

Event term	Adverse events		Adverse drug reactions	
	SOF/RBV (N = 207)	Placebo (N = 71)	SOF/RBV (N = 207)	Placebo (N = 71)
Any event	185 (89.4)	55 (77.5)	150 (72.5)	40 (56.3)
Fatigue	91 (44.0)	17 (23.9)	82 (39.6)	12 (16.9)
Nausea	46 (22.2)	13 (18.3)	37 (17.9)	10 (14.1)
Headache	43 (20.8)	14 (19.7)	30 (14.5)	12 (16.9)
Insomnia	39 (18.8)	3 (4.2)	33 (15.9)	3 (4.2)
Pruritus	23 (11.1)	6 (8.5)	15 (7.2)	6 (8.5)
Rash	18 (8.7)	6 (8.5)	14 (6.8)	5 (7.0)
Dizziness	19 (9.2)	5 (7.0)	13 (6.3)	5 (7.0)
Diarrhoea	19 (9.2)	4 (5.6)	13 (6.3)	1 (1.4)
Decreased appetite	7 (3.4)	7 (9.9)	7 (3.4)	6 (8.5)
Anaemia	27 (13.0)	0	26 (12.6)	0
Vomiting	11 (5.3)	5 (7.0)	8 (3.9)	2 (2.8)
Anxiety	13 (6.3)	4 (5.6)	8 (3.9)	1 (1.4)

80) Patient having received ≤12 weeks of treatment with IFN and then discontinued due to adverse drug reactions, etc.
81) Patient considered ineligible for treatment with IFN due to age or comorbidities such as autoimmune disorders, psychiatric disease, epilepsy, thyroid disease, retinal disease, and diabetes.
82) Patient having medical records of his/her decision to decline an IFN-based therapy ≥3 months prior to signing the informed consent.

Event term	Adverse events		Adverse drug reactions	
	SOF/RBV (N = 207)	Placebo (N = 71)	SOF/RBV (N = 207)	Placebo (N = 71)
Any event	185 (89.4)	55 (77.5)	150 (72.5)	40 (56.3)
Dyspnoea	19 (9.2)	1 (1.4)	14 (6.8)	1 (1.4)
Irritability	19 (9.2)	1 (1.4)	14 (6.8)	1 (1.4)
Arthralgia	16 (7.7)	1 (1.4)	10 (4.8)	0
Depression	15 (7.2)	1 (1.4)	9 (4.3)	1 (1.4)
Abdominal pain	6 (2.9)	4 (5.6)	3 (1.4)	1 (1.4)
Cough	11 (5.3)	2 (2.8)	7 (3.4)	1 (1.4)
Oedema peripheral	5 (2.4)	4 (5.6)	2 (1.0)	1 (1.4)
Oropharyngeal pain	5 (2.4)	4 (5.6)	2 (1.0)	1 (1.4)

n (%)

No deaths were reported. The following serious adverse events occurred including multiple events in the same subject: in 11 subjects in the SOF/RBV group, abdominal abscess, abnormal behaviour, cellulitis, drug withdrawal syndrome, eczema, fall, hepatic neoplasm malignant, hypersensitivity, hypoglycaemia, injury, non-cardiac chest pain, oedema peripheral, overdose, pyrexia, road traffic accident, and spinal compression fracture (1 subject each); and in 2 subjects in the placebo group, bile duct stone, bronchitis, and pancreatitis (1 subject each). Of these events, oedema peripheral and eczema (1 subject each) in the SOF/RBV group were assessed as related to study drug and the outcome was reported as resolved.

The following adverse events leading to study drug discontinuation occurred including multiple events in the same subject: in 5 subjects in the SOF/RBV group, abdominal pain upper, anaemia, anxiety, chest discomfort, injury, insomnia, muscle spasms, and road traffic accident (1 subject each); and in 3 subjects in the placebo group, ALT increased, oedema peripheral, rash, and pancreatitis (1 subject each). Of these events, anaemia and insomnia (1 subject each) in the SOF/RBV group and oedema peripheral and rash (1 subject each) in the placebo group were assessed as related to study drug and the outcome was reported as resolved except for insomnia (1 subject) in the SOF/RBV group and oedema peripheral and rash (1 subject each) in the placebo group.

4.(iii).A.(2).4) Foreign phase III study (5.3.5.1.3, Study GS-US-334-0108 [June 2012 to May 2013])

A randomized, double-blind, parallel-group study[83] was conducted at a total of 57 sites in 3 countries of the US, Canada, and New Zealand to investigate the efficacy and safety of the SOF+RBV regimen in chronic hepatitis C patients with or without compensated cirrhosis[84] (genotype 2 or 3) who failed to respond to prior treatment with an IFN-based regimen[85] (Target sample size of 200, 100 subjects each in the 12-week and 16-week treatment groups).

Subjects in the 12-week treatment group were to orally receive 12 weeks of SOF 400 mg QD + weight-based (1000 mg/day [body weight ≤75 kg] or 1200 mg/day [body weight >75 kg] in two divided doses) RBV (brand name, Ribasphere), followed by 4 weeks of matching placebo and subjects in the 16-week group were to orally receive 16 weeks of SOF 400 mg QD + RBV.

83) The subjects were stratified by compensated cirrhosis at screening (presence vs. absence) and HCV genotype (2 vs. 3) and randomized in a 1:1 ratio to the 12-week or 16-week treatment group.

84) Diagnosed by (1) liver biopsy, (2) Fibroscan (>12.5 kPa), or (3) Fibrosure score >0.75 and APRI score >2.

85) Of patients having received ≥12 weeks of treatment with an IFN-based regimen, those who failed to achieve undetectable HCV RNA levels or those with HCV RNA detected after once achieving undetectable HCV RNA levels.

Of 202 randomized subjects, 201 subjects received study drug (103 subjects in the 12-week group, 98 subjects in the 16-week group) and were included in the Safety Analysis Set and 195 subjects (100 subjects in the 12-week group, 95 subjects in the 16-week group), excluding 6 subjects who were found to have genotype 1 HCV infection after receiving study drug, were included in the FAS and the FAS was used for efficacy analyses.

The primary endpoint of the SVR12 rate was as shown in Table 23 and the lower bound of the 95% confidence interval for both groups was greater than the pre-specified historical control rate (25%[86)]), demonstrating their efficacy. The difference between the 12-week and 16-week groups was -23.4% [-35.4%, -11.4%].

Table 23. SVR12 rate (FAS)

	12-week treatment	16-week treatment
SVR12 rate	50.0 (50/100) [b)]	72.6 (69/95) [c)]
Between-group difference [95% CI] [a)]	-23.4 [-35.4,-11.4]	

% (n/N)
a) Cochran-Mantel-Haenszel test stratified by HCV genotype (2 vs. 3) and compensated cirrhosis (presence vs. absence)
b) SVR12 rate by genotype: 86.1% (31 of 36 subjects) for genotype 2 and 29.7% (19 of 64 subjects) for genotype 3.
c) SVR12 rate by genotype: 93.8% (30 of 32 subjects) for genotype 2 and 61.9% (39 of 63 subjects) for genotype 3.

The incidences of adverse events (including abnormal changes in laboratory values) were 89.3% (92 of 103 subjects) in the 12-week group and 87.8% (86 of 98 subjects) in the 16-week group. The incidences of adverse drug reactions[73)] (including abnormal laboratory changes) were 72.8% (75 of 103 subjects) in the 12-week group and 76.5% (75 of 98 subjects) in the 16-week group. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in either group were as shown in Table 24.

Table 24. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in either group

Event term	Adverse events		Adverse drug reactions	
Number of subjects	12-week treatment (N = 103)	16-week treatment (N = 98)	12-week treatment (N = 103)	16-week treatment (N = 98)
Any event	92 (89.3)	86 (87.8)	75 (72.8)	75 (76.5)
Fatigue	46 (44.7)	46 (46.9)	39 (37.9)	39 (39.8)
Headache	26 (25.2)	32 (32.7)	20 (19.4)	25 (25.5)
Insomnia	21 (20.4)	28 (28.6)	16 (15.5)	24 (24.5)
Nausea	22 (21.4)	20 (20.4)	17 (16.5)	17 (17.3)
Irritability	15 (14.6)	11 (11.2)	12 (11.7)	7 (7.1)
Cough	10 (9.7)	13 (13.3)	5 (4.9)	11 (11.2)
Diarrhoea	15 (14.6)	6 (6.1)	7 (6.8)	3 (3.1)
Arthralgia	11 (10.7)	9 (9.2)	8 (7.8)	7 (7.1)
Rash	7 (6.8)	12 (12.2)	5 (4.9)	11 (11.2)
Pruritus	12 (11.7)	7 (7.1)	10 (9.7)	7 (7.1)
Anxiety	8 (7.8)	9 (9.2)	1 (1.0)	4 (4.1)
Myalgia	8 (7.8)	9 (9.2)	7 (6.8)	7 (7.1)
Muscle spasms	8 (7.8)	8 (8.2)	5 (4.9)	5 (5.1)
Anaemia	11 (10.7)	4 (4.1)	11 (10.7)	4 (4.1)
Decreased appetite	9 (8.7)	5 (5.1)	7 (6.8)	2 (2.0)
Dyspnoea	8 (7.8)	5 (5.1)	8 (7.8)	5 (5.1)
Contusion	4 (3.9)	8 (8.2)	0	0
Depression	6 (5.8)	6 (6.1)	4 (3.9)	2 (2.0)
Dry skin	7 (6.8)	5 (5.1)	6 (5.8)	3 (3.1)
Abdominal pain	6 (5.8)	5 (5.1)	2 (1.9)	1 (1.0)
Dizziness	6 (5.8)	5 (5.1)	3 (2.9)	4 (4.1)
Upper respiratory tract infection	6 (5.8)	5 (5.1)	1 (1.0)	1 (1.0)
Back pain	5 (4.9)	5 (5.1)	1 (1.0)	0
Dysgeusia	3 (2.9)	6 (6.1)	3 (2.9)	6 (6.1)
Pain	4 (3.9)	5 (5.1)	3 (2.9)	2 (2.0)
Dyspepsia	6 (5.8)	3 (3.1)	4 (3.9)	3 (3.1)

86) The historical control rate was based on the SVR rate with 48 weeks of PegIFN/RBV in chronic hepatitis C (genotype 2 or 3) patients who failed IFN-based therapy (Poynard T, et al. *Gastroenterology*. 2009;136(5):1618-28 e2).

Event term	Adverse events		Adverse drug reactions	
Number of subjects	12-week treatment (N = 103)	16-week treatment (N = 98)	12-week treatment (N = 103)	16-week treatment (N = 98)
Any event	92 (89.3)	86 (87.8)	75 (72.8)	75 (76.5)
Constipation	2 (1.9)	5 (5.1)	0	1 (1.0)
Disturbance in attention	6 (5.8)	1 (1.0)	4 (3.9)	1 (1.0)

n (%)

No deaths were reported. The following serious adverse events occurred including multiple events in the same subjcts: in 5 subjects in the 12-week group, hepatic neoplasm malignant (3 subjects), abdominal pain, basal cell carcinoma, oesophageal varices haemorrhage, portal vein thrombosis, pyrexia, and upper limb fracture (1 subject each); and in 3 subjects in the 16-week group, non-cardiac chest pain, overdose, and suicide attempt (1 subject each). All of these events were assessed as unrelated to study drug. Adverse events leading to study drug discontinuation occurred in 1 subject in the 12-week group (abdominal pain and pyrexia), which were assessed as unrelated to study drug.

4.(iii).B Outline of the review

4.(iii).B.(1) Review strategy

Although the SOF+RBV regimen was studied in clinical studies submitted, RBV dosing recommendations are different in and out of Japan. Thus, PMDA decided to evaluate the efficacy and safety of this regimen, focusing on a Japanese phase III study (GS-US-334-0118) in which the same dosage regimen of RBV as approved in Japan was employed.

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

Based on the following considerations, PMDA concluded that the efficacy of the SOF+RBV regimen is expected in chronic hepatitis C patients with or without compensated cirrhosis (genotype 2).

However, as the information on resistance mutations obtained from clinical studies is limited, it is important to collect post-marketing information on resistance mutations to the SOF+RBV regimen, including the clinical course of patients after the end of treatment, and promptly provide the obtained findings to healthcare providers in medical settings.

The above conclusions by PMDA will be discussed at the Expert Discussion.

4.(iii).B.(2).1) Study design

PMDA asked the applicant to explain the appropriateness of employing an uncontrolled design for a Japanese phase III study (GS-US-334-0118).

The applicant explained as follows:

At the time of initiating the Japanese phase III study (June 2013), PegIFN alone or IFN-containing regimens such as PegIFN/RBV were recommended as treatment options for patients with chronic hepatitis C (genotype

2) in Japan,[87] but these regimens were considered inappropriate as a comparator for the following reasons.

● Since the majority of Japanese patients with chronic hepatitis C are elderly, many are ineligible for IFN.[81] Thus, in terms of feasibility, if PegIFN alone or an IFN-containing regimen such as PegIFN/RBV had been selected as a comparator, patient enrollment would not have been completed timely.

● Since the results from foreign phase III studies [see "4.(iii).A.(2) Phase III studies"] and an active-controlled clinical study of SOF+RBV vs. PegIFN+RBV,[88),89] which were available at the time of initiating the Japanese phase III study, revealed the outcomes of the SOF+RBV regimen, it was considered difficult to plan and conduct a controlled study using an IFN-containing regimen such as PegIFN/RBV as a comparator.

No Japanese clinical study investigating the efficacy of the PegIFN+RBV regimen in treatment-experienced chronic hepatitis C patients with or without compensated cirrhosis (genotype 2) has been reported and the optimal retreatment regimen for treatment-experienced patients with chronic hepatitis C (genotype 2) has not been established.

PMDA considers as follows:

At the time of initiating the Japanese phase III study, the efficacy and safety results in chronic hepatitis C patients with or without compensated cirrhosis (genotype 2) from Japanese and foreign clinical studies of PegIFN alone or in combination with RBV and from foreign clinical studies of the SOF+RBV regimen were available, which suggested, for the safety aspects, that the SOF+RBV regimen may be better tolerated than PegIFN alone or in combination with RBV and, for the efficacy aspects, that the SVR12 rate is expected to be higher with the SOF+RBV regimen compared to PegIFN alone or in combination with RBV. Taking account of these findings, in terms of feasibility, the applicant had no choice but to employ an uncontrolled design, instead of conducting an active-controlled, Japanese phase III study using an IFN-containing regimen such as PegIFN/RBV as a comparator.

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

The applicant explained the efficacy of the SOF+RBV regimen in chronic hepatitis C patients with or without compensated cirrhosis (genotype 2) as follows:

In a Japanese phase III study, the SVR12 rate [95% CI] in the non-cirrhotic treatment-naïve patients with chronic hepatitis C was 97.3% (73 of 75 subjects) [90.7%, 99.7%] and the lower bound of the 95% confidence interval was greater than the adjusted historical null rate (69%), which was based on the historical SVR rates with 24 weeks of PegIFN/RBV, demonstrating the efficacy of SOF. The SVR12 rate in the overall population (chronic hepatitis C patients with or without compensated cirrhosis [genotype 2]) was 96.4% (135 of 140 subjects)

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87) Drafting Committee for Hepatitis Management Guidelines, Japan Society of Hepatology ed. *Guidelines for the Management of Hepatitis C Virus Infection (First Edition)*, 2012

88) In a foreign phase III study in treatment-naïve patients with chronic hepatitis C (genotype 2) (P7977-1231), the SVR12 rates were 97.1% in the SOF/RBV group and 77.6% in the PegIFN/RBV group. The SVR24 rates with PegIFN/RBV combination therapy in treatment-experienced patients with chronic hepatitis C (genotype 2) have been reported to be approximately 50% (Oze T, et al. *J Gastroenterol*. 2011;46(8):1031-1037, Kanda T, et al. Dig Dis Sci. 2011;56(11):3335-3342).

89) In Study P7977-1231, the incidences of overall adverse events (including laboratory abnormalities) were 85.9% in the SOF/RBV group and 95.9% in the PegIFN/RBV group. The incidences of adverse events leading to study drug discontinuation were 1.2% in the SOF/RBV group and 11.9% in the PegIFN/RBV group. The incidences of Grade 3 or higher laboratory abnormalities were 14.2% in the SOF/RBV group and 40.9% in the PegIFN/RBV group.

(97.6% [81 of 83 subjects] in the treatment-naïve patients, 94.7% [54 of 57 subjects] in the treatment-experienced patients) [see "4.(iii).A.(2).1) Japanese phase III study"], demonstrating the efficacy of the SOF+RBV regimen in these patients. The SVR24 rate in the overall population was 96.4% (135 of 140 subjects).

The results of subgroup analyses were as shown in Table 25 Table 25and the SVR12 rate was ≥90% in most subgroups.

Table 25. SVR12 rates in subgroups (Efficacy analysis set)

Patient characteristics		SVR12		
		Treatment-naïve (N = 83)	Treatment-experienced (N = 57)	Overall (N = 140)
Overall		81/83 (97.6)	54/57 (94.7)	135/140 (96.4)
Age	<65 years	68/69 (98.6)	37/39 (94.9)	105/108 (97.2)
	≥65 years	13/14 (92.9)	17/18 (94.4)	30/32 (93.8)
Cirrhosis	No	73/75 (97.3)	48/50 (96.0)	121/125 (96.8)
	Yes	8/8 (100)	6/7 (85.7)	14/15 (93.3)
IFN eligibility	IFN-eligible	69/71 (97.2)	—	—
	IFN-ineligible	5/5 (100)	—	—
	Unwilling to take IFN	7/7 (100)	—	—
Response to prior treatment	Nonresponse [a)]	—	13/13 (100)	—
	Relapse/breakthrough [b)]	—	38/41 (92.7)	—
	IFN-intolerant [c)]	—	3/3 (100)	—
HCV RNA level	<5 Log_{10} IU/ml	12/12 (100)	1/1 (100)	13/13 (100)
	≥5 Log_{10} IU/ml	69/71 (97.2)	53/56 (94.6)	122/127 (96.1)
IL28B	CC	68/69 (98.6)	41/43 (95.3)	109/112 (97.3)
	Non CC	13/14 (92.9)	13/14 (92.9)	26/28 (92.9)

n/N (%)
a) Patient did not achieve undetectable HCV RNA levels on treatment with IFN.
b) Patient achieved undetectable HCV RNA levels during treatment with IFN or within 4 weeks after treatment, but did not achieve SVR.
c) Patient completed ≤12 weeks of treatment with IFN and discontinued treatment due to adverse drug reactions, etc.

PMDA considers as follows:

In the Japanese phase III study, the SVR12 rate [95% CI] in the non-cirrhotic treatment-naïve patients with chronic hepatitis C was 97.3% (73 of 75 subjects) [90.7%, 99.7%] and the lower bound of the 95% confidence interval was greater than the adjusted historical null rate (69%) [see "4.(iii).A.(2).1) Japanese phase III study"]. Thus, it can be concluded that the efficacy of the SOF+RBV regimen was demonstrated. Since the SVR12 rates [95% CI] with the SOF+RBV regimen were 94.7% (54 of 57 subjects) [85.4%, 98.9%] in the treatment-experienced patients and 93.3% (14 of 15 subjects) [68.1%, 99.8%] in the patients with chronic hepatitis C and compensated cirrhosis, the efficacy of the SOF+RBV regimen is expected in these patients.

4.(iii).B.(2).3) Viral resistance mutations

The applicant explained the emergence of SOF-resistant variants and the impact of resistant variants on the efficacy of the SOF+RBV regimen as follows:

In *in vitro* resistance selection experiments in replicon cells, the NS5B S282T substitution was detected in all replicon genotypes examined. Studies using S282T mutant replicon cells suggested that the S282T substitution confers decreased susceptibility to SOF [see "3.(i).A.(1).2) *In vitro* resistance selection"].

For patients who experienced virologic failure[90] in a Japanese phase III study (5 subjects), the NS5B region was deep-sequenced at baseline and at the timepoint of virologic failure. As a result, the S282T substitution or any other nucleotide NS5B polymerase inhibitor resistance-associated amino acid substitution (L159F and L320F)[91] was not detected.

One of 300 virologic failure subjects with NS5B sequences available[92] for foreign phase II and III studies[93] had a treatment-emergent S282T substitution. None of the treatment-emergent amino acid substitutions other than S282T showed a reduction in susceptibility to SOF or RBV. The correlations between amino acid substitutions in the NS5B region at baseline and treatment outcome were investigated.[94] As a result, none of the subjects had the S282T substitution at baseline and there were no correlations between the presence of any variant in the NS5B region at baseline and the efficacy of SOF-containing regimens.

PMDA considers as follows:
The S282T substitution, which has been suggested to be associated with reduced susceptibility to SOF, was detected in 1 subject in the foreign phase II and III studies. Although the S282T substitution or any other nucleotide NS5B polymerase inhibitor resistance-associated amino acid substitution was not detected in the Japanese phase III study, as the information obtained from clinical studies is limited, it is important to collect post-marketing information on resistance mutations in patients who have failed treatment with the SOF+RBV regimen, including their clinical course after the end of treatment, and promptly provide the obtained findings to healthcare providers in medical settings.

4.(iii).B.(3) Safety
PMDA conducted its safety review of the SOF+RBV regimen as shown in the following 1) to 4) and concluded as follows:
A precautionary statement about anemia-related events in the package insert is necessary. As there is limited clinical experience in Japanese IFN-ineligible, IFN-intolerant, and elderly patients, post-marketing information concerning use in these patients should be collected.

As long as physicians with adequate knowledge and experience in the treatment of viral liver disease perform periodic blood tests for monitoring and management of adverse events and take appropriate actions such as interruption/discontinuation of treatment, the SOF+RBV regimen is tolerable in chronic hepatitis C patients

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90) Subjects who met any of the following criteria.
- Nonresponse: HCV RNA level persistently ≥ LLOQ (25 IU/mL) through 8 weeks of treatment.
- Breakthrough: HCV RNA levels once dropped to< LLOQ, and then returned to ≥ LLOQ during the treatment.
- Rebound: >1 Log_{10}IU/mL increase in HCV RNA level from on-treatment nadir.
- Relapse: Although HCV RNA level achieved was < LLOQ at the end of treatment, HCV RNA level returned to ≥ LLOQ during the posttreatment period. .

91) Levin J, et al. *AASLD 2012*. 2012, Boston.

92) A patient with chronic hepatitis C (genotype 2b) who received SOF monotherapy. The patient relapsed at Week 4 post-treatment and S282T substitution was detected, but it was no longer detectable at Week 12 post-treatment by deep sequencing.

93) Five foreign phase II studies (P7977-0221, P7977-0422, P7977-0724, P7977-0523, P2938-0721) and 4 foreign phase III clinical studies (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

94) The NS5B region of subjects in foreign phase II and III studies (P7977-0422, P7977-0724, GS-US-334-0110, GS-US-334-0107, GS-US-334-0108, P7977-1231) was analyzed at baseline using population sequencing and the correlations between the pre-existence of NS5B substitutions at baseline and relapse at SVR4 or SVR12 time points were investigated.

with or without compensated cirrhosis (genotype 2).

The above conclusions by PMDA will be discussed at the Expert Discussion.

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

The applicant explained the safety of SOF+RBV in chronic hepatitis C patients with or without compensated cirrhosis (genotype 2) as follows:

In a Japanese phase III study, the incidence of adverse events was 75.0% (105 of 140 subjects). The incidence of Grade 3[95] or higher adverse events was 2.1% (3 of 140 subjects), the incidence of serious adverse events was 1.4% (2 of 140 subjects), and the incidence of adverse events leading to study drug dose reduction or interruption was 13.6% (19 of 140 subjects) or 1.4% (2 of 140 subjects), respectively, and there were no deaths or adverse events leading to treatment discontinuation.

Adverse events (including abnormal changes in laboratory values) reported in ≥5% of subjects were nasopharyngitis (43 subjects [30.7%]), anemia (16 subjects [11.4%]), headache (14 subjects [10.0%]), malaise (11 subjects [7.9%]), pruritus (9 subjects [6.4%]), constipation (7 subjects [5.0%]), and nausea (7 subjects [5.0%]). Adverse events leading to RBV dose reduction were anemia (14 subjects), hemoglobin decreased (4 subjects), dizziness (1 subject), and nausea (1 subject), including mulitiple events in the same subjects, and adverse events leading to RBV interruption were anemia (1 subject) and nasopharyngitis (1 subject). One subject had an adverse event leading to SOF interruption (nasopharyngitis). Adverse events occurred in all of 5 IFN-ineligible patients (anemia, and malaise [2 subjects each], nasopharyngitis, constipation, headache, arthralgia, back pain, pruritus, hot flush, asteatosis, acne, and spinal compression fracture [1 subject each], including multiple events in the same subjects), of which anemia (2 subjects) led to RBV dose reduction, but both cases were non-serious. One of 3 IFN-intolerant patients had adverse events (abdominal discomfort and anemia) and anemia led to RBV dose reduction, but both adverse events were non-serious.

In foreign phase III studies (P7977-1231, GS-US-334-0107, GS-US-334-0108), the incidence of adverse events with 12 weeks of SOF+RBV was 87.6% (496 of 566 subjects). The incidence of Grade 3 or higher adverse events was 7.2% (41 of 566 subjects), the incidence of serious adverse events was 3.9% (22 of 566 subjects), the incidence of adverse events leading to study drug dose reduction or interruption was 11.1% (63 of 566 subjects), the incidence of adverse events leading to treatment discontinuation was 1.6% (9 of 566 subjects), and the incidence of fatal adverse events was 0.2% (1 of 566 subjects).

Adverse events with an incidence of ≥5% were fatigue (229 subjects [40.5%]), headache (132 subjects [23.3%]), nausea (114 subjects [20.1%]), insomnia (91 subjects [16.1%]), pruritus (53 subjects [9.4%]), rash (48 subjects [8.5%]), anemia (58 subjects [10.2%]), irritability (58 subjects [10.2%]), diarrhoea (57 subjects [10.1%]), dizziness (52 subjects [9.2%]), dyspnoea (45 subjects [8.0%]), arthralgia (42 subjects [7.4%]), cough (39 subjects [6.9%]), myalgia (35 subjects [6.2%]), depression (34 subjects [6.0%]), decreased appetite (33 subjects

[95] The severity of adverse events was assessed using the Grading Scale for Severity of Adverse Events and Laboratory Abnormalities established by Gilead Sciences, Inc. (Omata M, et al. *J Viral Hepat*. 2014;21(11):762-768).

[5.8%]), vomiting (33 subjects [5.8%]), and anxiety (31 subjects [5.5%]). The main adverse event leading to RBV dose reduction or interruption was anemia (37 subjects [6.5%]). There were no adverse events leading to SOF interruption. Adverse events leading to study drug discontinuation (9 subjects) were anemia, abdominal pain, abdominal pain upper, chest discomfort, chest pain, pyrexia, injury, road traffic accident, blood creatine phosphokinase increased, weight decreased, decreased appetite, muscle spasms, depression, insomnia, anxiety, abnormal dreams, agitation, and apathy (1 subject each), including multiple events in the same subjects . Toxicity to various agents (cocaine and heroin intoxication) was a fatal adverse event (1 subject), which was assessed as unrelated to study drug.

PMDA considers as follows:
Based on the incidences of Grade 3 or higher adverse events and serious adverse events in the Japanese phase III and foreign clinical studies, the SOF+RBV regimen is tolerable. However, since anemia and hemoglobin decreased led to RBV dose reduction or interruption in some subjects, the details will be examined in the following section. The occurrence of hepatic dysfunction characteristically associated with other anti-HCV agents and safety in the elderly will also be examined in details in the following sections. Since there is limited clinical experience in Japanese patients who are ineligible for or intolerant of IFN, post-marketing information concerning use in these patients should be collected.

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

PMDA asked the applicant to explain the occurrence of anemia-related events associated with the SOF+RBV regimen.

The applicant explained as follows:
In a Japanese phase III study, the incidence of anemia-related events[96] was 15.7% (22 of 140 subjects; anemia [16 subjects], hemoglobin decreased [6 subjects], red blood cell count decreased, haematocrit decreased [0 subjects each]). When classified by severity, Grade 1 events occurred in 19 subjects (anemia [15 subjects], hemoglobin decreased [4 subjects]), Grade 2 events in 2 subjects (anemia and hemoglobin decreased [1 subject each]), and Grade 3 event in 1 subject (anemia), and no Grade 4 events were reported. The incidence of laboratory abnormalities in hemoglobin[97] was 40.7% (57 of 140 subjects) and when classified by severity, Grade 1 abnormalities occurred in 32 subjects, Grade 2 abnormalities in 20 subjects, and Grade 3 abnormalities in 5 subjects, and no Grade 4 abnormalities were reported.

Hemoglobin levels over time were as shown in Figure 2 and hemoglobin declined following the initiation of treatment and remained low throughout the treatment period, but returned to baseline levels at Week 4 post-

96) Anemia-related events were identified by the MedDRA preferred terms “anaemia” and “haemoglobin decreased”. No adverse events of “red blood cell count decreased” or “haematocrit decreased” were reported.

97) Based on hemoglobin values in the laboratory test results database, subjects with laboratory abnormalities in hemoglobin were identified using the following pre-defined criteria for severity of laboratory abnormalities.
Grade 1: absolute hemoglobin value (g/dL) of ≥10.0 and ≤10.9 or hemoglobin decrease from baseline of ≥2.5 and <3.5,
Grade 2: absolute hemoglobin value (g/dL) of ≥9.0 and <10.0 or hemoglobin decrease from baseline of ≥3.5 and <4.5,
Grade 3: absolute hemoglobin value (g/dL) of ≥7.0 and <9.0 or hemoglobin decrease from baseline of ≥4.5,
Grade 4: absolute hemoglobin value (g/dL) of <7.0.

treatment. The maximum hemoglobin change from baseline was greater in elderly subjects aged ≥ 65 years (-1.9 g/dL) than in non-elderly subjects aged <65 years (-1.3 g/dL).

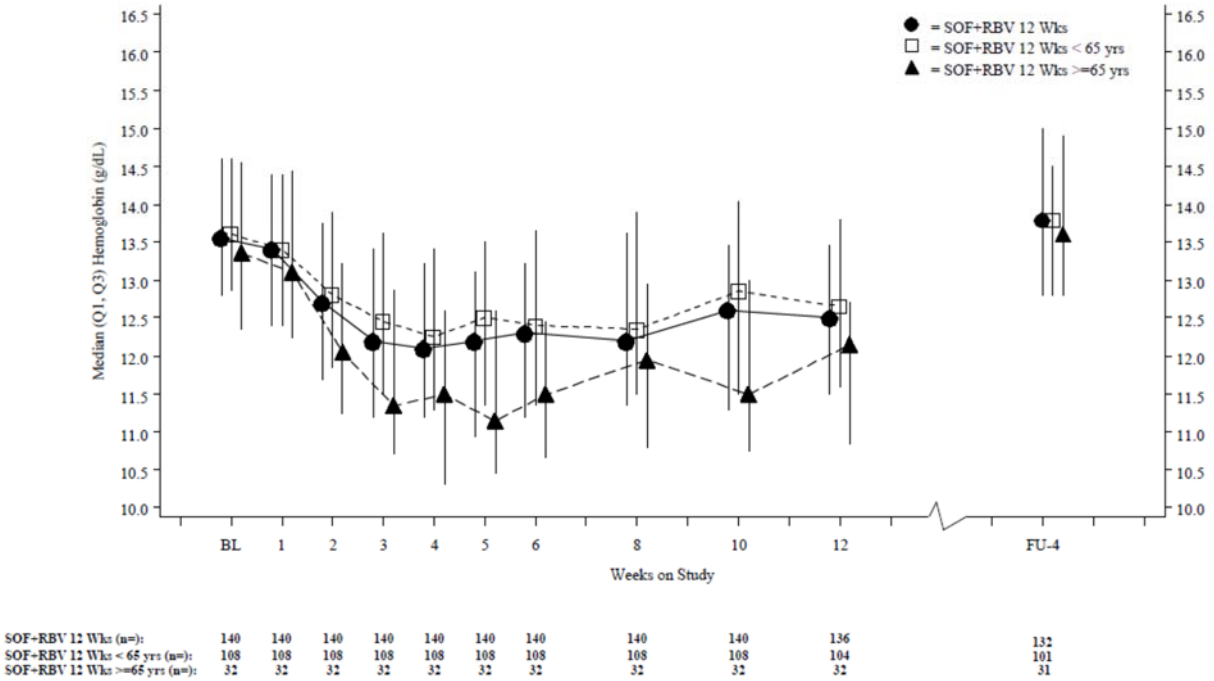

Figure 2. **Hemoglobin levels (median) over time (Japanese phase III study)**
Error bars represent the 25th to 75th percentile.

Two of 32 patients with Grade 1 abnormalities of hemoglobin decreased and 8 of 20 patients with Grade 2 abnormalities of hemoglobin decreased required RBV dose reduction[98] but none of the patients required RBV interruption. Of 5 patients with Grade 3 abnormalities of hemoglobin decreased, 4 patients required RBV dose reduction and 1 patient required RBV interruption. Following RBV dose reduction or interruption, all patients were able to complete the SOF+RBV regimen.

PMDA asked the applicant to explain the impact of RBV dose reduction or interruption on the efficacy of the SOF+RBV regimen.

The applicant explained as follows:
The SVR12 rates by RBV adherence[99] were 100% (7 of 7 subjects) in <80% adherence, 100% (9 of 9 subjects) in ≥80% to <90% adherence, and 96% (119 of 124 subjects) for subjects with ≥90% adherence. RBV adherence in the 5 patients who did not achieve SVR12 ranged from 93.7% to 100% while even patients with <90% adherence achieved SVR12. Therefore, RBV dose reduction or interruption is not considered to affect the efficacy of the SOF+RBV regimen.

PMDA considers as follows:
In the Japanese phase III study, RBV dose was reduced or interrupted in response to the occurrence of anemia-

98) RBV dose was to be reduced or interrupted in patients who developed anemia-related events in the Japanese phase III study, based on the RBV package insert for Japan [Copegus Tablet 200 mg package insert (14th edition, November 2013)].
99) Actual doses taken/doses planned at the start of treatment

related events. As a result, patients who developed anemia-related events were able to continue on the SOF+RBV regimen and it was confirmed that RBV dose reduction or interruption does not significantly affect SVR with the SOF+RBV regimen. As long as measures against anemia-related events are taken in medical settings including periodic blood tests to monitor hemoglobin values etc., and appropriate actions such as dose reduction and interruption upon the occurrence of anemia-related events, anemia-related events associated with the SOF+RBV regimen can be managed.

It is necessary to appropriately provide safety information concerning these events in order to ensure appropriate monitoring and actions by physicians with adequate knowledge and experience in the treatment of viral liver disease and to advise physicians to consult the RBV (Copegus Tablet 200 mg) package insert as well when treating patients.

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

Hepatic dysfunction has been reported with other anti-HCV agents. PMDA asked the applicant to explain the occurrence of hepatic dysfunction associated with SOF+RBV.

The applicant explained as follows:

In a Japanese phase III study, no hepatic function-related adverse events were reported except for hyperbilirubinaemia (2.9% [4 of 140 subjects]).

In these 4 subjects, hyperbilirubinaemia occurred between Days 8 and 15 and was assessed as related to study drug, and the outcome was reported as resolved. In any of these subjects, hyperbilirubinaemia was not associated with laboratory abnormalities (e.g. ALT increased, AST increased) or adverse events (e.g. increased bleeding, jaundice, encephalopathy) suggestive of hepatic dysfunction.

With respect to liver function test abnormalities of at least a 1-Grade exacerbation from baseline, the incidences of blood ALT increased,[100)] blood AST increased,[101)] blood ALP increased,[102)] and blood bilirubin total increased[103)] were 3.6% (5 of 140 subjects), 1.4% (2 of 140 subjects), 1.4% (2 of 140 subjects), and 23.6% (33 of 140 subjects), respectively, and Grade 3 or higher abnormality was blood bilirubin total increased in 1 subject (Grade 3).

Blood total bilirubin levels peaked during the first 1 to 2 weeks of treatment and then returned close to baseline levels at Week 3. Grade 3 or higher blood total bilirubin increased occurred on Day 8 and returned to baseline levels after the completion of study treatment. Although blood total bilirubin increased, other abnormal changes

100) Grade 1, blood ALT (IU/L) >1.25 to 2.50×ULN; Grade 2, blood ALT >2.50 to 5.00×ULN; Grade 3, blood ALT >5.00 to 10.00×ULN; Grade 4, blood ALT >10.00×ULN

101) Grade 1, blood AST (IU/L) >1.25 to 2.50×ULN; Grade 2, blood AST >2.50 to 5.00×ULN; Grade 3, blood AST >5.00 to 10.00×ULN; Grade 4, blood AST >10.00×ULN

102) Grade 1, blood ALP (IU/L) >1.25 to 2.50×ULN; Grade 2, blood ALP >2.50 to 5.00×ULN; Grade 3, blood ALP >5.00 to 10.00×ULN; Grade 4, blood ALP >10.00×ULN

103) Grade 1, total bilirubin (mg/dL) >1.0 to 1.5×ULN; Grade 2, total bilirubin >1.5 to 2.5×ULN; Grade 3, total bilirubin >2.5 to 5.0×ULN; Grade 4, total bilirubin >5.0×ULN

in other liver function tests (ALT or AST increased, etc.) were not found.

As described above, hyperbilirubinaemia (4 subjects) was reported as hepatic dysfunction-related adverse events and the most commonly reported liver function test abnormality was blood total bilirubin increased. The observed hyperbilirubinaemia or blood total bilirubin increased was not associated with other events or worsening of laboratory values suggestive of hepatic dysfunction, did not require dose adjustment of SOF or RBV or other action, and resolved during study treatment or after the completion of treatment.

Regarding the cause for the observed hepatic dysfunction associated with SOF+RBV, it has been reported that hyperbilirubinaemia is secondary to RBV-associated haemolytic anemia.[104)] In the Japanese phase III study, 3 of 4 subjects with hyperbilirubinaemia had anemia-related events (anemia [1 subject], hemoglobin decreased [2 subjects]) and 1 subject with Grade 3 or higher blood total bilirubin increased had Grade 3 blood hemoglobin decreased. Based on the above, the observed hyperbilirubinaemia and blood total bilirubin increased associated with the SOF+RBV regimen appear consistent with RBV-associated haemolytic anemia.

PMDA considers as follows:
As it has been reported that hyperbilirubinaemia is secondary to RBV-associated haemolytic anemia,[104)] the hyperbilirubinaemia and blood total bilirubin increased observed in the Japanese phase III study do not necessarily indicate direct SOF+RBV-induced hepatic dysfunction. The hepatic dysfunction observed with the SOF+RBV regimen in the Japanese phase III study is tolerable because it was mild and reversible. Therefore, the SOF+RBV regimen can be used, if attention is paid to blood bilirubin values over time.

4.(iii).B.(3).4) Elderly

PMDA asked the applicant to explain the safety of the SOF+RBV regimen in the elderly.

The applicant explained as follows:
A Japanese phase III study included 32 patients aged ≥65 years (22.9% of the subjects).[105)] A summary of safety in elderly patients aged ≥65 years and non-elderly patients aged <65 years was as shown inTable 26.

Table 26. Summary of safety in elderly and non-elderly patients (Japanese phase III study)

Event term	<65 years	≥65 years	Total
	N = 108	N = 32	N = 140
Any adverse event	79 (73.1)	26 (81.3)	95 (75.0)
Grade 3 or higher adverse event	1 (0.9)	2 (6.3)	3 (2.1)
Serious adverse event	2 (1.9)	0	2 (1.4)
Adverse event leading to study drug dose reduction	7 (6.5)	12 (37.5)	19 (13.6)
Adverse event leading to study drug interruption	2 (1.9)	0	2 (1.4)

n (%)

Adverse events reported in ≥5% of elderly subjects were nasopharyngitis (37.5% [12 of 32 subjects] in the elderly, 28.7% [31 of 108 subjects] in the non-elderly), anemia (28.1% [9 of 32 subjects] in the elderly, 6.5%

104) Dusheiko G, et al. *J Hepatol*. 1996;25(5):591-598, Bodenheimer HC, et al. *Hepatology*. 1997;26(2):473-477, Reichard O, et al. *Lancet*. 1991;337(8749):1058-1061, Di Biscegie AM, et al. *Hepatology*. 1992;16(3): 649-654.

105) The intended study population was patients aged ≥20 years and subjects aged between 34 and 74 years (age at baseline) were enrolled in the study.

[7 of 108 subjects] in the non-elderly), hemoglobin decreased (15.6% [5 of 32 subjects] in the elderly, 0.9% [1 of 108 subjects] in the non-elderly), abdominal discomfort (15.6% [5 of 32 subjects] in the elderly, 0% [0 of 108 subjects] in the non-elderly), pruritus (12.5% [4 of 32 subjects] in the elderly, 4.6% [5 of 108 subjects] in the non-elderly), headache (9.4% [3 of 32 subjects] in the elderly, 10.2% [11 of 108 subjects] in the non-elderly), malaise (9.4% [3 of 32 subjects] in the elderly, 7.4% [8 of 108 subjects] in the non-elderly), hyperbilirubinaemia (9.4% [3 of 32 subjects] in the elderly, 0.9% [1 of 108 subjects] in the non-elderly), constipation (6.3% [2 of 32 subjects] in the elderly, 4.6% [5 of 108 subjects] in the non-elderly), fatigue (6.3% [2 of 32 subjects] in the elderly, 1.9% [2 of 108 subjects] in the non-elderly), dizziness (6.3% [2 of 32 subjects] in the elderly, 1.9% [2 of 108 subjects] in the non-elderly), and hypokalaemia (6.3% [2 of 32 subjects] in the elderly, 0% [0 of 108 subjects] in the non-elderly). Concerning the events reported at a ≥5% higher incidence in the elderly than in the non-elderly (nasopharyngitis, anemia, hemoglobin decreased, abdominal discomfort, pruritus, hyperbilirubinaemia, hypokalaemia), the differences in the incidences are likely attributable to the small number of elderly subjects and are not clinically relevant except for anemia-related events (anemia and hemoglobin decreased) and hyperbilirubinaemia. Since the change in hemoglobin level from baseline was greater [see "4.(iii).B.(3).2) Anemia-related events"] and it has been reported that old age is generally a risk factor for RBV-associated anemia,[106)] attention should be paid to the possible occurrence of anemia, but anemia-related events (anemia and hemoglobin decreased) in the elderly as well as in the non-elderly can be managed by taking appropriate measures, i.e., RBV dose reduction or interruption based on hemoglobin values [see "4.(iii).B.(3).2) Anemia-related events"]. Hyperbilirubinaemia is considered to be an event secondary to anemia [see "4.(iii).B.(3).3) Hepatic dysfunction"].

Information on the safety profile of SOF+RBV in elderly patients in routine medical use will continue to be collected via post-marketing surveillance.

PMDA considers as follows:

The applicant's following explaination is understood: higher incidences of some adverse events in elderly subjects than in non-elderly subjects in the Japanese phase III study are not clinically relevant except for anemia-related events (anemia and hemoglobin decreased) and hyperbilirubinaemia. Regarding anemia-related events and hyperbilirubinaemia, as examined in "4.(iii).B.(3).2) Anemia-related events" and "4.(iii).B.(3).3) Hepatic dysfunction", all patients were able to continue on the SOF+RBV regimen following RBV dose reduction or interruption. As long as monitoring by periodic blood tests is performed and appropriate actions are taken upon the occurrence of an event, the SOF+RBV regimen is tolerable in elderly patients as well as in non-elderly patients. However, since there is limited clinical experience in Japanese elderly patients and the elderly often have reduced physiological function etc., and the possibility of adverse events cannot be ruled out, post-marketing information concerning use in the elderly should also be collected.

106) Borroni G, et.al. *J Viral Hepat*. 2013;20 (4):e90-5.

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

Given that Japanese and foreign clinical studies have demonstrated the efficacy and safety of the SOF+RBV regimen in genotype 2 chronic hepatitis C patients with or without compensated cirrhosis [see "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety"] and taking account of the indications for similar drugs and the following considerations, PMDA concluded that the appropriate indication for SOF should be as shown below. With respect to the indications for Copegus Tablet 200 mg, since the efficacy and safety of RBV when used in combination with SOF, one of anti-HCV agents, have been confirmed, "in combination with anti-HCV agents (excluding interferon)" (the proposed indication statement) should be replaced with "in combination with Sofosbuvir".

[SOF]

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

[Copegus Tablet 200 mg] (Underlined text indicates an addition.)

1. Suppression of viremia in either of the following patients with chronic hepatitis C, in combination with Peginterferon Alfa-2a (Genetical Recombination):
   (1) patients with serogroup 1 (genotype I [1a] or II [1b]) and high HCV-RNA levels, or
   (2) patients who have failed to respond to or relapsed following interferon monotherapy
2. Suppression of viremia in patients with chronic hepatitis C and compensated cirrhosis, in combination with Peginterferon Alfa-2a (Genetical Recombination).
3. <u>Suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients with or without compensated cirrhosis, in combination with Sofosbuvir.</u>

The above conclusions by PMDA will be discussed at the Expert Discussion.

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

PMDA asked the applicant to explain efficacy by subtype of genotype 2.

The applicant explained as follows:

In a Japanese phase III study, the SVR12 rates for subtypes 2a and 2b were 95.3% (82 of 86 subjects) and 98.1% (53 of 54 subjects), respectively. The SVR12 rates for other subtypes in foreign phase III studies were 100% (2 of 2 subjects) for 2c,[107)] 100% (1 of 1 subject) for 2i,[108)] 100% (1 of 1 subject) for 2j,[107)] and 100% (1 of 1 subject) for 2r.[107)] The above results indicate that there are no differences in the efficacy of the SOF+RBV regimen among different subtypes.

[107)] Study GS-US-334-0107 (CTD5.3.5.1.2)
[108)] Study GS-US-334-0108 (CTD5.3.5.1.3)

PMDA considers as follows:

There were no differences in the SVR12 rate with the SOF+RBV regimen between subtypes 2a and 2b in the Japanese phase III study. Although the information on other subtypes is limited, foreign phase III studies have shown that the SOF+RBV regimen achieved SVR for other subtypes. Thus, the SOF+RBV regimen can be indicated for "serogroup 2 (genotype 2)" chronic hepatitis C patients.

4.(iii).B.(4).2) Use in cirrhotic patients

The applicant explained the efficacy and safety of the SOF+RBV regimen in cirrhotic patients as follows:

The SVR12 rates in chronic hepatitis C patients with or without compensated cirrhosis (genotype 2) in Japanese and foreign phase III studies were as shown in Table 27.

Table 27. SVR12 rates in chronic hepatitis C patients with or without compensated cirrhosis

		Study population	Overall	Compensated cirrhotic patients	Noncirrhotic patients
Japan	GS-US-334-0118	Treatment-naïve and treatment-experienced patients	96.4 (135/140)	93.3 (14/15) [a)]	96.8 (121/125) [b)]
Overseas	P7977-1231	Treatment-naïve patients	97.1 (68/70)	90.9 (10/11)	98.3 (58/59)
	GS-US-334-0107	Patients intolerant of, ineligible for, or unwilling to receive IFN	95.3 (101/106)	94.1 (16/17)	92.4 (85/92)
	GS-US-334-0108	Patients who failed prior treatment with an IFN-based regimen	86.1 (31/36)	60.0 (6/10)	96.2 (25/26)

% (n/N)

a) The SVR12 rate in treatment-naïve patients was 100% (8 of 8 subjects) and the SVR12 rate in treatment-experienced patients was 85.7% (6 of 7 subjects).

b) The SVR12 rate in treatment-naïve patients was 97.3% (73 of 75 subjects) and the SVR12 rate in treatment-experienced patients was 96.0% (48 of 50 subjects).

Adverse events (including laboratory abnormalities) reported in ≥5% of either compensated cirrhotic or non-cirrhotic patients with chronic hepatitis C in the Japanese phase III study were as shown in Table 28 and the safety profile and the incidence of adverse events in compensated cirrhotic patients were similar to those in non-cirrhotic patients.

Table 28. Adverse events reported in ≥5% of either compensated cirrhotic or non-cirrhotic patients with chronic hepatitis C (Japanese phase III study)

Event term	Compensated cirrhotic patients (N = 15)	Noncirrhotic patients (N = 125)
Any adverse event	11 (75.2)	94 (73.3)
Anaemia	0	16 (12.8)
Supraventricular extrasystoles	1 (6.7)	0
Constipation	0	7 (5.6)
Nausea	0	7 (5.6)
Diarrhoea	1 (6.7)	3 (2.4)
Abdominal pain upper	1 (6.7)	3 (2.4)
Stomatitis	1 (6.7)	4 (3.2)
Malaise	0	10 (8.0)
Hyperbilirubinaemia	1 (6.7)	3 (2.4)
Nasopharyngitis	4 (26.7)	39 (31.2)
Cystitis	1 (6.7)	3 (2.4)
Haemoglobin decreased	1 (6.7)	5 (4.0)
Myalgia	1 (6.7)	4 (3.2)
Back pain	2 (13.3)	4 (3.2)
Musculoskeletal stiffness	1 (6.7)	0
Headache	0	14 (11.2)
Cough	1 (6.7)	3 (2.4)
Pruritus	1 (6.7)	8 (6.4)
Alopecia	1 (6.7)	2 (1.6)
Dermatitis contact	1 (6.7)	1 (0.8)

n (%)

The above results indicate that the safety and tolerability of the SOF+RBV regimen are similar between

compensated cirrhotic and non-cirrhotic patients with chronic hepatitis C and that similar efficacy can be expected between compensated cirrhotic and non-cirrhotic patients.

PMDA considers as follows:
In the Japanese phase III study, the SVR12 rate with the SOF+RBV regimen in compensated cirrhotic patients with chronic hepatitis C was similar to that in non-cirrhotic patients and there were no particular safety issues. Thus, the SOF+RBV regimen can be used in patients with chronic hepatitis C and compensated cirrhosis. However, as the SOF+RBV regimen was studied in a limited number of patients with chronic hepatitis C and compensated cirrhosis, it is necessary to collect safety and efficacy information from chronic hepatitis C patients with compensated cirrhosis via post-marketing surveillance.

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

Based on the following considerations, PMDA concluded that the appropriate dosage and administration statements for SOF and Copegus Tablet 200 mg should be as shown below. PMDA considers that the SOF and Copegus Tablet 200 mg package inserts should advise physicians to refer to the package insert of the other drug used in combination, and that SOF information leaflet etc., should contain the recommended doses of RBV and the guidelines for RBV dose reduction/discontinuation etc.

[SOF]
The usual adult dosage is 400 mg of Sofosbuvir, taken orally, once daily. Sovaldi should be used in combination with Ribavirin for 12 weeks.

[Copegus Tablet 200 mg] (Underlined denotes added text.additional text indicated underlined)
Copegus should be used in combination with Peginterferon Alfa-2a (Genetical Recombination) or Sofosbuvir.
The usual adult oral dosage of Copegus is provided in the following table. The dose should be reduced or discontinued or other appropriate measures should be taken according to the patient's condition.

Body weight	Ribavirin daily dose	After breakfast	After evening meal
≤60 kg	600 mg	200 mg	400 mg
>60 kg and ≤80 kg	800 mg	400 mg	400 mg
>80 kg	1000 mg	400 mg	600 mg

The above conclusions by PMDA will be discussed at the Expert Discussion.

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

The applicant explained the rationale for dosage and administration of SOF as follows:
The results of exposure-response analyses using the data from foreign phase I and II studies among patients with chronic hepatitis C (genotype 1) indicated that the SOF 400 mg dose has potent antiviral effect [see "4.(ii).A.(6) Exposure-response analyses"].

A foreign phase II study (P7977-0422)[109] investigated the efficacy and safety of the triple regimen of SOF 200 or 400 mg (12-week treatment) and PegIFN+RBV (24- or 48-week treatment)[110] in treatment-naïve patients with chronic hepatitis C (genotype 1). The SVR12 rates were 89.6% (43 of 48 subjects) in the 200 mg group and 91.5% (43 of 47 subjects) in the 400 mg group. Three subjects in the 200 mg group experienced virologic breakthrough[111] during treatment with PegIFN+RBV following treatment with SOF+PegIFN+RBV, but none of the subjects in the 400 mg group experienced virologic breakthrough. Safety and tolerability were comparable between the 200 mg and 400 mg groups. Thus, a SOF dose of 400 mg was selected for phase III studies. When treatment-naïve patients with genotype 1, 2, or 3 chronic hepatitis C received SOF 400 mg in combination with PegIFN+RBV, there were no differences in early change from baseline in HCV RNA levels[112] among the different genotypes.

In a foreign phase II study (P7977-0523),[113] the SVR12 rates with SOF alone, SOF+RBV, and SOF+PegIFN+RBV (12 weeks) in treatment-naïve patients with chronic hepatitis C (genotypes 2 or 3) were 60% (6 of 10 subjects), 100% (10 of 10 subjects), and 100% (11 of 11 subjects), respectively. These results indicated that there is little need to add PegIFN to the combine and that the efficacy can be expected only with the SOF+RBV regimen.

In addition to the above results, because no obvious differences were observed for the pharmacokinetics of SOF between Japanese and Caucasian subjects [see "4.(ii).A.(1).1 Foreign phase I single-dose study in Japanese and Caucasian healthy adult subjects"], 12 weeks of treatment with SOF 400 mg in combination with RBV was selected for Japanese and foreign phase III studies (GS-US-334-0118, P7977-1231, GS-US-334-0107, GS-US-334-0108). High SVR12 rates were observed and there were no particular safety issues in these studies.

Based on the above, 12 weeks of treatment with SOF 400 mg in combination with RBV was proposed for chronic hepatitis C patients with or without compensated cirrhosis (genotype 2).

PMDA considers that SOF 400 mg taken orally, once daily, in combination with RBV, for 12 weeks can be proposed for chronic hepatitis C patients with or without compensated cirrhosis (genotype 2).

4.(iii).B.(5).2) Dosage and administration for Copegus Tablet 200 mg

The applicants, Chugai Pharmaceutical Co., Ltd. and Gilead Sciences K.K. explained the rationale for dosage and administration of Copegus Tablet as follows:

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109) CTD5.3.5.1.5

110) The incidences of adverse events (including laboratory abnormalities) were 97.9% (47 of 48 subjects) in the 200 mg group and 97.9% (46 of 47 subjects) in the 400 mg group. Serious adverse events were reported by 1 subject in the 200 mg group and 3 subjects in the 400 mg group. Adverse events leading to discontinuation of any study drug occurred in 2 subjects in the 200 mg group and 3 subjects in the 400 mg group and a causal relationship to SOF was denied for all events.

111) HCV RNA level returned to ≥ LLOQ after achieving a level < LLOQ, during the course of treatment.

112) When treatment-naïve patients with chronic hepatitis C (genotype 1, 2, or 3) received SOF 400 mg in combination with PegIFN+RBV, the mean changes from baseline in HCV RNA levels (the estimated maximum percent reduction) were 3.64 Log_{10}IU/mL (85.4%) for genotype 1, 3.62 Log_{10}IU/mL (85.0%) for genotype 2, and 3.47 Log_{10}IU/mL (81.5%) for genotype 3 [Study P7977-0523 (CTD5.3.5.1.6) and Study P7977-0221 (CTD5.3.4.2.1)].

113) CTD5.3.5.1.6

For all Japanese and foreign phase III studies, the dosage and administration, and dose reduction/discontinuation guidelines regarding safety for the RBV in the SOF+RBV regimen were established based on the Japanese or foreign package insert of RBV approved as in the PegIFN+RBV regimen.

In a Japanese phase III study, adverse events leading to RBV dose reduction or interruption occurred in 19 subjects (13.6%) or 2 subjects (1.4%), respectively, which included 19 cases (13.6%) of anemia or hemoglobin decreased. Action was taken in accordance with the guidelines for dose reduction or discontinuation provided in the Japanese package insert and as a result, all patients completed treatment with the SOF+RBV regimen, a high SVR12 rate was achieved, and there were no particular safety issues.

Based on the above, it was decided that the current dosage, dose regimen, and dose reduction/discontinuation guidelines regarding safety for Copegus Tablet 200 mg shall be used and the package insert of SOF (used in combination with RBV) shall be referred during RBV treatment.

PMDA considers as follows:
There is no particular problem with referring to the current RBV package insert in establishing the dosage and administration, and dose reduction/discontinuation guidelines regarding safety for the RBV in the SOF+RBV regimen, juding from the obtained results of Japanese and foreign phase III studies. Since the Japanese phase III study demonstrated the efficacy of 12 weeks of treatment with SOF+RBV and no Japanese clinical study has investigated >12 weeks of treatment with SOF+RBV etc., the recommended duration of treatment with RBV when used in combination with SOF should be 12 weeks.

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

The applicant explained the clinical positioning of the SOF+RBV regimen in chronic hepatitis C patients with or without compensated cirrhosis (genotype 2) as follows:
The Japanese Hepatitis Management Guidelines[114] recommend PegIFN+RBV combination therapy (24-48 weeks) etc., for chronic hepatitis C patients with or without compensated cirrhosis (genotype 2). Since PegIFN requires once-weekly subcutaneous injections and may cause adverse reactions or tolerability problems, most of treatment-naïve patients in Japan are ineligible for an IFN-based regimen or unwilling to take IFN[115),116] and currently these patients have no treatment option. IFN-intolerant patients and patients who have failed prior treatment with an IFN-based regimen also have limited treatment options.

The results from a Japanese phase III study showed a high SVR12 rate in patients with chronic hepatitis C (genotype 2) who received the SOF+RBV regimen, regardless of prior treatment experience or compensated cirrhosis. Regarding safety, none of the subjects in the Japanese phase III study had an adverse event leading to study drug discontinuation and there should be no particular tolerability issues [see "4.(iii).B.(2) Efficacy", "4.(iii).B.(3) Safety", and "4.(iii).B.(4) Indications"]. The SOF+RBV regimen is an all-oral, IFN-free treatment

114) Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology ed. *Guidelines for the Management of Hepatitis C Virus Infection (3.1th edition)*, 2014.
115) Tanaka J, et al. *Intervirology*. 2004;47(1):32-40.
116) Asahina Y, et al. *Hepatology*. 2010;52(2):518-527.

regimen, enabling a cure in 12 weeks.

Based on the above, the SOF+RBV regimen can become a first-line treatment for chronic hepatitis C patients with or without compensated cirrhosis (genotype 2).

PMDA considers as follows:
While the Japanese phase III study was an open-label, uncontrolled study which makes a rigorous comparative evaluation of SOF+RBV and existing therapies difficult, it was concluded that the efficacy of the SOF+RBV regimen in chronic hepatitis C patients with or without compensated cirrhosis (genotype 2) can be expected [see "4.(iii).B.(2) Efficacy"]. Regarding safety, attention should be paid to the possible occurrence of anemia-related events etc., but there are no particular tolerability issues. Therefore, as long as physicians with adequate knowledge and experience in the treatment of viral liver disease perform periodic blood tests, monitor and manage adverse events, and take appropriate actions such as interruption/discontinuation of treatment, the SOF+RBV regimen can become a new treatment option for chronic hepatitis C patients with or without compensated cirrhosis (genotype 2).

4.(iii).B.(7) Post-marketing investigations

4.(iii).B.(7).1) SOF

The applicant is planning the following post-marketing surveillance study of SOF.
[Drug use-results survey]
● Objectives: To collect information about and evaluate safety and efficacy in routine clinical practice.
● Planned sample size: 1000 patients (including 200 chronic hepatitis C patients with compensated cirrhosis)
Basis for sample size determination
The planned sample size of 1000 patients provides a 95% probability of detecting at least one case of an adverse drug reaction with an incidence of 0.3%. As approximately 20% of patients with chronic hepatitis C at medical institutions in Japan had compensated cirrhosis, this survey is intended to enroll 20% of chronic hepatitis C patients with compensated cirrhosis (200 patients).
● Observation period: The observation period for safety will be continued from the start of treatment with SOF in combination with RBV up to 4 weeks after its completion (or its discontinuation) and the observation period for efficacy will be continued from the start of treatment with SOF in combination with RBV up to 36 weeks (including a 24-week post-treatment follow-up period).
● Survey period: 3 years

Information on SOF resistance mutations will be collected from spontaneous reports, literature, academic meetings, etc.

In addition to the investigations proposed by the applicant, PMDA considers that it is necessary to collect the following information during the post marketing period.
● Safety and efficacy in IFN-ineligible or -intolerant patients
● Safety and efficacy in the elderly

● Safety and efficacy in compensated cirrhotic patients

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

4.(iii).B.(7).2) Copegus Tablet 200 mg

The applicant, Chugai Pharmaceutical Co., Ltd., explained that no new or greater risk has been identified with Copegus Tablet 200 mg in combination with SOF compared with Copegus Tablet 200 mg in combination with PegIFNα-2a.

Taking account of the reviews in "4.(iii).B.(3) Safety", PMDA considers that the applicant's explanation is acceptable.

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

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

The assessment is currently ongoing and its results and the conclusion by PMDA will be reported in the Review Report (2).

IV. Overall Evaluation

Based on the submitted data, the efficacy of the SOF+RBV regimen in chronic hepatitis C patients with or without compensated cirrhosis (genotype 2) has been demonstrated and its safety is acceptable in view of its observed benefits. However, it is necessary to continue to collect the following post-marketing information.

● Safety and efficacy in IFN-ineligible or -intolerant patients
● Safety and efficacy in the elderly
● Safety and efficacy in compensated cirrhotic patients

PMDA considers that the SOF+RBV regimen may be approved for chronic hepatitis C patients with or without compensated cirrhosis (genotype 2) if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

February 23, 2015

I. Products Submitted for Registration

[Brand name]	(a) Sovaldi Tablets 400 mg
	(b) Copegus Tablet 200 mg
[Non-proprietary name]	(a) Sofosbuvir
	(b) Ribavirin
[Name of applicant]	(a) Gilead Sciences K.K.
	(b) Chugai Pharmaceutical Co., Ltd.
[Date of application]	(a) June 27, 2014
	(b) September 18, 2014

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 products 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).

Based on the comments from the expert advisors, PMDA conducted an additional review of the following points and took necessary actions, but otherwise PMDA's conclusions described in the Review Report (1) were supported.

(1) Draft risk management plan

(1).1) Sofosbuvir

PMDA's conclusion on a post-marketing surveillance study of Sofosbuvir (SOF) [see "Review Report (1), II.4.(iii).B.(7).1) SOF"] was supported by the expert advisors.

PMDA considers that it is necessary to collect the following information via post-marketing surveillance and provide the obtained information to healthcare providers in clinical settings as soon as the information is accumulated.

- Safety and efficacy in interferon (IFN)-ineligible or -intolerant patients
- Safety and efficacy in the elderly
- Safety and efficacy in compensated cirrhotic patients

Post-marketing information on resistance mutations should be collected from literature etc. It is necessary to collect information on resistance mutations as much as possible in patients who have failed to respond to the treatment with the SOF+Ribavirin (RBV) regimen, including their clinical course after the end of treatment, and

promptly provide the obtained findings to healthcare providers in clinical settings.

PMDA instructed the applicant (Gilead Sciences K.K.) to address the above points and the applicant agreed and responded appropriately.

Taking account of the above discussion, PMDA concluded that the safety specification and efficacy concerns as shown in Table 29 should be included in the current draft risk management plan and that additional pharmacovigilance activities and risk minimization activities as shown in Table 30 should be conducted. An outline of the draft drug use-results survey plan as shown in Table 31 was submitted.

Table 29. Safety specification and efficacy concerns of the draft risk management plan for SOF

Safety specification		
Important identified risks	Important potential risks	Important missing information
None.	· Anemia · Use in patients with severe renal impairment or ESRD requiring dialysis	None.
Efficacy concerns		
· Efficacy in routine clinical settings · Drug resistance		

Table 30. Summary of additional pharmacovigilance activities and risk minimization activities in the draft risk management plan for SOF

Additional pharmacovigilance activities	Additional risk minimization activities
· Early Post-marketing Phase Vigilance (EPPV) · Drug use-results survey	· EPPV

Table 31. Outline of the draft drug use-results survey plan for SOF

Objectives	To evaluate the safety and efficacy of the SOF+RBV regimen in routine clinical settings.
Survey method	Central registry system
Patients to be surveyed	Chronic hepatitis C patients with or without compensated cirrhosis
Survey period (Observation period)	3 years (up to 24 weeks after the end of treatment)
Planned sample size	1000 patients (including 200 chronic hepatitis C patients with compensated cirrhosis)
Main information to be collected	Safety and efficacy in IFN-ineligible or -intolerant patients, safety and efficacy in the elderly, safety and efficacy in compensated cirrhotic patients etc.

(1).2) Copegus Tablet 200 mg

The expert advisors made the following comment on PMDA's conclusion on a post-marketing surveillance study of Copegus Tablet 200 mg [see "4.(iii).B.(7).2) Copegus Tablet 200 mg" of Review Report (1)].

- Regarding the safety of RBV, the applicant's following explanation is understood: In Japanese and foreign clinical studies of RBV+SOF, no new or greater risk has been identified with RBV in combination with SOF compared to RBV in combination with Peginterferon Alfa-2a [Genetical Recombination]. However, there is no sufficient clinical experience with the SOF+RBV regimen in Japanese chronic hepatitis C patients with or without compensated cirrhosis. Therefore, it is necessary to collect information on the safety of RBV when used in combination with SOF via post-marketing surveillance.

Based on the comment from the expert advisors, PMDA instructed the applicant (Chugai Pharmaceutical Co., Ltd.) to conduct a post-marketing surveillance study of Copegus Tablet 200 mg as well and collect information on the safety of RBV when used in combination with SOF and the applicant agreed and responded appropriately.

Taking account of the above discussion, PMDA concluded that the safety specification and efficacy concerns as shown in Table 32 should be included in the current draft risk management plan and that additional pharmacovigilance activities and risk minimization activities as shown in Table 33 should be conducted. A drug use-results survey of both RBV and SOF will be conducted because the survey is for chronic hepatitis C patients with or without compensated cirrhosis receiving the SOF+RBV regimen. The specific survey method etc., are under discussion between Chugai Pharmaceutical Co., Ltd. and Gilead Sciences K.K.

Table 32. Safety specification and efficacy concerns of the draft risk management plan for Copegus Tablet 200 mg

Safety specification		
Important identified risks	Important potential risks	Important missing information
· Cytopenia · Thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS) · Aplastic anemia, aplasia pure red cell · Interstitial lung disease · Neuropsychiatric symptoms · Hepatic dysfunction · Autoimmune phenomena · Psoriasis · Cardiovascular disorders · Infections · Cerebrovascular disorders · Diabetes · Thyroid dysfunction · Skin disorders such as oculomucocutaneous syndrome, toxic epidermal necrolysis, and erythema multiforme · Hypersensitivity · Eye disorders · Teratogenicity · Acute renal failure, nephrotic syndrome · Gastrointestinal bleeding (melaena, bloody stool, etc.), peptic ulcer, colitis ischaemic	· Growth impairment in pediatric patients	None.
Efficacy concerns		
· Efficacy of RBV in combination with SOF in routine clinical use		

Table 33. Summary of additional pharmacovigilance activities and risk minimization activities in the draft risk management plan for Copegus Tablet 200 mg

Additional pharmacovigilance activities	Additional risk minimization activities
· EPPV · Drug use-results survey	· EPPV

(2) Others

The applicant (Gilead Sciences K.K.) reported failure to comply with the following obligations (some of the foreign post-marketing safety information was not reported or notified appropriately) during a Japanese phase III study (GS-US-334-0118): reporting to the Minister of Health, Labour and Welfare in accordance with Article 273 of the Ordinance for Enforcement of the Pharmaceutical Affairs Act ([also with the relevant provisons of the revised ordinance, which is the Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics] the Ordinance of the Ministry of Health and Welare [MHW] No.1 of 1961; hereinafter referred to as the “Enforcement Ordinance”); and notifying the investigators and the heads of the medical

institutions in accordance with Article 20 of the Ministerial Ordinance on Good Clinical Practice (MHW Ordinance No.28 of 1997; hereinafter referred to as the "GCP Ministerial Ordinance"). The unreported safety information was reported to the Minister of Health, Labour and Welfare, notified to the investigators and the heads of the medical institutions, and reported to the institutional review boards after this issue was revealed.

PMDA assessed the safety of SOF, including whether there was any unknown adverse reactions etc., among the unreported events, and then concluded that there are no new safety concerns other than those examined in the section " 4.(iii).B.(3) Safety" of Review Report (1) and that no additional precautionary statement in the package insert is needed at present. PMDA also asked the applicant to explain the cause for failure to appropriately report the SOF safety information etc., and future corrective actions.

The applicant explained as follows:
Due to the sponsor (Gilead Sciences, Inc.)'s insufficient understanding of Article 273 of the Enforcement Ordinance and Article 20 of the GCP Ministerial Ordinance, "Clinical Trial Safety Reporting Procedures" (CTSRP), which were developed jointly by the sponsor and the clinical trial in-country representative (hereinafter referred to as "In-country Representative") for the Japanese phase III study, did not require reporting etc., of foreign post-marketing safety information. Consequently, some of the foreign post-marketing safety information was not appropriately reported to the Minister of Health, Labour and Welfare or notified to the investigators and the heads of the medical institutions. The following corrective actions and preventive measures etc., for future improvements will be implemented promptly and appropriately.

- Set up a new division promptly to ensure the understanding of the Japanese regulations within the organization.
- Revise the CTSRP review procedure to allow for the development of appropriate CTSRP in accordance with local regulatory requirements, etc.
- Develop a guidance to ensure appropriate exchange of safety information with contract research organizations.
- Establish a procedure to promptly report to PMDA for the suspected cases of noncompliance with the Japanese regulations, etc.
- Constantly check if the measures or actions have been implemented appropriately and review and modify the measures to prevent similar situations from recurring etc., as needed.

PMDA considers as follows:
Some of the SOF safety information was not appropriately reported etc., during the drug development in Japan and such failure to comply with the statutory obligations should be corrected, also in terms of ensuring the safety of subjects in clinical trials, etc. Although the above corrective actions and preventive measures proposed by the applicant are acceptable at present, the applicant will need to appropriately implement these measures and promptly prepare an internal system etc., to prevent similar situations from recurring.

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 inspection and data integrity assessment

A document-based 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

Outcome of assessment: Conditional compliance

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.2.1).

As a result, since noncompliance with the GCP for Drugs was found at the sponsor (In-country Representative) site, actions such as exclusion of the data from the relevant subjects from the submitted application documents were necessary, but PMDA concluded that there should be no problem with conducting a regulatory review based on the application documents excluding the data in question.

There were findings requiring improvement for some trial sites and the sponsor (In-country Representative) as shown below, though not significantly affecting the overall assessment of the study, which were notified to the heads of the relevant medical institutions, the applicant, and the sponsor (In-country Representative).

[Noncompliance with the GCP for Drugs]

<u>Sponsor (In-country Representative)</u>

Parexel International K.K., which had been designated as the In-country Representative by Gilead Sciences, Inc. (the sponsor), performed its duties related to the preparation and management of the clinical trial such as monitoring activity.

[redacted]

In addition, the above monitoring reports were not adequately checked or followed-up. Since the sponsor (In-country Representative) could not foresee and prevent this issue from occurring, it is hard to say that appropriate written procedures were in place and a quality assurance and quality control system based on the written procedures was implemented and maintained to assure the clinical trial is conducted in compliance with the GCP requirements and the protocol.

[Findings requiring improvements]

Trial sites

- Inconsistencies between the source documents and the CRF (inconsistencies in the date and time of the last dose taken before blood collection etc.; undocumented adverse events).
- Subjects were to be informed prior to collection of additional blood and their willingness to continue participation in the clinical trial was to be also confirmed. However, the completion of such procedures was not documented for some subjects.

Sponsor (In-country Representative)

- Some of serious, unexpected adverse drug reactions etc., collected overseas were not immediately notified to the investigators and the heads of the medical institutions.

Its details were as described below:

In spite of knowing the cases that fall under Article 273, Paragraph 1 of the Ordinance for Enforcement of the Pharmaceutical Affairs Act (also under the relvant provisions of the revised ordinance, which is the Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics) (e.g., suspected cases of adverse reactions to a product used in foreign countries that has an identical active ingredient to the test drug), Gilead Sciences, Inc. (the sponsor) did not report the cases to the Minister of Health, Labour and Welfare within the timeframe stipulated by the MHLW Ordinance and did not notify the investigators or the heads of the medical institutions of them. After this issue was revealed, the unreported adverse drug reactions etc., were reported to the Minister of Health, Labour and Welfare. The investigators and the heads of the medical institutions were notified of them and all investigators concluded that no amendments to the protocol and the informed consent document were necessary and that the clinical trial could be continued. This conclusion was reported to and accepted by the institutional review boards. The sponsor concluded that an analysis for unexpected adverse events identified no new safety concerns about SOF.

- Inconsistencies between the source documents and the CRF (inconsistencies in the date and time of the last dose taken before blood collection, etc.) were not appropriately detected during monitoring visits.
- Inconsistencies between the source documents and the CRF (undocumented adverse events) were not appropriately checked.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that approval may be granted after modifying the indication and dosage and administration statements as shown below, with the following condition. As SOF is a drug with a new active ingredient and used in combination with Copegus Tablet 200 mg, the re-examination period is 8 years for both Sovaldi Tablets 400 mg and Copegus Tablet 200 mg; and neither the drug substance nor drug product of Sovaldi Tablets 400 mg is classified as a poisonous drug or a powerful drug, and the product is not classified as a biological product or a specified biological product.

[Indications]

[Sovaldi Tablets 400 mg]
Suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients with or without compensated cirrhosis.

[Copegus Tablets 200 mg] (Underline denotes added text.)
1. Suppression of viremia in either of the following patients with chronic hepatitis C, in combination with Peginterferon Alfa-2a (Genetical Recombination):
(1) patients with serogroup 1 (genotype I [1a] or II [1b]) and high levels of HCV-RNA, or
(2) patients who have failed to respond to or relapsed following interferon monotherapy
2. Suppression of viremia in patients with chronic hepatitis C and compensated cirrhosis, in combination with Peginterferon Alfa-2a (Genetical Recombination).
3. Suppression of viremia in serogroup 2 (genotype 2) chronic hepatitis C patients with or without compensated cirrhosis, in combination with Sofosbuvir.

[Dosage and administration]

[Sovaldi Tablets 400 mg]
The usual adult dosage is 400 mg of Sofosbuvir, administered orally once daily in combination with Ribavirin for 12 weeks.

[Copegus Tablets 200 mg] (Underline denotes added text.)
Ribavirin should be used in combination with Peginterferon Alfa-2a (Genetical Recombination) or Sofosbuvir.
The usual adult oral dosage of Ribavirin is provided in the following table. The dose should be reduced or discontinued, or other appropriate measures should be taken, depending on the patient's condition.

Body weight	Ribavirin daily dose	After breakfast	After evening meal
≤60 kg	600 mg	200 mg	400 mg
>60 kg and ≤80 kg	800 mg	400 mg	400 mg
>80 kg	1000 mg	400 mg	600 mg

[Condition for approval]

[Sovaldi Tablets 400 mg] and [Copegus Tablet 200 mg]
The applicant (of each product) is to develop a risk management plan for the product and implement it appropriately.