Review Report

February 22, 2017
Pharmaceuticals and Medical Devices Agency

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

Brand Name	(a) Sovaldi Tablets 400 mg
	(b) Rebetol Capsules 200 mg
	(c) Copegus Tablets 200 mg
Non-proprietary Name	(a) Sofosbuvir
	(b) and (c) Ribavirin (JAN*)
Applicant	(a) Gilead Sciences K.K.
	(b) MSD K.K.
	(c) Chugai Pharmaceutical Co., Ltd.
Date of Application	(a) August 31, 2016
	(b) September 27, 2016
	(c) November 18, 2016
Dosage Form/Strength	(a) Tablets: Each tablet contains 400 mg of Sofosbuvir.
	(b) Capsules: Each capsule contains 200 mg of Ribavirin.
	(c) Tablets: Each tablet contains 200 mg of Ribavirin.
Application Classification	(a) Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
	(b) Prescription drug, (4) Drug with a new indication
	(c) Prescription drug, (4) Drug with a new indication
Items Warranting Special Mention	
	Expedited review (PSEHB/PED Notification No. 0930-5 dated September 30, 2016; PSEHB/PED Notification No. 1122-1 dated November 22, 2016, issued by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the combination regimen of Sovaldi Tablets 400 mg and Rebetol Capsules 200 mg and the combination regimen of Sovaldi Tablets 400 mg and Copegus Tablets 200 mg have efficacy in patients with chronic hepatitis C with or without compensated cirrhosis (genotypes 3-6), and that the regimens have acceptable safety in view of the benefits (see Attachment).

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

Indications

(a) Sovaldi Tablets 400 mg

(Underline denotes additions or changes)

1. Suppression of viremia in either of the following patients with chronic hepatitis C with or without compensated cirrhosis:
   (1) patients infected with serogroup 2 (genotype 2) HCV, or
   (2) patients infected with HCV that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2)

(b) Rebetol Capsules 200 mg

(Underline denotes additions or changes)

1. Suppression of viremia in either of the following patients with chronic hepatitis C in combination with Interferon Alfa-2b (Genetical Recombination), Peginterferon Alfa-2b (Genetical Recombination), or Interferon Beta:
   (1) patients with high levels of HCV RNA in blood, 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-2b (Genetical Recombination)
3. Suppression of viremia in either of the following patients with chronic hepatitis C with or without compensated cirrhosis in combination with Sofosbuvir:
   (1) patients infected with serogroup 2 (genotype 2) HCV, or
   (2) patients infected with HCV that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2)
4. Suppression of viremia in patients with serogroup 2 (genotype 2) chronic hepatitis C in combination with the Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir fixed-dose combination tablet

(c) Copegus Tablets 200 mg

(Underline denotes additions or changes)

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 <u>either of the following</u> patients with chronic hepatitis C with or without compensated cirrhosis in combination with Sofosbuvir:
   <u>(1) patients infected with serogroup 2 (genotype 2) HCV, or</u>
   <u>(2) patients infected with HCV that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2)</u>

Dosage and Administration

(a) Sovaldi Tablets 400 mg

(Underline denotes additions)

1. <u>When used in patients infected with serogroup 2 (genotype 2) HCV:</u>
   The usual adult dosage is 400 mg of Sofosbuvir, administered orally once daily in combination with Ribavirin for 12 weeks.
2. <u>When used in patients infected with HCV that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2):</u>
   <u>The usual adult dosage is 400 mg of Sofosbuvir, administered orally once daily in combination with Ribavirin for 24 weeks.</u>

Conditions of Approval

(a) Sovaldi Tablets 400 mg

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

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

January 6, 2017

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

Products Submitted for Approval

Brand Name	(a) Sovaldi Tablets 400 mg
	(b) Rebetol Capsules 200 mg
	(c) Copegus Tablets 200 mg
Non-proprietary Name	(a) Sofosbuvir
	(b) and (c) Ribavirin
Applicant	(a) Gilead Sciences K.K.
	(b) MSD K.K.
	(c) Chugai Pharmaceutical Co., Ltd.
Date of Application	(a) August 31, 2016
	(b) September 27, 2016
	(c) November 18, 2016
Dosage Form/Strength	(a) Tablets: Each tablet contains 400 mg of Sofosbuvir.
	(b) Capsules: Each capsule contains 200 mg of Ribavirin.
	(c) Tablets: Each tablet contains 200 mg of Ribavirin.

Proposed Indications

(a) Sovaldi Tablets 400 mg

(Underline denotes changes)

Suppression of viremia in patients with chronic hepatitis C with or without compensated cirrhosis <u>(any serogroup [genotype] other than serogroup 1 [genotype 1])</u>

(b) Rebetol Capsules 200 mg

(Underline denotes changes)

1. Suppression of viremia in either of the following patients with chronic hepatitis C in combination with Interferon Alfa-2b (Genetical Recombination), Peginterferon Alfa-2b (Genetical Recombination), or Interferon Beta:
   (1) patients with high levels of HCV RNA in blood, 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-2b (Genetical Recombination)
3. Suppression of viremia in patients with chronic hepatitis C with or without compensated cirrhosis (any serogroup [genotype] other than serogroup 1 [genotype 1]) in combination with Sofosbuvir
4. Suppression of viremia in patients with serogroup 2 (genotype 2) chronic hepatitis C in combination with the Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir fixed-dose combination tablet

(c) Copegus Tablets 200 mg

(Underline denotes changes)

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 patients with chronic hepatitis C with or without compensated cirrhosis (any serogroup [genotype] other than serogroup 1 [genotype 1]) in combination with Sofosbuvir

Proposed Dosage and Administration

(a) Sovaldi Tablets 400 mg

(Underline denotes additions)

1. Suppression of viremia in patients with serogroup 2 (genotype 2) chronic hepatitis C with or without compensated cirrhosis:
   The usual adult dosage is 400 mg of Sofosbuvir, administered orally once daily in combination with Ribavirin for 12 weeks.
2. Suppression of viremia in non-cirrhotic or compensated cirrhotic patients with chronic hepatitis C infection that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2):
   The usual adult dosage is 400 mg of Sofosbuvir, administered orally once daily in combination with Ribavirin for 24 weeks.

(b) Rebetol Capsules 200 mg

(No changes)

1. 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.

- When used in combination with Interferon Alfa-2b (Genetical Recombination), Interferon Beta, Sofosbuvir, or the Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir fixed-dose combination tablet

Body weight	Dose of 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

- When used in combination with Peginterferon Alfa-2b (Genetical Recombination)

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

Body weight	Dose of 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

(2) Patients with chronic hepatitis C and compensated cirrhosis with baseline hemoglobin level <14 g/dL

Body weight	Dose of Ribavirin		
	Daily dose	After breakfast	After evening meal
≤60 kg	400 mg	200 mg	200 mg
>60 kg and ≤80 kg	600 mg	200 mg	400 mg
>80 kg	800 mg	400 mg	400 mg

(c) Copegus Tablets 200 mg

(No changes)

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	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

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List of Abbreviations

3TC	Lamivudine
Amio	Amiodarone
APRI	Aspartate aminotransferase to platelet ratio index
AUC	Area under the plasma concentration versus time curve
AUC_{last}	AUC from time of administration up to the last time point with a measurable concentration after dosing
AUC_{tau}	AUC over the dosing interval
C_{max}	Maximum plasma concentration
DAA	Direct acting anti-virals
DCV	daclatasvir
EC_{50}	50% effective concentration
ETR	Etravirine
FAS	Full analysis set
FTC	Emtricitabine
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IFN	Interferon
LDV	Ledipasvir
MVC	Maraviroc
PegIFN	Peginterferon
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
QD	quaque die
RAL	Raltegravir
RBV	Ribavirin
RTV	Ritonavir
SMV	Simeprevir
SOF	Sofosbuvir
SOF+RBV regimen	Combination regimen of sofosbuvir and ribavirin
SVR	Sustained virologic response

SVR12	Sustained virologic response of week 12
SVR24	Sustained virologic response of week 24
TDF	Tenofovir disoproxil fumarate
TVR	Telaprevir

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

Sofosbuvir (SOF), the active ingredient of Sovaldi Tablets 400 mg, is a nucleotide analog. The active metabolite of SOF, the uridine triphosphate form, suppresses hepatitis C virus (HCV) proliferation by inhibiting NS5B, which is essential for HCV replication. Ribavirin (RBV), the active ingredient of Rebetol Capsules 200 mg and Copegus Tablets 200 mg, is a nucleoside analog that shows antiviral activity against some DNA and RNA viruses. In Japan, a combination regimen of SOF and RBV (hereinafter, the SOF + RBV regimen) was approved in March 2015 for the indication of "suppression of viremia in patients with serogroup 2 (genotype 2) chronic hepatitis C with or without compensated cirrhosis" with a 12-week treatment period.

An estimated 1.5 to 2.0 million people have been infected with HCV in Japan (Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. Guidelines for the Management of Hepatitis C Virus Infection version 5.2. 2016). Among them, approximately 2800 patients are estimated to be infected with HCV genotype 3 and a very small number of patients are infected with HCV genotype 4, 5, or 6 (*J Gastroenterol.* 1996; 31: 801-5; *Hepatol Res.* 2009; 39: 657-63; etc.).

The 28th meeting of the Study Group on Unapproved and Off-label Drugs of High Medical Need which was established by the Ministry of Health, Labour and Welfare (MHLW), was held in August 2016. At the meeting, the study group concluded that a particularly high medical need existed for the SOF + RBV regimen in the "suppression of viremia in patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis." Based on this conclusion, MHLW requested the marketing authorization holders of SOF and RBV products to develop this regimen ("Request for the Development of Unapproved and Off-label Drugs" HPB/RDD Notification No. 0830-1, dated August 30, 2016, issued by the Research and Development Division, Health Policy Bureau and PSEHB/PED Notification No. 0830-2, dated August 30, 2016, issued by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

In response to the request from MHLW, the marketing authorization holders have filed a partial change application for Sovaldi Tablets 400 mg, Rebetol Capsules 200 mg, and Copegus Tablets 200 mg based on the results of the foreign clinical studies and Japanese clinical research study.

The SOF+RBV regimen for treatment of patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis has been approved in 69 countries/regions including Europe and the United State (US) as of December 2016.

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

No new study data were submitted by any of the applicants in the present applications for a new indication and/or dosage.

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

The results of a primary pharmacodynamic study and safety pharmacology studies were submitted by the applicant of Sovaldi Tablets 400 mg in support of the present application for new indication and dosage.

3.1 Primary pharmacodynamics

Antiviral activity of SOF against mutant viruses (CTD 4.2.1.1.1[1)])

A study was conducted to investigate the effects of HCV NS5B variants on the antiviral activity of SOF. Fold changes in susceptibility to SOF were evaluated using cells containing HCV replicons (genotypes 1a, 1b, 2a, 2b[2)], 3a, 4a, 5a[2)], and 6a[2)]) bearing NS5B substitutions reported in previous clinical studies or *in vitro* resistance selection studies of SOF (Package Insert of Sovaldi Tablets 400 mg, Version 6). The EC_{50} values of SOF against all the HCV genotype replicons encoding S282T substitution were 2.4- to 18.1-fold higher than the wild-type EC_{50}, showing decreased susceptibility to SOF. The EC_{50} values of SOF against HCV replicons bearing NS5B substitutions other than S282T (154 substitutions including L159F and V321A) were <2.5-fold those against the wild type.

3.2 Safety pharmacology (CTD 4.2.1.3.1, 4.2.1.3.2, 4.2.1.3.3, 4.2.1.3.4)

According to foreign post-marketing data on Sovaldi Tablets 400 mg, symptomatic bradycardia was reported in some patients receiving amiodarone (Amio) concomitantly with SOF and other direct acting anti-virals[3)] (DAAs). Taking the above findings into account, safety pharmacology studies were conducted to investigate the effects of amiodarone in combination with SOF and other DAAs on the cardiac conduction system. The results of the studies were newly submitted for the present application for a new indication and dosage (Table 1).

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1) In this Review Report (1), CTD numbers refer to those of the CTD submitted by the applicant of Sovaldi Tablets 400 mg unless otherwise stated.

2) The chimeric genotype 1b replicon cells encoding NS5B sequences from HCV genotype 2b, 5a, or 6a were used in this study.

3) Antiviral agents targeting NS3/4A, NS5A, and NS5B, non-structural regions that are not embedded in HCV particles. Ribavirin is not included.

Table 1. Summary of safety pharmacology studies

Study system	Endpoint, evaluation method, etc.	Concentration (μmol/L)	Route of administration	Noteworthy findings
Isolated guinea pig heart (≥4 samples/ concentration)	Atrial-His bundle (A-H) interval	Amio: 2 μmol/L DCV: 3 μmol/L SMV: 1 μmol/L SOF: 1 μmol/L GS-331007: 3 μmol/L	*ex vivo*	Change from baseline in A-H interval Amio: 13.8 ms Amio + DCV: 35.7 ms Amio + SMV: 24.7 ms Amio + SOF: 19.5 ms Amio + SOF + DCV: 47.0 ms (Atrioventricular block occurred in 2 of 5 tests) Amio + SOF + SMV: 26.8 ms Amio + GS-331007 + DCV: 21.3 ms
CHO cells expressing human L-type calcium channel (≥3 samples/ concentration)	hCav1.2 calcium current	Amio: 0.07 μmol/L SOF: 1, 10, 30, 100 μmol/L LDV: 0.3, 1 μmol/L DCV: 1, 3 μmol/L SMV: 0.3, 1 μmol/L GS-331007: 30, 100 μmol/L	*in vitro*	Amio: inhibited by 23% Amio + SOF (1, 10, 30, 100 μmol/L): inhibited by 39.5%, 67.4%, 42.2%, and 81.8%, respectively Amio + LDV (0.3, 1 μmol/L): inhibited by 41.9% and 58.9%, respectively Amio + SOF (1 μmol/L) + LDV (0.3 μmol/L): inhibited by 44.1% Amio + SOF (1 μmol/L) + DCV (3 μmol/L): inhibited by 43.2% Combination of Amio with DCV, SMV, or GS-331007 had no effect on the inhibitory action of Amio.
HEK-293 cells expressing human T-type calcium channel (≥3 samples/ concentration)	hCav3.2 calcium current	Amio: 0.3 μmol/L DCV: 1, 3 μmol/L SMV: 0.1, 0.3 μmol/L SOF: 30, 100 μmol/L LDV: 0.3, 1 μmol/L GS-331007: 30, 100 μmol/L	*in vitro*	Amio (0.3 μmol/L): inhibited by 25.3% Combination of Amio (0.3 μmol/L) with DCV, SMV, SOF, LDV, or GS-331007 had no effect on the inhibitory action of Amio.
HEK-293 cells expressing human hyperpolarization-activated cyclic nucleotide-gated channel (≥3 samples/ concentration)	hHCN4 potassium current	Amio: 0.3 μmol/L DCV: 1, 3 μmol/L SMV: 0.3, 1 μmol/L SOF: 1, 10 μmol/L LDV: 0.3, 1 μmol/L GS-331007: 3, 10 μmol/L	*in vitro*	Neither Amio (0.3 μmol/L) alone nor Amio (0.3 μmol/L) in combination with 2 components of various DAAs had any effect.

hCav1.2, human L-type calcium channel 1.2; hCav3.2, human T-type calcium channel 3.2; hHCN4, human hyperpolarization-activated cyclic nucleotide-gated channel 4; Amio, amiodarone; DCV, daclatasvir; SMV, simeprevir; LDV, ledipasvir; GS-331007, major metabolite of SOF in plasma

The applicant of Sovaldi Tablets 400 mg provided the following explanation about the effects of amiodarone in combination with SOF or other DAAs on the cardiac conduction system:

The effects of amiodarone in combination with SOF or other DAAs on atrial-His bundle (A-H) intervals (time), an index of atrioventricular nodal conduction, were evaluated in *ex vivo* studies[4)] using isolated guinea pig hearts. Prolongation of A-H intervals (time) was observed after the addition of 2 components (amiodarone + daclatasvir, simeprevir, or SOF) compared with after the addition of amiodarone alone. Addition of 3 components (amiodarone + SOF + daclatasvir) induced further prolongation of A-H intervals (time).

4) The concentrations of test substances used in each study were determined based on the estimated maximum plasma concentration of each substance administered at its clinical dose.

To clarify the mechanism of A-H interval (time) prolongation, the effects of amiodarone and each of the DAAs on 3 types of ion channels were investigated by the patch clamp technique. No changes in current were observed in the human T-type calcium channel 3.2 (hCav3.2) or human hyperpolarization-activated cyclic nucleotide-gated channel 4 (hHCN4) after the addition of 2 components (amiodarone + each DAA) compared with after the addition of amiodarone alone, suggesting that neither hCav3.2 nor hHCN4 is involved in the prolongation of the A-H interval (time). In an experiment with the human L-type calcium channel 1.2 (hCav1.2), inhibitory action on the hCav1.2 calcium current was greater after the addition of 2 components (amiodarone + SOF or ledipasvir) than after the addition of amiodarone alone, but no effects were observed after the addition of amiodarone in combination with other DAAs. As shown above, the results of these studies were not consistent with those of *ex vivo* studies using guinea pig hearts.

3.R Outline of the review conducted by PMDA

3.R.1 Antiviral activity of SOF and RBV

Each applicant provided the following explanation about the antiviral activity of SOF and that of the combination of SOF and RBV:

The *in vitro* EC_{50} values of SOF against HCV replicons (genotype 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a) were 14 to 110 nmol/L (Review Report of Sovaldi Tablets 400 mg [dated February 23, 2015]), showing that SOF can be expected to have antiviral activity against any of these HCV genotypes.

The antiviral activity of SOF or RBV was evaluated using wild-type replicon cells of HCV genotypes 1 to 6. The EC_{50} values of RBV against HCV genotypes 3 to 6 replicons were 1.5 to 7.1 μmol/L, showing no marked differences from those against HCV genotypes 1 and 2 replicons (Table 2).

Table 2. Antiviral activity of SOF or RBV against wild-type HCV replicon cells

HCV genotype (wild-type)	EC_{50} (nmol/L)	EC_{50} (μmol/L)
	SOF	RBV
1a	30.2	26.1
1b	21.5	6.6
2a	146.8	8.3
2b	13.3	2.6
3a	33.9	6.7
4a	35.8	6.2
5a	21.9	1.5
6a	45.5	7.1
Mean		

In the experiment using HCV genotype 1a replicon cells, a weak synergistic interaction was observed after the addition of SOF in combination with RBV (Review Report of Sovaldi Tablets 400 mg [dated February 23, 2015]).

The above results suggest that SOF and RBV can be expected to have antiviral activity against HCV genotypes 3 to 6.

PMDA's view:

Taking into account the results of studies using HCV replicon cells, SOF and RBV can be expected to have antiviral activity against HCV genotypes 3 to 6. The efficacy of the SOF + RBV regimen in patients with genotype 3 to 6 chronic hepatitis C with or without compensated cirrhosis is evaluated in Sections 7.R.2 and 7.R.4.

3.R.2 Resistance to SOF

The applicant of Sovaldi Tablets 400 mg provided the following explanation about the SOF resistance profiles of HCV genotypes:

In the *in vitro* resistance selection studies of SOF using HCV genotypes 1 to 6 replicon cells, the NS5B S282T substitution was detected in all the HCV genotype replicon cells evaluated. Reduced susceptibility to SOF was observed in all the HCV genotype replicons bearing an S282T substitution and the EC_{50} values were increased to 2.4- to 18.1-fold compared to the wild-type replicon (Package Insert of Sovaldi Tablets 400 mg, version 5). These findings suggested that the S282T substitution was a resistance-associated variant for SOF in all the HCV genotypes. However, an S282T substitution rarely emerges, and there are no available data showing the detection of this substitution before the first dose of SOF (*Clin Infect Dis.* 2014; 59: 1666-74).

Besides the S282T substitution, L159F and V321A substitutions were found in approximately 15% and 5%, respectively, of patients who did not achieve sustained virologic response (SVR) after treatment with an SOF-containing regimen, and the incidence of these substitutions was similar in patients with genotype 1, 2, or 3 HCV infection (*J Infect Dis.* 2016; 213: 1240-47). The L159F substitution, which was detected in approximately 10% of patients with genotype 1b HCV infection at baseline, rarely emerged in patients infected with other HCV genotypes. Although patients with genotype 1b HCV infection in whom the L159F substitution had been detected at baseline underwent the 24-week SOF + RBV regimen, there were no effects of the substitution on SVR12 rates. The V321A substitution was rarely detected in patients with any genotype HCV infection and was hardly detected at baseline. An analysis of the outcomes of patients with any genotype HCV infection who were treated properly with an SOF-containing regimen showed that baseline variants in the NS5B region were not related with treatment failure in patients treated with the SOF+RBV regimen.

Therefore, any of HCV genotypes 1 to 6 is unlikely to become resistant to SOF.

PMDA's view:

The results of *in vitro* studies using HCV replicon cells bearing NS5B substitutions reported in clinical studies or *in vitro* resistance selection studies of SOF indicated that the S282T substitution in the NS5B region contributes to a reduction in susceptibility to SOF in any HCV genotype [see Section 3.1]. The emergence of resistance mutations is important information related to the efficacy of the SOF + RBV regimen. Information on resistance to SOF should continue to be collected in the post-marketing setting, and any new findings should be promptly provided to healthcare professionals in clinical practice. The

relationship between resistance mutations reported in clinical studies and the efficacy of the SOF + RBV regimen is evaluated in Section 7.R.2.2.

3.R.3 Cardiac toxicity

The applicant of Sovaldi Tablets 400 mg provided the following explanation about the potential impact of effects of amiodarone in combination with SOF on the cardiac conduction system:

Outside Japan, symptomatic bradycardia was reported in some patients treated with amiodarone in combination with SOF and other DAAs. The mechanism of the onset of this clinical symptom, though investigated in non-clinical studies, was not clarified [see Sections 3.2, 4.1, and 5.1]. According to the currently available safety information on Sovaldi Tablets 400 mg, including post-marketing information, there is no evidence suggesting any relationship between cardiac conduction system-related adverse events and the co-administration of amiodarone, SOF, and RBV without other DAAs. In Japan, Sovaldi Tablets 400 mg is approved only for the treatment of HCV infection in combination with RBV and is unlikely to be used in combination with other DAAs. Based on the above, at present, no new precautionary statements about the risk of bradycardia resulting from the co-administration of amiodarone and SOF are necessary in the package insert of Sovaldi Tablets 400 mg.

PMDA's view:

The applicant of Sovaldi Tablets 400 mg has claimed that no new precautionary statement about the risk of bradycardia resulting from the co-administration of Sovaldi Tablets 400 mg and amiodarone is necessary in the package insert. The applicant's claim is understandable. However, the applicant should continue to collect information on the occurrence of cardiac conduction system-related adverse events.

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

The results of non-clinical pharmacokinetic studies were newly submitted by the applicant of Sovaldi Tablets 400 mg in support of the present application for a new indication and dosage.

4.1 Drug interaction with amiodarone

4.1.1 Drug interaction mediated by plasma protein binding (CTD 4.2.2.6.3)

The effects of 10 μmol/L SOF on the plasma protein binding of 10 μmol/L amiodarone and its active metabolite, *N*-desethylamiodarone (10 μmol/L), were evaluated using human plasma. SOF had no impact on the plasma protein binding of amiodarone or *N*-desethylamiodarone.

4.1.2 Drug interaction mediated by tissue binding (CTD 4.2.2.6.4)

The effects of 10 μmol/L SOF on the binding of 20 μmol/L amiodarone and 20 μmol/L *N*-desethylamiodarone to the atrial tissue were evaluated using human atrial tissue homogenate. SOF had no impact on the binding of amiodarone or *N*-desethylamiodarone to human atrial tissue.

4.R Outline of the review conducted by PMDA

PMDA concluded that there are no particular pharmacokinetic concerns in the data submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The results of a repeated-dose toxicity study in rats conducted to evaluate the cardiac toxicity of SOF were newly submitted by the applicant of Sovaldi Tablets 400 mg in support of the present application for a new indication and dosage.

5.1 Seven-day repeated oral dose study in rats with a 4-week recovery period (CTD 4.2.3.2.1)

Rats (n = 15/sex/group) orally received SOF at 0 (vehicle[5)]), 500, or 1000 mg/kg twice daily for 7 days in a repeated-dose study (including evaluation of reversibility after a 4-week recovery period and measurement of concentrations of GS-331007, the major metabolite of SOF in plasma, in the cardiac tissue). No deaths occurred in any of the dose groups. Histopathological examination of the heart showed no abnormal findings. At ≥500 mg/kg, the incidence of soft feces, etc. tended to increase, this change had no impact on body weight gain or general condition. Thus, the change was of little toxicological significance, according to the applicant of Sovaldi Tablets 400 mg. No abnormalities were found in other test parameters in any groups including the recovery group (n = 5/sex). Based on the above, the no-observed-adverse-effect level (NOAEL) in the study was determined to be 2000 mg/kg/day.

GS-331007 was detected in the cardiac tissue. The plasma exposure to GS-331007 in rats following administration of SOF at 2000 mg/kg/day (C_{max}, 11.0 μg/mL for males and 12.8 μg/mL for females; AUC_{last}, 193 μg·h/mL for males and 223 μg·h/mL for females) was compared with that in humans[6)] following administration of SOF at the clinical dose (400 mg/day) (C_{max}, 0.582 μg/mL; AUC_{tau}, 7.12 μg·h/mL). The C_{max} and AUC in rats were 19- to 22-fold and 27- to 31-fold, respectively, of those in humans.

5.R Outline of the review conducted by PMDA

PMDA concluded that there are no particular toxicological concerns with the data submitted to support the clinical use of SOF.

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

6.1 Biopharmaceutic studies and associated analytical methods

No new biopharmaceutic data were submitted for the present applications for new indication and/or dosage.

Liquid chromatography/tandem mass spectrometry was used to determine the concentrations of SOF and its major metabolite, GS-331007, in human plasma (lower limit of quantitation [LLOQ], 5 ng/mL for SOF and 10 ng/mL for GS-331007).

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5) 95% polyethylene glycol 400 and 5% polysorbate 80

6) Exposure to GS-331007 in patients with chronic hepatitis C (genotypes 1-6) after administration of 400 mg SOF, which was estimated from a PPK model developed based on the results of foreign clinical studies of SOF (Review Report of Sovaldi Tablets 400 mg dated February 23, 2015)

6.2 Clinical pharmacology

The results of a foreign clinical study in patients with chronic hepatitis C with or without compensated cirrhosis were newly submitted by the applicant of Sovaldi Tablets 400 mg in support of the present application for a new indication and dosage. The results of *in vitro* studies using human biomaterials are presented in the section for non-clinical pharmacokinetics [see Section 4.1]. In the following sections, doses are expressed as doses of active ingredients and pharmacokinetic (PK) parameters are expressed as mean values.

Foreign phase III study (CTD 5.3.5.1.1, Study GS-US-334-0123 [July 2012 to February 2014])

HIV co-infected patients with genotype 1, 2, or 3 chronic hepatitis C with or without compensated cirrhosis orally received SOF 400 mg once daily in combination with RBV (brand name, Ribasphere Tablets [note: a generic product of Rebetol Capsules 200 mg; not approved in Japan]) for 12 or 24 weeks. Data on plasma concentrations of SOF and GS-331007 in the patients treated (2172 plasma concentration data from 221 patients) were used for analysis. Steady-state PK parameters of SOF and GS-331007 were estimated by the population pharmacokinetic (PPK) model developed based on the results of previous foreign clinical studies of SOF (Review Report of Sovaldi Tablets 400 mg dated February 23, 2015). The estimated C_{max} and AUC_{tau} were 480 ng/mL and 1011 ng·h/mL, respectively, for SOF and 1015 ng/mL and 8053 ng·h/mL, respectively, for GS-331007. The estimated C_{max} and AUC_{tau} values of SOF and GS-331007 were similar irrespective of HCV genotype, presence or absence of concomitant anti-HIV agents, or type of anti-HIV agents used concomitantly.[7)]

6.R Outline of the review conducted by PMDA

PMDA concluded that there are no particular concerns with the clinical pharmacology data submitted.

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

The results of the foreign clinical studies and Japanese clinical research study were submitted by the applicant of Sovaldi Tablets 400 mg as efficacy and safety data in support of the present application for a new indication and dosage. The applicants of Rebetol Capsules 200 mg and Copegus Tablets 200 mg also submitted identical data. The data from clinical studies and clinical research study submitted by each applicant are summarized in Table 3.

7) Efavirenz/FTC/TDF, rilpivirine/FTC/TDF, raltegravir/FTC/TDF, darunavir/RTV/FTC/TDF, atazanavir/RTV/FTC/TDF, and other anti-HIV agents

Table 3. Summary of main clinical studies conducted to evaluate the efficacy and safety of the SOF+RBV regimen

Study No. (phase)	Study population	n	Dosage regimen
Foreign clinical studies (evaluation data)			
GS-US-334-0133 (III)	Patients with genotype 2 or 3 chronic hepatitis C with or without compensated cirrhosis	419	12 or 24 weeks[a)] of SOF 400 mg QD + RBV or placebo QD
GS-US-334-0153 (III)	Patients with genotype 2 or 3 chronic hepatitis C with or without compensated cirrhosis	592	16 or 24 weeks of SOF 400 mg QD + RBV or 12 weeks of SOF 400 mg QD + RBV + PegIFN 180 µg/week
GS-US-334-0123 (III)	Patients with genotype 1, 2, or 3 chronic hepatitis C with or without compensated cirrhosis, who were co-infected with HIV	223	12 or 24 weeks of SOF 400 mg QD + RBV
GS-US-334-0124 (III)	Patients with genotype 1, 2, 3, or 4 chronic hepatitis C with or without compensated cirrhosis, who were co-infected with HIV	274	12 or 24 weeks of SOF 400 mg QD + RBV
Japanese clinical research study (reference data)			
—	Patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis, who were co-infected with HIV	4	24 weeks of SOF 400 mg QD + RBV

a) Based on the results of another clinical study (GS-US-334-0108), the duration of treatment with SOF 400 mg QD + RBV for patients with genotype 3 HCV infection was changed from 12 weeks to 24 weeks.

7.1 Foreign clinical studies

7.1.1 Foreign phase III study (CTD 5.3.5.1.3, Study GS-US-334-0133 [September 2012 to January 2014])

A randomized, double-blind, parallel group study[8)] was conducted at 77 sites in 10 countries including France, Germany, Italy, and the UK to assess the efficacy and safety of the SOF+RBV regimen in patients with genotype 2 or 3 chronic hepatitis C with or without compensated cirrhosis[9)] (target sample size of 400 subjects [320 subjects for the SOF+RBV group and 80 subjects for the placebo group]).

In the initial study plan, the treatment duration was 12 weeks for the SOF + RBV group and the placebo group (randomization ratio of 4 to 1). Based on the results of a foreign clinical study (GS-US-334-0108), the treatment duration for subjects with genotype 3 HCV infection in the SOF + RBV group was changed to 24 weeks.[10)]

According to the changed dosage regimen, subjects in the SOF + RBV group received SOF 400 mg QD in combination with RBV (brand name, Ribasphere Tablets [note: a generic product of Rebetol Capsules 200 mg; not approved in Japan]) at a weight-based dose (1000 mg/day [body weight ≤75 kg] or 1200 mg/day [body weight >75 kg] in two divided doses) for 12 weeks (genotype 2 or 3) or 24 weeks (genotype 3), and subjects in the placebo group received SOF placebo QD with RBV placebo for 12 weeks.

8) Randomized based on the presence or absence of prior treatment with IFN and the presence or absence of cirrhosis as randomization factors

9) Diagnosed by (a) liver biopsy findings, (b) Fibroscan (>12.5 kPa), or (c) Fibrotest score of >0.75 and aspartate aminotransferase to platelet ratio index (APRI) score of >2

10) Data from a foreign phase III study (Study GS-US-334-0108) become available during the treatment period of Study GS-US-334-0133, showing that the SVR12 rate in subjects infected with genotype 3 HCV receiving the SOF + RBV regimen for 12 weeks and 16 weeks was 30% (19 of 64 subjects) and 62% (39 of 63 subjects), respectively. This results suggested that patients infected with genotype 3 HCV would obtain clinical benefits from ≥12-week treatment with the SOF + RBV regimen. Based on the above findings, the blinding code was broken, and the treatment duration was changed to 24 weeks for all the subjects infected with genotype 3 HCV in the SOF+RBV group who had not completed or discontinued the 12-week treatment.

A total of 419 subjects received at least 1 dose of the study drug; 334 subjects in the SOF + RBV group (84 subjects [genotype 2, n = 73; genotype 3, n = 11] treated for 12 weeks and 250 subjects [genotype 3] treated for 24 weeks) and 85 subjects in the placebo group (genotype 2, n = 18; genotype 3, n = 67). All of these subjects were included in the safety analysis set, and 334 subjects in the SOF + RBV group (84 subjects [genotype 2, n = 73; genotype 3, n = 11] treated for 12 weeks and 250 subjects [genotype 3] treated for 24 weeks) were included in the full analysis set (FAS). The FAS was the efficacy analysis set.

The primary efficacy endpoint was the SVR12 rate.[11)] The results are shown in Table 4. In the SOF+RBV group, the SVR24 rate in subjects treated for 12 weeks was 93.2% (68 of 73 subjects; genotype 2) and 27.3% (3 of 11 subjects; genotype 3), and that in subjects treated for 24 weeks was 85.2% (213 of 250 subjects; genotype 3). In the placebo group, no subjects' HCV RNA levels fell below the LLOQ.

Table 4. SVR12 rates (FAS)

		SVR12 rate [95% CI][a)]		
		Genotype 2	Genotype 3	
		12-week SOF + RBV	12-week SOF + RBV	24-week SOF + RBV
Overall population		93.2 [84.7, 97.7] (68/73)	27.3 [6.0, 61.0] (3/11)	85.2 [80.2, 89.4] (213/250)
Prior treatment (IFN-based regimen)	Yes	90.2 [76.9, 97.3] (37/41)	33.3 [7.5, 70.1] (3/9)	78.6 [71.0, 85.0] (114/145)
	No	96.9 [83.8, 99.9] (31/32)	0 (0/2)	94.3 [88.0, 97.9] (99/105)
Subjects with chronic hepatitis C		95.2 [86.5, 99.0] (59/62)	33.3 [7.5, 70.1] (3/9)	90.5 [85.4, 94.3] (172/190)
Subjects with chronic hepatitis C and compensated cirrhosis		81.8 [48.2, 97.7] (9/11)	0 (0/2)	68.3 [55.0, 79.7] (41/60)

% (n/N)
a) 95% confidence interval (CI) was calculated by the Clopper-Pearson method.

Safety data were analyzed. The incidence of adverse events (including abnormal changes in laboratory values) in the 12-week SOF + RBV group, 24-week SOF + RBV group, and placebo group was 85.7% (72 of 84 subjects), 91.6% (229 of 250 subjects), and 70.6% (60 of 85 subjects), respectively. The incidence of adverse drug reactions[12)] (including abnormal changes in laboratory values) in the 12-week SOF+RBV group, 24-week SOF+RBV group, and placebo group was 72.6% (61 of 84 subjects), 74.4% (186 of 250 subjects), and 42.4% (36 of 85 subjects), respectively. The adverse events and adverse drug reactions occurring in ≥10% of subjects treated with any regimen are shown in Table 5.

11) The proportion of subjects with a HCV RNA level below the LLOQ at 12 weeks after the end of treatment
12) Adverse events considered by the investigators (sub-investigators) to be related to the study drug

Table 5. Adverse events and adverse drug reactions occurring in ≥10% of subjects in any group (safety analysis set)

Name of event	Adverse events			Adverse drug reactions		
	12-week SOF + RBV (N = 84)	24-week SOF + RBV (N = 250)	Placebo (N = 85)	12-week SOF + RBV (N = 84)	24-week SOF + RBV (N = 250)	Placebo (N = 85)
Overall	72 (85.7)	229 (91.6)	60 (70.6)	61 (72.6)	186 (74.4)	36 (42.4)
Headache	24 (28.6)	74 (29.6)	23 (27.1)	17 (20.2)	51 (20.4)	13 (15.3)
Fatigue	19 (22.6)	75 (30.0)	16 (18.8)	19 (22.6)	63 (25.2)	13 (15.3)
Pruritus	20 (23.8)	67 (26.8)	8 (9.4)	16 (19.0)	52 (20.8)	8 (9.4)
Asthenia	21 (25.0)	53 (21.2)	4 (4.7)	17 (20.2)	50 (20.0)	2 (2.4)
Nausea	26 (31.0)	33 (13.2)	9 (10.6)	22 (26.2)	27 (10.8)	7 (8.2)
Insomnia	9 (10.7)	41 (16.4)	2 (2.4)	6 (7.1)	32 (12.8)	1 (1.2)
Nasopharyngitis	4 (4.8)	36 (14.4)	9 (10.6)	0	4 (1.6)	0
Dry skin	8 (9.5)	31 (12.4)	5 (5.9)	8 (9.5)	23 (9.2)	4 (4.7)
Dyspnoea	12 (14.3)	27 (10.8)	1 (1.2)	9 (10.7)	22 (8.8)	1 (1.2)
Cough	8 (9.5)	27 (10.8)	4 (4.7)	3 (3.6)	14 (5.6)	2 (2.4)
Diarrhoea	4 (4.8)	30 (12.0)	4 (4.7)	2 (2.4)	17 (6.8)	0
Arthralgia	3 (3.6)	25 (10.0)	6 (7.1)	1 (1.2)	12 (4.8)	3 (3.5)
Irritability	4 (4.8)	26 (10.4)	3 (3.5)	4 (4.8)	26 (10.4)	2 (2.4)

n (%)

No deaths were reported in the study. Serious adverse events occurred in 10 subjects in the 24-week SOF + RBV group (amylase increased, lipase increased, arrhythmia, biliary colic, road traffic accident, complex regional pain syndrome, haemorrhoidal haemorrhage, hepatocellular carcinoma, hyperglycaemia, invasive ductal breast carcinoma, and suicide attempt in 1 subject each [some subjects had more than 1 event]) and 2 subjects in the placebo group (adenocarcinoma of colon and gastroenteritis in 1 subject each). The suicide attempt in 1 subject in the 24-week SOF+RBV group was considered related to the study drug. The outcomes of all the serious adverse events were "resolved," except for those in 3 subjects who were being followed (hepatocellular carcinoma, invasive ductal breast carcinoma, and adenocarcinoma of colon).

Adverse events leading to discontinuation of SOF occurred in 1 subject in the 12-week SOF + RBV group (malaise and headache [the subject had more than 1 event]), 1 subject in the 24-week SOF + RBV group (suicide attempt), and 1 subject in the placebo group (liver function test abnormal). All these adverse events were considered related to the study drug and their outcomes were all "resolved."

Adverse events leading to dose reduction or interruption of RBV occurred in 6 subjects in the 12-week SOF + RBV group (anaemia in 4 subjects; and fatigue, dry skin, and gastroenteritis in 1 subject each [some subjects had more than 1 event]), 14 subjects in the 24-week SOF + RBV group (anaemia in 9 subjects; asthma in 2 subjects; and fatigue, abdominal pain, dyspnoea, pruritus, and rash generalised in 1 subject each [some subjects had more than 1 event]), and 1 subject in the placebo group (anaemia in 1 subject).

7.1.2 Foreign phase III study (CTD 5.3.5.1.4, Study GS-US-334-0153 [September 2013 to March 2015])

A randomized, double-blind, parallel group study[13] was conducted at 80 sites in 5 countries comprising the UK, the US, Australia, Canada, and New Zealand to assess the efficacy and safety of the SOF + RBV regimen versus the SOF + PegIFN + RBV regimen in patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis and those with genotype 2 chronic hepatitis C and compensated cirrhosis[14] (target sample size of 600 subjects [200 subjects each for the 16-week SOF + RBV group, 24-week SOF + RBV group, and 12-week SOF + PegIFN + RBV group]).

Subjects in the SOF + RBV group received SOF 400 mg QD in combination with RBV (brand name, Ribasphere Tablets [note: a generic product of Rebetol Capsules 200 mg; not approved in Japan]) at a weight-based dose (1000 mg/day [body weight ≤75 kg] or 1200 mg/day [body weight >75 kg] in two divided doses) for 16 or 24 weeks. Subjects in the 12-week SOF + PegIFN + RBV group received SOF 400 mg QD in combination with RBV at a weight-based dose (1000 mg/day [body weight ≤75 kg] or 1200 mg/day [body weight >75 kg] in two divided doses) and Peginterferon Alfa-2a (Genetical Recombination) 180 μg (once weekly) for 12 weeks.

A total of 592 randomized subjects received at least 1 dose of the study drug (the 16-week SOF + RBV group, n = 196; the 24-week SOF + RBV group, n = 199; and the 12-week SOF + PegIFN + RBV group, n = 197). All of the subjects were included in the FAS, safety analysis set, and efficacy analysis set.

The primary efficacy endpoint was the SVR12 rate. The results are shown in Table 6. The between-group difference in SVR12 rate in subjects with genotype 3 chronic hepatitis C with or without compensated cirrhosis was calculated using the Cochran-Mantel-Haenszel method with the presence or absence of previous IFN treatment and the presence or absence of compensated cirrhosis as stratification factors. The difference [95% confidence interval (CI)] in SVR12 rate between the 16-week SOF + RBV group and the 24-week SOF + RBV group was −13.1% [−21.5%, −4.7%], and the lower bound of the 95% CI was below the pre-specified non-inferiority margin (−12%); therefore, the non-inferiority of the 16-week SOF + RBV regimen to the 24-week SOF + RBV regimen was not confirmed.[15] The difference [95% CI] in SVR12 rate between the 24-week SOF + RBV group and the 12-week SOF + PegIFN + RBV group was −8.8% [−15.5%, −2.1%], and the lower bound of the 95% CI was below the pre-specified non-inferiority margin (−12%); therefore, the non-inferiority of the 24-week SOF + RBV regimen to the 12-week SOF + PegIFN + RBV regimen was not confirmed.[15]

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13) Randomized based on HCV genotype, the presence or absence of cirrhosis, and the presence or absence of prior treatment as randomization factors

14) Diagnosed by (a) liver biopsy findings or (b) Fibroscan (>12.5 kPa)

15) The study was intended to (a) verify the non-inferiority of the 16-week SOF + RBV regimen to the 24-week SOF + RBV regimen or to (b) verify the non-inferiority of the 24-week SOF + RBV regimen to the 12-week SOF + PegIFN + RBV regimen (non-inferiority margin of 12%). The gatekeeping method was used to control the probability of type I error (familywise error rate).

The SVR24 rate was 86.7% (13 of 15 subjects) in the 16-week SOF + RBV group (genotype 2), 70.7% (128 of 181 subjects) in the 16-week SOF + RBV group (genotype 3), 100.0% (17 of 17 subjects) in the 24-week SOF + RBV group (genotype 2), 83.0% (151 of 182 subjects) in the 24-week SOF + RBV group (genotype 3), 93.8% (15 of 16 subjects) in the 12-week SOF + PegIFN + RBV group (genotype 2), and 93.4% (169 of 181 subjects) in the 12-week SOF + PegIFN + RBV group (genotype 3).

Table 6. SVR12 rate (FAS)

			SVR12 rate [95% CI][a)]		
			16-week SOF + RBV	24-week SOF + RBV	12-week SOF + PegIFN + RBV
Genotype 2	Overall subjects		86.7 [59.5, 98.3] (13/15)	100 [80.5, 100] (17/17)	93.8 [69.8, 99.8] (15/16)
	Prior treatment (IFN-based regimen)	Yes	86.7 [59.5, 98.3] (13/15)	100 [80.5, 100] (17/17)	93.8 [69.8, 99.8] (15/16)
		No	–	–	–
	Subjects with chronic hepatitis C		–	–	–
	Subjects with chronic hepatitis C and compensated cirrhosis		86.7 [59.5, 98.3] (13/15)	100 [80.5, 100] (17/17)	93.8 [69.8, 99.8] (15/16)
Genotype 3	Overall subjects		70.7 [63.5, 77.2] (128/181)	84.1 [77.9, 89.1] (153/182)	92.8 [88.0, 96.1] (168/181)
	Prior treatment (IFN-based regimen)	Yes	64.4 [53.7, 74.3] (58/90)	79.5 [69.6, 87.4] (70/88)	90.8 [82.7, 95.9] (79/87)
		No	76.9 [66.9, 85.1] (70/91)	88.3 [80.0, 94.0] (83/94)	94.7 [88.0, 98.3] (89/94)
	Subjects with chronic hepatitis C		79.8 [71.7, 86.5] (99/124)	86.5 [79.3, 91.9] (109/126)	95.1 [89.7, 98.2] (117/123)
	Subjects with chronic hepatitis C and compensated cirrhosis		50.9 [37.3, 64.4] (29/57)	78.6 [65.6, 88.4] (44/56)	87.9 [76.7, 95.0] (51/58)

% (n/N); −, not calculated
a) 95% CI was calculated using the Clopper-Pearson method.

Safety data were analyzed. The incidence of adverse events (including abnormal changes in laboratory values) in the 16-week SOF + RBV group, 24-week SOF + RBV group, and 12-week SOF + PegIFN + RBV group was 94.4% (185 of 196 subjects), 94.5% (188 of 199 subjects), and 99.0% (195 of 197 subjects), respectively. The incidence of adverse drug reactions[12)] (including abnormal changes in laboratory values) in the 16-week SOF + RBV group, 24-week SOF + RBV group, and 12-week SOF + PegIFN + RBV group was 79.1% (155 of 196 subjects), 78.4% (156 of 199 subjects), and 95.9% (189 of 197 subjects), respectively. The adverse events and adverse drug reactions occurring in ≥10% of subjects in any group are shown in Table 7.

Table 7. Adverse events and adverse drug reactions occurring in ≥10% of subjects in any group (safety analysis set)

Name of event	Adverse events			Adverse drug reactions		
	16-week SOF + RBV (N = 196)	24-week SOF + RBV (N = 199)	12-week SOF + PegIFN + RBV (N = 197)	16-week SOF + RBV (N = 196)	24-week SOF + RBV (N = 199)	12-week SOF + PegIFN + RBV (N = 197)
Overall	185 (94.4)	188 (94.5)	195 (99.0)	155 (79.1)	156 (78.4)	189 (95.9)
Fatigue	74 (37.8)	83 (41.7)	92 (46.7)	64 (32.7)	77 (38.7)	89 (45.2)
Headache	61 (31.1)	72 (36.2)	70 (35.5)	46 (23.5)	54 (27.1)	61 (31.0)
Insomnia	47 (24.0)	56 (28.1)	50 (25.4)	40 (20.4)	47 (23.6)	47 (23.9)
Nausea	32 (16.3)	34 (17.1)	50 (25.4)	24 (12.2)	29 (14.6)	42 (21.3)
Rash	24 (12.2)	27 (13.6)	39 (19.8)	17 (8.7)	19 (9.5)	31 (15.7)
Dyspnoea exertional	22 (11.2)	22 (11.1)	30 (15.2)	19 (9.7)	19 (9.5)	27 (13.7)
Pruritus	21 (10.7)	24 (12.1)	22 (11.2)	19 (9.7)	20 (10.1)	16 (8.1)
Diarrhoea	21 (10.7)	18 (9.0)	27 (13.7)	11 (5.6)	8 (4.0)	20 (10.2)
Decreased appetite	13 (6.6)	16 (8.0)	35 (17.8)	11 (5.6)	12 (6.0)	32 (16.2)
Myalgia	12 (6.1)	19 (9.5)	33 (16.8)	8 (4.1)	14 (7.0)	31 (15.7)
Irritability	17 (8.7)	25 (12.6)	21 (10.7)	13 (6.6)	21 (10.6)	21 (10.7)
Dry skin	15 (7.7)	22 (11.1)	25 (12.7)	12 (6.1)	20 (10.1)	22 (11.2)
Cough	10 (5.1)	19 (9.5)	28 (14.2)	3 (1.5)	12 (6.0)	21 (10.7)
Influenza like illness	7 (3.6)	8 (4.0)	39 (19.8)	2 (1.0)	3 (1.5)	35 (17.8)
Arthralgia	10 (5.1)	15 (7.5)	25 (12.7)	5 (2.6)	8 (4.0)	20 (10.2)
Vomiting	10 (5.1)	21 (10.6)	19 (9.6)	5 (2.6)	9 (4.5)	15 (7.6)
Skeletal muscle pain	9 (4.6)	22 (11.1)	11 (5.6)	4 (2.0)	9 (4.5)	9 (4.6)
Pyrexia	5 (2.6)	7 (3.5)	29 (14.7)	2 (1.0)	8 (4.0)	27 (13.7)
Chills	3 (1.5)	4 (2.0)	21 (10.7)	3 (1.5)	2 (1.0)	18 (9.1)

n (%)

No deaths were reported in the study. Serious adverse events occurred in 8 subjects in the 16-week SOF + RBV group (depression, suicidal ideation, pancreatitis, acute coronary syndrome, adenocarcinoma of colon, arthritis, cellulitis, chest pain, and orthostatic hypotension in 1 subject each [some subjects had more than 1 event]), 10 subjects in the 24-week SOF + RBV group (atrial fibrillation, subcutaneous abscess, pancreatitis, syncope, abdominal pain, alcohol abuse, drug abuse, flank pain, hepatocellular carcinoma, miscarriage of partner, musculoskeletal chest pain, and overdose in 1 subject each [some subjects had more than 1 event]), and 12 subjects in the 12-week SOF + PegIFN + RBV group (atrial fibrillation, depression, syncope, alcohol withdrawal syndrome, haemoglobin decreased, hallucination, loss of consciousness, pleuritic pain, pneumonia, respiratory infection, snake bite, nausea, and vomiting in 1 subject each [some subjects had more than 1 event]). The events reported in 1 subject in the 16-week SOF + RBV group (depression and suicidal ideation [the subject had more than 1 event]), 1 subject in the 24-week SOF + RBV group (miscarriage of partner), and 5 subjects in the 12-week SOF + PegIFN + RBV group (pneumonia, respiratory infection, haemoglobin decreased, depression, and hallucination in 1 subject each) were considered related to the study drug. The outcomes of all these serious adverse events, excluding alcohol abuse, were “resolved.”

Adverse events leading to discontinuation of SOF occurred in 3 subjects in the 16-week SOF + RBV group (acute coronary syndrome, angina pectoris, sleep disorder, depression, and suicidal ideation in 1 subject each [some subjects had more than 1 event]), 2 subjects in the 24-week SOF + RBV group (alcohol abuse and drug abuse in 1 subject each), and 1 subject in the 12-week SOF + PegIFN + RBV group (depression). The events occurring in 1 subject in the 12-week SOF + PegIFN + RBV group

(depression) and 2 subjects in the 16-week SOF + RBV group (depression, suicidal ideation, and sleep disorder in 1 subject each [some subjects had more than 1 event]) were considered related to the study drug, and the outcomes of all these events, excluding sleep disorder and alcohol abuse, were "resolved."

Main adverse events leading to dose reduction or interruption of RBV occurred in 8 subjects in the 16-week SOF+RBV group (anaemia and fatigue in 3 subjects each; nausea in 2 subjects; and haemoglobin decreased, respiratory infection, abdominal pain, and pyrexia in 1 subject each [some subjects had more than 1 event]), 17 subjects in the 24-week SOF + RBV group (anaemia in 6 subjects; haemoglobin decreased and fatigue in 4 subjects each; and dizziness, depression, drug abuse, irritability, and rash in 1 subject each), and 26 subjects in the 12-week SOF + PegIFN + RBV group (haemoglobin decreased in 10 subjects; anaemia in 9 subjects; fatigue, dizziness, asthenia, dizziness postural, dyspnoea, dyspnoea exertional, and headache in 2 subjects each; and depression, respiratory infection, alcohol withdrawal syndrome, cardiac discomfort, disorientation, lethargy, mood swings, and tinnitus in 1 subject each [some subjects had more than 1 event]).

7.1.3 Foreign phase III study (CTD 5.3.5.1.1, Study GS-US-334-0123 [July 2012 to February 2014])

An open-label, uncontrolled study was conducted at 34 sites in the US and Puerto Rico to assess the efficacy and safety of the SOF + RBV regimen in patients with chronic hepatitis C with or without compensated cirrhosis[16] who were co-infected with HIV (target sample size of 230 subjects: treatment-naïve subjects [genotype 1], n = 115; treatment-naïve or IFN treatment-experienced subjects [genotype 2 or 3], n = 115).

SOF 400 mg QD in combination with RBV (brand name, Ribasphere Tablets [note: a generic product of Rebetol Capsules 200 mg; not approved in Japan]) at a weight-based dose (1000 mg/day [body weight ≤75 kg] or 1200 mg/day [body weight >75 kg] in two divided doses) was administered for 12 weeks to treatment-naïve subjects (genotype 2 or 3) and for 24 weeks to treatment-naïve subjects (genotype 1) and IFN treatment-experienced subjects (genotype 2 or 3).

A total of 223 subjects received at least 1 dose of the study drug (genotype 1, 114 treatment-naïve subjects; genotype 2, 26 treatment-naïve and 24 treatment-experienced subjects; genotype 3, 42 treatment-naïve and 17 treatment-experienced subjects). All of the subjects were included in the FAS and safety analysis set. The FAS also served as the efficacy analysis set.

The primary efficacy endpoint was the SVR12 rate. The results are shown in Table 8.

The SVR24 rate was 75.4% (86 of 114 subjects) in the 24-week SOF + RBV group (genotype 1), 88.5% (23 of 26 subjects) in the 12-week SOF + RBV group (genotype 2), 91.7% (22 of 24 subjects) in the 24-

16) Diagnosed by (a) liver biopsy findings, (b) Fibroscan (>12.5 kPa), or (c) Fibrotest score >0.75 and APRI score >2

week SOF + RBV group (genotype 2), 66.7% (28 of 42 subjects) in the 12-week SOF + RBV group (genotype 3), and 88.2% (15 of 17 subjects) in the 24-week SOF + RBV group (genotype 3).

Table 8. SVR12 rate (FAS)

		SVR12 rate [95% CI][a)]				
		Genotype 1	Genotype 2		Genotype 3	
		24-week SOF + RBV	12-week SOF + RBV	24-week SOF + RBV	12-week SOF + RBV	24-week SOF + RBV
Overall subjects		76.3 [67.4, 83.8] (87/114)	88.5 [69.8, 97.6] (23/26)	91.7 [73.0, 99.0] (22/24)	66.7 [50.5, 80.4] (28/42)	94.1 [71.3, 99.9] (16/17)
Prior treatment (IFN-based regimen)	Yes	–	–	91.7 [73.0, 99.0] (22/24)	–	94.1 [71.3, 99.9] (16/17)
	No	76.3 [67.4, 83.8] (87/114)	88.5 [69.8, 97.6] (23/26)	–	66.7 [50.5, 80.4] (28/42)	–
Subjects with chronic hepatitis C		77.1 [68.0, 84.6] (84/109)	88.0 [68.8, 97.5] (22/25)	90.0 [68.3, 98.8] (18/20)	66.7 [49.0, 81.4] (24/36)	100 [71.5, 100.0] (11/11)
Subjects with chronic hepatitis C and compensated cirrhosis		60.0 [14.7, 94.7] (3/5)	100 [2.5, 100.0] (1/1)	100 [39.8, 100.0] (4/4)	66.7 [22.3, 95.7] (4/6)	83.3 [35.9, 99.6] (5/6)

% (n/N); −, not calculated
a) 95% CI was calculated using the Clopper-Pearson method.

Safety data were analyzed. The incidence of adverse events (including abnormal changes in laboratory values) in the 12-week SOF + RBV group (treatment-naïve subjects [genotype 2 or 3]) and the 24-week SOF + RBV group (genotype 1 or treatment-experienced subjects [genotype 2 or 3]) was 83.8% (57 of 68 subjects) and 92.3% (143 of 155 subjects), respectively. The incidence of adverse drug reactions[12)] (including abnormal changes in laboratory values) in the 12-week SOF + RBV group (treatment-naïve subjects [genotype 2 or 3]) and the 24-week SOF + RBV group (genotype 1 or treatment-experienced subjects [genotype 2 or 3]) was 60.3% (41 of 68 subjects) and 66.5% (103 of 155 subjects), respectively. The adverse events and adverse drug reactions occurring in ≥10% of subjects in either group are shown in Table 9.

Table 9. Adverse events and adverse drug reactions occurring in ≥10% of subjects in either group (safety analysis set)

Name of event	Adverse events		Adverse drug reactions	
	12-week SOF + RBV (genotype 2 or 3) (N = 68)	24-week SOF + RBV (genotype 1, 2, or 3) (N = 155)	12-week SOF + RBV (genotype 2 or 3) (N = 68)	24-week SOF + RBV (genotype 1, 2, or 3) (N = 155)
Overall	57 (83.8)	143 (92.3)	41 (60.3)	103 (66.5)
Fatigue	24 (35.3)	60 (38.7)	22 (32.4)	55 (35.5)
Insomnia	14 (20.6)	23 (14.8)	14 (20.6)	12 (7.7)
Nausea	12 (17.6)	24 (15.5)	9 (13.2)	15 (9.7)
Headache	9 (13.2)	21 (13.5)	7 (10.3)	17 (11.0)
Upper respiratory tract infection	8 (11.8)	18 (11.6)	0	1 (0.6)
Diarrhoea	6 (8.8)	17 (11.0)	2 (2.9)	4 (2.6)
Cough	4 (5.9)	18 (11.6)	0	4 (2.6)
Irritability	7 (10.3)	16 (10.3)	7 (10.3)	12 (7.7)
Anaemia	6 (8.8)	16 (10.3)	6 (8.8)	15 (9.7)

n (%)

Death occurred in 1 subject (completed suicide) in the 12-week SOF + RBV group (treatment-naïve subject [genotype 3]), and was considered unrelated to the study drug.

Serious adverse events occurred in 5 subjects in the 12-week SOF + RBV group (treatment-naïve, genotype 2 or 3) (drug abuse, acute myocardial infarction, septic shock, pneumonia, staphylococcal sepsis, encephalitis, acute renal failure, respiratory failure, intentional overdose, suicide attempt, fracture, incision site infection, completed suicide, and pulmonary embolism in 1 subject each [some subjects had more than 1 event]), 1 subject in the 24-week SOF + RBV group (treatment-experienced, genotype 2 or 3) (pneumonia, chronic obstructive pulmonary disorder, and leukocytoclastic vasculitis in 1 subject each [the subject had more than 1 event]), and 8 subjects in the 24-week SOF + RBV group (genotype 1) (cellulitis and acute renal failure in 2 subjects each; and intentional overdose, leukocytosis, atrial fibrillation, atrial flutter, diabetic ketoacidosis, altered state of consciousness, anaemia, colitis, enterocolitis, gastroenteritis salmonella, abdominal pain, bipolar disorder, respiratory tract infection, and chest pain in 1 subject each [some subjects had more than 1 event]). All of these events were considered unrelated to the study drug. The outcomes of all these serious adverse events, excluding pulmonary embolism, were "resolved."

Adverse events leading to discontinuation of SOF occurred in 3 subjects in the 12-week SOF + RBV group (treatment-naïve, genotype 2 or 3) (abnormal loss of weight, decreased appetite, headache, drug abuse, acute myocardial infarction, septic shock, pneumonia, staphylococcal bacteraemia, encephalopathy, acute renal failure, respiratory failure, intentional overdose, and suicide attempt in 1 subject each [some subjects had more than 1 event]), 1 subject in the 24-week SOF + RBV group (treatment-experienced, genotype 2 or 3) (dyspnoea), and 3 subjects in the 24-week SOF + RBV group (genotype 1) (sensation of foreign body, anxiety, insomnia, and agitation in 1 subject each [some subjects had more than 1 event]). The events occurring in 2 subjects in the 12-week SOF + RBV group (abnormal loss of weight, decreased appetite, and headache in 1 subject each [some subjects had more than 1 event]) and in 5 subjects in the 24-week SOF + RBV group (insomnia, sensation of foreign body, agitation, anxiety, and dyspnoea in 1 subject each) were considered related to the study drug. The outcomes of all these events, excluding headache, were "resolved."

Adverse events leading to dose reduction or interruption of RBV occurred in 4 subjects in the 12-week SOF + RBV group (treatment-naïve, genotype 2 or 3) (anaemia in 3 subjects, and fatigue and haemoglobin decreased in 1 subject each [some subjects had more than 1 event]) and 19 subjects in the 24-week SOF + RBV group (genotype 1; or treatment experienced, genotype 2 or 3) (anaemia in 12 subjects, fatigue in 4 subjects, dizziness in 3 subjects, etc.).

7.1.4 Foreign phase III study (CTD 5.3.5.1.2, Study GS-US-334-0124 [January 2013 to July 2014])

An open-label, uncontrolled study was conducted at 39 sites in Australia, France, Germany, Italy, Spain, and the UK to assess the efficacy and safety of the SOF+RBV regimen in patients with chronic hepatitis

C with or without compensated cirrhosis[17] who were co-infected with HIV (target sample size of 270 subjects [genotype 1, n = 100; genotype 2 or 3, n = 150; genotype 4, n = 20]).

SOF 400 mg QD in combination with RBV (brand name, Ribasphere Tablets [note: a generic product of Rebetol Capsules 200 mg; not approved in Japan]) at a weight-based dose (1000 mg/day [body weight ≤75 kg] or 1200 mg/day [body weight >75 kg] in two divided doses) was administered for 12 weeks to treatment-naïve subjects (genotype 2) and for 24 weeks to treatment-naïve subjects (genotype 1, 3, or 4) and IFN treatment-experienced subjects (genotype 2 or 3).

A total of 274 subjects received at least 1 dose of the study drug (genotype 1, 112 treatment-naïve subjects; genotype 2, 19 treatment-naïve and 6 IFN treatment-experienced subjects; genotype 3, 57 treatment-naïve and 49 IFN treatment-experienced subjects; genotype 4, 31 treatment-naïve subjects). All of the subjects were included in the FAS and safety analysis set. The FAS also served as the efficacy analysis set.

The primary efficacy endpoint was the SVR12 rate. The results are shown in Table 10.

The SVR24 rate was 83.0% (93 of 112 subjects) in the 24-week SOF + RBV group (genotype 1), 89.5% (17 of 19 subjects) in the 12-week SOF + RBV group (genotype 2), 83.3% (5 of 6 subjects) in the 24-week SOF + RBV group (genotype 2), 87.7% (93 of 106 subjects) in the 24-week SOF + RBV group (genotype 3), and 80.6% (25 of 31 subjects) in the 24-week SOF + RBV group (genotype 4).

Table 10. SVR12 rate (FAS)

		SVR12 rate [95% CI][a]				
		Genotype 1	Genotype 2		Genotype 3	Genotype 4
		24-week SOF + RBV	12-week SOF + RBV	24-week SOF + RBV	24-week SOF + RBV	24-week SOF + RBV
Overall subjects		84.8 [76.8, 90.9] (95/112)	89.5 [66.9, 98.7] (17/19)	83.3 [35.9, 99.6] (5/6)	88. [81.1, 94.0] (94/106)	83.9 [66.3, 94.5] (26/31)
Prior treatment (IFN–based regimen)	Yes	–	–	83.3 [35.9, 99.6] (5/6)	85.7 [72.8, 94.1] (42/49)	–
	No	84.8 [76.8, 90.9] (95/112)	89.5 [66.9, 98.7] (17/19)	–	91.2 [80.7, 97.1] (52/57)	83.9 [66.3, 94.5] (26/31)
Subjects with chronic hepatitis C		88.4 [80.2, 94.1] (84/95)	88.9 [65.3, 98.6] (16/18)	75.0 [19.4, 99.4] (3/4)	91.3 [82.8, 96.4] (73/80)	82.6 [61.2, 95.0] (19/23)
Subjects with chronic hepatitis C and compensated cirrhosis		64.7 [38.3, 85.8] (11/17)	100 [2.5, 100.0] (1/1)	100 [15.8, 100.0] (2/2)	80.8 [60.6, 93.4] (21/26)	87.5 [47.3, 99.7] (7/8)

% (n/N); −, not calculated
a) 95% CI was calculated using the Clopper-Pearson method.

Safety data were analyzed. The incidence of adverse events (including abnormal changes in laboratory values) in the 12-week SOF + RBV group (treatment-naïve subjects [genotype 2]), 24-week SOF + RBV group (treatment-experienced subjects [genotype 2 or 3]), and 24-week SOF + RBV group (treatment-naïve subjects [genotype 1, 3, or 4]) was 89.5% (17 of 19 subjects), 85.5% (47 of 55 subjects), and

17) Diagnosed by (a) liver biopsy findings, (b) Fibroscan (>12.5 kPa), or (c) Fibrotest score >0.75 and APRI score >2

91.0% (182 of 200 subjects), respectively. The incidence of adverse drug reactions[12] (including abnormal changes in laboratory values) in the 12-week SOF + RBV group (treatment-naïve subjects [genotype 2]), 24-week SOF + RBV group (treatment-experienced subjects [genotype 2 or 3]), and 24-week SOF + RBV group (treatment-naïve subjects [genotype 1, 3, or 4]) was 73.7% (14 of 19 subjects), 54.5% (30 of 55 subjects), and 67.5% (135 of 200 subjects), respectively. The adverse events and adverse drug reactions occurring in ≥10% of subjects treated with any regimen are shown in Table 11.

Table 11. Adverse events and adverse drug reactions with an incidence of ≥10% in any group (safety analysis set)

Name of event	Adverse events		Adverse drug reactions	
	12-week SOF + RBV treatment-naïve (genotype 2) (N = 19)	24-week SOF + RBV treatment-naïve (genotype 1, 3, or 4) or treatment-experienced (genotype 2 or 3) (N = 255)	12-week SOF + RBV treatment-naïve (genotype 2) (N = 19)	24-week SOF + RBV treatment-naïve (genotype 1, 3, or 4) or treatment-experienced (genotype 2 or 3) (N = 255)
Overall	17 (89.5)	229 (89.8)	14 (73.7)	165 (64.7)
Fatigue	5 (26.5)	51 (20.0)	5 (26.3)	42 (16.5)
Asthenia	1 (5.3)	43 (16.9)	1 (5.3)	26 (10.2)
Insomnia	3 (15.8)	41 (16.1)	3 (15.8)	22 (8.6)
Headache	1 (5.3)	42 (16.5)	1 (5.3)	23 (9.0)
Nausea	3 (15.8)	36 (14.1)	1 (5.3)	27 (10.6)
Diarrhoea	1 (5.3)	29 (11.4)	1 (5.3)	9 (3.5)
Irritability	1 (5.3)	26 (10.2)	1 (5.3)	15 (5.9)
Dyspnoea	2 (10.5)	18 (7.1)	2 (10.5)	11 (4.3)
Rash	2 (10.5)	18 (7.1)	1 (5.3)	12 (4.7)
Nasopharyngitis	3 (15.8)	16 (6.3)	0	0
Dyspnoea exertional	2 (10.5)	16 (6.3)	1 (5.3)	12 (4.7)
Abdominal pain upper	3 (15.8)	10 (3.9)	1 (5.3)	4 (1.6)
Dermatitis	2 (10.5)	5 (2.0)	1 (5.3)	3 (1.2)
Depressed mood	2 (10.5)	4 (1.6)	2 (10.5)	2 (0.8)

n (%)

No deaths occurred during the adverse event evaluation period (up to 4 weeks after the end of treatment) but 1 death occurred after this period in the 24-week SOF + RBV group (treatment-experienced subjects [genotype 3]) (hepatic cancer). The death was considered unrelated to the study drug.[18]

Serious adverse events occurred in 5 subjects in the 24-week SOF + RBV group (treatment-experienced subjects [genotype 2 or 3]) (anaemia, alcoholism, bile duct stone, headache, and hepatic cancer in 1 subject each) and 10 subjects in the 24-week SOF + RBV group (treatment-naïve subjects [genotype 1, 3, or 4]) (anaemia, cholecystitis, atypical pneumonia, drug abuse, rhabdomyolysis, acute renal failure, gastroenteritis, mania, thrombocytopenia, petechiae, psychotic disorder, pyrexia, supraventricular tachycardia, and tooth abscess in 1 subject each [some subjects had more than 1 event]). Of these events, anaemia in 2 subjects and mania, thrombocytopenia, and petechiae in 1 subject each were considered related to the study drug. The outcomes of all these serious adverse events, excluding hepatic cancer in 1 subject (resulting in death), were "resolved."

[18] Hepatic cancer (male subject aged 50 years). The subject completed the 24-week study treatment and died of hepatocellular carcinoma 221 days after the end of treatment. The hepatocellular carcinoma in the subject had been detected by the nuclear magnetic resonance image diagnostic system on Day 1 of treatment.

Adverse events leading to discontinuation of SOF occurred in 6 subjects in the 24-week SOF + RBV group (treatment-experienced subjects [genotype 2 or 3] or treatment-naïve subjects [genotype 1, 3, or 4]) (supraventricular tachycardia, mania, headache, feeling hot, lethargy, abdominal distension, chest pain, pruritus, thrombocytopenia, petechiae, and photophobia in 1 subject each [some subjects had more than 1 event]).

Main adverse events leading to dose reduction or interruption of RBV occurred in 1 subject in the 12-week SOF + RBV group (treatment-naïve subjects [genotype 2]) (haemoglobin decreased) and 21 subjects in the 24-week SOF + RBV group (treatment-experienced subjects [genotype 2 or 3] or treatment-naïve subjects [genotype 1, 3, or 4]) (anaemia in 12 subjects, haemoglobin decreased in 4 subjects, asthenia in 3 subjects, and dyspnoea and fatigue in 2 subjects each).

7.2 Japanese clinical research study (reference data, CTD 5.3.5.4.1 [20 to 20])

An open-label, uncontrolled study was conducted at to assess the efficacy and safety of the SOF + RBV regimen in 4 patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis who were co-infected with HIV.

Subjects received SOF 400 mg QD in combination with RBV (Copegus Tablets 200 mg) at a weight-based dose (600 mg/day [body weight ≤60 kg], 800 mg/day [body weight >60 and ≤80 kg], or 1000 mg/day [body weight >80 kg] in two divided doses) for 24 weeks. The dose of RBV was reduced or interrupted as needed in accordance with the package insert of Copegus Tablets 200 mg.

The baseline characteristics of the individual subjects are shown in Table 12.

Table 12. Baseline characteristics of Japanese subjects with genotype 3 chronic hepatitis C with or without compensated cirrhosis

	Subject A	Subject B	Subject C	Subject D
Age	4	5	3	5
Sex	Male	Male	Male	Male
CD4 (cell/μL)	337	497	536	474
Compensated cirrhosis	Yes	Yes	Yes	No
Duration of HIV infection	>35 years	>35 years	>35 years	>35 years
History of AIDS defining illness	No	No	No	No
HIV treatment	RAL/FTC/TDF	ETR/RAL/MVC	ETR/RAL/3TC	ETR/RAL/FTC/TDF
Hemophilia type	A	A	A	A
Prior treatment of HCV	PegIFN/RBV	PegIFN/RBV	PegIFN/RBV/TVR	None
Response to prior treatment of HCV	Non-response	Partial response	Non-response	–
Baseline HCV RNA level	5.5 $\log_{10}$ IU/mL	6.8 $\log_{10}$ IU/mL	6.7 $\log_{10}$ IU/mL	5.1 $\log_{10}$ IU/mL

RAL, raltegravir; ETR, etravirine; MVC, maraviroc; 3TC, lamivudine; TVR, telaprevir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate

Three of the 4 subjects achieved SVR12, and relapse was observed in 1 subject (subject C) at 4 weeks after the end of treatment. Drug resistance-associated mutations were not evaluated.

No adverse events occurred during the study treatment period. None of the subjects experienced study drug discontinuation or adjustment.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

IFN-based regimens are currently available in Japan for treatment of patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis. However, IFN is known to cause specific adverse events such as depression and influenza-like symptoms. There is a high medical need to develop novel regimens that do not contain IFN for this patient population. The clinical data package submitted for the present application does not include data from Japanese clinical studies.

PMDA's view:

Because a very small percentage of the Japanese population is affected by genotype 3 chronic hepatitis C with or without compensated cirrhosis, it would take a long time to conduct a clinical study in this patient population in Japan. Taking the above into account and based on the results of the evaluation conducted by the Study Group on Unapproved and Off-label Drugs of High Medical Need, the early clinical development of the SOF + RBV regimen is desirable. The efficacy and safety of the SOF + RBV regimen in patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis can be evaluated based mainly on the results from foreign studies, for the following reasons:

- No clear ethnic differences have been observed in the pharmacokinetics of SOF between Japanese and non-Japanese patients (Review Report of Sovaldi Tablets 400 mg [dated February 23, 2015]).
- The efficacy and safety of the SOF + RBV regimen were demonstrated in Japanese and foreign clinical studies in patients with genotype 2 chronic hepatitis C with or without compensated cirrhosis (Review Report of Sovaldi Tablets 400 mg [dated February 23, 2015]).
- The results of non-clinical studies showed no effects of genotypes on the antiviral activity of SOF against wild-type HCV replicon cells. In a Japanese clinical study, the SVR12 rates for subtypes 2a and 2b were 95.3% (82 of 86 subjects) and 98.1% (53 of 54 subjects), respectively, showing no marked differences between these subtypes (Review Report of Sovaldi Tablets 400 mg [dated February 23, 2015]).
- Data from the Japanese clinical research study on the SOF + RBV regimen in patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis are consistent with the efficacy and safety data of the regimen from foreign studies [see Section 7.2].

7.R.2 Efficacy

Based on the following considerations, PMDA concluded that the 24-week SOF + RBV regimen can be expected to be effective in patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis.

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

7.R.2.1 Efficacy

The applicant of Sovaldi Tablets 400 mg provided the following explanation about the efficacy of the SOF + RBV regimen in patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis:

Data from foreign clinical studies (Studies GS-US-334-0133, GS-US-334-0153, GS-US-334-0123, and GS-US-334-0124) were analyzed to identify the SVR12 rates in overall subjects and in each subgroup. The results are shown in Table 13. Data from the subgroups of non-cirrhotic patients with chronic hepatitis C were analyzed by the duration of the SOF + RBV treatment, and the SVR12 rate was 81.5% to 100% after 24-week treatment, which was higher than that after 12- or 16-week treatment (0% to 82.9%). Data from the subgroups of patients with chronic hepatitis C and compensated cirrhosis were analyzed by the duration of the SOF + RBV treatment, and the SVR12 rate was 61.7% to 100% after 24-week treatment, which was higher than that after 12- or 16-week treatment (0% to 66.7%). In the Japanese clinical research study, 3 of 4 patients who were co-infected with HCV (genotype 3) and HIV achieved SVR12 after 24-week treatment.

The above results from the foreign clinical studies and Japanese clinical research study suggested that 24-week SOF + RBV regimen has a certain degree of efficacy in patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis.

Table 13. SVR12 rate in patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis (FAS)

			Overall	Chronic hepatitis C	Compensated cirrhosis
Study GS-US-334-0133[a)]	12-week SOF + RBV	Treatment-naïve	0% (0/2)	0% (0/2)	0% (0/0)
		Treatment-experienced	33.3% (3/9)	42.9% (3/7)	0% (0/2)
	24-week SOF + RBV	Treatment-naïve	94.3% (99/105)	94.6% (87/92)	92.3% (12/13)
		Treatment-experienced	78.6% (114/145)	86.7% (85/98)	61.7% (29/47)
Study GS-US-334-0153	16-week SOF + RBV	Treatment-naïve	76.9% (70/91)	82.9% (58/70)	57.1% (12/21)
		Treatment-experienced	64.4% (58/90)	75.9% (41/54)	47.2% (17/36)
	24-week SOF + RBV	Treatment-naïve	88.3% (83/94)	90.3% (65/72)	81.8% (18/22)
		Treatment-experienced	79.5% (70/88)	81.5% (44/54)	76.5% (26/34)
Study GS-US-334-0123	12-week SOF + RBV	Treatment-naïve	66.7% (28/42)	66.7% (24/36)	66.7% (4/6)
		Treatment-experienced	–	–	–
	24-week SOF + RBV	Treatment-naïve	–	–	–
		Treatment-experienced	94.1% (16/17)	100% (11/11)	83.3% (5/6)
Study GS-US-334-0124	24-week SOF + RBV	Treatment-naïve	91.2% (52/57)	90.7% (49/54)	100.0% (3/3)
		Treatment-experienced	85.7% (42/49)	92.3% (24/26)	78.3% (18/23)

% (n/N)

a) The protocol was amended to change the duration of treatment from 12 weeks to 24 weeks for subjects (genotype 3) who had not completed or discontinued.

PMDA's view:

In the foreign studies (Studies GS-US-334-0133, GS-US-334-0153, GS-US-334-0123, and GS-US-334-0124), the SVR12 rates in patients with genotype 3 chronic hepatitis C and those with genotype 3 chronic hepatitis C and compensated cirrhosis after treatment with the 24-week SOF + RBV regimen were 81.5% to 100% and 61.7% to 100%, respectively, which were higher than those after 12- or 16-week

treatment. The above results suggest that the 24-week SOF + RBV regimen has a certain degree of efficacy.

7.R.2.2 Viral resistance mutations

Each of the applicants provided the following explanation about the emergence of SOF-resistant variants and the impact of resistant variants on the efficacy of the SOF + RBV regimen:

The results from a non-clinical study conducted to evaluate the antiviral activity of SOF against HCV replicons containing NS5B substitutions suggest that the S282T substitution in the NS5B region contributes to a reduction in susceptibility to SOF in all HCV genotypes studied and that the other NS5B substitutions evaluated (e.g., S96T, N142T, L159F/V321A) do not affect the antiviral activity of SOF [see Section 3.1]. Samples collected from patients (n = 302) with genotype 3 chronic hepatitis C with or without compensated cirrhosis enrolled in foreign studies (Studies GS-US-334-0133, GS-US-334-0153, GS-US-334-0123, and GS-US-334-0124) were used to analyze[19] NS5B genes at baseline. As a result, no NS5B substitutions[20] were detected at baseline. Among subjects who experienced virologic failure[21] (n = 77), NS5B substitutions were detected in 17 subjects (L159F substitution in 13 subjects and V321A substitution in 5 subjects [both substitutions were detected in some subjects]) at the time of virologic failure. However, none of these substitutions in the NS5B region caused a notable change in susceptibility to SOF in non-clinical studies. Therefore, what impact these variants have on the efficacy of the SOF + RBV regimen remains unknown. The NS5B S282T substitution was not detected in any clinical study.

PMDA's view:

The NS5B S282T substitution involved in a reduction in susceptibility to SOF was not detected in any subjects in foreign studies. NS5B HCV variants were identified in subjects who experienced virologic failure, though the impact of the variants on the SOF + RBV regimen in those subjects is unknown. Since the information on HCV variants obtained from clinical studies is limited, the applicant should collect post-marketing information on baseline HCV variants in patients who are to start the SOF + RBV regimen or on HCV variants in patients experiencing virologic failure after treatment with the SOF + RBV regimen, including information from the literature. Any new findings should be promptly communicated to healthcare professionals in clinical practice.

7.R.3 Safety

PMDA's views:

Evaluation of the safety of the 24-week SOF + RBV regimen is summarized in the sections below. The occurrence of anemia-related events should continue to be monitored during treatment with the 24-week SOF + RBV regimen as stated in the current package inserts of SOF and RBV products. However, The safety of this regimen can be managed, similarly to the currently available 12-week SOF + RBV regimen,

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19) The assay cut-off of 1% was used for deep sequence analysis.
20) S96T, N142T, L159F, S282T or other, M289L/I, L320F, V321A
21) Subjects who experienced virologic breakthrough during treatment or who failed to respond to or relapsed following the 24-week treatment with the SOF+RBV regimen

if it is used under the supervision of a physician with sufficient knowledge and experience in the treatment of viral liver diseases, taking appropriate measures such as monitoring and management of adverse events and interruption/discontinuation of treatment. Nevertheless, given that there is very limited clinical experience with the 24-week SOF + RBV regimen in Japanese patients, the applicant should collect post-marketing information about the safety of this regimen. Any new findings should be promptly communicated to healthcare professionals in clinical practice.

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

7.R.3.1 Duration of treatment and safety

Each of the applicants provided the following explanation about the safety of the 24-week SOF + RBV regimen:

The pooled safety data from foreign clinical studies (Studies GS-US-334-0133, GS-US-334-0153, GS-US-334-0123, and GS-US-334-0124) were analyzed to assess the safety profile of the 24-week SOF + RBV regimen versus the 12-week SOF + RBV regimen. The analysis results are summarized in Table 14.

Table 14. Safety profile of the SOF + RBV regimen (pooled analysis of 4 foreign phase III studies)

	12-week SOF + RBV regimen			24-week SOF + RBV regimen		
	Non-cirrhotic patients with chronic hepatitis	Compensated cirrhotic patients with chronic hepatitis	Total	Non-cirrhotic patients with chronic hepatitis	Compensated cirrhotic patients with chronic hepatitis	Total
Number of subjects	150	21	171	658	201	859
Overall AEs	126 (84.0)	20 (95.2)	146 (85.4)	602 (91.5)	187 (93.0)	789 (91.9)
Study drug-related AEs	98 (65.3)	18 (85.7)	116 (67.8)	470 (71.4)	140 (69.7)	610 (71.0)
Grade ≥3[a)] AEs	11 (7.3)	0	11 (6.4)	37 (6.1)	19 (9.5)	56 (6.5)
Serious AEs	5 (3.3)	0	5 (2.9)	26 (4.0)	18 (9.0)	44 (5.1)
Deaths	1 (0.6)	0	1 (0.6)	0	0	0
AEs leading to study discontinuation	4 (2.7)	0	4 (2.3)	14 (2.1)	2 (1.0)	16 (1.9)

n (%)

a) The severity of each adverse event was assessed using the grading scale for the severity of adverse events and laboratory abnormalities established by Gilead Sciences, Inc. (Omata M, et al. *J Viral Hepat*. 2014; 21(11):762-768).

The incidences of overall adverse events and serious adverse events by duration of treatment were higher in subjects treated with the 24-week SOF + RBV regimen than in those treated with the 12-week SOF + RBV regimen. On the other hand, there were no marked differences in the incidences of Grade ≥3 adverse events and adverse events leading to study discontinuation between subjects treated with the 24-week regimen and those treated with the 12-week regimen.

In foreign clinical studies, the main adverse events reported were fatigue (28.0%), nausea (23.9%), headache (19.9%), insomnia (15.2%), and itching sensation (15.2%) in subjects treated with the 12-week SOF+RBV regimen, and fatigue (31.3%), headache (24.3%), insomnia (18.7%), nausea (14.8%),

and pruritus (13.9%) in subjects receiving the 24-week SOF+RBV regimen, showing no marked differences in the safety profile of the regimen associated with the prolonged duration of treatment.

Most of the adverse events reported in subjects treated with the 12- or 24-week SOF + RBV regimen were Grade 1 or 2 in severity. The Grade ≥3 adverse events occurring in ≥2 subjects were anaemia (3 subjects), fatigue (3 subjects), chest pain (2 subjects), hyperbilirubinaemia (2 subjects), and acute renal failure (2 subjects) among those treated with the 24-week SOF + RBV regimen and fatigue (2 subjects) among those treated with the 12-week regimen.

One of the subjects treated with the 12-week regimen died (completed suicide), and the death was considered unrelated to the study drug. No serious adverse events considered related to the study drug were reported in any subjects treated with the 12-week SOF + RBV regimen. Serious adverse events considered related to the study drug were reported by 6 subjects treated with the 24-week SOF + RBV regimen (anaemia in 2 subjects and suicide attempt, miscarriage of partner, mania, thrombocytopenia, and petechiae in 1 subject each [some subjects had more than 1 event]). The outcomes of all these study drug-related serious adverse events were “resolved.”

Adverse events leading to study discontinuation occurred in 4 subjects treated with the 12-week SOF + RBV regimen (headache, abnormal loss of weight, decreased appetite, drug abuse, acute myocardial infarction, septic shock, intentional overdose, malaise, and headache in 1 subject each [some subjects had more than 1 event]) and in 16 subjects treated with the 24-week SOF + RBV regimen (anxiety in 2 subjects, and drug abuse, alcohol abuse, suicide attempt, insomnia, agitation, sensation of foreign body, dyspnoea, atypical pneumonia, supraventricular tachycardia, mania, feeling hot, headache, diarrhoea, nausea, pyrexia, lethargy, chest pain, abdominal distension, pruritus, thrombocytopenia, petechiae, and photophobia in 1 subject each [some subjects had more than 1 event]). The outcomes of all these events, excluding ongoing alcohol abuse in 1 subject, were assessed as resolved.

The above results suggest that the safety profile of the 24-week SOF + RBV regimen is similar to that of the approved 12-week SOF + RBV regimen.

The safety of the regimen in elderly patients (≥65 years of age) was assessed. The incidence of adverse events in subjects aged ≥65 years in foreign clinical studies was 100% (15 of 15 subjects) in subjects mono-infected with HCV and 87.5% (7 of 8 subjects) in subjects co-infected with HCV and HIV. No deaths, serious adverse events, or adverse events leading to study discontinuation occurred. While no conclusion on the safety of the regimen in elderly patients can be drawn based on the above results obtained from a small number of subjects, it seems unnecessary to include any new precautionary statements for elderly patients in the package insert at this stage.

PMDA's view:
The incidences of Grade ≥3 adverse events and serious adverse events in foreign clinical studies showed that the safety profile of the 24-week SOF + RBV regimen was similar to that of the approved 12-week SOF + RBV regimen, indicating no new concerns associated with the prolonged duration of treatment. Although the occurrence of anemia-related events should continue to be monitored as advised in the current package inserts of SOF and RBV products, the safety of the 24-week SOF + RBV regimen can be managed, similarly to the approved 12-week SOF + RBV regimen, provided that it is used under the supervision of a physician with sufficient knowledge and experience in the treatment of viral liver diseases, taking appropriate measures such as monitoring and management of adverse events and interruption/discontinuation of treatment.

The risk of hepatic dysfunction is described in the following section.

7.R.3.2 Hepatic dysfunction

In a foreign clinical study in patients co-infected with HCV and HIV, the incidence of Grade 3 bilirubin increased was high in subjects receiving SOF+RBV in combination with atazanavir. PMDA asked the applicants to explain the risk of hepatic dysfunction in patients treated with SOF+RBV in combination with atazanavir.

Each applicant's explanation:
In the foreign clinical study in patients who were co-infected with HCV and HIV, the incidence of Grade ≥3 bilirubin increased was 78.9% (60 of 76 subjects) in subjects treated with SOF+RBV plus atazanavir, which was higher than that in subjects treated with SOF+RBV alone(3.0% [10 of 334 subjects]). On the other hand, no subjects experienced Grade ≥3 hepatic dysfunction-related events around the time (± 2 weeks) when Grade ≥3 bilirubin increased occurred. Taking into account that subjects who had their Grade ≥3 bilirubin total increased when concomitantly receiving atazanavir did not exhibit an increase in direct bilirubin or transaminase and that the level of total bilirubin in these subjects returned to the baseline level after the end of treatment, the bilirubin total increased observed in the study should not be interpreted as evidence suggesting hepatic dysfunction. In general, an increase in blood bilirubin associated with RBV-induced hemolytic anemia is observed in patients receiving RBV. Atazanavir, which is a uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1) inhibitor, inhibits bilirubin conjugation. Therefore, the possible mechanism of an increase in bilirubin observed after co-administration of SOF+RBV plus atazanavir is as follows: RBV-induced hemolytic anemia led to increased blood bilirubin, which resulted in delayed excretion.

The above results indicated that there is no need to include a new precautionary statement regarding the risk of hepatic dysfunction in patients treated with the 24-week SOF + RBV regimen with or without atazanavir in the relevant package inserts.

PMDA's view:

In a foreign clinical study in patients who were co-infected with HCV and HIV, the incidence of Grade ≥3 bilirubin increased was as high as 78.9% (60 of 76 subjects) in subjects treated with SOF+RBV plus atazanavir. However, the following explanation of the applicants is acceptable: Given that no subjects developed Grade ≥3 liver function test abnormal concurrently with increased bilirubin and that indirect bilirubin mainly increased in the study with no increase in direct bilirubin, the cases of increased bilirubin observed in the study do not necessarily suggest the risk of hepatic dysfunction caused by the SOF + RBV regimen; therefore, there is no need to include a new precautionary statement about hepatic dysfunction in patients treated with the 24-week SOF + RBV regimen in the relevant package inserts. Nevertheless, when atazanavir is concomitantly used, patients should be monitored for increased bilirubin, as advised in the package insert of atazanavir. In addition, given that there is very limited clinical experience with the 24-week SOF + RBV regimen in Japanese patients co-infected with HCV and HIV, any findings obtained in the post-marketing setting should be promptly communicated to healthcare professionals in clinical practice.

7.R.4 Indication and dosage and administration

Based on the reviews presented in Sections 7.R.2 and 7.R.3 as well as the following, PMDA concluded that Sovaldi Tablets 400 mg, Rebetol Capsules 200 mg, and Copegus Tablets 200 mg can be indicated for the treatment of "patients with chronic hepatitis C with or without compensated cirrhosis, which is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2)" and that "SOF 400 mg QD administered orally for 24 weeks in combination with RBV" is acceptable for the dosage and administration of Sovaldi Tablets 400 mg.

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

7.R.4.1 Dosage and administration of Sovaldi Tablets 400 mg

The applicant of Sovaldi Tablets 400 mg provided the following explanation about the dosage and administration of SOF:

Based on the results from foreign dose-finding studies of SOF (Studies P7977-0221 and P7977-0422) and a pharmacokinetic study in Japanese and Caucasian healthy adults (Study GS-US-334-0111) (Review Report of Sovaldi Tablets 400 mg [dated February 23, 2015]), SOF 400 mg QD was proposed as the dosage and administration for a new indication, similarly to that for the treatment of HCV genotype 2.

In earlier foreign clinical studies of the 12-week SOF + RBV regimen in patients with genotype 2 or 3 chronic hepatitis C with or without compensated cirrhosis (Studies GS-US-334-0107 and P7977-1231), the SVR12 rates in non-cirrhotic patients with genotype 3 chronic hepatitis C and patients with genotype 3 chronic hepatitis C and compensated cirrhosis (61.2% and 55.7%, respectively) were lower than those in non-cirrhotic patients with genotype 2 chronic hepatitis C and patients with genotype 2 chronic hepatitis and compensated cirrhosis (92.7% and 97.1%, respectively). Consequently, the duration of

treatment with SOF + RBV was extended in subsequent studies. In foreign clinical studies (Studies GS-US-334-0133, GS-US-334-0153, GS-US-334-0123, and GS-US-334-0124), the efficacy and safety of the 24-week SOF + RBV regimen were demonstrated in patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis [see Sections 7.R.2 and 7.R.3].

Based on the above, the following dosage and administration statement was proposed for Sovaldi Tablets 400 mg: "The usual adult dosage is 400 mg of sofosbuvir, administered orally once daily in combination with ribavirin for 24 weeks."

Based on the results from the foreign clinical studies and Japanese clinical research study, PMDA concluded that the proposed dosage and administration (SOF 400 mg QD administered orally for 24 weeks in combination with RBV) is acceptable for patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis.

7.R.4.2 Dosage and administration of Copegus Tablets 200 mg and Rebetol Capsules 200 mg

PMDA's view on the dosage and administration of RBV:

In the foreign clinical studies, the dosage and administration and the dose adjustment method of RBV were selected in accordance with the label information of RBV products approved outside Japan. The dosage and administration and the dose adjustment method employed in the foreign clinical studies were different from the dosage and administration of RBV products approved in Japan and the dose adjustment method described in the Japanese package insert of RBV. Meanwhile, when Sovaldi Tablets 400 mg and Copegus Tablets 200 mg were co-administered for 24 weeks in Japanese clinical research study, Copegus Tablets 200 mg was administered to Japanese patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis at a dose specified for co-administration with SOF. The dose was adjusted in accordance with the dose adjustment method described in the "Precautions for the Dosage and Administration" section of its Japanese package insert. The results from these patients included in this research study, though small in number, were consistent with the results from foreign clinical studies. In clinical practice in Japan, no RBV products have been administered in accordance with in their label information approved outside Japan.

Based on the above, the dosage and administration and the dose adjustment method of Copegus Tablets 200 mg for the SOF + RBV regimen should be the same as specified in its Japanese package insert for co-administration with SOF.

There is no available information on the 24-week combination regimen of Sovaldi Tablets 400 mg and Rebetol Capsules 200 mg in Japanese patients. However, given that the dosage and administration and the dose adjustment method of Rebetol Capsules 200 mg in the 12-week SOF + RBV regimen are the same as those of Copegus Tablets 200 mg, the dosage and administration and the dose adjustment method of Copegus Tablets 200 mg should be applicable to Rebetol Capsules 200 mg in the SOF + RBV regimen.

There is no need to change the current dosage and administration of Rebetol Capsules 200 mg and Copegus Tablets 200 mg because the duration of treatment is stated in the "Dosage and Administration" section of the package insert of Sovaldi Tablets 400 mg, which is to be co-administered with Rebetol Capsules 200 mg or Copegus Tablets 200 mg.

7.R.4.3 Indications

HCV genotypes 1 to 6 have been identified. The proposed indication for the present application is "suppression of viremia in patients with chronic hepatitis C with or without compensated cirrhosis (any serogroup [genotype] other than serogroup 1 [genotype 1])."

PMDA performed the following evaluation of the efficacy of the SOF + RBV regimen in patients with chronic hepatitis C genotype 4, 5, or 6, with or without compensated cirrhosis:
The SVR12 rates observed in the foreign clinical study in patients with genotype 4 chronic hepatitis C with or without compensated cirrhosis (Study GS-US-334-0124) are shown in Table 15. Since the safety of the 24-week SOF + RBV regimen is considered manageable, the 24-week SOF + RBV regimen is likely to be usable in patients with genotype 4 chronic hepatitis C with or without compensated cirrhosis.

Table 15. SVR12 rates in subjects with genotype 4 chronic hepatitis C with or without compensated cirrhosis

			Overall	Non-cirrhotic patients with chronic hepatitis	Compensated cirrhotic patients with chronic hepatitis
Study GS-US-334-0124	24-week SOF + RBV	Treatment-naïve	83.9% (26/31)	82.6% (19/23)	87.5% (7/8)
		Treatment-experienced	–	–	–
Study GS-US-334-0114 [a)]	12-week SOF + RBV	Treatment-naïve	78.6% (11/14)	90.9% (10/11)	33.3% (1/3)
		Treatment-experienced	58.8% (10/17)	61.5% (8/13)	50.0% (2/4)
	24-week SOF + RBV	Treatment-naïve	100% (14/14)	100% (11/11)	100% (3/3)
		Treatment-experienced	86.7% (13/15)	81.8% (9/11)	100% (4/4)
Study GS-US-334-0138 [b)]	12-week SOF + RBV	Treatment-naïve	84.0% (21/25)	86.4% (19/22)	66.7% (2/3)
		Treatment-experienced	70.4% (19/27)	72.7% (16/22)	60.0% (3/5)
	24-week SOF + RBV	Treatment-naïve	91.7% (22/24)	90.5% (19/21)	100% (3/3)
		Treatment-experienced	88.9% (24/27)	95.2% (20/21)	66.7% (4/6)

% (n/N)
a) A randomized, parallel-group study conducted in Egyptian patients with genotype 4 chronic hepatitis C with or without compensated cirrhosis to evaluate the efficacy and safety of the SOF + RBV regimen [see CTD 5.3.4.2.1]
b) A randomized, parallel-group study conducted in Egyptian patients with genotype 4 chronic hepatitis C with or without compensated cirrhosis to evaluate the efficacy and safety of the SOF + RBV regimen [see CTD 5.3.5.1.5]

HCV genotype 5 is found primarily in South Africa and genotype 6 in East/Southeast Asia. The genotypes are rarely detected in Japan, Europe, or the US (*Hepatology.* 2015; 61: 77-87). No clinical studies have been conducted to evaluate the efficacy and safety of the SOF + RBV regimen in patients with HCV genotype 5 or 6. Meanwhile, as the world is increasingly globalized, a growing number of people move across national boundaries. Under the circumstances, it would be meaningful, from the viewpoint of public health, to make the 24-week, IFN-free, SOF + RBV regimen available in clinical practice in Japan for the treatment of genotype 5 or 6 HCV infection as well as genotype 3 HCV infection, provided that the characteristics (including genotypes) of patients participating in clinical studies of the

SOF + RBV regimen are appropriately communicated to healthcare professionals and patients and that both the physician and the patient select the SOF + RBV regimen based on a thorough understanding of its efficacy. The above decision is based on the following reasons:

- The SOF + RBV regimen is to be selected and used for eligible patients based on the judgment of a physician with sufficient knowledge and experience in the treatment of viral liver diseases.
- The safety of the 24-week SOF + RBV regimen is likely to be manageable.
- The antiviral activity of SOF and RBV against all genotypes was demonstrated in non-clinical studies.

Given that there is very limited clinical experience with the 24-week SOF + RBV regimen in Japanese patients, the applicant should collect information on the safety and efficacy of this regimen (including information on genotype) in patients with chronic hepatitis C with or without compensated cirrhosis. Any findings should be promptly communicated to healthcare professionals in clinical practice.

7.R.4.4 Use in compensated cirrhotic patients with chronic hepatitis C

PMDA's view on the use in compensated cirrhotic patients with chronic hepatitis C:

The SVR12 rates in compensated cirrhotic patients with chronic hepatitis C treated with the 24-week SOF + RBV regimen were 61.7% to 100% in foreign phase III studies, indicating that the safety of the regimen in this patient population can be managed [see Section 7.R.3] and that it is clinically meaningful to make the 24-week SOF + RBV regimen available also to compensated cirrhotic patients with chronic hepatitis C. However, given that there is limited clinical experience with the 24-week SOF + RBV regimen in compensated cirrhotic Japanese patients with chronic hepatitis C, the applicant should collect post-marketing information on the safety and efficacy of the regimen in this patient population.

7.R.5 Clinical positioning

Each of the applicants provided the following explanation about the clinical positioning of the 24-week SOF + RBV regimen in patients with chronic hepatitis C with or without compensated cirrhosis:

In Japan, IFN-based therapy is the only treatment option for patients with genotypes 3 through 6 chronic hepatitis C with or without compensated cirrhosis. IFN-based therapy cannot necessarily be used in all of patients with genotypes 3 through 6 because of intolerance to IFN or other reasons. The results from the foreign clinical studies and Japanese clinical research study have demonstrated the efficacy and favorable safety profile of the 24-week SOF + RBV regimen. Therefore, this regimen is expected to become a new treatment option for these patient populations.

PMDA's view:

As stated in Sections 7.R.2 and 7.R.3, the efficacy of the 24-week SOF + RBV regimen is promising in patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis and its safety can be managed. As stated in Section 7.R.4.3, the 24-week SOF + RBV regimen can be a new treatment option for patients with genotypes 3 through 6 chronic hepatitis C with or without compensated cirrhosis provided that a physician with sufficient knowledge and experience in the treatment of viral liver

diseases selects patients eligible for this regimen based on a full understanding of the results of clinical and non-clinical studies.

7.R.6 Post-marketing investigations

7.R.6.1 SOF

The applicant of Sovaldi Tablets 400 mg is planning the following post-marketing surveillance study of the SOF + RBV regimen.

[Specified drug use-results survey]

- Objectives: To collect information on the safety and efficacy of the 24-week SOF + RBV regimen in clinical practice.
- Planned sample size: 50 patients

  [Rationale]

  Given that the number of Japanese patients with genotypes 3 through 6 chronic hepatitis C with or without compensated cirrhosis is very small, the sample size was determined to be 50 in consideration of the feasibility of the survey.
- Observation period: The observation period for safety will be up to approximately 28 weeks, from the start of treatment with the SOF + RBV regimen up until 4 weeks after its completion or discontinuation; and the observation period for efficacy will be up to approximately 48 weeks, from the start of treatment with the SOF + RBV regimen up until 24 weeks after its completion or discontinuation.
- Survey period: 3 years (registration period of 2 years)

In addition to the investigations proposed by the applicant of Sovaldi Tablets 400 mg, PMDA considers that the applicant should collect post-marketing information on the safety and efficacy of the regimen in patients infected with each HCV genotype.

Information on SOF resistance-associated mutations from sources including the published literature should continue to be collected. Any new findings should be promptly communicated to healthcare professionals in clinical practice.

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

7.R.6.2 RBV

The applicants of Rebetol Capsules 200 mg and Copegus Tablets 200 mg do not intend to perform any post-marketing surveillance, and they intend to obtain and evaluate information collected through the specified drug use-results survey performed by the applicant of Sovaldi Tablets 400 mg, for the following reasons:

- Information on the safety and efficacy of the 24-week SOF + RBV regimen can be collected through the specified drug use-results survey planned for SOF.

- The safety of RBV when used in combination with IFN or PegIFN for ≥24 weeks has been demonstrated.
- The safety profile of RBV was assessed in foreign clinical studies conducted by the applicant of Sovaldi Tablets 400 mg, and no new risk was identified.

On the basis of the considerations presented in Section 7.R.3 and the experience with use of RBV in clinical practice, PMDA concluded that the explanations provided by the applicants of Rebetol Capsules 200 mg and Copegus Tablets 200 mg are acceptable and that there is no need to include any additional pharmacovigilance activities in the risk management plan.

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

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

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

The assessment is currently underway. Its results and the conclusion of PMDA will be reported in the Review Report (2).

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

The assessment is currently underway. Its results and the conclusion of PMDA will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that demonstrate the efficacy of the 24-week SOF + RBV regimens (Sovaldi Tablets 400 mg and Rebetol Capsules 200 mg or Copegus Tablets 200 mg) in the treatment of patients with chronic hepatitis C with or without compensated cirrhosis (genotypes 3-6) and that the regimens have acceptable safety in view of their benefits. The 24-week SOF + RBV regimen is clinically meaningful because it offers a new treatment option for patients with chronic hepatitis C with or without compensated cirrhosis (genotypes 3-6).

PMDA has concluded that Sovaldi Tablets 400 mg, Rebetol Capsules 200 mg, and Copegus Tablets 200 mg used for the 24-week SOF + RBV regimen may be approved if this regimen is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 22, 2017

Products Submitted for Approval

Brand Name	(a) Sovaldi Tablets 400 mg
	(b) Rebetol Capsules 200 mg
	(c) Copegus Tablets 200 mg
Non-proprietary Name	(a) Sofosbuvir
	(b) and (c) Ribavirin
Applicant	(a) Gilead Sciences K.K.
	(b) MSD K.K.
	(c) Chugai Pharmaceutical Co., Ltd.
Date of Application	(a) August 31, 2016
	(b) September 27, 2016
	(c) November 18, 2016

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Section "7.R.2 Efficacy" of Review Report (1).

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

1.1 Hepatocellular carcinoma

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Section "7.R.3 Safety" of Review Report (1). The expert advisors made the following comments concerning the risk of hepatocellular carcinoma in patients treated with interferon (IFN)-free, direct acting anti-viral (DAA) regimens:

- Given that data suggesting a relationship between an IFN-free DAA therapy and the risk of hepatocellular carcinoma were reported recently, this issue should continue to be investigated.

PMDA asked the applicants to explain the risk of hepatocellular carcinoma in patients treated with IFN-free DAA regimens.

The applicant of Sovaldi Tablets 400 mg provided the following explanation:
After the first use of IFN-free DAA regimens in clinical practice, relationships between the achievement of SVR following a DAA therapy and the prevention of liver disease progression or the decreased incidence of hepatocellular carcinoma were reported (*J Hepatol.* 2016; 65: 741-7; *Gastroenterology.* 2016; 152: 142-56; and other articles). On the other hand, data showing a relationship between an IFN-free DAA regimen and the increased incidence of hepatocellular carcinoma after treatment with this regimen were also reported (*J Hepatol.* 2016; 65: 1070-1). At present, there seems to be insufficient scientific evidence suggesting that an IFN-free DAA regimen increases the incidence of hepatocellular carcinoma.

PMDA's view:
Currently, only limited information is available regarding the long-term outcomes of patients achieving SVR after an IFN-free DAA therapy. It is difficult to reach a conclusion at this stage regarding a possible relationship between IFN-free DAA regimens and the risk of hepatocellular carcinoma. Therefore, the relationship between DAA regimens and the risk of hepatocellular carcinoma should continue to be investigated. The applicant should collect information from Japanese and foreign clinical research reports based on long-term observation of patients treated with IFN-free DAA regimens. Any new findings should be adequately communicated to healthcare professionals in clinical practice.

1.2 Indication and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Section "7.R.4 Indication and dosage and administration" of Review Report (1).

On the basis of the comment from the Expert Discussion, PMDA concluded that the applicant should provide information on the efficacy and safety of the 24-week SOF + RBV regimen in patients with genotypes 4 through 6 chronic hepatitis C with or without compensated cirrhosis to healthcare professionals in clinical practice and that the indication and the dosage and administration of Sovaldi Tablets 400 mg, Rebetol Capsules 200 mg, and Copegus Tablets 200 mg should be as shown below.

[Indications]
(Underline denotes additions or changes)

Sovaldi Tablets 400 mg	Suppression of viremia in <u>either of the following</u> patients with chronic hepatitis C with or without compensated cirrhosis: <u>(1) patients infected with serogroup 2 (genotype 2) HCV, or</u> <u>(2) patients infected with HCV that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2)</u>

Rebetol Capsules 200 mg	1. to 2. (Omitted) 3. Suppression of viremia in <u>either of the following</u> patients with chronic hepatitis C with or without compensated cirrhosis in combination with sofosbuvir: <u>(1) patients infected with serogroup 2 (genotype 2) HCV, or</u> <u>(2) patients infected with HCV that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2)</u> 4. (Omitted)
Copegus Tablets 200 mg	1. to 2. (Omitted) 3. Suppression of viremia in <u>either of the following</u> patients with chronic hepatitis C with or without compensated cirrhosis in combination with sofosbuvir: <u>(1) patients infected with serogroup 2 (genotype 2) HCV, or</u> <u>(2) patients infected with HCV that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2)</u>

[Dosage and administration]

Sovaldi Tablets 400 mg	(Underline denotes additions or changes) <u>1. When used in patients infected with serogroup 2 (genotype 2) HCV:</u> The usual adult dosage is 400 mg of Sofosbuvir, administered orally once daily in combination with Ribavirin for 12 weeks. <u>2. When used in patients infected with HCV that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2):</u> <u>The usual adult dosage is 400 mg of Sofosbuvir, administered orally once daily in combination with Ribavirin for 24 weeks.</u>
Rebetol Capsules 200 mg	(No changes) 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. • When used in combination with Interferon alfa-2b (Genetical Recombination), Interferon Beta, Sofosbuvir, or the Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir fixed-dose combination tablet

Body weight	Dose of 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

• When used in combination with Peginterferon Alfa-2b (Genetical Recombination)

<table>
<tr><td></td><td>(1) Patients with chronic hepatitis C or patients with chronic hepatitis C and compensated cirrhosis with baseline hemoglobin level ≥14 g/dL
<table>
<tr><th rowspan="2">Body weight</th><th colspan="3">Dose of Ribavirin</th></tr>
<tr><th>Daily dose</th><th>After breakfast</th><th>After evening meal</th></tr>
<tr><td>≤60 kg</td><td>600 mg</td><td>200 mg</td><td>400 mg</td></tr>
<tr><td>>60 kg and ≤80 kg</td><td>800 mg</td><td>400 mg</td><td>400 mg</td></tr>
<tr><td>>80 kg</td><td>1000 mg</td><td>400 mg</td><td>600 mg</td></tr>
</table>
(2) Patients with chronic hepatitis C and compensated cirrhosis with baseline hemoglobin level <14 g/dL
<table>
<tr><th rowspan="2">Body weight</th><th colspan="3">Dose of Ribavirin</th></tr>
<tr><th>Daily dose</th><th>After breakfast</th><th>After evening meal</th></tr>
<tr><td>≤60 kg</td><td>400 mg</td><td>200 mg</td><td>200 mg</td></tr>
<tr><td>>60 kg and ≤80 kg</td><td>600 mg</td><td>200 mg</td><td>400 mg</td></tr>
<tr><td>>80 kg</td><td>800 mg</td><td>400 mg</td><td>400 mg</td></tr>
</table></td></tr>
<tr><td>Copegus Tablets 200 mg</td><td>(No changes)
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.
<table>
<tr><th>Body weight</th><th>Daily dose</th><th>After breakfast</th><th>After evening meal</th></tr>
<tr><td>≤60 kg</td><td>600 mg</td><td>200 mg</td><td>400 mg</td></tr>
<tr><td>>60 kg and ≤80 kg</td><td>800 mg</td><td>400 mg</td><td>400 mg</td></tr>
<tr><td>>80 kg</td><td>1000 mg</td><td>400 mg</td><td>600 mg</td></tr>
</table></td></tr>
</table>

Given that there is no clinical experience with the 24-week SOF + RBV regimen in Japanese patients with genotypes 4 through 6 chronic hepatitis C with or without compensated cirrhosis, a physician with sufficient knowledge and experience in the treatment of viral liver diseases should treat this patient population with this regimen based on a full understanding of the results of clinical studies and the efficacy and safety of the regimen.

Based on the above review, PMDA instructed the applicant of Sovaldi Tablets 400 mg to present the following precautionary statement in the “Precautions for Indications” section of the package insert: use of the SOF + RBV regimen in patients infected with HCV that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2) should be decided by a physician with a full understanding of the results of clinical and non-clinical studies of the regimen. PMDA also instructed all the applicants to provide healthcare professionals with currently available data from foreign clinical studies of the 24-week SOF + RBV regimen in patients with genotype 4 chronic hepatitis C with or without compensated cirrhosis and information on *in vitro* antiviral activity by genotype appropriately via the package inserts of Sovaldi Tablets 400 mg and Ribavirin products. Each applicant agreed to these instructions.

1.3 Risk management plan (draft)

1) SOF

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in "7.R.6 Post-marketing investigations" of Review Report (1). The expert advisors made the following comments concerning the measures to actively collect information on Japanese patients with genotypes 3 through 6 chronic hepatitis C with or without compensated cirrhosis:

- Considering that there is very limited clinical experience with the 24-week SOF + RBV regimen in Japanese patients with genotypes 3 through 6 chronic hepatitis C with or without compensated cirrhosis, it is extremely important to actively collect information on the post-marketing safety and efficacy (including information on genotype) of the regimen and to communicate it to healthcare professionals in clinical practice. However, since the number of Japanese patients with genotypes 3 through 6 chronic hepatitis C with or without compensated cirrhosis is very small, it would be difficult to collect the above information in the patient populations only through the usual post-marketing surveillance. The applicant should collaborate with relevant academic societies and medical institutions to collect information on the efficacy and safety of the 24-week SOF + RBV regimen actively and efficiently. Through such a collaboration, information should be gathered from medical institutions in which these patients are treated for hepatitis or cirrhosis.

Based on the comment from the Expert Discussion, PMDA performed the following review:
In Japan, the 24-week SOF + RBV regimen has been administered to a very small number of patients with genotype 3 chronic hepatitis C with or without compensated cirrhosis and to none of those with genotype 4, 5, or 6 chronic hepatitis C with or without compensated cirrhosis. For this reason, post-marketing information on the efficacy and safety of this regimen in these patient populations should be collected at the earliest possible time and any new findings should be communicated appropriately to healthcare professionals in clinical practice. Since the number of Japanese patients are affected by genotypes 3 through 6 chronic hepatitis C with or without compensated cirrhosis is very small, the applicant should undertake post-marketing surveillance in collaboration with relevant academic societies and medical institutions to gather information from medical institutions in which these patients are treated for hepatitis or cirrhosis. The applicant also should establish a system to reliably and promptly collect information on the efficacy and safety of the 24-week SOF + RBV regimen in Japanese patients with genotypes 3 through 6 chronic hepatitis C with or without compensated cirrhosis.

PMDA instructed the applicant to address the above points in post-marketing surveillance, and the applicant agreed to the instruction.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for Sovaldi Tablets 400 mg should include the safety and efficacy specifications presented in Table 16, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 17. PMDA accepted an outline of the specified use-results survey plan (draft) shown in Table 18.

Table 16. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Reactivation of hepatitis B virus (HBV) in patients with history of or current HBV infection • Hypertension • Cerebrovascular disorder	• Anemia • Use in patients with severe renal impairment or renal failure requiring dialysis	Not applicable
Efficacy specification		
• Efficacy in clinical settings • Drug resistance		

Table 17. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Use-results survey (patients with serogroup 2 [genotype 2] chronic hepatitis C with or without compensated cirrhosis) • Specified use-results survey (patients with chronic hepatitis C with or without compensated cirrhosis that is neither serogroup 1 [genotype 1] nor serogroup 2 [genotype 2])	Not applicable

Table 18. Outline of specified use-results survey plan (draft)

Objectives	To collect information on the safety and efficacy of the 24-week SOF + RBV regimen in patients with chronic hepatitis C with or without compensated cirrhosis that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2) in clinical settings
Survey method	Patients treated with the 24-week SOF + RBV regimen are to be enrolled
Population	Patients with chronic hepatitis C with or without compensated cirrhosis that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2)
Survey period (observation period)	3 years (48 weeks [up to 24 weeks after the end of treatment])
Planned sample size	50 patients
Main survey items	Anemia, use in patients with severe renal impairment or renal failure requiring dialysis, reactivation of HBV in patients with history of or current HBV infection, hypertension, cerebrovascular disorder, and efficacy

2) RBV

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in "7.R.6 Post-marketing investigations" of Review Report (1).

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The drug application data (CTD 5.3.5.1.3[22)]) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. 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. The application was submitted for new indication and new dosage and administration of Sovaldi Tablets 400 mg and for new indication of Rebetol Capsules 200 mg and Copegus Tablets 200 mg. However, taking into account that the remainder of the re-examination period for the initial approval of Sovaldi Tablets 400 mg is more than 4 years and that Rebetol Capsules 200 mg or Copegus Tablets 200 mg is to be used in combination with Sovaldi Tablets 400 mg, the re-examination period for the present application should be equal to the remainder of the re-examination period for the initial approval of Sovaldi Tablets 400 mg (until March 25, 2023) for Sovaldi Tablets 400 mg and until March 25, 2023 for both Rebetol Capsules 200 mg and Copegus Tablets 200 mg similarly to Sovaldi Tablets 400 mg.

[Indications]

Sovaldi Tablets 400 mg

(Underline denotes additions, and strikeout denotes deletion)

1. Suppression of viremia in <u>either of the following</u> patients with chronic hepatitis C with or without compensated cirrhosis ~~(any serogroup [genotype] other than serogroup 1 [genotype 1])~~:
   (1) <u>patients infected with serogroup 2 (genotype 2) HCV, or</u>
   (2) <u>patients infected with HCV that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2)</u>

Rebetol Capsules 200 mg

(Underline denotes additions, and strikeout denotes deletion)

1. Suppression of viremia in either of the following patients with chronic hepatitis C in combination with Interferon Alfa-2b (Genetical Recombination), Peginterferon Alfa-2b (Genetical Recombination), or Interferon Beta:
   (1) patients with high levels of HCV RNA in blood, 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-2b (Genetical Recombination)

22) Data submitted by each applicant

3. Suppression of viremia in either of the following patients with chronic hepatitis C with or without compensated cirrhosis ~~(any serogroup [genotype] other than serogroup 1 [genotype 1])~~ in combination with Sofosbuvir:
   (1) patients infected with serogroup 2 (genotype 2) HCV, or
   (2) patients infected with HCV that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2)
4. Suppression of viremia in patients with serogroup 2 (genotype 2) chronic hepatitis C in combination with the Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir fixed-dose combination tablet

Copegus Tablets 200 mg
(Underline denotes additions, and strikeout denotes deletion)
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 either of the following patients with chronic hepatitis C with or without compensated cirrhosis ~~(any serogroup [genotype] other than serogroup 1 [genotype 1])~~ in combination with Sofosbuvir:
   (1) patients infected with serogroup 2 (genotype 2) HCV, or
   (2) patients infected with HCV that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2)

Dosage and Administration
Sovaldi Tablets 400 mg
(Underline denotes additions, and strikeout denotes deletion)
1. When used in patients infected with ~~Suppression of viremia in patients with~~ serogroup 2 (genotype 2) HCV ~~chronic hepatitis C with or without compensated cirrhosis~~:
   The usual adult dosage is 400 mg of Sofosbuvir, administered orally once daily in combination with Ribavirin for 12 weeks.
2. When used in patients infected with HCV ~~Suppression of viremia in non-cirrhotic or compensated patients with cirrhotic hepatitis C infection~~ that is neither serogroup 1 (genotype 1) nor serogroup 2 (genotype 2):
   The usual adult dosage is 400 mg of Sofosbuvir, administered orally once daily in combination with Ribavirin for 24 weeks.

Condition of Approval
Sovaldi Tablets 400 mg
The applicant is required to develop and appropriately implement a risk management plan.