Report on the Deliberation Results

June 3, 2015

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

[Brand name]	Harvoni Combination Tablets
[Non-proprietary name]	Ledipasvir Acetonate/Sofosbuvir (JAN*)
[Name of applicant]	Gilead Sciences K.K.
[Date of application]	September 24, 2014

[Results of deliberation]
In the meeting held on May 28, 2015, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

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

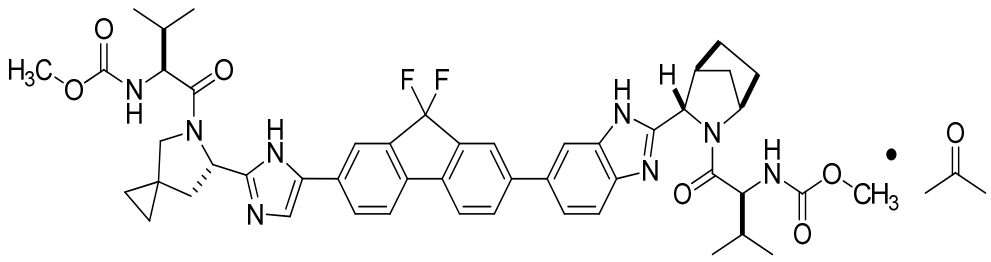
**Japanese Accepted Name (modified INN)*

Review Report

May 14, 2015
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Harvoni Combination Tablets
[Non-proprietary name]	Ledipasvir Acetonate/Sofosbuvir
[Applicant]	Gilead Sciences K.K.
[Date of application]	September 24, 2014
[Dosage form/Strength]	Tablets: Each tablet contains 90 mg of Ledipasvir and 400 mg of Sofosbuvir.
[Application classification]	Prescription drug, (1) Drug with a new active ingredient and (2) New combination drug
[Chemical structure]	Ledipasvir Acetonate



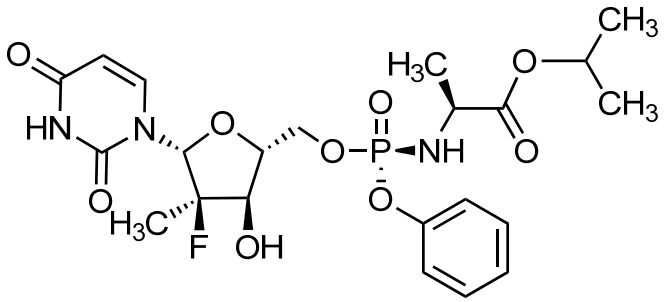
Molecular formula: $C_{49}H_{54}F_2N_8O_6 \cdot C_3H_6O$

Molecular weight: 947.08

Chemical name:

Methyl{(1*S*)-1-[(1*R*,3*S*,4*S*)-3-(5-{9,9-difluoro-7-[2-((6*S*)-5-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-azaspiro[2.4]hept-6-yl)-1*H*-imidazol-4-yl]-9*H*-fluoren-2-yl}-1*H*-benzimidazol-2-yl)-2-azabicyclo[2.2.1]heptane-2-carbonyl]-2-methylpropyl}carbamate monoacetonate

Sofosbuvir



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

Molecular weight: 529.45

Chemical name:

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

[Items warranting special mention]	Priority Review (Notification No. 1008-2 of Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated October 8, 2014)
[Reviewing office]	Office of New Drug IV

Review Results

May 14, 2015

[Brand name]	Harvoni Combination Tablets
[Non-proprietary name]	Ledipasvir Acetonate/Sofosbuvir
[Applicant]	Gilead Sciences K.K.
[Date of application]	September 24, 2014

[Results of review]
Based on the submitted data, the efficacy of Harvoni Combination Tablets in serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis has been demonstrated and its safety is acceptable in view of its observed benefits.

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

[Indications]	Suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis.
[Dosage and administration]	The usual adult dosage is one tablet (90 mg of Ledipasvir and 400 mg of Sofosbuvir), administered orally once daily for 12 weeks.
[Condition for approval]	The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

April 8, 2015

I. Product Submitted for Registration

[Brand name]	Harvoni Combination Tablets
[Non-proprietary name]	Ledipasvir Acetonate/Sofosbuvir
[Name of applicant]	Gilead Sciences K.K.
[Date of application]	September 24, 2014
[Dosage form/Strength]	Tablets: Each tablet contains 90 mg of Ledipasvir and 400 mg of Sofosbuvir.
[Proposed indications]	Serogroup 1 (genotype 1) chronic hepatitis C virus (HCV) infection with or without compensated cirrhosis
[Proposed dosage and administration]	The usual adult dosage is one tablet (90 mg of Ledipasvir and 400 mg of Sofosbuvir), administered orally once daily. The recommended duration of treatment is 12 weeks.

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

The data submitted by the applicant and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. Data on the quality of the Sofosbuvir (SOF) drug substance, one of the active substances in Harvoni Combination Tablets (LDV/SOF) as well as non-clinical and clinical data on SOF (excluding study data on SOF in combination with Ledipasvir [LDV]) have already been submitted by the applicant in support of the new drug application for Sovaldi Tablets 400 mg, which contains SOF as the active substance.

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

LDV/SOF is a combination product that contains two active ingredients, 90 mg of LDV and 400 mg of SOF. LDV is a compound discovered by Gilead Sciences, Inc. (the US) and it is considered to suppress viral proliferation by inhibiting the NS5A protein, which is required for hepatitis C virus (HCV) replication. SOF is the active substance of Sovaldi Tablets 400 mg, which was approved for the treatment of HCV (genotype 2) infection in March 2015 and its active metabolite, the uridine triphosphate form, is considered to suppress viral proliferation by inhibiting NS5B polymerase, which is required for HCV replication. Outside Japan, the clinical development of LDV/SOF was undertaken by Gilead Sciences, Inc. (the US). As of February 2015, LDV/SOF has been approved for the treatment of HCV infection in 34 countries including the US and the EU nations.

The number of people infected with HCV is estimated to be approximately 180 million globally[1)] and 1.3 to

1) Ghany MG, et al., *Hepatology*. 2009;49(4):1335-1374.

2.4 million in Japan (genotype 1 comprising approximately 70% of infections in Japan).[2)] Currently in Japan, interferon preparations, ribavirin, NS3/4A protease inhibitors (telaprevir, simeprevir sodium, asunaprevir, vaniprevir), and an HCV NS5A inhibitor (daclatasvir hydrochloride) have been approved for the treatment of patients with chronic hepatitis C (genotype 1).

Since the results from a Japanese clinical study of LDV/SOF in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) became available, the applicant has filed a marketing application for LDV/SOF.

2. Data relating to quality

2.A Summary of the submitted data

The submitted data relating to the quality of Ledipasvir (LDV) are presented in the sections below. Since the Sofosbuvir (SOF) drug substance is the same as that used in Sovaldi Tablets 400 mg and the data on the quality of the SOF drug substance were submitted in support of the new drug application for Sovaldi Tablets 400 mg, a description of quality studies of the SOF drug substance has been omitted.

2.A.(1) Drug substance (Ledipasvir Acetonate)

2.A.(1).1) Characterization

The drug substance is a white to tinted (off-white, tan, yellow, orange, or pink) powder. It has been characterized by solubility, melting point, hygroscopicity, dissociation constant (pKa), partition coefficient, polymorphism, and stereochemistry. [redacted]

The chemical structure of the drug substance has been elucidated by elemental analysis, ultraviolet spectroscopy, infrared spectroscopy, nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR), mass spectrometry, and single-crystal X-ray diffraction.[3)] Although the Ledipasvir Acetonate drug substance has six asymmetric carbons, the commercial manufacturing process is controlled to produce only [redacted] stereoisomers[4)] [see "2.B. Control of Ledipasvir Acetonate drug substance" for the control of LDV drug substance as Ledipasvir Acetonate].

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

[redacted]

2) Sievert W, et al., *Liver Int*. 2011;31 Suppl 2:61-80.
3) [redacted]
4) [redacted]

[redacted]

[redacted]

[redacted]

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

The proposed drug substance specifications consist of content, appearance, identification (identification of LDV, ultraviolet-visible spectrophotometry and liquid chromatography [HPLC]; identification of acetone, gas chromatography [GC]), purity (clarity of solution, elemental impurities [inductively coupled plasma mass spectrometry], related substances [HPLC], residual solvents [GC]), acetone (GC), water content, and assay (HPLC).

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

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

Table 1. Stability studies on drug substance

Study	Scale	Temperature	Humidity	Storage period	Storage package
Long-term	4 pilot-scale batches	25°C	60%RH	18 or 24 months[a)]	Double polyethylene bags/a brown high-density polyethylene container
	3 commercial-scale batches			12, 18, or 24 months[b)]	
Accelerated	4 pilot-scale batches	40°C	75%RH	6 months	
	3 commercial-scale batches			6 months	

a) 18 months for 2 batches and 24 months for 2 batches
b) 12 months for 1 batch, 18 months for 1 batch, and 24 months for 1 batch

Based on the above, a re-test period of [redacted] months has been proposed for the drug substance when stored protected from light in double polyethylene bags within a high-density polyethylene container at room temperature. The long-term testing will be continued up to [redacted] months for pilot-scale batches and up to [redacted] months for commercial-scale batches.

2.A.(2) Drug product

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

The proposed drug product is a film-coated tablet containing 90 mg LDV and 400 mg SOF and the excipients microcrystalline cellulose, lactose monohydrate, copovidone, croscarmellose sodium, magnesium stearate, light anhydrous silicic acid, and Opadry II Orange.

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

[redacted]

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

The proposed drug product specifications include strength, appearance, identification (ultraviolet-visible spectrophotometry and HPLC), purity [related substances of LDV (HPLC) and related substances of SOF (HPLC)], water content, uniformity of dosage units (content uniformity testing), dissolution, and assay (HPLC).

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

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

Table 2. Stability studies on drug product

Study	Scale	Temperature	Humidity	Storage period	Storage package
Long-term	3 pilot-scale batches	25°C	60%RH	18 months	A high-density polyethylene container (with a silica gel desiccant)
Intermediate	3 pilot-scale batches	30°C	75%RH	18 months	
Accelerated	3 pilot-scale batches	40°C	75%RH	6 months	

In accordance with the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No.0603004 dated June 3, 2003), a shelf-life of 30 months has been proposed for the drug product when stored in a high-density polyethylene container (with a silica gel desiccant) at room temperature. The long-term testing will be continued up to [redacted] months.

2.B Outline of the review by PMDA

On the basis of the submitted data and the following considerations, PMDA concluded that the quality of the LDV drug substance and the drug product is adequately controlled.

Control of Ledipasvir Acetonate drug substance

The applicant's explanation on the appropriateness of controlling the drug substance as Ledipasvir Acetonate:

[redacted]

[redacted][5)][redacted]

Based on the above, it is appropriate to control the drug substance as Ledipasvir Acetonate.

In accordance with the "Guideline for Residual Solvents in Pharmaceuticals" (PMSB/ELD Notification No.307 dated March 30, 1998) and based on the acetone content in batches used for Japanese and foreign clinical

5) [redacted]

studies ([redacted]%-[redacted]%), the acetone content acceptance criterion for the Ledipasvir Acetonate drug substance has been set at ≤[redacted]%.

[redacted]

The applicant explained that the acetone content acceptance criterion for Ledipasvir Acetonate drug substance will be in the range of [redacted]% to [redacted]% based on the results of batch analyses etc.

PMDA's view:
There is no particular problem with the control of the LDV drug substance as Ledipasvir Acetonate and the applicant's response regarding the acetone content acceptance criterion is also acceptable.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

Primary pharmacodynamic studies of Ledipasvir (LDV) were conducted to determine inhibition of hepatitis C virus (HCV) replicon replication, LDV resistance mutations, and pharmacodynamic interactions with other anti-HCV agents or anti-human immunodeficiency virus (HIV) agents. Secondary pharmacodynamic studies were performed to determine the activity against other non-HCV viruses, cytotoxicity, activity against HCV proteins, and the effects on a panel of receptors, ion channels, and enzyme activities. Safety pharmacology studies were performed to assess the effects on the function of the central nervous, cardiovascular, and respiratory systems.

Since the pharmacologic data on Sofosbuvir (SOF) were submitted in support of the new drug application for Sovaldi Tablets 400 mg, a description of pharmacology studies of SOF has been omitted.

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

3.(i).A.(1).1) *In vitro* antiviral activity (4.2.1.1.1; Reference data 4.2.1.1.2, 4.2.1.1.4)

LDV has not been tested for the inhibition of NS5A. The applicant explained as follows: Given that (i) LDV has been reported to bind to domain 1 of NS5A;[6)] (ii) when HCV replicon cells were cultured in the presence of LDV, resistance mutations were detected in the NS5A gene [see "3.(i).A.(1).2) *In vitro* resistance selection"]; and (iii) no inhibition of other HCV proteins such as NS3/4A protease was observed with LDV [see "3.(i).A.(2).4) Activity against HCV proteins"], LDV binds to NS5A to inhibit its function.

In HCV replicon assays (a luciferase reporter gene assay),[7)] the antiviral activity of LDV against different

6) Ascher DB, et al., *Scientific reports*. 2014;4:4765.
7) Lohmann V, et al., *Science*. 1999;285(5424):110-113.

genotypes was determined by quantifying HCV replicon replication. The 50% effective concentrations (EC_{50}) are as shown in Table 3.

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

Genotype (strain)	EC_{50} (nmol/L)
1a (H77)	0.031
1b (Con-1)	0.004
2a (JFH-1, L31 in NS5A [a)])	21
2a (J6, M31 in NS5A [b)]) [c)]	249
2b (MD2b8-2, L31 in NS5A [a)]) [d)]	16
2b (MD2b-1, M31 in NS5A [b)]) [e)]	530
3a (S52)	168
4a (ED43)	0.39
5a (SA13) [f)]	0.15
6a (HK6a Consensus)	1.1
6e (D88) [g)]	264

Geometric mean
a) Leucine at amino acid position 31 in NS5A
b) Methionine at amino acid position 31 in NS5A
c) The chimeric genotype 2a (JFH-1) replicon encoding NS5A from genotype 2a (J6)
d) The chimeric genotype 2a (JFH-1) replicon encoding NS5A from genotype 2b (MD2b8-2)
e) The chimeric genotype 2a (JFH-1) replicon encoding NS5A from genotype 2b (MD2b-1)
f) The chimeric genotype 1b (Con-1) replicon encoding NS5A amino acids 9-184 from genotype 5a (SA13)
g) The chimeric genotype 1b (Con-1) replicon encoding NS5A amino acids 9-184 from genotype 6e (D88)

HCV genotype 1a clinical isolates (30 samples) and HCV genotype 1b clinical isolates (3 samples) with no baseline NS5A resistance-associated variant were obtained from patients enrolled in LDV foreign phase II and SOF foreign phase III studies.[8)] The antiviral activity of LDV against chimeric replicons encoding NS5A sequences in these clinical isolates were evaluated, and the EC_{50} values were 0.022 for genotype 1a and 0.006 nmol/L for genotype 1b.

The effect of human serum on the antiviral activity of LDV was assessed. The EC_{50} of LDV against HCV genotype 1a (H77) replicon was 11.6 times higher in the presence than in the absence of 40% (v/v) human serum.

3.(i).A.(1).2) *In vitro* resistance selection (4.2.1.1.6 to 4.2.1.1.8; Reference data 4.2.1.1.9)

HCV genotype 1b replicon cells (1b-Rluc-2) were cultured in the presence of LDV 0.31, 0.63, or 1.25 nmol/L (75-, 150-, or 300-fold the EC_{50} value, respectively) for 3 weeks to determine their LDV resistance profiles. The NS5A substitution Y93H was identified in all 15 LDV-resistant clones and in the pool of the remaining resistant colonies and Q54H and P299T/Q were observed in 2 clones each. F127L, T135N, R262Q, N276S, S297P, A300E, A393T, S401Y, D430N, and S437R were observed in a single clone each. M2I and C446R, amino acid substitutions at the NS5A-5B junction, were observed in a single clone each.

NS5A substitutions observed in *in vitro* resistance selection studies of LDV[9)] or Daclatasvir Hydrochloride[10)] (DCV, another NS5A inhibitor) were introduced into HCV genotype 1b replicons (PI-HRluc). These replicon cells were used to evaluate the susceptibility to LDV, DCV, or 2'-C-Methyl-Adenosine (a nucleotide NS5B

8) Studies GS-US-256-0124 and GS-US-334-0110
9) NS5A substitutions observed more than once in the *in vitro* resistance selection studies (Q54H, Y93H, P299T, P299Q) were endoced, but a replicon carrying Q54H failed to replicate. Substitutions in the NS5A-5B junction (M2I, C446R) were also encoded, but a replicon carrying C446R failed to replicate.
10) Gao M, et al., New BMS HCV NS5A Inhibitor From Screen Hit to Clinic [Meeting Presentation], 15th International Symposium on Hepatitis C Virus and Related Viruses, 2008 October 5-9; San Antonio, Texas, USA.

polymerase inhibitor, "2' C-Me-A") (Table 4).

Table 4. Fold resistance to LDV, DCV, or 2' C-Me-A for genotype 1b mutant replicons [a)]

Mutations	LDV	DCV	2'-C-Me-A
M2I	2	1.6	1.3
L31F	10	13	1.6
L31M	12	11	1.5
L31V	133	17	1.3
Y93H	3310	44	1.5
P299Q	3.6	2.4	1.5
P299T	2.2	1.3	1.6

a) EC_{50} for mutant replicon/EC_{50} for wild-type replicon
The EC_{50} values of LDV, DCV, and 2'-C-Me-A against wild-type genotype 1b replicon were 0.001, 0.003, and 120 nmol/L, respectively.

HCV genotype 1a replicon cells (1a-HRlucP) were cultured in the presence of LDV 10, 20, or 40 nmol/L (50-, 100-, or 200-fold the EC_{50} value, respectively) for 3 weeks to determine their LDV resistance profiles. Amino acid substitutions identified in the NS5A genes [11)] were Q30E and Y93H. The fold-changes in LDV susceptibility[12)] for the Q30E and Y93H substitutions in HCV genotype 1a replicons (1a-HRlucP) were 997-fold and 3029-fold, respectively, and the fold-changes in SOF susceptibility were 1.0-fold and 0.7-fold, respectively. These substitutions and amino acid substitutions resistant to DCV[13)] were introduced into HCV genotype 1a replicons (PI-HRluc) and the replicon cells were used to evaluate the susceptibility to LDV or DCV (Table 5).

Table 5. Fold resistance to LDV or DCV for genotype 1a mutant replicons

Fold resistance [a)]	Mutations	
	LDV	DCV
≤3	K24Q, A25T, M28I/L/V, Q30V, H58P/R, E62D/G, R81K/W	K24E/N/Q/R, A25T, M28I/L/V, Q30L/V, H58L/P/R, E62D/G, R81K/W
>3 and ≤20	K24E/R, Q30L/T, H58L	K24G, Q30T
>20 and <100	K24G/N, M28T	L31I
≥100	M28A/G, Q30E/G/H/K/R, L31I/M/V, P32L, H58D, Y93C/H/N/S	M28A/G/T, Q30E/G/H/K/R, L31M/V, P32L, H58D, Y93C/H/N/S

a) EC_{50} for mutant replicon/EC_{50} for wild-type replicon
The EC_{50} values of LDV and DCV against wild-type genotype 1a replicon were 0.051 and 0.023 nmol/L, respectively.

3.(i).A.(1).3) Cross-resistance with other anti-HCV agents (4.2.1.1.8, 4.2.1.1.10)

The effects of substitutions associated with resistance to NS3/4A protease inhibitors or nucleoside and nonnucleoside[14)] NS5B polymerase inhibitors (Table 6)[15)] on the antiviral activity of LDV were evaluated using HCV genotype 1a and 1b NS3 and NS5B mutant replicon cells. The fold-change in the EC_{50} value of LDV[12)] was <2-fold for all mutants tested.

11) Amino acid substitutions detected in ≥2 colonies in the LDV 20 and 40 nmol/L selections. Q30E and Y93H were identified also in the pool of resistant colonies (10 nmol/L selection).

12) EC_{50} for mutant replicon/EC_{50} for wild-type replicon

13) Fridell RA, et al., *Hepatology*. 2011;54(6):1924-1935.

14) S282T was tested as a resistance substitution to nucleoside NS5B polymerase inhibitors; and M414T, L419M/S, R422K, M423I/T/V, Y448H, I482L, A486I/T/V, V494A, Y448H + Y452H, and C316Y + C445F + Y452H were tested as resistance substitutions to nonnucleoside NS5B polymerase inhibitors (Nguyen TT, et al., *Antimicrob Agents Chemother*. 2003;47(11):3525-3530, Shih IH, et al., *Antimicrob Agents Chemother*. 2011;55(9):4196-4203, Dvory-Sobol H, et al., *Antimicrob Agents Chemother*. 2014;58(11):6599-6606, Rupp D, et al., *Semin Liver Dis*. 2014;34(1):9-21).

15) Le Pogam S, et al., *J Virol*. 2006;80 (12):6146-6154, He Y, et al., *Antimicrob Agents Chemother*. 2008;52 (3):1101-1110, Lenz O, et al., *Antimicrob Agents Chemother*. 2010;54 (5):1878-1887, Lam AM, et al., *Antimicrob Agents Chemother*. 2012;56 (6):3359-3368.

Table 6. Substitutions associated with resistance to NS3/4A protease inhibitors or NS5B polymerase inhibitors

	HCV genotype	Resistance-associated variants tested
NS3 mutants	1a	Q80K, R155G/I/K/M/S/T/W, A156T, D168A/E/G/H/N/V/Y, I170T
	1b	V36A/M, T54A/S, R155C/G/K/L/Q/W, A156D/G/S/T/V, D168A/E/G/H/N/T/V/Y
NS5B mutants	1a	S282T, L419M/S, R422K, M423I/T/V, I482L, A486V, V494A
	1b	S282T, M414T, L419M/S, R422K, M423I/T/V, Y448H, I482L, A486I/T/V, V494A, Y448H + Y452H, C316Y + C445F + Y452H

3.(i).A.(1).4) Antiviral activity in combination with other anti-HCV agents (4.2.1.1.13, 4.2.1.1.14, 4.2.1.4.1 to 4.2.1.4.3)

The antiviral effects of LDV in combination with other anti-HCV agents (SOF, boceprevir [an NS3/4A protease inhibitor], simeprevir sodium [an NS3/4A protease inhibitor], telaprevir [an NS3/4A protease inhibitor], DCV [an NS5A inhibitor], interferon, ribavirin) were evaluated in HCV genotype 1a and 1b replicon cells. The results are as shown in Table 7.

Table 7. Antiviral activity of LDV in combination with other anti-HCV agents

HCV genotype	Compound	Volume [(μmol/L)^2%] [a)]	Interaction [b)]
Genotype 1a	LDV/SOF	3.3	Additive
	LDV/boceprevir	2.3	Additive
	LDV/simeprevir sodium	3.7	Additive
	LDV/telaprevir	0.7	Additive
	LDV/DCV	4.3	Additive
Genotype 1b	LDV/SOF	9.25	Additive
	LDV/interferon	32	Weak synergistic
	LDV/ribavirin	61	Moderate synergistic

Mean

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

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

3.(i).A.(1).5) Combined activity of LDV and HIV inhibitors (4.2.1.4.3)

Since there are HCV- and HIV-coinfected patients, the effects of HIV inhibitors[16)] on the antiviral activity of LDV were assessed in HCV genotype 1a replicon cells. The EC_{50} value of LDV was similar regardless of the presence of any of the HIV inhibitors at 0.15 to 15 μmol/L. The effects of LDV on the antiviral activity of HIV inhibitors[16)] were examined in HIV-1 (IIIB)-infected MT-4 cells (adult T cell leukemia cell line). The EC_{50} values for all of the HIV inhibitors tested were similar regardless of the presence of LDV at concentrations corresponding to 1- to 20-fold the EC_{50} value.

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

3.(i).A.(2).1) Antiviral activity against other non-HCV viruses (4.2.1.2.1, 4.2.1.2.2)

The antiviral activity of LDV was tested against human rhinovirus, influenza A and B viruses, bovine viral diarrhea virus, RS virus, hepatitis B virus, HIV-1, and a panel of flaviviruses (West Nile virus, yellow fever virus, dengue type 2 virus, and banzi virus) (Table 8).

16) efavirenz, elvitegravir, tenofovir, darunavir, emtricitabine, atazanavir, rilpivirine, and raltegravir

Table 8. Antiviral activity of LDV against other non-HCV viruses

Virus	EC_{50} (μmol/L)
Human rhinovirus (HRV) [a)]	> 50
Influenza A virus	> 100
Influenza B virus	> 100
Bovine viral diarrhea virus	19.3
RS virus	> 10
Hepatitis B virus	> 10
HIV-1	> 2.8
West Nile virus	> 100
Yellow fever virus	> 100
Dengue type 2 virus	> 41
Banzi virus	> 100

Mean
a) Infectious mixture of HRV1A, HRV14 and HRV16

3.(i).A.(2).2) *In vitro* cytotoxicity (4.2.1.2.1, 4.2.1.2.3)

The cytotoxicity of LDV was determined in HCV replicon cell lines (1b-Rluc-2, Huh-luc, 1a-HRlucP, and SL-3) and human hepatocarcinoma cell line HepG2 by calculating 50% cytotoxic concentration (CC_{50}) (Table 9).

Table 9. Cytotoxicity of LDV in multiple cell lines

	CC_{50} (μmol/L)				
	1b-Rluc-2	Huh-luc	1a-HRlucP	SL-3	HepG2
3 days of LDV exposure	36.65	> 50	16.17	> 50	5.91
7 days of LDV exposure	19.75	27.96	6.31	—	4.03

Mean
—: Not determined

Cytotoxicity in MT-4 cells (adult T-cell Leukemia cell line) was also tested in a 5-day assay and yielded a CC_{50} value of 2.79 μmol/L.

Cytotoxicity associated with the combination of LDV (0.014-1760 nmol/L) and SOF (320 nmol/L) in HCV genotype 1b (Con-1), 2a (JFH-1), 3a (S52), and 4a (ED43) replicon cells was tested. The combination of LDV and SOF showed no increase in cytotoxicity.

3.(i).A.(2).3) Effects on ligand binding to receptors and ion channels or on enzyme activities (4.2.1.2.4)

LDV was tested using ligand binding assays against a panel of 68 receptors and ion channels and evaluated *in vitro* for possible interactions with enzyme activities. As a result, the IC_{50} values of LDV were 0.21 and 3.47 μmol/L against the sodium channel and the N-binding site of L-type calcium channel, respectively. LDV (10 μmol/L) inhibited ligand binding to the D-binding site of L-type calcium channel and the androgen receptor by approximately 50%, but did not show ≥50% inhibition or induction of any other enzyme activity or ligand binding.

3.(i).A.(2).4) Activity against HCV proteins (4.2.1.2.5, 4.2.1.2.6)

LDV was tested for its ability to inhibit HCV enzymes and HCV internal ribosome entry site (IRES) (Table 10).

Table 10. LDV activity against HCV enzymes and the HCV IRES

Compound	IC_{50} (nmol/L)			
	NS3/4A protease	NS5B polymerase	NS3 helicase	IRES
LDV	> 20,000	> 2700	> 11,000	> 100,000
Positive control [a)]	1.2	62	1430	393

Mean
a) [redacted]

Since phosphorylation of NS5A has been reported to play a role in HCV replication,[17)] LDV activity against 442 protein kinases was assessed using quantitative PCR. LDV competitively inhibited binding of Bruton's tyrosine kinase and homeodomain-interacting protein kinase-1 to their ligands at 0.1 μmol/L. LDV did not inhibit binding of other kinases.

3.(i).A.(3) Safety pharmacology (4.2.1.3.1 to 4.2.1.3.4)

The effects of LDV on the central nervous, cardiovascular, and respiratory systems were assessed (Table 11). LDV 0.5 μmol/L (444.5 ng/mL) corresponded to systemic exposure levels approximately 1200-fold[18)] the clinical exposure.

Table 11. Summary of safety pharmacology studies

Organ systems evaluated	Test system	Parameters evaluated/evaluation method etc.	Route of administration	Doses or concentrations	No. per group [a)]	Noteworthy findings
Central nervous system	SD rat	Irwin test	Oral	0, 10, 30, 100 mg/kg	6	None.
Cardiovascular system	HEK-293 cells	hERG current	*In vitro*	0.25, 0.5 μmol/L	—	0.3% inhibition at 0.25 μmol/L. 0.8% inhibition at 0.5 μmol/L.
	Beagle dog	Telemetry	Oral	0, 3, 10, 30 mg/kg	4	None.
Respiratory system	SD rat	tidal volume, respiration rate, minute volume	Oral	0, 10, 30, 100 mg/kg	8	None.

a) Since no gender-related differences were observed in LDV repeat-dose toxicity studies in rats and dogs, male animals only were used in safety pharmacology studies.

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

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

PMDA's view:

The submitted data has demonstrated the antiviral activity of LDV against HCV. The antiviral activity of SOF was evaluated for the registration of Sovaldi Tablets 400 mg.[19)] The antiviral activity of the combination of LDV and SOF was tested in HCV replicon cells, which indicated that the combination of SOF and LDV is expected to exhibit additive antiviral activity. The efficacy of the combination of SOF and LDV in chronic hepatitis C patients with or without compensated cirrhosis is described in "4.(iii).B.(2) Efficacy."

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

The applicant's explanation on the SOF and LDV resistance profiles of HCV:

In vitro studies identified the SOF resistance-associated NS5B substitution S282T in genotype 1b. Reduced

17) Huang Y, et al., *Virology*. 2007;364(1):1-9.

18) A population pharmacokinetic analysis was performed using the plasma drug concentration data from non-Japanese healthy adult subjects and chronic hepatitis C patients orally given LDV/SOF (90 mg/400 mg, the proposed dosage and dose regimen) once daily. Calculation was based on the C_{max} of LDV (estimate), 0.364 μg/mL [see "4.(ii).A.(2).2).(a) Foreign studies"], and the free fraction of LDV in human plasma, 0.1% [see "3.(ii).A.(2).1) Protein binding"].

19) Sovaldi Tablets 400 mg/Copegus Tablet 200 mg Review Report (February 23, 2015)

susceptibility to SOF was observed for genotype 1a and 1b NS5B S282T mutant replicons compared to the corresponding wild-type replicons. On the other hand, no reduction in the antiviral activity of SOF was observed for replicons encoding resistance substitutions to nonnucleoside NS5B polymerase inhibitors, NS3 protease inhibitors, and NS5A inhibitors.[19)]

The NS5A substitutions Q30E and Y93H in genotype 1a and Y93H in genotype 1b were identified as LDV resistance substitutions in *in vitro* studies. Reduced susceptibility to LDV was observed for NS5A Q30E or Y93H mutant replicons compared to the wild-type replicon. Reduced susceptibility to LDV was observed for mutant replicons containing substitutions at positions M28, Q30, L31, or Y93, etc. (i.e., amino acid substitutions resistant to DCV, another currently approved NS5A inhibitor). On the other hand, no reduction in the antiviral activity of LDV was observed for replicons encoding resistance substitutions to nucleoside and nonnucleoside NS5B polymerase inhibitors and NS3 protease inhibitors [see "3.(i).A.(1).2) *In vitro* resistance selection" and "3.(i).A.(1).3) Cross-resistance with other anti-HCV agents"].

PMDA's view:
Reduced susceptibility to SOF was associated with the NS5B substitution S282T in genotypes 1a and 1b. The results of *in vitro* resistance selection studies showed that reduced susceptibility to LDV was associated with the NS5A substitutions Q30E and Y93H, and that there is cross-resistance between LDV and DCV (a currently approved NS5A inhibitor) [see "3.(i).A.(1).2) *In vitro* resistance selection"]. The association between the emergence of resistance mutations and the efficacy of the combination of LDV and SOF in clinical studies is discussed in "4.(iii).B.(2) Efficacy." The presence or absence of resistance-associated variants is important information on the efficacy of SOF and LDV. Therefore, it is important to collect post-marketing information on resistance to SOF or LDV. New findings should be provided to healthcare professionals promptly when they become available.

3.(ii) Summary of pharmacokinetic studies

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

The pharmacokinetics of LDV were studied in mice, rats, rabbits, dogs and monkeys after intravenous or oral administration of ^{14}C-LDV or unlabeled LDV. Liquid chromatography/tandem mass spectrometry was utilized for the determination of plasma LDV concentrations (lower limit of quantitation [LLOQ], 2 or 50 ng/mL). Radioactivity levels in biomaterials were determined using liquid scintillation counting and tissue radioactivity levels were determined using quantitative whole-body autoradiography. Liquid chromatography/tandem mass spectrometry coupled with a radio flow-through detector was utilized for metabolite analysis.

Since the pharmacokinetic data on SOF were submitted in support of the new drug application for Sovaldi Tablets 400 mg, a description of pharmacokinetic studies of SOF has been omitted.

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

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

The apparent permeability of LDV through Caco-2 cell monolayers was determined. The ratio of the apparent

permeability coefficient determined in the basolateral to apical direction to that determined in the apical to basolateral direction (efflux ratio) was 0.38 at 1 μmol/L. The applicant explained that the results of the assay may be less reliable because LDV had low permeability values even when the wells without cells were used in the assay, suggesting LDV adsorption to the wells/the membrane.

3.(ii).A.(1).2) Single-dose studies (4.2.2.2.2 to 4.2.2.2.5, 4.2.2.2.8, 4.2.2.2.9)

Rats (n = 3 males/group) received a single oral dose of LDV 5 mg/kg or a single intravenous dose of LDV 1 mg/kg, dogs (n = 3 males/group) received a single oral dose of LDV 0.5 mg/kg or a single intravenous dose of LDV 0.2 mg/kg, and monkeys (n = 3 males/group) received a single oral dose of LDV 1 mg/kg or a single intravenous dose of LDV 0.5 mg/kg. The absolute bioavailability of LDV was 33%, 53%, and 42% in rats, dogs, and monkeys, respectively.

The maximum plasma concentration (C_{max}) and the area under the plasma concentration versus time curve from time 0 to 24 hours (AUC_{0-24}) following single oral doses of LDV to mice, rats, and rabbits were determined. The results are as shown in Table 12. Dose-proportional or less than dose-proportional increases in exposure were observed in mice and rats. In rabbits, the increases in exposure were more than dose-proportional over the dose range of 10 to 100 mg/kg and less than dose-proportional over the dose range of 100 to 300 mg/kg. There was no further increase in exposure from 300 to 600 mg/kg. There were no sex differences in the results of mice and rats.

Table 12. Single-dose pharmacokinetic parameters

Species	Dose (mg/kg)	Number of animals	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)
Mouse	30	3 males/time point	2740	33,900
	100	3 males/time point	5210	78,800
	100	3 females/time point	5860	64,900
	300	3 males/time point	11,000	151,000
Rat	10	3 males	571	5430
	30	3 males	1510	14,850
	100	3 males	1700	20,100
	300	3 males	2020	29,800
	100	5 males	1900	26,400
	100	5 females	1350	17,500
	300	3 males	2000	37,900
	600	3 males	1850	32,600
Rabbit	10	3 females	48.4	333
	30	3 females	341	1960
	100	3 females	1390	8990
	300	3 females	1350	18,400
	600	3 females	1060	15,400

Mean

3.(ii).A.(1).3) Repeated-dose studies (Toxicokinetics) (4.2.3.2.3, 4.2.3.2.5)

Table 13 shows plasma AUC_{0-24} values in rats and dogs following repeated oral doses of LDV. The results indicated accumulation of LDV after repeated doses. The AUC_{0-24} was higher in male rats than in female rats. The AUC_{0-24} was higher in female dogs than in male dogs at Week 39.

Table 13. AUC_{0-24} values at different time points

Animal species Duration of dosing	Dose (mg/kg/day)	Number of animals	Day 1 AUC_{0-24} (ng·h/mL)		Week 13 AUC_{0-24} (ng·h/mL)		After the last dose AUC_{0-24} (ng·h/mL)	
			Male	Female	Male	Female	Male	Female
Rat 26 weeks	10	3/sex/time point	4667	2703	11,699	5256	16,067	7703
	30	3/sex/time point	12,561	10,361	26,866	16,835	36,189	23,563
	100	3/sex/time point	26,807	19,340	51,097	43,728	60,842	51,175
Dog 39 weeks	3	7/sex	4602	4259	5239	4455	5673	8249
	10	7/sex	13,080	16,772	15,142	25,323	15,897	32,178
	30	9/sex	25,178	19,226	35,199	45,685	41,318	80,268

Mean

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

3.(ii).A.(2).1) Protein binding (4.2.2.3.3)

Plasma protein binding of LDV (2 and 10 µmol/L) was ≥99.9% in all species tested (mice, rats, dogs, monkeys, and humans).

3.(ii).A.(2).2) Tissue distribution (4.2.2.3.1, 4.2.2.3.2)

Tissue distribution was examined in mice (n = 1 male/time point) following a single 20 mg/kg oral dose of ^{14}C-LDV and in albino and pigmented rats (n = 1 male/time point) following a single 10 mg/kg oral dose of ^{14}C-LDV. Concentrations of radioactivity in tissues of mice peaked at 3 or 8 hours post-dose and were below the LLOQ by 168 hours post-dose except for the adrenal gland, bone marrow, thymus, liver, kidneys, kidney medulla, kidney cortex, spleen, thyroid, testis, pancreas, and salivary gland. The high levels of radioactivity (excluding the gastrointestinal tract) were detected in the gallbladder, liver, harderian gland, and kidneys (the maximum concentrations were 43,100, 34,900, 15,600, and 15,100 ng eq./g, respectively). In rats, concentrations of radioactivity peaked at 4 or 8 hours post-dose and were below the LLOQ in most tissues (except for the kidneys, kidney medulla, kidney cortex, pituitary gland, and adrenal gland in albino rats and the uveal tract in pigmented rats) by 168 hours post-dose. The high levels of radioactivity (excluding the gastrointestinal tract) were detected in the liver, adrenal gland, urinary bladder, kidneys, and spleen in both albino and pigmented rats (The maximum concentrations were 9720, 3920, 3700, 3330, and 1530 ng eq./g, respectively, in albino rats and 9540, 3590, 1150, 2900, and 1270 ng eq./g, respectively, in pigmented rats). In pigmented rats, radioactivity in the uveal tract was low, but persistently detectable. However, there were no differences in the distribution of LDV to skin between albino and pigmented rats. The applicant explained that the detection of radioactivity in the uveal tract was not related to direct binding of LDV to melanin.

Up to 24 hours post-dose, the blood to plasma ratio of radioactivity ranged from 0.539 to 0.638 in mice and from 0.589 to 0.752 in rats.

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

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

Based on the results of assessments in "3.(ii).A.(3).2) *In vivo* metabolism" and "3.(ii).A.(3).3) *In vitro* metabolism," the metabolic pathway of LDV has been proposed as shown in Figure 1. LDV metabolites were primarily formed via *N*-demethylcarboxylation and oxidation. No metabolites unique to humans were identified.

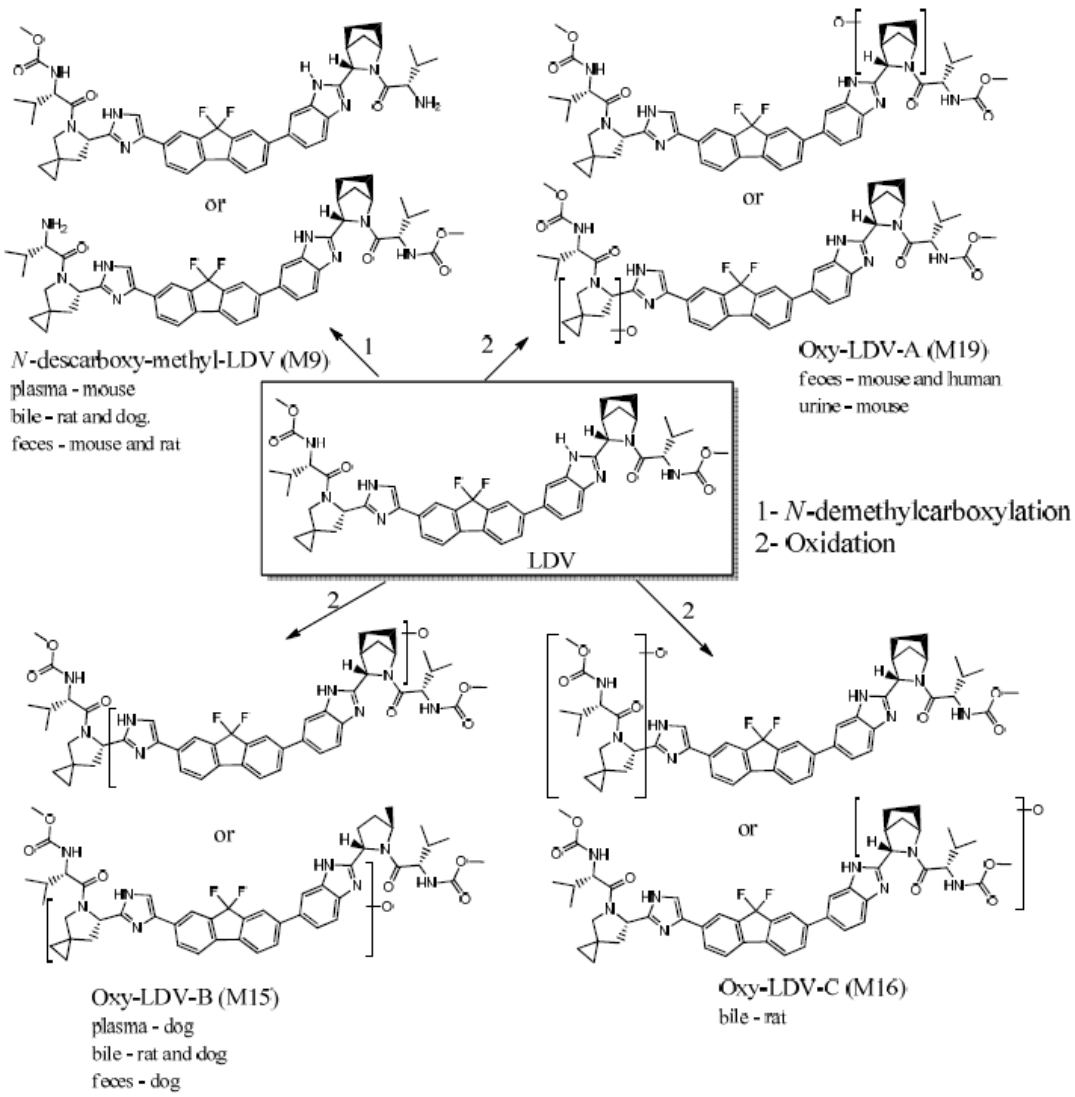


Figure 1. Proposed metabolic pathway of LDV

or: Since the difinitive structures of compounds detected cannot be determined by mass spectrometry, more than one possible structural formula is given.

3.(ii).A.(3).2) *In vivo* metabolism (4.2.2.4.1 to 4.2.2.4.3)

Following a single 20 mg/kg oral dose of ^{14}C-LDV in mice (4 males), unchanged parent drug represented 96.9% of total plasma radioactivity and M9 represented 1.1% of total plasma radioactivity. Unchanged parent drug, M1, M3, M4, M6, M19, M23, and M31 were detected in urine. Unchanged parent drug accounted for 80.1% of total radioactivity in feces and M9 and M19 were also detected in feces.

Bile-duct cannulated and intact rats (3 males each) were given a single 10 mg/kg oral dose of ^{14}C-LDV. In intact rats, unchanged parent drug accounted for 87.1% of total radioactivity in plasma; M1, M3, and M10 were also present in plasma and unchanged parent drug accounted for 85.8% of total radioactivity in feces; and M1, M2, and M9 were also detected in feces. Unchanged parent drug and 15 different metabolites were detected in bile from bile-duct cannulated rats.

Bile-duct cannulated and intact dogs (3 males each) were given a single 10 mg/kg oral dose of ^{14}C-LDV. In intact dogs, unchanged parent drug and M15 accounted for 87.5% and 5.29%, respectively, of total radioactivity in plasma; 7 different metabolites were detected, but no unchanged parent drug detected, in urine; and unchanged parent drug represented 76.7% of total radioactivity in feces; and M6 and M15 were also detected in feces. Unchanged parent drug and M8, M9, and M15 were detected in bile from bile-duct cannulated dogs.

Unchanged parent drug and M19 were present in feces of human [see "4.(ii).A.(1).2).(b) Mass balance"].

3.(ii).A.(3).3) *In vitro* metabolism (4.2.2.4.4 to 4.2.2.4.6)

LDV was stable metabolically, as assessed *in vitro* in hepatic microsomes from mice, rats, dogs, monkeys, and humans when LDV 3 µmol/L was added and in human hepatocytes when LDV 2 µmol/L was added. When LDV 5 µmol/L was added to human cytochrome P450 (CYP) expression system (CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4), LDV was minimally metabolized, indicating that LDV is not a substrate of the CYP enzymes tested.

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

3.(ii).A.(4).1) Urinary and fecal excretion and biliary excretion (4.2.2.3.1, 4.2.2.3.2, 4.2.2.5.1, 4.2.2.5.2)

Following a single 20 mg/kg oral dose of ^{14}C-LDV in mice (4 males), 77.9% of the total radioactive dose was excreted by 24 hours post-dose and 0.838% and 93.9% of the total dose were excreted in urine and feces, respectively, by 168 hours post-dose.

Following a single 10 mg/kg oral dose of ^{14}C-LDV in bile-duct cannulated and intact rats (3 males each), 69.4% and 82.4%, respectively, of the administered radioactivity were excreted by 24 hours post-dose. In bile-duct cannulated rats, 0.49%, 85.2%, and 3.01% of the administered radioactivity were excreted in urine, feces, and bile, respectively, by 168 hours post-dose. In intact rats, 0.29% and 92.9% of the administered radioactivity were excreted in urine and feces, respectively, by 168 hours post-dose.

Following a single 10 mg/kg oral dose of ^{14}C-LDV in bile-duct cannulated and intact dogs (3 males each), 81.7% and 81.8%, respectively, of the administered radioactivity were excreted by 48 hours post-dose. In bile-duct cannulated dogs, 0.355%, 72.7%, and 18.8% of the administered radioactivity were excreted in urine, feces, and bile, respectively, by 168 hours post-dose. In intact dogs, 0.357% and 95.8% of the administered radioactivity were excreted in urine and feces, respectively, by 168 hours post-dose.

Following a single 0.25 mg/kg intravenous dose of LDV in bile-duct cannulated dogs (3 males), 0.23% and 70.9% of the total dose were excreted in urine and bile, respectively, by 24 hours post-dose.

3.(ii).A.(4).2) Excretion in milk (Toxicokinetics) (4.2.3.5.3.1)

Rats (n = 3 females/time point) orally received 10, 30, or 100 mg/kg/day of LDV from gestation day 6 through postpartum day 10. The $AUC_{0\text{-}24}$ values of LDV were 2.62 (10 mg/kg/day group) to 37.6 (100 mg/kg/day group) µg·h/mL in female rats on postpartum day 10 and 0.598 (10 mg/kg/day group) to 9.77 (100 mg/kg/day group) µg·h/mL in neonatal rats on postnatal day 10. Assuming that the half-life of LDV in neonatal rats is similar to

that in maternal animals (<8 hours), LDV detected in the plasma of neonatal rats on postnatal day 10 was due to the excretion of LDV in milk, which was explained by the applicant.

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

3.(ii).A.(5).1) Enzyme inhibition or induction (4.2.2.6.1 to 4.2.2.6.3, 4.2.2.6.12, 4.2.2.6.13)

The potential of LDV to inhibit the activities of CYP isozymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A) was evaluated using human liver microsomes. The results indicated that LDV hardly inhibits CYP enzymes (IC_{50}, 9.9 and >25 μmol/L[20)] for CYP3A; IC_{50} >25 μmol/L for other CYP isozymes). The human uridine diphosphate-glucuronyltransferase (UGT) 1A1 expression system was used to evaluate the potential of LDV to inhibit UGT1A1. The results indicated that LDV is not an inhibitor of UGT1A1 (IC_{50}, 7.95 μmol/L).

The potential of LDV to induce CYP isozymes (CYP1A2, 2B6, 2C9, 3A), UGT1A1, and human P-glycoprotein (P-gp) was evaluated using human hepatocytes. The results showed that LDV is not an inducer.[21)]

Cells expressing the human pregnane X receptor (PXR) and cells expressing the human aryl hydrocarbon receptor (AhR) were used to evaluate the potential of LDV to activate AhR and PXR and potentiate induction of drug metabolizing enzymes. At 10 μmol/L, LDV did not activate AhR and the activation of PXR by LDV was weaker than that by androstanol, a weak PXR activator. Thus, the applicant explained that LDV does not cause clinically relevant induction via AhR (e.g., CYP1A2) or PXR (e.g., CYP3A4).

3.(ii).A.(5).2) Drug transporter substrate assays (4.2.2.6.4, 4.2.2.6.5, 4.2.2.6.7, 4.2.2.6.9)

LDV (^{3}H-LDV, 0.5 μmol/L) accumulation in P-gp-overexpressing Madin-Darby canine kidney type II (MDCKII) cells was approximately 30% of that in wild-type MDCKII cells. In the presence of P-gp inhibitors verapamil and cyclosporine, LDV accumulation in P-gp-overexpressing MDCKII cells was comparable to that in wild-type MDCKII cells. These results indicated that LDV is a substrate of P-gp.

LDV (^{3}H-LDV, 0.5 μmol/L) accumulation in breast cancer resistance protein (BCRP)-overexpressing MDCKII cells was approximately 38.0% of that in wild-type cells. In the presence of BCRP inhibitor cyclosporine, LDV accumulation in BCRP-overexpressing MDCKII cells was comparable to that in wild-type MDCKII cells. These results indicated that LDV is a substrate of BCRP.

The LDV (0.1 μmol/L) uptake rates were 1.5, 1.3, and 3.4 pmol/min/10^6cells in Chinese hamster ovary (CHO) cells transfected with organic anion transporting polypeptide (OATP) 1B1, CHO cells transfected with OATP1B3, and wild-type CHO cells, respectively, and the OATP1B1 and OATP1B3 inhibitor rifampicin did not influence LDV uptake rate, indicating that LDV is not a substrate of OATP1B1 or OATP1B3.

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20) Testosterone and midazolam were used as CYP3A substrates.

21) The potential of LDV (1-10 μmol/L) to induce CYP isozymes, UGT1A1, and P-gp was evaluated. As a result, LDV increased the activity and mRNA expression level of CYP1A2 by 1.10- to 1.13-fold and 0.55- to 1.40-fold, respectively, the activity and mRNA expression level of CYP2B6 by 1.50- to 2.47-fold and 1.87- to 2.23-fold, respectively, the activity and mRNA expression level of CYP3A by 1.33- to 4.87-fold and 2.57- to 14.4-fold, respectively, the mRNA expression level of CYP2C9 by 1.41- to 1.70-fold, the mRNA expression level of UGT1A1 by 1.27- to 1.57-fold, and the mRNA expression level of P-gp by 1.33- to 1.50-fold. Small increases in the activity of CYP2B6 and the activity and mRNA level of CYP3A were <15% of those caused by the positive controls.

LDV (1 and 5 μmol/L) accumulation in CHO cells transfected with organic cation transporter (OCT) 1 was approximately 1.25- to 1.33-fold that observed in wild-type CHO cells, indicating that LDV is not a substrate of OCT1.

3.(ii).A.(5).3) Drug transporter inhibition assays (4.2.2.6.6, 4.2.2.6.8 to 4.2.2.6.10)

LDV was evaluated as inhibitors of P-gp, BCRP, multidrug resistance-associated protein (MRP) 2, OATP1B1, OATP1B3, OCT1, bile salt export pump (BSEP), MRP4, OCT2, OAT1, OAT3, and multidrug and toxin extrusion (MATE) transporter 1. On the basis of the plasma LDV concentration in humans (total concentration, 409 nmol/L) [see "4.(ii).A.(2).2).(a) Foreign studies"] and the IC_{50} values against these transporters, the applicant explained that LDV is an inhibitor of P-gp, BCRP, and BSEP.[22)]

3.(ii).A.(5).4) Effect on permeability (4.2.2.6.11, 4.2.2.6.14)

The effect of SOF 1000 μmol/L or LDV 1, 5, and 25 μmol/L on the permeability of tenofovir disoproxil fumarate (TDF) 50 μmol/L through Caco-2 cell monolayers was determined. The efflux ratio of TDF was approximately 18. SOF reduced the efflux ratio to 2.1 and LDV concentration-dependently reduced the efflux ratio to 1.5 at 25 μmol/L. The applicant explained that SOF or LDV has the potential to increase intestinal absorption of TDF.

The effect of LDV 1 μmol/L on the permeability of SOF 10 μmol/L in Caco-2 cell monolayers was determined. The efflux ratio of SOF was 43.6 and the addition of LDV to SOF reduced the efflux ratio to 22.9. The applicant explained that LDV has the potential to increase SOF intestinal absorption.

3.(ii).A.(5).5) Effect of LDV on the active metabolite of SOF (4.2.2.6.15)

The effect of LDV on GS-461203 (the active metabolite of SOF) concentration in human primary hepatocytes was assessed. In the presence and absence of LDV, the intracellular concentrations of GS-461203 were 49.7 and 69.8 pmol/10^6cell, respectively, indicating that LDV does not significantly affect SOF metabolism.

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

PMDA's view:

Although it is difficult to say that the results of an *in vitro* study to determine the efflux ratio for transport of LDV across Caco-2 cell monolayers were assessed appropriately, there is no particular problem with the submitted data from other non-clinical pharmacokinetic studies of LDV.

22) Discussed in accordance with the FDA Guidance for industry: Drug interaction studies-Study design, data analysis, implications for dosing, and labeling recommendations. Draft Guidance, 2012. LDV inhibited P-gp and BCRP by 46.3% and 38.1%, respectively, at 1 μmol/L and LDV inhibited BSEP by 51% at 6 μmol/L. Thus, the discussion led to an IC_{50} value of approximately 1 μmol/L for P-gp and BCRP and an IC_{50} value of approximately 6 μmol/L for BSEP.

3.(iii) Summary of toxicology studies

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

The applicant submitted the following toxicity data on LDV: the results from repeat-dose toxicity, genotoxicity, carcinogenicity,[23] reproductive and developmental toxicity, local tolerance, and other toxicity studies (a skin sensitization study, a study on impurities, a phototoxicity study, comparison of the toxicity profiles of LDV and the D-tartrate salt of LDV[24]), using LDV, the D-tartrate salt of LDV, or Ledipasvir Acetonate. Since SOF toxicity data were submitted in support of the new drug application for Sovaldi Tablets 400 mg, a description of toxicity studies of SOF has been omitted.

Unless otherwise specified, 45% propylene glycol (PG) and 15% Solutol HS-15 in 40% reverse osmosis (RO) water was used as the vehicle for the test article.

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

Oral toxicity studies of LDV were conducted in mice, rats, and dogs. No toxicological findings were observed up to the highest doses tested in all studies. No target organs of LDV toxicity were identified.

The no-observed-adverse-effect levels (NOAELs) were determined in mouse 4-week study (300 mg/kg/day), rat 26-week study (100 mg/kg/day), and dog 39-week toxicity study (30 mg/kg/day). LDV plasma exposures (AUC) at the NOAELs were approximately 32/19-fold (mice, male/female), 7.1/6.0-fold (rats, male/female), and 4.8/9.4-fold (dogs, male/female) the human plasma exposure[25] at the maximum recommended clinical dose (90 mg/day).

3.(iii).A.(1).1) Mouse 4-week toxicity study (4.2.3.2.1)

Ledipasvir Acetonate 0 (vehicle[26]), 20, 60, or 300 mg/kg/day (free base equivalent) was administered orally to rasH2 mice (n = 10/sex/group) for 29 days. All examinations revealed no abnormalities. The NOAEL for both males and females was determined to be 300 mg/kg/day.

3.(iii).A.(1).2) Rat 2-week toxicity study (4.2.3.2.2)

LDV 0 (vehicle), 10, 30, or 100 mg/kg/day was administered orally to SD rats (n = 10/sex/group) for 14 days. All examinations revealed no abnormalities. The NOAEL for both males and females was determined to be 100 mg/kg/day.

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[23] Although an assessment of carcinogenic potential is not required based on duration of clinical dosing of LDV/SOF (12 weeks) and "Guidelines for Carcinogenicity Studies of Drugs" etc., the results from a 26-week oral carcinogenicity study in rasH2 mice were submitted.

[24] During the late development stage of the drug substance manufacturing process, a final crystalline form with improved physical properties was needed for the isolation of drug substance and a better drug product performance; thus the crystalline D-tartrate salt of LDV and the crystalline acetonate of LDV were discovered.

[25] Based on a population pharmacokinetic analysis using the plasma pharmacokinetic data from non-Japanese healthy adult subjects and chronic hepatitis C patients orally administered LDV/SOF (90 mg/400 mg, the proposed dosage and dose regimen) once daily, the estimated AUC_{tau} of LDV was 8.53 μg·h/mL [see "4.(ii).A.(2).2).(a) Foreign studies"].

[26] 0.2% hydroxypropyl methylcellulose, 0.2% polysorbate 20, and 0.9% benzyl alcohol in RO water

3.(iii).A.(1).3) Rat 26-week toxicity study with a 4-week recovery phase (4.2.3.2.3)

LDV 0 (vehicle), 10, 30, or 100 mg/kg/day was administered orally to SD rats (n = 10/sex/group) for 26 weeks.[27)] The reversibility of toxicity following a 4-week recovery period was evaluated in animals from the LDV 0 and 100 mg/kg/day groups (n = 5/sex/group). Four females given 100 mg/kg/day died or were sacrificed moribund. According to the applicant's explanation, 3 of these 4 deaths were attributed to gavage error and the cause of death in the remaining 1 animal was undetermined. All examinations otherwise revealed no abnormalities. Since only one death of undetermined cause occurred during the early phase of dosing (Day 57), the NOAEL for both males and females was determined to be 100 mg/kg/day.

3.(iii).A.(1).4) Dog 2-week toxicity study (4.2.3.2.4)

LDV 0 (vehicle), 3, 10, or 30 mg/kg/day was administered orally to beagle dogs (n = 3/sex/group) for 15 days. Body weight loss and lower food consumption were observed during Week 1 of the dosing phase in animals given 30 mg/kg/day. Based on the above, the NOAEL for both males and females was determined to be 10 mg/kg/day.

3.(iii).A.(1).5) Dog 39-week toxicity study with a 4-week recovery phase (4.2.3.2.5)

LDV 0 (vehicle), 3, 10, or 30 mg/kg/day was administered orally to beagle dogs (n = 4/sex/group) for 39 weeks.[28)] The reversibility of toxicity following a 4-week recovery period was evaluated in animals from the LDV 0 and 30 mg/kg/day groups (n = 2/sex/group). One male in the 10 mg/kg/day group and 2 males in the 30 mg/kg/day group were sacrificed moribund. According to the applicant's explanation, the 1 death in the 10 mg/kg/day group and the 1 death in the 30 mg/kg/day group were attributed to gavage error and the cause of death in the remaining 1 animal was bacterial infection. All examinations otherwise revealed no abnormalities. The NOAEL for both males and females was determined to be 30 mg/kg/day.

3.(iii).A.(2) Genotoxicity (4.2.3.3.1.1, 4.2.3.3.1.2, 4.2.3.3.2.1)

LDV was not genotoxic in a bacterial reverse mutation assay, a chromosomal aberration assay using cultured mammalian cells, or a rat bone marrow micronucleus assay.

3.(iii).A.(3) Carcinogenicity (4.2.3.4.1)

Ledipasvir Acetonate 0 (RO water), 0 (vehicle[26)]), 20, 60, or 300 mg/kg/day was administered orally to rasH2 mice (n = 25/sex/group) for 26 weeks. No treatment-related effects on survival were observed and a minimal increase in body weight gain was noted. No neoplastic lesions were found and the no-observed-effect level (NOEL) was determined to be 300 mg/kg/day. LDV plasma exposure (AUC) at the NOEL was >26-fold the human plasma exposure[25)] at the maximum recommended clinical dose (90 mg/day).

3.(iii).A.(4) Reproductive and developmental toxicity

Reproductive and development toxicity studies of LDV consisted of a rat study of fertility and early embryonic development to implantation, embryo-fetal development studies in rats and rabbits, and a rat study of effects

[27)] LDV 0 (vehicle), 10, 30, or 100 mg/kg/day was administered orally to SD rats (10/sex/group) for 13 weeks for an interim necropsy.
[28)] LDV 0 (vehicle), 3, 10, or 30 mg/kg/day was administered orally to beagle dogs (3/sex/group) for 13 weeks for an interim necropsy.

on pre- and postnatal development, including maternal function. The main LDV-related findings were a reduction in body weight gain, decreased food consumption, and reductions in the numbers of corpora lutea, implantations, and viable embryos in rat dams and reduced body weight gain in rat pups. LDV plasma exposures (AUC) at the NOAELs in the rat and rabbit embryo-fetal development studies (rats, 100 mg/kg/day; rabbits, 180 mg/kg/day) were 4.6- and 2.4-fold the human plasma exposure,[25)] respectively, at the maximum recommended clinical dose (90 mg/day) and LDV plasma exposure (AUC) at the NOAELs in the rat study of effects on pre- and postnatal development, including maternal function (30 mg/kg/day for F_1 neonatal development; 100 mg/kg/day for F_1 development; 100 mg/kg/day for F_2 survival) were 1.3-, 4.4-, and 4.4-fold the human plasma exposure, respectively.

3.(iii).A.(4).1) Study of fertility and early embryonic development to implantation (4.2.3.5.1.1)

SD rats (n = 22/sex/group) orally received Ledipasvir Acetonate 0 (vehicle), 10, 30, or 100 mg/kg/day (free base equivalent) from 28 days prior to mating through the day before necropsy for males and from 15 days prior to mating through gestation day 7 for females. There were no parental general toxicities or treatment-related male reproductive abnormalities. Female reproductive toxicity was assessed. The numbers of corpora lutea, implantation sites, and viable embryos were slightly reduced in the 100 mg/kg/day group. The NOAELs for parental general toxicity and male reproductive toxicity were determined to be 100 mg/kg/day and the NOAELs for female reproductive toxicity and early embryonic development were determined to be 30 mg/kg/day.

3.(iii).A.(4).2) Embryo-fetal development studies

3.(iii).A.(4).2).(a) Rat study (4.2.3.5.2.2)

Pregnant SD rats (n = 25/group) orally received LDV 0 (vehicle), 10, 30, or 100 mg/kg/day from gestation day 6 to gestation day 17. Decreases in maternal body weight gain and food consumption were observed in the 100 mg/kg/day group. There were no treatment-related embryo/fetal abnormalities. The NOAEL for maternal general toxicity was determined to be 30 mg/kg/day and the NOAEL for embryo-fetal developmental toxicity was determined to be 100 mg/kg/day.

3.(iii).A.(4).2).(b) Rabbit study (4.2.3.5.2.4)

Pregnant NZW rabbits (n = 20/group) orally received LDV 0 (vehicle[29)]), 30, 60, or 180 mg/kg/day from gestation day 7 to gestation day 20. Two animals each in the control and 60 mg/kg/day groups and 3 animals in the 180 mg/kg/day group died or were sacrificed moribund. The applicant did not attribute the deaths to LDV because the deaths were associated with dosing errors or poor pregnancy outcomes (early delivery/abortion) and did not occur in a dose-related manner. There were no other treatment-related maternal or embryo/fetal abnormalities. Based on the above, the NOAELs for maternal general toxicity and embryo-fetal developmental toxicity were determined to be 180 mg/kg/day.

[29)] 75% PG and 25% Solutol HS-15

3.(iii).A.(4).3) Study of effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1)

Pregnant SD rats (n = 25/group) orally received Ledipasvir Acetonate 0 (vehicle), 10, 30, or 100 mg/kg/day (free base equivalent) from gestation day 6 through lactation day 20. One animal in the 100 mg/kg/day group was sacrificed moribund on gestation day 18. In dams, body weight loss (during the early phase of dosing), decreased body weight gain, and lower food consumption were observed in the 100 mg/kg/day group. In pups (F_1), reduced body weight gain was noted between postnatal days 4 and 7 and between postnatal days 17 and 21 in the 100 mg/kg/day group. Based on the above, the NOAELs for maternal general toxicity and F_1 neonatal development were determined to be 30 mg/kg/day and the NOAELs for F_1 physical development, behavior, and reproductive performance and F_2 survival were determined to be 100 mg/kg/day.

3.(iii).A.(5) Other toxicity studies

3.(iii).A.(5).1) Ocular irritation study and dermal irritation study (4.2.3.6.1, 4.2.3.6.2)

An *in vitro* bovine corneal opacity and permeability assay to assess the eye irritation potential of LDV and a dermal irritation study of LDV in NZW rabbits were performed. No eye or dermal irritation was observed in the studies.

3.(iii).A.(5).2) Murine local lymph node assay (4.2.3.7.1.1)

Female CBA/Ca mice (n = 5/group) were treated with 25 μL of 0 (vehicle, dimethylformamide), 10%, 25%, or 50% (w/v) Ledipasvir Acetonate (the concentrations are expressed in terms of the free base) by topical application at the dorsum of each ear for 3 days. At 3 days after the last topical application, the mice were intravenously injected with ^{3}H-methylthymidine. At 5 hours after the intravenous injection, incorporated radioactivity in the auricular lymph nodes was measured. No erythema of the ear was observed. The comparison of incorporated radioactivity in the treated group vs. the control group indicated that LDV is not a skin sensitizer.

3.(iii).A.(5).3) Toxicity assessment of impurities

Rat 2-week toxicity study (4.2.3.7.6.1)

In order to assess LDV manufacturing process-related impurities,[30] the toxicity profile in SD rats (n = 10 males/group) orally given 0 (vehicle[31]), 30, or 100 mg/kg/day of LDV spiked with impurities (Lot number [redacted]; % purity, 98.3%) for 2 weeks was compared to that in animals given the control lot Ledipasvir Acetonate (Lot number [redacted]; % purity, 99.3%) 100 mg/kg/day (free base equivalent) for 2 weeks. No treatment-related abnormalities were observed in any group.

3.(iii).A.(5).4) Phototoxicity study in hairless mice (4.2.3.7.7.1)

SKH1-hr hairless mice (n = 6 females/group) were orally given the D-tartrate salt of LDV 0 (vehicle[32]), 22.3, 74.5, 224, or 300 mg/kg/day. The mice were exposed to UVA (100 J/m^2) for 0.5 hours at 4 hours after administration. Neither erythema nor edema occur in any group.

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30) Related Substance A, Related Substance B, Related Substance C, Related Substance D, Related Substance E, Related Substance F, and Related Substance G

31) 45% PG and 15% Kolliphor HS-15 in 40% RO water

32) 0.2% hydroxypropyl methylcellulose, 0.2% polysorbate 20, and 0.9% benzyl alcohol in RO water

3.(iii).A.(5).5) Rat 2-week toxicity study comparing LDV to D-tartrate salt of LDV (4.2.3.7.7.2)

SD rats (n = 10/sex/group) were orally given LDV 0 (vehicle) or 100 mg/kg/day or the D-tartrate salt of LDV 0 (vehicle[32)]), 30, or 100 mg/kg/day for 14 days. No treatment-related abnormalities were observed in any group. The NOAEL was determined to be 100 mg/kg/day for both LDV and the D-tartrate salt of LDV.

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

PMDA's view on the toxicity of the combination of LDV and SOF:

Since the maximum dose was limited to lower levels due to the low solubility of LDV,[33)] the toxicity studies conducted do not allow for a complete characterization of the toxicological profile of LDV. However, maximum feasible oral doses were used in all toxicity studies and acceptable safety margins were observed. The safety evaluation can therefore be made to the minimum necessary extent from a toxicological point of view. The studies produced no noteworthy toxicological findings relevant to the safety of LDV. The toxicity of SOF has been evaluated for the registration of Sovaldi Tablets 400 mg[34)] and the primary target organs of toxicity were the gastrointestinal tract and cardiovascular system in rats and the gastrointestinal tract, hepatobiliary system, and hematopoietic (red blood cells) system in dogs. The results of these toxicity studies of LDV or SOF suggests LDV is unlikely to potentiate the toxicity of SOF over the clinical dose range. Taking also into account that no adverse events of particular concern have so far been reported in clinical studies of LDV/SOF [see "4.(iii).B.(3) Safety"], PMDA concluded that there is no particular toxicological concern about LDV/SOF.

4. Clinical data

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

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

[redacted][35)]

[redacted][36)]

This section summarizes the results from 1 relative bioavailability and food effect study of Harvoni Combination Tablets (LDV/SOF) (each containing LDV 90 mg/SOF 400 mg) in healthy non-Japanese adults.

Liquid chromatography/tandem mass spectrometry was utilized to determine the concentrations of LDV and SOF and its metabolites (GS-331007 and GS-566500) in human plasma and urine (LLOQ: 1 ng/mL for LDV in plasma, 5 ng/mL for SOF in plasma, 10 ng/mL for SOF metabolites in plasma).

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33) The applicant explained that the solubility of LDV is <0.01 mg/mL in sodium hydroxide solution (pH 7.5) and that LDV is practically insoluble.

34) Sovaldi Tablets 400 mg/Copegus Tablet 200 mg Review Report (February 23, 2015)

35) [redacted] Formulation 3 was developed to mitigate food effects, which had been observed with Formulations 1 and 2.

36) These formulations were used in the following main clinical studies. [redacted]

Since the biopharmaceutic data on SOF formulations were submitted in support of the new drug application for Sovaldi Tablets 400 mg, a description of biopharmaceutic studies of SOF has been omitted.

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

Relative bioavailability and food effect study (Reference data, 5.3.1.2.2; Study GS-US-337-0101 [July 2012 to October 2012])

A two-treatment, two-period, crossover study[37)] was conducted in healthy non-Japanese adults (28 subjects included in pharmacokinetic assessment) to evaluate the relative bioavailability of the LDV/SOF fixed-dose combination (FDC) tablet formulation (LDV 90 mg/SOF 400 mg) relative to concurrent administration of the individual tablet formulations (LDV 90 mg + SOF 400 mg).[38)] Subjects received single oral doses of study drug under fasted conditions.

Table 14 shows the area under the plasma concentration versus time curve extrapolated to infinite time (AUC_{inf}), the maximum plasma concentration (C_{max}), and the geometric least-squares mean ratio [90% confidence interval (CI)] (LDV/SOF FDC vs. LDV+SOF). Similar AUC_{inf} and C_{max} values were achieved upon administration of the LDV/SOF FDC tablet or LDV+SOF. Thus, the LDV/SOF FDC tablet used in this study was chosen as the to-be-marketed formulation.

Table 14. Pharmacokinetic parameters following administration of LDV/SOF FDC or LDV+SOF

	LDV/SOF FDC (N = 28)	LDV+SOF (N = 28)	Geometric least-squares mean ratio [90% CI] [b)]
SOF			
AUC_{inf} (ng·h/mL)	1349.1 (37.6)	1552.3 (38.7)	0.88 [0.78, 0.98]
C_{max} (ng/mL)	1323.7 (68.3)	1545.9 (46.1)	0.82 [0.71, 0.95]
GS-566500 [a)]			
AUC_{inf} (ng·h/mL)	1686.4 (29.9)	2005.2 (27.7)	0.85 [0.77, 0.94]
C_{max} (ng/mL)	419.7 (31.7)	508.7 (28.7)	0.85 [0.74, 0.96]
GS-331007 [a)]			
AUC_{inf} (ng·h/mL)	11,861.9 (23.3)	12,475.6 (23.1)	0.95 [0.90, 1.01]
C_{max} (ng/mL)	761.1 (30.6)	764.1 (27.3)	0.99 [0.91, 1.07]
LDV			
AUC_{inf} (ng·h/mL)	9529.5 (46.8)	9533.3 (46.4)	0.96 [0.79, 1.17]
C_{max} (ng/mL)	313.9 (45.2)	313.9 (40.5)	0.98 [0.82, 1.18]

Mean (CV%)
a) SOF metabolites, b) LDV/SOF FDC vs. LDV+SOF

The pharmacokinetics of a single oral dose of the LDV/SOF FDC tablet were assessed in healthy non-Japanese adults (30 subjects included in pharmacokinetic assessment[39)]) under fasted or fed conditions (high-fat meal [approximately 1000 kcal, approximately 50% fat] or moderate-fat meal [approximately 600 kcal, approximately 25%-30% fat]) using a three-treatment, three-period crossover design.[40)]

The AUC_{inf} and C_{max} values and the geometric least-squares mean ratios [90% CIs] (high-fat meal/fasted) after administration of the LDV/SOF FDC tablet under fasted or fed condisions are as shown in Table 15. Neither

37) [redacted]

38) A 9-day washout period was included between doses.

39) Analysis was performed for 29 subjects receiving the dose after high-fat meal and for 29 subjects receiving the dose under fasted conditions.

40) A 9-day washout period was included between doses.

C_{max} nor AUC_{inf} of LDV was altered by food. Food increased the C_{max} and AUC_{inf} of SOF and its metabolite GS-566500. For GS-331007 (the predominant metabolite of SOF), lower C_{max} was observed upon administration with food, with no change in AUC_{inf}. The applicant explained as follows: These results (food effects on the pharmacokinetic parameters of SOF and its metabolites following administration of SOF as a component of the LDV/SOF FDC tablet) were largely consistent with the study results submitted in support of the new drug application for Sovaldi Tablets 400 mg[41)] and neither C_{max} nor AUC_{inf} of LDV was altered by food. Therefore as with Sovaldi Tablets 400 mg, the LDV/SOF FDC tablet can also be administered without regard to food.

Table 15. Pharmacokinetic parameters following administration of a single dose of LDV/SOF FDC under fasted or fed conditions

	High-fat meal (N = 29)	Moderate-fat meal (N = 30)	Fasted (N = 29)	Geometric least-squares mean ratio [90% CI] [b)]
SOF				
AUC_{inf} (ng·h/mL)	2571.4 (34.0)	2862.2 (33.4)	1522.6 (39.5)	1.79 [1.62, 1.98]
C_{max} (ng/mL)	1354.6 (42.5)	1523.7 (39.8)	1240.1 (49.6)	1.15 [0.99, 1.34]
GS-566500 [a)]				
AUC_{inf} (ng·h/mL)	2833.1 (22.2)	2791.9 (21.4)	1676.7 (42.0)	1.81 [1.66, 1.96]
C_{max} (ng/mL)	555.1 (26.8)	549.3 (22.2)	390.4 (42.7)	1.54 [1.39, 1.71]
GS-331007 [a)]				
AUC_{inf} (ng·h/mL)	12,946.5 (18.5)	13,841.9 (17.7)	11,832.2 (23.0)	1.12 [1.07, 1.18]
C_{max} (ng/mL)	599.7 (22.9)	699.6 (19.5)	865.4 (26.6)	0.70 [0.65, 0.76]
LDV				
AUC_{inf} (ng·h/mL)	9215.6 (36.1)	10,644.3 (35.6)	10,567.0 (57.2)	1.03 [0.88, 1.19]
C_{max} (ng/mL)	254.8 (25.9)	318.5 (24.8)	323.8 (44.8)	0.88 [0.76, 1.03]

Mean (CV%)
a) SOF metabolites, b) High-fat meal/fasted

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

PMDA concluded that there are no particular problems with the submitted biopharmaceutical data.

4.(ii) Summary of clinical pharmacology studies

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

The data submitted in this application included the results from foreign phase I studies (a comparative pharmacokinetic study in healthy adult subjects, pharmacokinetic studies in subjects with hepatic or renal impairment, drug interaction studies, etc.) and the results of population pharmacokinetic (PPK) analyses using the data from foreign phase I, II, and III studies or a Japanese phase III study. *In vitro* studies using human biomaterials are described in "3.(ii).A.(2) Distribution," "3.(ii).A.(3) Metabolism," and "3.(ii).A.(5) Pharmacokinetic drug interactions."

Since the clinical pharmacology data on SOF formulations were submitted in support of the new drug application for Sovaldi Tablets 400 mg, a description of clinical pharmacology studies of SOF has been omitted.

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

41) Sovaldi Tablets 400 mg/Copegus Tablet 200 mg Review Report (February 23, 2015)

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

4.(ii).A.(1).1) Phase I study in Japanese and Caucasian subjects (5.3.3.1.3, Study GS-US-334-0111 [April 2012 to November 2012])

The pharmacokinetics of SOF, GS-566500, GS-331007, and LDV following administration of a single oral dose of LDV/SOF (LDV 90 mg/SOF 400 mg) to healthy adultsunder fasted conditions (16 subjects included in pharmacokinetic assessment [8 Japanese subjects and 8 Caucasian subjects]) were investigated at 1 site in the US.[42)]

The results are as shown in Table 16. The geometric mean ratios of C_{max} and AUC extrapolated to infinite time (AUC_{inf}) of the substances detected in Japanese subjects versus Caucasian subjects were 0.94 and 0.91, respectively, for SOF, 1.30 and 1.13, respectively, for GS-566500, 0.94 and 0.85, respectively, for GS-331007, and 1.26 and 1.07, respectively, for LDV.

Table 16. Pharmacokinetic parameters following a single dose of LDV/SOF

	N	C_{max} (ng/mL)		AUC_{inf} (ng·h/mL)		T_{max}[a)] (h)		$t_{1/2}$ (h)	
		Japanese	Caucasian	Japanese	Caucasian	Japanese	Caucasian	Japanese	Caucasian
SOF	8	1316.0 (34.1)	1412.0 (33.8)	1576.0 (51.5)	1615.7 (46.3)	0.5 [0.5, 2.1]	0.5 [0.5, 2.0]	0.4 (25.2)	0.6 (39.3)
GS-566500	8	606.0 (32.4)	472.2 (37.3)	2151.9 (37.9)	1916.5 (42.2)	1.5 [0.5, 3.0]	1.0 [1.0, 2.0]	2.0 (6.0)	2.1 (8.6)
GS-331007	8	876.9 (35.8)	904.3 (33.2)	12,074.2 (29.8)	14,269.2 (34.8)	2.5 [1.0, 3.1]	4.3 [1.5, 4.5]	29.5 (26.9)	32.6 (20.4)
LDV	8	420.7 (49.0)	308.1 (29.0)	13,958.9 (53.6)	12,427.8 (39.8)	5.0 [5.0, 5.0]	5.0 [4.5, 5.0]	50.0 (17.6)	48.3 (23.1)

Mean (CV%), T_{max}: time to maximal plasma concentration, $t_{1/2}$: half-life
a) Median [Range]

4.(ii).A.(1).2) Phase I studies in foreign subjects

4.(ii).A.(1).2).(a) Phase I study (Reference data, 5.3.3.1.1, Study GS-US-256-0101 [April 2010 to June 2010])

[redacted][43)][redacted]

[redacted] The PK parameters following fasted administration of single oral doses are as shown in Table 17. The C_{max} and AUC_{inf} of LDV were dose-proportional over the dose range of 3 to 100 mg.

Table 17. [redacted]

Dose	N	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	T_{max} [a)] (h)	$t_{1/2}$ (h)
3 mg	8	6.0 (37.2)	218.0 (60.6)	6.0 [4.0, 6.0]	45.8 (53.9)
10 mg	8	18.9 (36.4)	618.0 (32.3)	5.0 [4.0, 6.0]	46.1 (36.9)
30 mg	8	73.1 (50.8)	2415.9 (60.3)	6.0 [4.0, 8.0]	39.1 (30.7)
60 mg	8	118.3 (50.0)	4711.1 (58.2)	6.0 [4.0, 6.0]	49.1 (20.6)
100 mg	8	215.5 (34.6)	7697.1 (34.3)	6.0 [4.0, 6.1]	43.3 (24.0)

Mean (CV%)
a) Median [Range]

42) The pharmacokinetics of SOF, GS-566500, and GS-331007 following administration of 200 to 800 mg of SOF were also investigated (Sovaldi Tablets 400 mg/Copegus Tablet 200 mg Review Report, February 23, 2015).

43) The pharmacokinetics of LDV after administration under fasted and fed conditions [high-fat meal (784 kcal, approximately 58% fat)] were investigated for the 30 mg cohort and 5 subjects from the 30 mg (fasted) cohort were reenrolled in the 30 mg (fed) cohort.

4.(ii).A.(1).2).(b) Mass balance (Reference data, 5.3.3.1.2, Study GS-US-256-0108 [March 2012 to May 2012])

The mass balance of a single oral dose of ^{14}C-LDV 90 mg with a standardized meal (400 kcal, 13 g fat) was determined in healthy non-Japanese adults (8 subjects included in pharmacokinetic assessment).

By 216 hours post-dose, 86.1% of the administered radioactivity (1.2% in urine and 84.9% in feces) was recovered. No unchanged parent drug was detected in urine. Unchanged LDV was the major component excreted in feces (approximately 70% of the administered dose), followed by M19 (2.2% of the administered dose). The blood to plasma ratio ranged from 0.51 to 0.66 up to 24 hours post-dose.

4.(ii).A.(1).2).(c) Interaction between LDV and SOF (Reference data, 5.3.3.4.9, Study GS-US-334-0101 [February 2012 to May 2012])

Healthy non-Japanese adults (17 subjects included in pharmacokinetic assessment) received the LDV 90-mg tablet and the SOF 400-mg tablet, alone or in combination,[44] to evaluate the potential for pharmacokinetic drug-drug interaction between LDV and SOF.

The geometric mean ratios [90% CIs] of C_{max} and AUC[45] (coadministration/administration alone) were 2.21 [1.76, 2.78] and 2.29 [1.91, 2.76], respectively, for SOF; 1.82 [1.54, 2.16] and 1.79 [1.55, 2.07], respectively, for GS-566500; 0.81 [0.77, 0.86] and 1.19 [1.13, 1.26], respectively, for GS-331007; and 0.97 [0.90, 1.04] and 0.96 [0.92, 1.00], respectively, for LDV. SOF did not alter the C_{max} or AUC over the dosing interval (AUC_{tau}) of LDV. The C_{max} and AUC_{inf} of SOF and GS-566500 were increased by LDV, but the findings were considered of no safety concern by the applicant.[46]

4.(ii).A.(2) Patient studies

4.(ii).A.(2).1) Foreign phase I study (Reference data, 5.3.3.2.1, Study GS-US-256-0102 [July 2010 to December 2011])

Single-agent tablets of LDV 1 to 90 mg were orally administered once daily under fasted conditions for 3 days to treatment-naïve patients with chronic hepatitis C (genotype 1) (59 subjects included in pharmacokinetic assessment [10 subjects/group[47]]) to evaluate the pharmacokinetics of LDV. The results are as shown in Table 18.

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44) Subjects received a single dose of SOF 400 mg followed by 3 days of washout, then LDV 90 mg once daily for 10 days and a single dose of LDV 90 mg + SOF 400 mg.

45) AUC_{inf} for SOF, AUC over the dosing interval (AUC_{tau}) for LDV

46) The increases in the C_{max} and AUC of SOF and GS-566500 observed in a drug-drug interaction study of SOF and cyclosporine were not considered of safety concern (Sovaldi Tablets 400 mg/Copegus Tablet 200 mg Review Report, February 23, 2015) and the increases in the C_{max} and AUC of SOF and GS-566500 in the present study remained within this range.

47) Genotype 1a and 1b patients were enrolled to receive 10 mg (9 and 10 subjects included in pharmacokinetic assessment, respectively). Patients assigned to other dose groups were all Genotype 1a.

Table 18. [redacted]

	N	C_{max} (ng/mL)		AUC [a] (ng·h/mL)		T_{max} [b] (h)		$t_{1/2}$ (h)	
		Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3
1 mg (GT1a)	10 [c]	1.6 (20.2)	2.2 (39.7)	30.9 (51.8)	34.0 (29.8)	4.0 [4.0, 6.0]	6.0 [4.0, 6.0]	12.7 (81.3)	14.2 (55.5)
3 mg (GT1a)	10	4.5 (33.3)	6.1 (56.6)	103.1 (85.1)	89.7 (54.6)	5.0 [3.0, 8.0]	6.0 [3.0, 8.0]	18.6 (72.8)	29.8 (86.5)
10 mg (GT1a)	9	18.1 (49.6)	22.2 (31.4)	359.8 (40.7)	323.6 (27.9)	6.0 [2.0, 16.0]	6.0 [4.0, 12.0]	20.6 (57.5)	43.0 (21.7)
10 mg (GT1b)	10	19.4 (24.3)	28.0 (42.7)	413.6 (38.4)	409.5 (42.5)	5.0 [4.0, 6.0]	6.0 [3.0, 8.0]	16.1 (25.5)	34.9 (34.8)
30 mg (GT1a)	10	67.0 (45.9)	103.3 (57.5)	1,491.0 (57.0)	1,592.4 (59.5)	6.0 [4.0, 12.0]	5.0 [0, 6.0]	16.9 (47.4)	40.4 (37.7)
90 mg (GT1a)	10	166.6 (44.5)	247.7 (45.4)	4,137.4 (67.1)	3,815.5 (42.1)	6.0 [2.0, 8.0]	6.0 [2.0, 10.0]	21.0 (38.2)	54.2 (42.4)

Mean (CV%), GT1a: genotype 1a, GT1b: genotype 1b
a) AUC_{inf} for Day 1, AUC_{tau} for Day 3
b) Median [Range]
c) N = 8 for C_{max} and T_{max} on Day 1, and AUC and $t_{1/2}$ on Day 3. N = 6 for AUC and $t_{1/2}$ on Day 1.

The relationship between LDV AUC_{tau} and change from baseline in hepatitis C virus (HCV) RNA levels in chronic hepatitis C patients (genotype 1a) was evaluated using a sigmoid maximal effect (E_{max}) model. The analysis predicted that >95% of the maximal effect would be achieved after administration of ≥30 mg of LDV.

4.(ii).A.(2).2) PPK analyses

4.(ii).A.(2).2).(a) Foreign studies (5.3.3.5.1 to 5.3.3.5.3)

PPK analysis (NONMEM ver. 7.1.2) was performed using the plasma concentration data from foreign phase I, II, and III studies[48] in healthy adult subjects or patients with chronic hepatitis C (genotypes 1-3) (SOF, n = 1455, 7602 sampling points; GS-331007, n = 1966, 17,072 sampling points; LDV, n = 2150, 20,146 sampling points). The final population pharmacokinetic model for SOF best described the plasma concentration data with a 1-compartment model with first-order absorption, first-order elimination, and an absorption lag time. The final population pharmacokinetic model for GS-331007 or LDV best described the plasma concentration data with a 2-compartment model with first-order absorption, first-order elimination, and an absorption lag time.

HCV infection status and creatinine clearance were selected as covariates of SOF oral clearance (CL/F) and meal status was selected as a covariate of absorption rate constant (Ka) of SOF. Creatinine clearance, sex, ribavirin (RBV) usage, and race were selected as covariates of GS-331007 CL/F; creatinine clearance, RBV usage, and HCV infection status were selected as covariates of GS-331007; apparent central volume of distribution (Vc/F), HCV infection status and meal status were selected as covariates of GS-331007 Ka; and meal status was selected as a covariate of GS-331007 relative bioavailability. Sex, body weight, RBV usage, and HCV infection status were selected as covariates of LDV CL/F; body weight was selected as a covariate of LDV Vc/F; and HCV infection status was selected as a covariate of LDV relative bioavailability.[49]

48) The data from 1455 subjects for SOF (209 healthy adult subjects and 1246 patients with chronic hepatitis C) and 1966 subjects for GS-331007 (207 healthy adult subjects and 1759 patients with chronic hepatitis C) in 5 phase I studies (Studies GS-US-334-0101, GS-US-334-0111, GS-US-344-0102, GS-US-337-0101, and GS-US-337-0127) and 5 phase II or III studies (Studies GS-US-337-0118, P7977-0523, GS-US-337-0102, GS-US-337-0108, and GS-US-337-0109) were used in the SOF and GS-331007 PPK analyses.
The data from 2150 subjects (391 healthy adult subjects and 1759 patients with chronic hepatitis C) in 9 phase I studies (Studies GS-US-334-0101, GS-US-334-0111, GS-US-334-0146, GS-US-344-0101, GS-US-344-0102, GS-US-344-0108, GS-US-344-0109, GS-US-337-0101, and GS-US-337-0127) and 5 phase II or III studies (Studies GS-US-337-0118, P7977-0523, GS-US-337-0102, GS-US-337-0108, and GS-US-337-0109) were used in the LDV PPK analysis.

49) Age, sex, race, body weight, creatinine clearance, cirrhosis, meal status, RBV usage, HCV infection status, HCV genotype, IL28B genotype, and concomitant medication were tested as covariates.

The C_{max} and AUC_{tau} values after oral administration of LDV/SOF in patients with chronic hepatitis C, estimated from the final models, were 659 ng/mL and 1380 ng·h/mL, respectively, for SOF, 736 ng/mL and 12,500 ng·h/mL, respectively, for GS-331007, and 364 ng/mL and 8530 ng·h/mL, respectively, for LDV.

4.(ii).A.(2).2).(b) Japanese study (5.3.5.1.1, Study GS-US-337-0113 [October 2013 to June 2014])

LDV/SOF was administered orally once daily with or without RBV (SOF, n = 51; GS-331007, n = 318; LDV, n = 318) to patients with chronic hepatitis C (genotype 1). PPK analysis (NONMEM ver. 7.1.2) was performed using the SOF, GS-331007, and LDV plasma concentration data from these patients. Previously-built models as mentioned in "4.(ii).A.(2).2).(a) Foreign studies" were used as the final models. The C_{max} and AUC_{tau} values after oral administration of LDV/SOF in patients with chronic hepatitis C (which were estimated from the final models) were 556 ng/mL and 1568 ng·h/mL, respectively, for SOF, 716 ng/mL and 12,516 ng·h/mL, respectively, for GS-331007, and 488 ng/mL and 11,684 ng·h/mL, respectively, for LDV.

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

4.(ii).A.(3).1) Study in subjects with hepatic impairment (Reference data, 5.3.3.3.2, Study GS-US-344-0101 [October 2012 to May 2013])

The pharmacokinetics of LDV were studied in non-Japanese subjects with normal hepatic function or severe hepatic impairment (Child-Pugh C) (10 subjects with normal hepatic function and 10 subjects with severe hepatic impairment included in pharmacokinetic assessment) following a single oral dose of the LDV 90-mg tablet.

The results are as shown in Table 19. An approximately 35% decrease in C_{max} and prolonged $t_{1/2}$ were observed in subjects with severe hepatic impairment as compared to subjects with normal hepatic function (48.1 hours in subjects with normal hepatic function and 94.6 hours in subjects with severe hepatic impairment), suggesting decreased absorption and decreased systemic clearance, but the AUC_{inf} values were similar. On basis of the above findings, the applicant explained that no dose adjustment of LDV is required for HCV-infected patients with hepatic impairment. The protein binding of LDV was 99.9% and 99.8%, respectively, demonstrating a lack of alteration in LDV protein binding in subjects with severe hepatic impairment.

Table 19. Pharmacokinetic parameters following a single oral dose of LDV 90 mg in subjects with normal hepatic function or severe hepatic impairment

	N	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	T_{max} [a] (h)	$t_{1/2}$ (h)	Geometric mean ratio [90% CI] [b]	
						C_{max}	AUC_{inf}
Normal hepatic function	10	197.4 (35.2)	7615.7 (30.9)	6.0 [6.0, 10.0]	48.1 (15.2)	—	—
Severe hepatic impairment	10	134.3 (43.9)	9567.2 (67.7)	6.0 [4.0, 8.0]	94.6 (40.8)	0.65 [0.45, 0.92]	1.08 [0.70, 1.65]

Mean (CV%)
a) Median [range], b) Severe hepatic impairment/normal hepatic function

4.(ii).A.(3).2) Pharmacokinetic study in subjects with renal impairment (Reference data, 5.3.3.3.3, Study GS-US-344-0108 [April 2013 to July 2013])

The pharmacokinetics of LDV were studied in non-Japanese subjects with normal renal function or severe renal impairment (creatinine clearance <30 mL/min) (9 subjects with normal renal function and 10 subjects with severe renal impairment included in pharmacokinetic assessment) following a single oral dose of the LDV 90-mg tablet.

The results are as shown in Table 20. The C_{max} and AUC_{inf} values of LDV were similar between subjects with severe renal impairment and subjects with normal renal function. The applicant explained that no dose adjustment of LDV is required for HCV-infected patients with renal impairment.

Table 20. Pharmacokinetic parameters following a single oral dose of LDV 90 mg in subjects with normal renal function or severe renal impairment

	N	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	T_{max} [a)] (h)	$t_{1/2}$ (h)	Geometric mean ratio [90% CI] [b)]	
						C_{max}	AUC_{inf}
Normal renal function	9	341.7 (32.7)	12,875.1 (40.0)	6.0 [4.0, 8.0]	54.7 (17.4)	—	—
Severe renal impairment	10	311.2 (30.2)	13,162.0 (35.0)	6.0 [3.0, 8.0]	60.6 (22.5)	0.92 [0.70, 1.21]	1.06 [0.75, 1.48]

Mean (CV%)
a) Median [range]
b) Severe renal impairment/normal renal function

4.(ii).A.(4) Drug interaction studies (Reference data, 5.3.3.4.6, Study GS-US-248-0125 [August 2011 to November 2011]; Reference data, 5.3.3.4.8, Study GS-US-256-0129 [December 2010 to February 2011]; Reference data, 5.3.3.4.10, Study GS-US-334-0146 [November 2012 to March 2013], Reference data, 5.3.3.4.12, Study GS-US-337-0127 [May 2013 to June 2013]; Reference data 5.3.3.4.13, Study GS-US-337-0128 [June 2013 to August 2013]; Reference data, 5.3.3.4.14, Study GS-US-344-0102 [September 2012 to February 2013]; Reference data, 5.3.3.4.16, Study GS-US-337-1306 [February 2014 to June 2014]; Reference data, 5.3.3.4.17, Study GS-US-337-1501 [July 2014 to September 2014])

Eight pharmacokinetic interaction studies were conducted to assess possible instraction of LDV single agent or LDV/SOF and other drugs. The geometric mean ratios [90% CIs] of C_{max}, AUC, and C_{min} of LDV or coadministered drugs (coadministration/administration alone) are as shown in Table 21 and Table 22.

Table 21. Impact of coadministered drug on pharmacokinetic parameters of LDV or LDV/SOF

Coadministered drug	Dosage regimen			N	Geometric mean ratios of LDV, SOF, and GS-331007 pharmacokinetic parameters [90% CIs]			
	Coadministered drug	LDV	SOF			C_{max}	AUC	C_{min}
ABC/3TC	600/300 mg QD	90 mg QD	400 mg QD	13	LDV	1.10 [1.01, 1.19]	1.18 [1.10, 1.28]	1.26 [1.17, 1.36]
					SOF	1.08 [0.85, 1.35]	1.21 [1.09, 1.35]	—
					GS	1.00 [0.94, 1.07]	1.05 [1.01, 1.09]	1.08 [1.01, 1.14]
ATV/RTV	300/100 mg QD	90 mg QD	400 mg QD	30	LDV	1.98 [1.78, 2.20]	2.13 [1.89, 2.40]	2.36 [2.08, 2.67]
					SOF	0.96 [0.88, 1.05]	1.08 [1.02, 1.15]	—
					GS	1.13 [1.08, 1.19]	1.23 [1.18, 1.29]	1.28 [1.21, 1.36]
ATV/RTV + FTC/TDF		90 mg QD	400 mg QD	24	LDV	1.68 [1.54, 1.84]	1.96 [1.74, 2.21]	2.18 [1.91, 2.50]
					SOF	1.01 [0.88, 1.15]	1.11 [1.02, 1.21]	—

Coadministered drug	Dosage regimen			N	Geometric mean ratios of LDV, SOF, and GS-331007 pharmacokinetic parameters [90% CIs]			
	Coadministered drug	LDV	SOF			C_{max}	AUC	C_{min}
	ATV/RTV 300/100 mg QD FTC/TDF 200/300 mg QD				GS	1.17 [1.12, 1.23]	1.31 [1.25, 1.36]	1.42 [1.34, 1.49]
DRV/RTV	800/100 mg QD	90 mg QD	—	23	LDV	1.45 [1.34, 1.56]	1.39 [1.28, 1.49]	1.39 [1.29, 1.51]
DRV/RTV + FTC/TDF	DRV/RTV 800/100 mg QD FTC/TDF 200/300 mg QD	90 mg QD	400 mg QD	23	LDV	1.11 [0.99, 1.24]	1.12 [1.00, 1.25]	1.17 [1.04, 1.31]
					SOF	0.63 [0.52, 0.75]	0.73 [0.65, 0.82]	—
					GS	1.10 [1.04, 1.16]	1.20 [1.16, 1.24]	1.26 [1.20, 1.32]
EFV/FTC/TDF	600/200/300 mg QD	90 mg QD	400 mg QD	14	LDV	0.66 [0.59, 0.75]	0.66 [0.59, 0.75]	0.66 [0.57, 0.76]
					SOF	1.03 [0.87, 1.23]	0.94 [0.81, 1.10]	—
					GS	0.86 [0.76, 0.96]	0.90 [0.83, 0.97]	1.07 [1.02, 1.13]
EVG/COBI	150/150 mg QD	90 mg QD	400 mg QD	29	LDV	1.63 [1.51, 1.75]	1.78 [1.64, 1.94]	1.91 [1.76, 2.08]
					SOF	1.33 [1.14, 1.56]	1.36 [1.21, 1.52]	—
					GS	1.33 [1.22, 1.44]	1.44 [1.41, 1.48]	1.53 [1.47, 1.59]
FTC/RPV/TDF	200/25/300 mg QD	90 mg QD	400 mg QD	15	LDV	1.01 [0.95, 1.07]	1.08 [1.02, 1.15]	1.16 [1.08, 1.25]
					SOF	1.05 [0.93, 1.20]	1.10 [1.01, 1.21]	—
					GS	1.06 [1.01, 1.11]	1.15 [1.11, 1.19]	1.18 [1.13, 1.23]
DTG + FTC/TDF	DTG 50 mg QD FTC/TDF 200/300 mg QD	90 mg QD	400 mg QD	29	LDV	0.85 [0.81, 0.90]	0.89 [0.84, 0.95]	0.89 [0.84, 0.95]
					SOF	1.06 [0.92, 1.21]	1.09 [1.00, 1.19]	—
					GS	0.99 [0.95, 1.03]	1.06 [1.03, 1.09]	1.06 [1.03, 1.10]
FAM	40 mg single dose simultaneously with LDV/SOF	90 mg single dose	400 mg single dose	12	LDV	0.80 [0.69, 0.93]	0.89 [0.76, 1.06]	—
					SOF	1.15 [0.88, 1.50]	1.11 [1.00, 1.24]	—
					GS	1.06 [0.97, 1.14]	1.06 [1.02, 1.11]	—
	40 mg single dose (staggered [12 hours] dosing of LDV/SOF)	90 mg single dose	400 mg single dose	12	LDV	0.83 [0.69, 1.00]	0.98 [0.80, 1.20]	—
					SOF	1.00 [0.76, 1.32]	0.95 [0.82, 1.10]	—
					GS	1.13 [1.07, 1.20]	1.06 [1.01, 1.12]	—
OPZ	20 mg QD	90 mg single dose	400 mg single dose	16	LDV	0.89 [0.61, 1.30]	0.96 [0.66, 1.39]	—
					SOF	1.12 [0.88, 1.42]	1.00 [0.80, 1.25]	—
					GS	1.14 [1.01, 1.29]	1.03 [0.96, 1.12]	—
RAL	400 mg BID	90 mg QD	—	28	LDV	0.92 [0.85, 1.00]	0.91 [0.84, 1.00]	0.89 [0.81, 0.98]
RFP [a)]	600 mg QD	90 mg single dose	—	31	LDV	0.65 [0.56, 0.76]	0.41 [0.36, 0.48]	—
SMV	150 mg QD	30 mg QD	—	22	LDV	1.81 [1.69, 2.94]	1.92 [1.77, 2.07]	—

QD: once daily, BID: twice daily, GS: GS-331007, C_{min}: plasma trough concentration, GS: GS-331007, —: Not available
ABC: abacavir, 3TC: lamivudine, ATV: atazanavir, RTV: ritonavir, FTC: emtricitabine, DRV: darunavir, EFV: efavirenz, EVG: elvitegravir, COBI: cobicistat, RPV: rilpivirine, FAM: famotidine, OPZ: omeprazole, RAL: raltegravir, RFP: rifampicin, SMV: simeprevir
a) This study was conducted in the presence of LDV, vedroprevir and tegobuvir.

Table 22. Impact of LDV or LDV/SOF on pharmacokinetic parameters of coadministered drug

Coadministered drug	Dosage regimen			N	Geometric mean ratios of pharmacokinetic parameters of coadministered drug [90% CIs]		
	Coadministered drug	LDV	SOF		C_{max}	AUC	C_{min}
ABC/3TC	ABC 600 mg QD	90 mg QD	400 mg QD	15	0.92 [0.87, 0.97]	0.90 [0.85, 0.94]	—
	3TC 300 mg QD				0.93 [0.87, 1.00]	0.94 [0.90, 0.98]	1.12 [1.05, 1.20]
ATV/RTV	ATV 300 mg QD	90 mg QD	400 mg QD	30	1.07 [1.00, 1.15]	1.33 [1.25, 1.42]	1.75 [1.58, 1.93]
	RTV 100 mg QD				0.93 [0.84, 1.02]	1.05 [0.98, 1.11]	1.56 [1.42, 1.71]
ATV/RTV + FTC/TDF	ATV 300 mg QD	90 mg QD	400 mg QD	24	1.07 [0.99, 1.14]	1.27 [1.18, 1.37]	1.63 [1.45, 1.84]
	RTV 100 mg QD				0.86 [0.79, 0.93]	0.97 [0.89, 1.05]	1.45 [1.27, 1.64]
	FTC 200 mg QD				0.98 [0.94, 1.02]	1.00 [0.97, 1.04]	1.04 [0.96, 1.12]
	TDF 300 mg QD				1.47 [1.37, 1.58]	1.35 [1.29, 1.42]	1.47 [1.38, 1.57]
DRV/RTV	DRV 800 mg QD	90 mg QD	—	23	1.02 [0.88, 1.19]	0.96 [0.84, 1.11]	0.97 [0.86, 1.10]
	RTV 100 mg QD				1.33 [1.20, 1.47]	1.37 [1.22, 1.55]	1.33 [1.07, 1.66]
DRV/RTV + FTC/TDF	DRV 800 mg QD	90 mg QD	400 mg QD	23	1.01 [0.96, 1.06]	1.04 [0.99, 1.08]	1.08 [0.98, 1.20]
	RTV 100 mg QD				1.17 [1.01, 1.35]	1.25 [1.15, 1.36]	1.48 [1.34, 1.63]
	FTC 200 mg QD				1.02 [0.96, 1.08]	1.04 [1.00, 1.08]	1.03 [0.97, 1.10]
	TDF 300 mg QD				1.64 [1.54, 1.74]	1.50 [1.42, 1.59]	1.59 [1.49, 1.70]
EFV/FTC/TDF	EFV 600 mg QD	90 mg QD	400 mg QD	15	0.87 [0.79, 0.97]	0.90 [0.84, 0.96]	0.91 [0.83, 0.99]
	FTC 200 mg QD				1.08 [0.97, 1.21]	1.05 [0.98, 1.11]	1.04 [0.98, 1.11]
	TDF 300 mg QD				1.79 [1.56, 2.04]	1.98 [1.77, 2.23]	2.63 [2.37, 2.97]
EVG/COBI	EVG 150 mg QD	90 mg QD	400 mg QD	29	0.88 [0.82, 0.95]	1.02 [0.95, 1.09]	1.36 [1.23, 1.49]
	COBI 150 mg QD				1.25 [1.18, 1.32]	1.59 [1.49, 1.70]	4.25 [3.47, 5.22]
FTC/RPV/TDF	FTC 200 mg QD	90 mg QD	400 mg QD	14	1.02 [0.98, 1.06]	1.05 [1.02, 1.08]	1.06 [0.97, 1.15]
	RPV 25 mg QD				0.97 [0.88, 1.07]	1.02 [0.94, 1.11]	1.12 [1.03, 1.21]
	TDF 300 mg QD				1.32 [1.25, 1.39]	1.40 [1.31, 1.50]	1.91 [1.74, 2.10]
DTG + FTC/TDF	DTG 50 mg QD	90 mg QD	400 mg QD	29	1.15 [1.07, 1.23]	1.13 [1.06, 1.20]	1.13 [1.06, 1.21]
	FTC 200 mg QD				1.02 [0.95, 1.08]	1.07 [1.04, 1.10]	1.05 [1.02, 1.09]
	TDF 300 mg QD				1.61 [1.51, 1.72]	1.65 [1.59, 1.71]	2.15 [2.05, 2.26]
Norelgestromin	Norgestimate 0.180/0.215/0.250 mg /ethinyl estradiol 0.025 mg QD	90 mg QD	—	15	1.02 [0.89, 1.16]	1.03 [0.90, 1.18]	1.09 [0.91, 1.31]
Norgestrel					1.03 [0.87, 1.23]	0.99 [0.82, 1.20]	1.00 [0.81, 1.23]
Ethinyl estradiol					1.40 [1.18, 1.66]	1.20 [1.04, 1.39]	0.98 [0.79, 1.22]
RAL	400 mg BID	90 mg QD	—	28	0.82 [0.66, 1.02]	0.85 [0.70, 1.02]	1.15 [0.90, 1.46]
SMV	150 mg QD	30 mg QD	—	22	2.61 [2.39, 2.86]	2.69 [2.44, 2.96]	—

QD: once daily, BID: twice daily, —: Not available
ABC: abacavir, 3TC: lamivudine, ATV: atazanavir, RTV: ritonavir, FTC: emtricitabine, DRV: darunavir, EFV: efavirenz, EVG: elvitegravir, COBI: cobicistat, RPV: rilpivirine, RAL: raltegravir, SMV: simeprevir

4.(ii).A.(5) QT/QTc study (5.3.4.1.1, Study GS-US-344-0109 [February 2013 to May 2013])

A six-treatment, three-period, crossover study was conducted in 60 healthy non-Japanese adults to evaluate the effect of LDV on the QT/QTc interval. A single oral dose of moxifloxacin 400 mg was administered as an active control and placebo or LDV 120 mg was orally administered twice daily for 10 days.

The largest mean difference in change from baseline in the QT interval corrected using the Fridericia formula (QTcF) between LDV and placebo [90% CI] was 1.5 [-0.5, 3.5] ms at 12 hours post-dose. The upper bound of the 90% confidence interval was below 10 ms. The applicant therefore explained that LDV at doses up to 120 mg does not prolong the QTcF interval.[50)] The C_{max} and AUC_{tau} following twice daily administration of LDV 120 mg were 1519.5 ng/mL and 15,932.9 ng·h/mL, respectively.

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

4.(ii).B.(1) Effects of LDV on pharmacokinetic parameters of pravastatin, rosuvastatin, digoxin, and cyclosporine

The applicant's explanation on the effects of LDV on the pharmacokinetic parameters of pravastatin sodium (pravastatin), rosuvastatin calcium (rosuvastatin), digoxin, and cyclosporine:

Pravastatin, rosuvastatin, digoxin, or cyclosporine was coadministered with LDV+vedroprevir (VDV)+tegobuvir (TGV) in a foreign phase I study (GS-US-248-0125). The geometric mean ratios of the C_{max} and AUC of each drug (coadministration/administration alone) [90% CIs] are as shown in Table 23.

Table 23. Effects of LDV+VDV+TGV on pharmacokinetic parameters of coadministered drug

Coadministered drug	Dosage regimen				N	Geometric mean ratios of pharmacokinetic parameters of coadministered drug [90% CIs]	
	Coadministered drug	LDV	VDV	TGV		C_{max}	AUC_{inf}
Pravastatin	40 mg single dose	90 mg QD	200 mg QD	30 mg BID	23	2.66 [2.23, 3.18]	2.68 [2.32, 3.09]
Rosuvastatin	10 mg single dose				23	17.69 [14.09, 22.23]	7.99 [6.97, 9.16]
Digoxin	0.25 mg single dose				10	1.25 [0.84, 1.86]	1.34 [1.17, 1.52]
Cyclosporine	300 mg single dose				32	0.95 [0.89, 1.02]	1.00 [0.91, 1.11]

QD: once daily, BID: twice daily

The C_{max} and AUC of rosuvastatin increased 17.7- and 8.0-fold, respectively, when coadministered with LDV+VDV+TGV, compared with those following single administration. Since rosuvastatin is a substrate of OATP, BCRP, and sodium-taurocholate cotransporting polypeptide (NTCP), these transporters were likely involved in the observed increases in rosuvastatin exposures. While LDV is an inhibitor of BCRP [see "3.(ii).A.(5).3) Drug transporter inhibition assays"], VDV also inhibits OATP, BCRP, and NTCP. Thus, the extent of the contribution of LDV to the increases in rosuvastatin C_{max} and AUC is unclear, but marked increases in rosuvastatin exposures have been observed in clinical studies. Therefore rosuvastatin will be listed in the

50) The largest mean difference in change from baseline in QTcF between moxifloxacin and placebo [two-sided 96.67% CI] was 9.1 [6.5, 11.7] ms at 3.5 hours post-dose.

section of precautions for concomitant use in the LDV/SOF package insert.

The C_{max} and AUC of digoxin both increased approximately 1.3-fold when coadministered with LDV+VDV+TGV, compared with those following single administration. Given that digoxin is a substrate of P-gp, that LDV and VDV are P-gp inhibitors [see "3.(ii).A.(5).3) Drug transporter inhibition assays"], and that digoxin has a narrow therapeutic window and an increase in digoxin exposure is considered clinically important, digoxin will be listed in the section of precautions for concomitant use in the LDV/SOF package insert.

PMDA's view:
Since VDV and TGV in addition to LDV were coadministered in the foreign phase I study (GS-US-248-0125), the contribution of LDV to changes in the pharmacokinetic parameters of pravastatin, rosuvastatin, digoxin, and cyclosporine is unclear at present. Given that rosuvastatin exposures increased markedly and that digoxin has a narrow therapeutic window, listing rosuvastatin and digoxin in the section of precautions for concomitant use in the LDV/SOF package insert is acceptable.

4.(ii).B.(2) Use in patients with renal impairment
Multiple reports on serious adverse events or deaths occurring in patients with severe renal impairment or end-stage renal disease (ESRD) treated with SOF 400 mg have been available from foreign marketing experience. Higher exposures to GS-331007 (the predominant metabolite of SOF) were observed in subjects with severe renal impairment or ESRD requiring hemodialysis. For these reasons, Sovaldi Tablets 400 mg is contraindicated in patients with severe renal impairment or ESRD requiring hemodialysis.

PMDA asked the applicant to explain the need for a precautionary statement regarding the use of LDV/SOF in patients with renal impairment.

The applicant's explanation:
Since LDV is primarily excreted unchanged in feces and renal elimination is minor [see "4.(ii).A.(1).2).(b) Mass balance"], the pharmacokinetics of LDV were similar between subjects with severe renal impairment and subjects with normal renal function [see "4.(ii).A.(3).2) Pharmacokinetic study in subjects with renal impairment"]. However, as Sovaldi Tablets 400 mg is contraindicated in patients with severe renal impairment or ESRD requiring hemodialysis, the proposed combination product that contains SOF as a component, will also be contraindicated in patients with severe renal impairment or ESRD requiring hemodialysis.

PMDA accepted the applicant's explanation.

4.(iii) Summary of clinical efficacy and safety

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

The efficacy and safety evaluation data submitted in the application consisted of the results from 1 Japanese study and 5 foreign studies. The reference data submitted consisted of the results from 37 foreign studies. Clinical studies submitted as the evaluation data are summarized in Table 24. Since the results from a phase I

study (GS-US-334-0111) were submitted in support of the new drug application for Sovaldi Tablets 400 mg, a description of this study has been omitted.

Table 24. Summary of clinical studies (Evaluation data)

	Phase	Study Number	Study Population	Primary objectives	Number of subjects	Dosage and Administration
Overseas	I	GS-US-344-0109	Healthy adults	QT/QTc	60	10 days of LDV 120 mg BID
Overseas	I	GS-US-334-0111	Healthy Japanese and Caucasian adults	PK Safety Tolerability	64	Single dose of SOF 200, 400, 800 mg, or LDV/SOF
Japan	III	GS-US-337-0113	Genotype 1 chronic hepatitis C patients with or without compensated cirrhosis (treatment-naïve or treatment-experienced)	Efficacy Safety	341	12 weeks of LDV/SOF QD or LDV/SOF QD+RBV BID
Overseas	III	GS-US-337-0102	Genotype 1 chronic hepatitis C patients with or without compensated cirrhosis (treatment-naïve)	Efficacy Safety	865	12 or 24 weeks of LDV/SOF QD or LDV/SOF QD+RBV BID
Overseas	III	GS-US-337-0108	Genotype 1 non-cirrhotic patients with chronic hepatitis C (treatment-naïve)	Efficacy Safety	647	8 or 12 weeks of LDV/SOF QD or 8 weeks of LDV/SOF QD+RBV BID
Overseas	III	GS-US-337-0109	Genotype 1 chronic hepatitis C patients with or without compensated cirrhosis (treatment-experienced)	Efficacy Safety	440	12 or 24 weeks of LDV/SOF QD or LDV/SOF QD+RBV BID

QD: once daily, BID: twice daily

4.(iii).A.(1) Phase I study (5.3.4.1.1, Study GS-US-344-0109 [February 2013 to May 2013])

A randomized, six-treatment, three-period, crossover study was conducted at 1 site in the US to evaluate the effect of LDV 120 mg on the QT/QTc interval in healthy adults(target sample size of 60 subjects; 10 per treatment sequence).

LDV 120 mg or placebo was to be administered orally twice daily (BID) for 10 days or a single oral dose of moxifloxacin 400 mg was to be administered once daily (QD).

Fifty-nine subjects treated with LDV, 60 subjects treated with placebo, and 60 subjects treated with moxifloxacin were included in the Safety Analysis Set.

Adverse events reported in ≥2 subjects following any treatment were upper respiratory tract infection (LDV, 0 of 59 subjects; placebo, 2 of 60 subjects; moxifloxacin, 0 of 60 subjects) and headache (LDV, 1 of 59 subjects; placebo, 3 of 60 subjects; moxifloxacin, 1 of 60 subjects), of which headache (LDV, 1 subject; placebo, 2 subjects; moxifloxacin, 1 subject) was assessed as causally related to the study drug and the outcome was reported as “resolved” for all cases.

Neither deaths nor serious adverse events were reported. An adverse event leading to discontinuation occurred in 1 subject following administration of moxifloxacin (exacerbation of hematuria) and its causal relationship to study drug was ruled out.

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

4.(iii).A.(2).1) Japanese study (5.3.5.1.1, Study GS-US-337-0113 [October 2013 to June 2014])

A randomized, open-label, parallel-group study[51] was conducted at 19 study sites in Japan to evaluate the efficacy and safety of the regimens of LDV/SOF with or without RBV (brand name, Copegus Tablet 200 mg) (LDV/SOF+RBV) in chronic hepatitis C patients with or without compensated cirrhosis[52] (genotype 1) (target sample size, 150 treatment-naïve[53] and 150 treatment-experienced[54] patients).

LDV/SOF was to be administered orally QD in both the LDV/SOF and LDV/SOF+RBV groups and RBV was to be administered orally BID. The duration of treatment was 12 weeks in both groups. RBV 600 mg/day (body weight ≤60 kg), 800 mg/day (body weight >60 kg and ≤80 kg), or 1000 mg/day (body weight >80 kg) was to be administered in two divided doses. Subjects in the LDV/SOF group were to take LDV/SOF once daily, without regard to food while subjects in the LDV/SOF+RBV group were to take LDV/SOF+RBV after breakfast and RBV after evening meal.

[redacted][55]

The primary endpoint, i.e., the proportion of patients with sustained virologic response 12 weeks after discontinuation of treatment (SVR12 rate[56]), was 100% (157 of 157 subjects) in the LDV/SOF group (treatment-naïve, 100% [78 of 78 subjects]; treatment-experienced, 100% [79 of 79 subjects]) (genotype 1a, 100% [6 of 6 subjects]; genotype 1b, 100% [151 of 151 subjects]) and 98.1% (158 of 161 subjects) in the LDV/SOF+RBV group (treatment-naïve, 96.3% [78 of 81 subjects]; treatment-experienced, 100% [80 of 80 subjects]) (genotype 1a, 100% [4 of 4 subjects]; genotype 1b, 98.1% [154 of 157 subjects]). Among treatment-naïve patients with chronic hepatitis C, the SVR12 rates [95% CIs] were 100% [94.5%, 100%] (65 of 65 subjects) in the LDV/SOF group and 97.1% [90.1%, 99.7%] (68 of 70 subjects) in the LDV/SOF+RBV group

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51) The randomization of treatment-naïve patients was stratified by the presence or absence of compensated cirrhosis at screening and the randomization of treatment-experienced patients was stratified by the presence or absence of compensated cirrhosis at screening and response to prior treatment (nonresponse, relapse/breakthrough, or IFN-intolerant) and subjects were randomized to the LDV/SOF or LDV/SOF+RBV group in a 1:1 ratio.

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

53) No prior exposure to any of interferon (IFN), RBV, and other HCV-specific direct-acting antiviral agents.

54) Patients who were previously treated with IFN and who fell under any one of the following. Patients with prior exposure to HCV-specific direct-acting antiviral agents other than NS3/4A protease inhibitors were ineligible.
- Patient who discontinued IFN treatment due to adverse drug reactions, etc.
- Patient who failed to achieve undetectable HCV RNA levels on treatment with IFN.
- Patient who achieved undetectable HCV RNA levels during treatment with IFN or within 4 weeks after the end of the treatment, but failed to achieve SVR.

55) The following protocol deviations were found in the trial site: delays in the submission of the investigator's brochure (revised version), delays in the reporting of some of the safety information to the investigators and the head of the medical institution, and forged entries in the monitoring reports. Due to this fact, 23 subjects enrolled at this trial site were excluded from the analysis populations.

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

and the lower bound of the 95% confidence interval was higher than the pre-specified adjusted historical SVR null rate (63%[57]) in each treatment group, demonstrating their efficacy. In the full analysis set (FAS), the SVR12 rates were 100% (171 of 171 subjects) in the LDV/SOF group (treatment-naïve, 100% [83 of 83 subjects]; treatment-experienced, 100% [88 of 88 subjects]) and 98.2% (167 of 170 subjects) in the LDV/SOF+RBV group (treatment-naïve, 96.4% [80 of 83 subjects]; treatment-experienced, 100% [87 of 87 subjects]).

The incidences of adverse events (including abnormal changes in laboratory values) were 66.2% (104 of 157 subjects) in the LDV/SOF group and 76.4% (123 of 161 subjects) in the LDV/SOF+RBV group. The incidences of adverse drug reactions[58] (including abnormal changes in laboratory values) were 21.7% (34 of 157 subjects) in the LDV/SOF group and 50.3% (81 of 161 subjects) in the LDV/SOF+RBV group. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in either group are as shown in Table 25.

Table 25. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in either group

Event term	Adverse events		Adverse drug reactions	
	LDV/SOF	LDV/SOF+RBV	LDV/SOF	LDV/SOF+RBV
N	157	161	157	161
Any event	104 (66.2)	123 (76.4)	34 (21.7)	81 (50.3)
Nasopharyngitis	45 (28.7)	39 (24.2)	0	1 (0.6)
Anaemia	3 (1.9)	23 (14.3)	2 (1.3)	23 (14.3)
Headache	11 (7.0)	14 (8.7)	3 (1.9)	7 (4.3)
Pruritus	6 (3.8)	13 (8.1)	5 (3.2)	7 (4.3)
Rash	4 (2.5)	11 (6.8)	2 (1.3)	11 (6.8)
Malaise	9 (5.7)	9 (5.6)	1 (0.6)	5 (3.1)
Stomatitis	6 (3.8)	10 (6.2)	4 (2.5)	3 (1.9)
Nausea	5 (3.2)	9 (5.6)	4 (2.5)	5 (3.1)

n (%)

One death occurred in the LDV/SOF+RBV group (cardiac arrest), which was assessed as causally related to study drug. Other serious adverse events occurred in 2 subjects in the LDV/SOF group (hepatocellular carcinoma and oesophageal varices haemorrhage [1 subject each]) and 1 subject in the LDV/SOF+RBV group (acute myocardial infarction). Of these adverse events, acute myocardial infarction was assessed as causally related to study drug and the outcome of this event was reported as resolved. An adverse event leading to discontinuation of all study drugs occurred in 1 subject in the LDV/SOF+RBV group (rash morbilliform [1 subject]). This event was assessed as causally related to study drug and the outcome was reported as resolved.

Among the 23 subjects excluded from the safety analysis set, the incidences of adverse events were 35.7% (5 of 14 subjects) in the LDV/SOF group and 44.4% (4 of 9 subjects) in the LDV/SOF+RBV group. Adverse events reported in ≥3 subjects in either group were nasopharyngitis (21.4% [3 of 14 subjects] in the LDV/SOF group, 0% [0 of 9 subjects] in the LDV/SOF+RBV group) and rash (7.1% [1 of 14 subjects] in the LDV/SOF group, 33.3% [3 of 9 subjects] in the LDV/SOF+RBV group). A serious adverse event occurred in 1 subject in the LDV/SOF group (wrist fracture) and its causal relationship to study drug was ruled out. There were no deaths or adverse events leading to study drug discontinuation.

57) A historical SVR rate of 73% was calculated from the data from a clinical study of a triple regimen of telaprevir+peginterferon (PegIFN)+RBV in treatment-naïve Japanese patients with chronic hepatitis C (genotype 1) (Kumada, et al. *J Hepatol*. 2012;56:78-84). The 63% null SVR rate was obtained after allowing for a trade-off in efficacy exchanged for an expected improved safety profile and shorter duration of treatment.

58) Adverse events assessed by the investigator (sub-investigator) as related to study drug.

4.(iii).A.(2).2) Foreign study (5.3.5.1.2, Study GS-US-337-0102 [September 2012 to April 2014])

A randomized, open-label, parallel-group study[59] was conducted at 100 study sites in 6 countries including the US, Germany, and France to evaluate the efficacy and safety of the regimens of LDV/SOF with or without RBV in treatment-naïve[53] chronic hepatitis C patients with or without compensated cirrhosis[60] (genotype 1) (target sample size of 800; 200 subjects each in the LDV/SOF 12-week, LDV/SOF 24-week, LDV/SOF+RBV [brand name, Ribasphere] 12-week, and LDV/SOF+RBV 24-week treatment groups).

LDV/SOF QD or LDV/SOF QD with RBV BID[61] was to be administered orally for 12 or 24 weeks.

Of 870 randomized subjects, 865 received study drug (214 in the LDV/SOF 12-week, 217 in the LDV/SOF 24-week, 217 in the LDV/SOF+RBV 12-week, and 217 in the LDV/SOF+RBV 24-week treatment groups). The 865 subjects were all included in the FAS and in the safety analysis set and the FAS was used for efficacy analyses.

The primary endpoint of the SVR12 rate[56] [95% CI] was 97.7% [94.6%, 99.2%] (209 of 214 subjects) in the LDV/SOF 12-week treatment group (genotype 1a, 96.5% [139 of 144 subjects]; genotype 1b, 100% [66 of 66 subjects]; others,[62] 100% [4 of 4 subjects]) and 97.2% [94.1%, 99.0%] (211 of 217 subjects) in the LDV/SOF+RBV 12-week treatment group (genotype 1a, 96.6% [143 of 148 subjects]; genotype 1b, 98.5% [67 of 68 subjects]; others,[63] 100% [1 of 1 subject]). The lower bound of the 95% confidence interval was higher than the pre-specified adjusted historical SVR null rate (60%[64]) in each treatment group, demonstrating their efficacy. The SVR12 rates among subjects who received 24 weeks of treatment were 98.2% [95.3%, 99.5%] (213 of 217 subjects) in the LDV/SOF 24-week treatment group and 99.1% [96.7%, 99.9%] (215 of 217 subjects) in the LDV/SOF+RBV 24-week treatment group.

The incidences of adverse events (including abnormal changes in laboratory values) were 78.5% (168 of 214 subjects) in the LDV/SOF 12-week treatment group, 84.8% (184 of 217 subjects) in the LDV/SOF+RBV 12-week treatment group, 81.6% (177 of 217 subjects) in the LDV/SOF 24-week treatment group, and 92.2% (200 of 217 subjects) in the LDV/SOF+RBV 24-week treatment group. The incidences of adverse drug reactions[58] (including abnormal changes in laboratory values) were 49.5% (106 of 214 subjects) in the LDV/SOF 12-week treatment group, 70.0% (152 of 217 subjects) in the LDV/SOF+RBV 12-week treatment group, 53.0% (115 of 217 subjects) in the LDV/SOF 24-week treatment group, and 78.3% (170 of 217 subjects) in the LDV/SOF+RBV 24-week treatment group. Adverse events and/or adverse drug reactions reported in ≥5% of

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59) The randomization was stratified by genotype (1a, 1b, or mixed 1a/b) and the presence or absence of cirrhosis at screening and subjects were randomized in a 1:1:1:1 ratio to the LDV/SOF 12- or 24-week or LDV/SOF+RBV 12- or 24-week treatment group.

60) Diagnosed by liver biopsy (Metavir score = 4, Ishak score ≥5, etc.), Fibroscan (>12.5 kPa), or FibroTest® score >0.75 and APRI score >2.

61) RBV 1000 mg/day (body weight <75kg) or 1200 mg/day (body weight ≥75 kg) was administered in two divided doses.

62) Genotype 1 (unknown subtype), 1 subject; genotype 4, 1 subject; unknown genotype, 2 subjects.

63) Genotype 1 (unknown subtype), 1 subject.

64) A historical SVR rate of 65% was obtained from the data from clinical studies of a triple regimen of telaprevir+PegIFN+RBV (Jacobson IM, et al., *N Engl J Med*. 2011;361(25):2405-2416) or a triple regimen of boceprevir+PegIFN+RBV (Poordad F, et al., *N Engl J Med*. 2011;364(13):1195-1206) in treatment-naïve patients with chronic hepatitis C (genotype 1) after adjusting for the expected proportion of subjects with cirrhosis (approximately 20%) in this study. The 60% null SVR rate was obtained after allowing for a trade-off in efficacy exchanged for an expected improved safety profile and shorter duration of treatment.

subjects in any group are as shown in Table 26.

Table 26. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in any group

Event term	Adverse events				Adverse drug reactions			
	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks
N	214	217	217	217	214	217	217	217
Any event	168 (78.5)	184 (84.8)	177 (81.6)	200 (92.2)	106 (49.5)	152 (70.0)	115 (53.0)	170 (78.3)
Fatigue	44 (20.6)	79 (36.4)	53 (24.4)	82 (37.8)	32 (15.0)	70 (32.3)	38 (17.5)	69 (31.8)
Headache	52 (24.3)	49 (22.6)	54 (24.9)	64 (29.5)	36 (16.8)	36 (16.6)	39 (18.0)	42 (19.4)
Insomnia	16 (7.5)	45 (20.7)	26 (12.0)	47 (21.7)	11 (5.1)	39 (18.0)	14 (6.5)	39 (18.0)
Nausea	24 (11.2)	37 (17.1)	29 (13.4)	32 (14.7)	17 (7.9)	28 (12.9)	24 (11.1)	26 (12.0)
Asthenia	14 (6.5)	23 (10.6)	20 (9.2)	26 (12.0)	13 (6.1)	21 (9.7)	15 (6.9)	22 (10.1)
Diarrhoea	24 (11.2)	18 (8.3)	24 (11.1)	14 (6.5)	10 (4.7)	16 (7.4)	16 (7.4)	7 (3.2)
Rash	16 (7.5)	21 (9.7)	15 (6.9)	27 (12.4)	7 (3.3)	16 (7.4)	12 (5.5)	24 (11.1)
Irritability	11 (5.1)	17 (7.8)	17 (7.8)	24 (11.1)	7 (3.3)	14 (6.5)	11 (5.1)	19 (8.8)
Cough	6 (2.8)	21 (9.7)	16 (7.4)	25 (11.5)	3 (1.4)	12 (5.5)	4 (1.8)	14 (6.5)
Pruritus	11 (5.1)	22 (10.1)	8 (3.7)	20 (9.2)	7 (3.3)	21 (9.7)	6 (2.8)	14 (6.5)
Arthralgia	9 (4.2)	14 (6.5)	20 (9.2)	11 (5.1)	2 (0.9)	6 (2.8)	8 (3.7)	4 (1.8)
Nasopharyngitis	14 (6.5)	9 (4.1)	13 (6.0)	17 (7.8)	2 (0.9)	0	1 (0.5)	1 (0.5)
Constipation	13 (6.1)	12 (5.5)	15 (6.9)	10 (4.6)	8 (3.7)	8 (3.7)	7 (3.2)	6 (2.8)
Dizziness	9 (4.2)	10 (4.6)	13 (6.0)	18 (8.3)	7 (3.3)	7 (3.2)	6 (2.8)	10 (4.6)
Anxiety	6 (2.8)	9 (4.1)	12 (5.5)	20 (9.2)	5 (2.3)	3 (1.4)	5 (2.3)	8 (3.7)
Anaemia	0	25 (11.5)	0	21 (9.7)	0	24 (11.1)	0	21 (9.7)
Myalgia	9 (4.2)	12 (5.5)	12 (5.5)	12 (5.5)	6 (2.8)	5 (2.3)	6 (2.8)	3 (1.4)
Dyspepsia	7 (3.3)	11 (5.1)	14 (6.5)	12 (5.5)	5 (2.3)	4 (1.8)	8 (3.7)	9 (4.1)
Back pain	12 (5.6)	5 (2.3)	12 (5.5)	14 (6.5)	3 (1.4)	1 (0.5)	1 (0.5)	2 (0.9)
Muscle spasms	7 (3.3)	14 (6.5)	9 (4.1)	12 (5.5)	4 (1.9)	5 (2.3)	2 (0.9)	2 (0.9)
Dyspnoea	3 (1.4)	18 (8.3)	5 (2.3)	15 (6.9)	3 (1.4)	16 (7.4)	3 (1.4)	14 (6.5)
Decreased appetite	10 (4.7)	12 (5.5)	8 (3.7)	9 (4.1)	9 (4.2)	7 (3.2)	4 (1.8)	7 (3.2)
Abdominal pain	12 (5.6)	9 (4.1)	7 (3.2)	8 (3.7)	7 (3.3)	4 (1.8)	4 (1.8)	3 (1.4)
Vomiting	7 (3.3)	9 (4.1)	6 (2.8)	12 (5.5)	1 (0.5)	4 (1.8)	5 (2.3)	6 (2.8)
Dry skin	2 (0.9)	14 (6.5)	3 (1.4)	12 (5.5)	1 (0.5)	12 (5.5)	1 (0.5)	11 (5.1)
Abdominal pain upper	5 (2.3)	11 (5.1)	6 (2.8)	8 (3.7)	3 (1.4)	7 (3.2)	3 (1.4)	6 (2.8)
Depression	5 (2.3)	6 (2.8)	5 (2.3)	11 (5.1)	3 (1.4)	4 (1.8)	2 (0.9)	6 (2.8)
Dyspnoea exertional	3 (1.4)	9 (4.1)	2 (0.9)	11 (5.1)	1 (0.5)	8 (3.7)	0	11 (5.1)
Gastrooesophageal reflux disease	4 (1.9)	7 (3.2)	3 (1.4)	11 (5.1)	1 (0.5)	2 (0.9)	1 (0.5)	8 (3.7)

n (%)

No deaths were reported. Serious adverse events occurred in 1 subject (chest pain) in the LDV/SOF 12-week treatment group, 7 subjects in the LDV/SOF+RBV 12-week treatment group (non-cardiac chest pain, pneumonia, anaemia, hypertension, intervertebral disc protrusion, migraine, and tibia fracture [1 subject each]), 18 subjects in the LDV/SOF 24-week treatment group (gastroenteritis and hand fracture [2 subjects each]; chest pain, non-cardiac chest pain, abdominal discomfort, breast mass, cellulitis, colitis, Factor VIII inhibition, fall, foot fracture, headache, lower limb fracture, lumbar spinal stenosis, mesenteric vein thrombosis, progressive multifocal leukoencephalopathy, salpingitis, and urinary tract infection [1 subject each]; a subject experiencing one or more events was counted for each of the events), and 6 subjects in the LDV/SOF+RBV 24-week treatment group (pneumonia, alcohol poisoning, alcohol withdrawal syndrome, calculus ureteric, carotid artery stenosis, concussion, depression, rib fracture, squamous cell carcinoma, and substance abuse [1 subject each]; a subject experiencing one or more events was counted for each of the events), of which salpingitis, headache, Factor VIII inhibition, and mesenteric vein thrombosis reported in the LDV/SOF 24-week treatment group were assessed as causally related to study drug and the outcome was reported as resolved except for headache and Factor VIII inhibition.

No adverse events leading to discontinuation of all study drugs were reported in the LDV/SOF 12-week treatment group or the LDV/SOF+RBV 12-week treatment group. Adverse events leading to discontinuation of all study drugs occurred in 4 subjects in the LDV/SOF 24-week treatment group (palpitations, chest pain, dizziness, Factor VIII inhibition, haemorrhage, and throat tightness [1 subject each]; a subject experiencing one or more events was counted for each of the events) and 5 subjects in the LDV/SOF+RBV 24-week treatment group (anxiety [1 subject]; palpitations, dyspnoea, ear pain, eyelid oedema, fatigue, gastrointestinal viral infection, headache, sensory disturbance, and vertigo [1 subject each] a subject experiencing one or more events was counted for each of the events), of which palpitations, Factor VIII inhibition, haemorrhage, and throat tightness reported in the LDV/SOF 24-week treatment group and dyspnoea, eyelid oedema, fatigue, headache, and sensory disturbance reported in the LDV/SOF+RBV 24-week treatment group were assessed as causally related to study drug and the outcome was reported as resolved except for Factor VIII inhibition, haemorrhage, eyelid oedema, headache, and sensory disturbance.

4.(iii).A.(2).3) Foreign study (5.3.5.1.3, Study GS-US-337-0108 [May 2013 to March 2014])

A randomized, open-label, parallel-group study[65)] was conducted at 59 study sites in the US to evaluate the efficacy and safety of the regimens of LDV/SOF with or without RBV in non-cirrhotic, treatment-naïve[53)] patients with chronic hepatitis C (genotype 1) (target sample size of 600; 200 subjects each in the LDV/SOF 8-week, LDV/SOF 12-week, and LDV/SOF+RBV (brand name, Ribasphere) 8-week treatment groups).

LDV/SOF QD was to be administered orally for 8 or 12 weeks or LDV/SOF QD with RBV BID[61)] was to be administered orally for 8 weeks.

All of 647 randomized subjects to receive study drug (215 in the LDV/SOF 8-week, 216 in the LDV/SOF 12-week, and 216 LDV/SOF+RBV 8-week treatment groups) were included in the FAS and in the safety analysis set and the FAS was used for efficacy analyses.

The primary endpoint of the SVR12 rate[56)] are as shown in Table 27. The lower bound of the 95% confidence interval was higher than the pre-specified adjusted historical SVR null rate (60%[66)]) in each treatment group, demonstrating their efficacy. The difference in the SVR12 rate between the 8-week treatment of LDV/SOF and 8-week treatment of LDV/SOF+RBV [95% CI] was 0.9% [-3.9%, 5.7%] and the difference between the 8-week treatment of LDV/SOF and 12-week treatment of LDV/SOF was -1.4% [-6.4%, 3.6%].

65) The randomization was stratified by genotype (1a or 1b [subjects with mixed genotype 1a/b were stratified as 1a]) at screening and subjects were randomized in a 1:1:1 ratio to the LDV/SOF 8-week treatment, LDV/SOF 12-week treatment, or LDV/SOF+RBV group.

66) A historical SVR rate of 65% was obtained from the data from clinical studies of a triple regimen of telaprevir+PegIFN+RBV (Jacobson IM, et al., *N Engl J Med*. 2011;361(25): 2405-2416) or a triple regimen of boceprevir+PegIFN+RBV (Poordad F, et al., *N Engl J Med*. 2011;364(13):1195-1206) in treatment-naïve patients with chronic hepatitis C (genotype 1) after adjusting for the expected proportion of IFN-ineligible subjects (approximately 8%) in this study. The 60% null SVR rate was obtained after allowing for a trade-off in efficacy exchanged for an expected improved safety profile and shorter treatment duration.

Table 27. SVR12 rate (FAS)

	LDV/SOF 8 weeks	LDV/SOF+RBV 8 weeks	LDV/SOF 12 weeks
SVR12 rate	94.0 (202/215) [b)]	93.1 (201/216) [c)]	95.4 (206/216) [d)]
Treatment difference vs. 8-week LDV/SOF+RBV [95% CI] [a)]	0.9 [-3.9, 5.7]		
Treatment difference vs. 12-week LDV/SOF [95% CI] [a)]	-1.4 [-6.4, 3.6]		
Treatment difference vs. 12-week LDV/SOF [95% CI] [a)]		-2.3 [-7.5, 2.9]	

% (n/N)
a) Mantel-Haenszel test adjusted for HCV genotype [genotype 1a or 1b]
b) genotype 1a, 93.0% (159 of 171 subjects); genotype 1b, 97.7% (42 of 43 subjects); genotype 1 (unknown subtype), 100% (1 of 1 subject)
c) genotype 1a, 92.4% (159 of 172 subjects); genotype 1b, 95.5% (42 of 44 subjects)
d) genotype 1a, 94.8% (163 of 172 subjects); genotype 1b, 97.7% (43 of 44 subjects)

The incidences of adverse events (including abnormal changes in laboratory values) were 67.4% (145 of 215 subjects) in the LDV/SOF 8-week treatment group, 76.4% (165 of 216 subjects) in the LDV/SOF+RBV 8-week treatment group, and 69.0% (149 of 216 subjects) in the LDV/SOF 12-week treatment group. The incidences of adverse drug reactions[58)] (including abnormal changes in laboratory values) were 38.1% (82 of 215 subjects) in the LDV/SOF 8-week treatment group, 61.6% (133 of 216 subjects) in the LDV/SOF+RBV 8-week treatment group, and 43.1% (93 of 216 subjects) in the LDV/SOF 12-week treatment group. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in any group were as shown in Table 28.

Table 28. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in any group

Event term	Adverse events			Adverse drug reactions		
	LDV/SOF 8 weeks	LDV/SOF+RBV 8 weeks	LDV/SOF 12 weeks	LDV/SOF 8 weeks	LDV/SOF+RBV 8 weeks	LDV/SOF 12 weeks
N	215	216	216	215	216	216
Any event	145 (67.4)	165 (76.4)	149 (69.0)	82 (38.1)	133 (61.6)	93 (43.1)
Fatigue	45 (20.9)	75 (34.7)	49 (22.7)	34 (15.8)	70 (32.4)	27 (12.5)
Headache	30 (14.0)	54 (25.0)	33 (15.3)	23 (10.7)	42 (19.4)	21 (9.7)
Nausea	15 (7.0)	38 (17.6)	24 (11.1)	13 (6.0)	33 (15.3)	16 (7.4)
Insomnia	11 (5.1)	26 (12.0)	15 (6.9)	7 (3.3)	21 (9.7)	10 (4.6)
Irritability	3 (1.4)	29 (13.4)	9 (4.2)	2 (0.9)	23 (10.6)	4 (1.9)
Diarrhoea	15 (7.0)	13 (6.0)	9 (4.2)	9 (4.2)	8 (3.7)	2 (0.9)
Arthralgia	9 (4.2)	11 (5.1)	16 (7.4)	8 (3.7)	8 (3.7)	7 (3.2)
Constipation	9 (4.2)	13 (6.0)	8 (3.7)	4 (1.9)	8 (3.7)	3 (1.4)
Dizziness	6 (2.8)	13 (6.0)	9 (4.2)	5 (2.3)	11 (5.1)	5 (2.3)
Rash	3 (1.4)	19 (8.8)	5 (2.3)	2 (0.9)	17 (7.9)	2 (0.9)
Pruritus	2 (0.9)	16 (7.4)	5 (2.3)	2 (0.9)	15 (6.9)	5 (2.3)
Cough	3 (1.4)	12 (5.6)	7 (3.2)	0	8 (3.7)	1 (0.5)
Anaemia	2 (0.9)	17 (7.9)	2 (0.9)	0	17 (7.9)	0
Muscle spasms	3 (1.4)	11 (5.1)	6 (2.8)	0	7 (3.2)	2 (0.9)
Dyspnoea	0	11 (5.1)	1 (0.5)	0	11 (5.1)	0

n (%)

No deaths were reported. Serious adverse events occurred in 4 subjects in the LDV/SOF 8-week treatment group (anaphylactic reaction, colitis, diabetes mellitus inadequate control, hypertension, and lower gastrointestinal haemorrhage [1 subject each] a subject experiencing one or more events was counted for each of the events), 1 subject in the LDV/SOF+RBV 8-week treatment group (pituitary tumour), and 5 subjects in the LDV/SOF 12-week treatment group (abdominal pain, bile duct stone, haemothorax, hypoglycaemia, intestinal perforation, jaundice, mental status changes, respiratory failure, rhabdomyolysis, road traffic accident, skeletal injury, and lung squamous cell carcinoma [1 subject each] a subject experiencing one or more events was counted for each of the events). A causal relationship to study drug was ruled out for all events and the outcome was reported as resolved except for skeletal injury and intestinal perforation. Adverse events leading to discontinuation of all study drugs occurred in 0 subjects in the LDV/SOF 8-week treatment group, 1 subject in the LDV/SOF+RBV 8-week treatment group (road traffic accident), and 2 subjects in the LDV/SOF 12-

week treatment group (arthralgia and lung squamous cell carcinoma [1 subject each]), of which arthralgia was assessed as causally related to study drug and the outcome of this event was reported as resolved.

4.(iii).A.(2).4) Foreign study (5.3.5.1.4, Study GS-US-337-0109 [January 2013 to February 2014])

A randomized, open-label, parallel-group study[67] was conducted at 64 study sites in the US to evaluate the efficacy and safety of the regimens of LDV/SOF with or without RBV in treatment-experienced[68] chronic hepatitis C patients with or without compensated cirrhosis[60] (genotype 1) (target sample size of 400; 100 subjects each in the LDV/SOF 12-week, LDV/SOF 24-week, LDV/SOF+RBV [brand name, Ribasphere] 12-week, and LDV/SOF+RBV 24-week treatment groups).

LDV/SOF QD or LDV/SOF QD with RBV BID[61] was to be administered orally for 12 or 24 weeks.

Of 441 randomized subjects, 440 received study drug (109 subjects each in the LDV/SOF 12- and 24-week treatment groups, 111 subjects each in the LDV/SOF+RBV 12- and 24-week treatment groups). The 440 subjects were all included in the FAS and in the safety analysis set and the FAS was used for efficacy analyses.

The primary endpoint of the SVR12 rate[56] [95% CI] was 93.6% [87.2%, 97.4%] (102 of 109 subjects) in the LDV/SOF 12-week treatment group (genotype 1a, 95.3% [82 of 86 subjects]; genotype 1b, 87.0% [20 of 23 subjects]), 96.4% [91.0%, 99.0%] (107 of 111 subjects) in the LDV/SOF+RBV 12-week treatment group (genotype 1a, 95.5% [84 of 88 subjects]; genotype 1b, 100% [23 of 23 subjects]), 99.1% [95.0%, 100.0%] (108 of 109 subjects) in the LDV/SOF 24-week treatment group (genotype 1a, 98.8% [84 of 85 subjects]; genotype 1b, 100% [24 of 24 subjects]), and 99.1% [95.1%, 100.0%] (110 of 111 subjects) in the LDV/SOF+RBV 24-week treatment group (genotype 1a, 98.9% [87 of 88 subjects]; genotype 1b, 100% [23 of 23 subjects]) and the lower bound of the 95% confidence interval was higher than the pre-specified adjusted historical SVR null rate (25%[69]) in each treatment group, demonstrating their efficacy.

The incidences of adverse events (including abnormal changes in laboratory values) were 67.0% (73 of 109 subjects) in the LDV/SOF 12-week treatment group, 86.5% (96 of 111 subjects) in the LDV/SOF+RBV 12-week treatment group, 80.7% (88 of 109 subjects) in the LDV/SOF 24-week treatment group, and 90.1% (100 of 111 subjects) in the LDV/SOF+RBV 24-week treatment group. The incidences of adverse drug reactions [58]

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67) The randomization was stratified by genotype (1a or 1b [subjects with mixed genotype 1a/b were stratified as 1a]) and the presence or absence of cirrhosis at screening and response to prior treatment (relapse/breakthrough or nonresponse) and subjects were randomized in a 1:1:1:1 ratio to the LDV/SOF 12-week, LDV/SOF 24-week, LDV/SOF+RBV 12-week, or LDV/SOF+RBV 24-week treatment group.

68) Patients who were previously treated with a PegIFN+RBV regimen or an NS3/4A protease inhibitor+PegIFN+RBV regimen and who fell under either of the following:
- Nonresponder: Patient who did not achieve undetectable HCV RNA levels on treatment.
- Relapse/breakthrough: Patient who achieved undetectable HCV RNA levels during treatment or within 4 weeks after the end of treatment, but did not achieve SVR.

69) (1) For patients who failed prior treatment with PegIFN+RBV and then received a protease inhibitor based triple therapy regimen, a historical retreatment SVR rate of 65% was obtained from the data from clinical studies of telaprevir+PegIFN+RBV (Zeuzem S, et al., *N Engl J Med*. 2011;364(25):2417-2428) or boceprevir+PegIFN+RBV (Bacon BR, et al., *N Engl J Med*. 2011;364(13):1207-1217) in treatment-experienced (e.g. PegIFN+RBV) chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) after adjusting for the expected proportion of subjects with cirrhosis (approximately 20%) in this study. (2) For chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) who have failed treatment with a triple regimen of an NS3/4A protease inhibitor+PegIFN+RBV, no retreatment options are currently available and a retreatment SVR rate of 5% was therefore used. Based on (1) and (2), a null SVR rate of 25% was obtained after adjusting for the expected proportion of subjects having had prior treatment with an NS3/4A protease inhibitor+PegIFN+RBV (approximately 50%) in this study and allowing for a discount in efficacy due to an expected improved safety profile and shorter duration of treatment.

(including abnormal changes in laboratory values) were 34.9% (38 of 109 subjects) in the LDV/SOF 12-week treatment group, 69.4% (77 of 111 subjects) in the LDV/SOF+RBV 12-week treatment group, 45.9% (50 of 109 subjects) in the LDV/SOF 24-week treatment group, and 76.6% (85 of 111 subjects) in the LDV/SOF+RBV 24-week treatment group. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in any group are as shown in Table 29.

Table 29. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in any group

Event term	Adverse events				Adverse drug reactions			
	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks
N	109	111	109	111	109	111	109	111
Any event	73 (67.0)	96 (86.5)	88 (80.7)	100 (90.1)	38 (34.9)	77 (69.4)	50 (45.9)	85 (76.6)
Fatigue	23 (21.1)	45 (40.5)	26 (23.9)	50 (45.0)	11 (10.1)	42 (37.8)	20 (18.3)	46 (41.4)
Headache	28 (25.7)	26 (23.4)	25 (22.9)	35 (31.5)	19 (17.4)	23 (20.7)	18 (16.5)	27 (24.3)
Nausea	13 (11.9)	20 (18.0)	7 (6.4)	25 (22.5)	6 (5.5)	15 (13.5)	5 (4.6)	22 (19.8)
Insomnia	10 (9.2)	18 (16.2)	4 (3.7)	19 (17.1)	8 (7.3)	16 (14.4)	4 (3.7)	16 (14.4)
Arthralgia	7 (6.4)	13 (11.7)	7 (6.4)	17 (15.3)	2 (1.8)	9 (8.1)	3 (2.8)	13 (11.7)
Cough	5 (4.6)	16 (14.4)	5 (4.6)	16 (14.4)	0	11 (9.9)	2 (1.8)	9 (8.1)
Diarrhoea	7 (6.4)	5 (4.5)	9 (8.3)	17 (15.3)	3 (2.8)	3 (2.7)	6 (5.5)	11 (9.9)
Rash	2 (1.8)	11 (9.9)	6 (5.5)	16 (14.4)	2 (1.8)	9 (8.1)	1 (0.9)	10 (9.0)
Irritability	2 (1.8)	13 (11.7)	4 (3.7)	12 (10.8)	2 (1.8)	11 (9.9)	3 (2.8)	10 (9.0)
Dizziness	3 (2.8)	8 (7.2)	7 (6.4)	12 (10.8)	1 (0.9)	5 (4.5)	5 (4.6)	7 (6.3)
Myalgia	5 (4.6)	6 (5.4)	8 (7.3)	10 (9.0)	3 (2.8)	3 (2.7)	5 (4.6)	9 (8.1)
Dyspnoea	0	16 (14.4)	3 (2.8)	9 (8.1)	0	15 (13.5)	1 (0.9)	7 (6.3)
Upper respiratory tract infection	4 (3.7)	6 (5.4)	7 (6.4)	11 (9.9)	0	0	0	1 (0.9)
Pruritus	5 (4.6)	10 (9.0)	2 (1.8)	10 (9.0)	4 (3.7)	10 (9.0)	2 (1.8)	9 (8.1)
Muscle spasms	1 (0.9)	8 (7.2)	2 (1.8)	12 (10.8)	1 (0.9)	5 (4.5)	1 (0.9)	8 (7.2)
Anaemia	0	9 (8.1)	1 (0.9)	12 (10.8)	0	9 (8.1)	1 (0.9)	12 (10.8)
Back pain	3 (2.8)	3 (2.7)	4 (3.7)	9 (8.1)	0	0	0	3 (2.7)
Dry skin	0	3 (2.7)	3 (2.8)	11 (9.9)	0	3 (2.7)	2 (1.8)	9 (8.1)
Nasopharyngitis	3 (2.8)	5 (4.5)	3 (2.8)	6 (5.4)	0	0	0	0
Sinusitis	1 (0.9)	6 (5.4)	3 (2.8)	7 (6.3)	1 (0.9)	0	0	1 (0.9)
Anxiety	2 (1.8)	7 (6.3)	4 (3.7)	3 (2.7)	1 (0.9)	2 (1.8)	3 (2.8)	2 (1.8)
Bronchitis	2 (1.8)	3 (2.7)	3 (2.8)	8 (7.2)	0	0	0	2 (1.8)
Constipation	2 (1.8)	4 (3.6)	6 (5.5)	3 (2.7)	0	3 (2.7)	3 (2.8)	1 (0.9)
Vomiting	2 (1.8)	3 (2.7)	0	9 (8.1)	1 (0.9)	1 (0.9)	0	5 (4.5)
Abdominal pain	6 (5.5)	2 (1.8)	0	5 (4.5)	2 (1.8)	0	0	1 (0.9)
Nasal congestion	6 (5.5)	3 (2.7)	1 (0.9)	3 (2.7)	0	1 (0.9)	0	1 (0.9)
Dyspnoea exertional	0	5 (4.5)	0	6 (5.4)	0	4 (3.6)	0	6 (5.4)
Oropharyngeal pain	1 (0.9)	3 (2.7)	0	6 (5.4)	0	0	0	2 (1.8)

n (%)

No deaths were reported. Serious adverse events occurred in 6 subjects in the LDV/SOF 24-week treatment group (angina unstable, convulsion, hepatic encephalopathy, intervertebral disc protrusion, non-cardiac chest pain, spondylolisthesis, and upper gastrointestinal haemorrhage [1 subject each]; a subject experiencing one or more events was counted for each of the events) and 3 subjects in the LDV/SOF+RBV 24-week treatment group (cholecystitis acute, vaginal prolapse, and wound infection [1 subject each]). A causal relationship to study drug was ruled out and the outcome was reported as resolved for all events.

There were no adverse events leading to discontinuation of all study drugs.

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

4.(iii).B.(1) The significance of LDV and SOF in the form of a single tablet regimen

The applicant's explanation on the significance of LDV and SOF in the form of a single tablet regimen:

Since HCV is an RNA virus, it exhibits high mutation rates during replication.[70] An antiviral drug inhibits viral replication by targeting a viral protein, resulting in the selection of drug-resistant virus variants with mutations in the targeted viral protein. Thus, the coadministration of antiviral drugs targeting different viral proteins is recommended.[71] Since LDV and SOF have different resistance profiles [see "3.(i).A.(1).3) Cross-resistance with other anti-HCV agents"], HCV variants resistant to one of the two drugs coadministered are susceptible to the other and *vice versa*. The efficacy of LDV+SOF+RBV was shown to be higher than that of SOF+RBV in foreign clinical studies in patients with chronic hepatitis C (genotype 1), demonstrating that a regimen containing LDV and SOF with different mechanisms of action has more potent antiviral efficacy. The combination was also confirmed to raise no particular safety concerns.

Combination regimens of drugs with different mechanisms of action are recommended for the treatment of HIV-infected patients[72] and the literature suggests that active substances in the form of a single tablet regimen is associated with higher adherence.[73] Similarly, combination regimens of drugs with different mechanisms of action are recommended for the treatment of HCV-infected patients as well.[74] Thus, a single tablet regimen has significance in terms of improving drug adherence.

Based on the above, a fixed-dose combination product that contains the active substances LDV and SOF in a single tablet has clinical significance.

PMDA's view:
Since the possibility that the LDV/SOF combination product is associated with higher adherence is based on the information on a disease for which the duration of treatment is different, etc., it is difficult to determine whether the clinical significance of a combination product is the same across different diseases. On the other hand, taking into account that combination regimens with drugs with different mechanisms of action are recommended for the treatment of HCV-infected patients,[74] the development of a fixed-dose combination product that contains LDV and SOF in a single tablet can be rational and the applicant's claim that it has clinical significance is understandble. No rules on dose reduction of LDV/SOF due to adverse events were specified in the clinical study protocol. Since the need for dose reduction of LDV or SOF due to adverse events and the treatment outcomes with reduced doses are unknown, there has so far been no medical need for the development of a combination regimen with LDV tablets and the currently approved SOF tablets, in addition to the LDV/SOF combination product.

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

Based on the following considerations [4.(iii).B.(2).1) and 4.(iii).B.(2).2)], PMDA concluded that the efficacy of LDV/SOF in patients with HCV infection can be expected.

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70) Neumann AD, et al., *Science*. 1998;282:103-107.
71) Gene E, et al., *Antivir Ther*. 2012;17:1201-1210.
72) 2013 Health and Labour Sciences Research Grant, Anti-AIDS Research Project, Group for "Research on HIV infection and its complications", *Anti-HIV Therapy Guideline*, March 2014.
73) Bangsberg DR, et al., *AIDS*. 2010;24(18):2835-2840.
74) Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology ed. *Guidelines for the Management of Hepatitis C Virus Infection (3.2th edition)*, 2014.

However, the information on resistance mutations obtained from clinical studies is limited. It is therefore important to collect post-marketing information on the association between the presence/absence of resistance-associated variants at baseline and the efficacy of LDV/SOF, and on resistance mutations in patients who did not achieve SVR after treatment with LDV/SOF. The obtained findings should be promptly provided to healthcare professionals.

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

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

PMDA asked the applicant to explain the appropriateness of employing an uncontrolled design when planning and conducting a Japanese study (Study GS-US-337-0113).

The applicant's response:

At the time of initiating the Japanese study (October 2013), IFN-containing regimens such as a dual or triple regimen (peginterferon [PegIFN]+RBV or triple regimen of PegIFN+RBV+telaprevir [TVR]) were recommended as treatment options for chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) in Japan,[75] but these regimens were considered inappropriate as a comparator for the following reasons.

- Since the proportion of elderly patients with chronic hepatitis C is higher in Japan than overseas,[76] the proportion of IFN-ineligible patients[77] is also high. Thus, if an IFN-containing regimen such as a triple regimen of TVR+PegIFN+RBV had been selected as a comparator, patient enrollment would not have been completed timely.
- According to the results from a foreign phase II study (Study GS-US-337-0118) which were available by the time of initiating the Japanese study, the SVR12 rates among treatment-naïve patients with chronic hepatitis C (genotype 1) were 95.0% in the LDV/SOF 8-week treatment group, 94.7% in the LDV/SOF 12-week treatment group, and 100% in the LDV/SOF+RBV 8-week treatment group. The SVR12 rates among treatment-experienced patients (genotype 1)[78] were 94.7% in the LDV/SOF 12-week treatment group and 100% in the LDV/SOF+RBV 12-week treatment group. The overall incidences of adverse events among treatment-naïve patients were 45.0% in the LDV/SOF 8-week treatment group, 42.1% in the LDV/SOF 12-week treatment group, and 57.1% in the LDV/SOF+RBV 8-week treatment group. The overall incidences of adverse events among treatment-experienced patients were 36.8% in the LDV/SOF 12-week treatment group and 57.1% in the LDV/SOF+RBV 12-week treatment group. No adverse events leading to study drug discontinuation were reported. On the other hand, the SVR24 rates for Japanese patients with chronic hepatitis C (genotype 1) treated with a triple regimen of TVR+PegIFN+RBV were 73.0%[79] in treatment-

75) Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology ed. *Guidelines for the Management of Hepatitis C Virus Infection (First edition)*, 2012
76) Tanaka J, et al., *Intervirilogy*. 2004;47(1):32-40.
77) Patient considered ineligible for treatment with IFN due to age or comorbidities such as autoimmune disorders, psychiatric disease, and diabetes.
78) Half of the patients had compensated cirrhosis and patients previously treated with NS3/4A protease inhibitors were included.
79) Kumada H, et al., *J Hepatol.* 2012;56(1):78-84.

naïve patients, 88.1% in patients with prior relapse, and 34.1%[80] in patients with prior nonresponse. All patients experienced adverse events and serious adverse events such as anaemia, skin disorders (rash, Stevens-Johnson syndrome, drug hypersensitivity syndrome), renal impairment, and renal failure were reported. Taking account of these results, it was considered that the majority of candidate trial sites would not accept the protocol for a study using an IFN-containing regimen as a comparator.

The applicant also explained the efficacy of LDV/SOF in Japanese chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) as follows:

In the Japanese study, the lower bound of the 95% confidence interval for the SVR12 rate following administration of LDV/SOF in treatment-naïve patients with chronic hepatitis C was higher than the pre-specified adjusted historical SVR null rate [see "4.(iii).A.(2).1) Japanese study"]. Subgroup analysis results for the LDV/SOF group in the Japanese study are as shown in Table 30. The SVR12 rates in all subgroups were 100%. In the overall population consisting of treatment-naïve and treatment-experienced chronic hepatitis C patients with or without compensated cirrhosis (genotype 1), the proportion of patients who achieved sustained virologic response 24 weeks after the end of treatment (SVR24 rate) in the LDV/SOF group was 100% (157 of 157 subjects).

Based on the above, the efficacy of LDV/SOF in Japanese chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) can be expected.

Table 30. SVR12 rates in subgroups (Efficacy Analysis Set)

Patient characteristics		LDV/SOF	
		Treatment-naïve (N = 78)	Treatment-experienced (N = 79)
Overall		78/78 (100)	79/79 (100)
Genotype	1a	1/1 (100)	5/5 (100)
	1b	77/77 (100)	74/74 (100)
Age	<65 years	56/56 (100)	44/44 (100)
	≥65 years	22/22 (100)	35/35 (100)
Degree of fibrosis	Chronic hepatitis	65/65 (100)	52/52 (100)
	Compensated cirrhosis	13/13 (100)	27/27 (100)
IFN eligibility	IFN-eligible	74/74 (100)	—
	IFN-ineligible	4/4 (100)	—
Response to prior treatment	Nonresponse [a)]	—	25/25 (100)
	Relapse/Breakthrough [b)]	—	39/39 (100)
	IFN-intolerant [c)]	—	15/15 (100)
HCV RNA level	<800,000 IU/ml	6/6 (100)	9/9 (100)
	≥800,000 IU/ml	72/72 (100)	70/70 (100)
IL-28B polymorphism rs12979860	CC	50/50 (100)	31/31 (100)
	Non CC	28/28 (100)	48/48 (100)

n/N (%), —: Not applicable

a) Patient who did not achieve undetectable HCV RNA levels on treatment with IFN.

b) Patient who achieved undetectable HCV RNA levels during treatment with IFN or within 4 weeks after treatment, but did not achieve SVR.

c) Patient who discontinued treatment with IFN due to adverse drug reactions, etc.

PMDA's view:

The results from a Japanese clinical study of a triple regimen of TVR+PegIFN+RBV in patients with chronic hepatitis C (genotype 1) and the results from a foreign phase II study of LDV/SOF in chronic hepatitis C

80) Hayashi N, et al., *J Viral Hepat*. 2012;19(2):e134-e142.

patients with or without compensated cirrhosis (genotype 1) were available at the time of initiating the Japanese study. This indicated that treatment with a regimen of LDV/SOF with or without RBV resulted in higher SVR12 rates compared to a triple regimen of TVR+PegIFN+RBV and was also well tolerated. Thus, there is some justification for the applicant's explanation that a study using an IFN-containing regimen such as TVR+PegIFN+RBV as a comparator was not planned in terms of feasibility.

In the Japanese study, the lower bound of the 95% confidence interval for the SVR12 rate in treatment-naïve patients with chronic hepatitis C treated with LDV/SOF was higher than the pre-specified adjusted historical SVR null rate. In addition, the SVR12 rates following treatment with LDV/SOF in all subgroups were 100%. Although the small number of subjects evaluated makes it difficult to derive a clear conclusion, these findings can support the efficacy of LDV/SOF in treatment-naïve and treatment-experienced Japanese chronic hepatitis C patients with or without compensated cirrhosis (genotype 1). However, since the currently available information is limited regarding use in patients who are ineligible for or intolerant of IFN-containing regimens, chronic hepatitis C patients with compensated cirrhosis, etc., it is important to collect post-marketing information regarding use in these patients. The obtained findings should be promptly provided to healthcare professionals.

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

The applicant's explanation on the emergence of LDV/SOF-resistant variants and the impact of resistant variants on the efficacy of LDV/SOF:

In *in vitro* resistance selection studies of LDV, the primary NS5A resistance substitutions were selected; Y93H and Q30E were detedcted in genotype 1a replicon cells and Y93H in genotype 1b replicon cells. These HCV mutants showed reduced susceptibility to LDV [see "3.(i).A.(1).2) *In vitro* resistance selection"]. The NS5B substitution S282T was identified as the primary resistance substitution to SOF in all replicon genotypes examined (1b, 2a, 2b, 3a, 4a, 5a, 6a).[81)]

In a Japanese study of LDV/SOF, 23.3% of subjects enrolled (74 of 318 subjects; 26.1% [41 of 157 subjects] in the LDV/SOF group and 20.5% [33 of 161 subjects] in the LDV/SOF+RBV group) had baseline NS5A resistance-associated polymorphisms.[82),83)] Among these subjects, the SVR12 rates were 100% (41 of 41 subjects) in the LDV/SOF group and 97.0% (32 of 33 subjects) in the LDV/SOF+RBV group. Table 31 shows the SVR12 rates by baseline NS5A resistance-associated polymorphisms in this study. Moreover, 2.5% of subjects enrolled (8 of 318 subjects; 3.2% [5 of 157 subjects] in the LDV/SOF group and 1.9% [3 of 161 subjects] in the LDV/SOF+RBV group) had baseline NS5B resistance-associated polymorphisms,[84),83)] but all the subjects with baseline NS5B resistance-associated polymorphisms achieved SVR12. There were no subjects whose virus had the S282T polymorphism at baseline in this study.[83)] Only 1 subject in the LDV/SOF+RBV

81) Sovaldi Tablets 400 mg/Copegus Tablet 200 mg Review Report (February 23, 2015)
82) NS5A resistance-associated polymorphisms in genotype 1a were defined as K24G/N/R, M28A/G/T, Q30E/G/H/L/K/R/T, L31I/F/M/V, P32L, S38F, H58D, A92K/T, and Y93C/F/H/N/S and NS5A resistance-associated polymorphisms in genotype 1b were defined as L31I/F/M/V, P32L, P58D, A92K, and Y93C/H/N/S.
83) Deep sequencing.
84) NS5B resistance-associated polymorphisms were defined as S96T, N142T, L159F, S282T, M289L, L320F, and V321A.

group did not achieve SVR12[85),86)] and the NS5A substitution Y93H was detected in this patient at both baseline and relapse while no NS5B resistance-associated substitution was detected.

Table 31. SVR12 rates by baseline NS5A resistance-associated polymorphisms (Japanese phase III study)

	NS5A resistance-associated variant at baseline	LDV/SOF		LDV/SOF+RBV	
		Genotype	SVR12 rate	Genotype	SVR12 rate
Single mutation	L31M	1b	5/5 (100)	1b	3/3 (100)
	L31I	1b	1/1 (100)	—	—
	L31F	1b	1/1 (100)	—	—
	L31V	1b	1/1 (100)	—	—
	Y93H	1b	30/30 (100)	1b	26/27 (96.3)
	Q30R	1a	1/1 (100)	—	—
Multiple/mixed mutations	L31I, Y93N, Y93C	—	—	1a	1/1 (100)
	L31I, Y93H	—	—	1b	1/1 (100)
	Y93S, Y93N, Y93H	—	—	1b	1/1 (100)
	Y93F, Y93H	1b	2/2 (100)	—	—
Total		41/41 (100)		32/33 (97.0)	

n/N (%)

According to a pooled analysis of foreign phase III studies (Studies GS-US-337-0102, GS-US-337-0108, and GS-US-337-0109), 15.8% of subjects enrolled (256 of 1618 subjects;[87)] 15.6% [192 of 1233 subjects] for genotype 1a and 15.8% [60 of 380 subjects] for genotype 1b) had baseline NS5A resistance-associated polymorphisms.[82),88)] Table 32 shows the SVR12 rates by baseline NS5A resistance-associated polymorphisms.

Table 32. SVR12 rates by baseline NS5A resistance-associated polymorphisms (Pooled foreign phase III studies)

		Treatment-naïve		Treatment-experienced	
		LDV/SOF (N = 697)	LDV/SOF+RBV (N = 483)	LDV/SOF (N = 218)	LDV/SOF+RBV (N = 221)
Presence of any baseline NS5A resistance-associated variants		109/116 (94.0)	71/78 (91.0)	26/30 (86.7)	29/32 (90.6)
NS5A resistance mutation category fold-change in susceptibility [a, b)]	>2.5-10	28/28 (100)	14/15 (93.3)	7/7 (100)	10/10 (100)
	>10-50	1/1 (100)	1/1 (100)	2/2 (100)	2/2 (100)
	>50-100	10/10 (100)	5/5 (100)	2/2 (100)	1/1 (100)
	>100-1000	29/32 (90.6)	29/30 (96.7)	8/9 (88.9)	4/6 (66.7)
	>1000	41/45 (91.1)	22/27 (81.5)	7/10 (70.0)	12/13 (92.3)
Absence of baseline NS5A resistance-associated variants		564/581 (97.1)	391/405 (96.5)	184/188 (97.9)	187/189 (98.9)

n/N (%)

a) 50% effective concentration (EC_{50}) for mutant replicon/EC_{50} for wild-type replicon

b) NS5A resistance-associated variants and fold-changes in susceptibility were as shown below.

Genotype 1a:

>2.5- to 10-fold resistance-associated variants (RAVs); K24R and Q30I/L/T: >10- to 50-fold RAVs; Y93F and Q30S: >50- to 100-fold RAVs; M28T and K24G: >100-to 1000-fold RAVs; L31I/M, Q30H/R, and Y93T: >1000-fold RAVs; M28A, Q30E, H58D, and Y93C/N/S/H

Genotype 1b:

>2.5- to 10-fold RAV; L31M: >10- to 50-fold RAVs; L31I/V: >100- to 1000-fold RAV; Y93S: >1000-fold RAV; Y93H

Of 172 subjects with NS5A resistance-associated polymorphisms corresponding to >100-fold resistance to LDV, 20 (11.6%) did not achieve SVR12, but all subjects with NS5A resistance-associated polymorphisms corresponding to ≤100-fold resistance to LDV (84 subjects) achieved SVR12. NS5B resistance-associated

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

86) A treatment-naïve patient (genotype 1b) in the LDV/SOF+RBV group. The patient experienced relapse 4 weeks after the end of study treatment.

87) Deep sequencing was performed for 1621 subjects in 3 foreign phase III studies (Studies GS-US-337-0102, GS-US337-0108, and GS-US-337-0109) and baseline NS5A sequences were obtained for 1618 subjects.

88) Population sequencing and deep sequencing.

polymorphisms were detected at baseline in 2.0% of subjects enrolled (26[89] of 1285 subjects;[90] 0.4% [4 of 994 subjects] for genotype 1a, 7.6% [22 of 288 subjects] for genotype 1b, and 0% [0 of 3 subjects] for others[91]) and all of them achieved SVR12. No S282T was detected at baseline in these foreign studies.

On the other hand, 37 subjects did not achieve SVR12[85] in the foreign phase III studies (Studies GS-US-337-0102, GS-US-337-0108, and GS-US-337-0109). Of these, 19 subjects' viruses had NS5A resistance-associated substitutions corresponding to >100-fold resistance to LDV (Y93H and Q30H) detected at post-baseline time points (these subjects' viruses had no baseline NS5A resistance-associated polymorphisms). According to the analysis of post-baseline NS5B substitutions, S282T was not detected and V321A and L159F[92] (1 subject each), which conferred <2-fold resistance to SOF, were detected in 2 genotype 1a relapsers in the LDV/SOF group. However, it is difficult to assess the impact on the efficacy of LDV/SOF because the number of subjects is small.

PMDA's view:
There were no patients whose viruses had the NS5B S282T substitution at baseline in Japanese or foreign clinical studies of LDV/SOF and patients with other NS5B resistance-associated polymorphisms achieved SVR12. On the other hand, the SVR12 rate in patients with baseline NS5A resistance-associated polymorphisms was 98.7% (73 of 74 subjects) in the Japanese study, but according to a pooled analysis of foreign phase III studies, the SVR12 rate following treatment with LDV/SOF tended to be low in patients with baseline NS5A resistance-associated polymorphisms corresponding to >100-fold resistance to LDV. Resistance analyses at the end of treatment showed a high proportion of subjects with NS5A resistance-associated variants (78.4% [29 of 37 subjects]). The information on the association between resistance-associated polymorphisms and the efficacy of LDV/SOF obtained from these Japanese and foreign clinical studies is limited. It is important to also collect post-marketing information on baseline resistance-associated polymorphisms, resistance mutations, etc., in patients who did not achieve SVR after treatment with LDV/SOF. The obtained findings should be provided to healthcare professionals promptly.

4.(iii).B.(3) Safety
PMDA conducted its safety review of LDV/SOF as shown in the sections below, 4.(iii).B.(3).1) to 4.(iii).B.(3).4), and concluded that the safety of LDV/SOF in Japanese chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) is acceptable.

However, as there is limited clinical experience of LDV/SOF in Japanese IFN-ineligible, IFN-intolerant, and elderly patients, post-marketing information concerning use in these patients should be collected. According to foreign post-marketing safety information, arrhythmic events such as bradycardia have been reported in patient

89) Twenty subjects had L159F+C316N, 3 subjects had N142T, and 1 subject each had L159F, S282G, and L320S.
90) Deep sequencing was performed for some subjects in a foreign phase III study (Study GS-US-337-0102) and all subjects in foreign phase III studies (Studies GS-US337-0108 and GS-US-337-0109) and NS5B sequences were obtained for 1285 subjects.
91) One subject each for genotype 1c, genotype 4d, and mixed genotype 1a/b.
92) The fold-changes in susceptibility for HCV V321A mutant replicon (EC_{50} for mutant replicon/EC_{50} for wild-type replicon) were 1.2-fold for genotype 1a and 1.4-fold for genotype 1b. The fold-changes in susceptibility for HCV L159F mutant replicon were 1.2-fold for genotype 1a and 1.3-fold for genotype 1b.

treated with LDV/SOF in combination with amiodarone. Thus, it is necessary to collect post-marketing information on the cardiac toxicity of LDV/SOF including arrhythmia.

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

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

The applicant's explanation on the safety of LDV/SOF in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1):

In the LDV/SOF group of a Japanese study, the incidence of adverse events was 66.2% (104 of 157 subjects). The incidence of Grade ≥3[93)] adverse events was 1.9% (3 of 157 subjects), the incidence of serious adverse events was 1.3% (2 of 157 subjects), and the incidence of adverse events leading to LDV/SOF interruption was 0.6% (1 of 157 subjects). Neither deaths nor adverse events leading to treatment discontinuation were reported.

Adverse events (including abnormal changes in laboratory values) reported by ≥5% of subjects in the LDV/SOF group were nasopharyngitis (28.7% [45 of 157 subjects]), headache (7.0% [11 of 157 subjects]), and malaise (5.7% [9 of 157 subjects]), of which headache (3 subjects) and malaise (1 subject) were assessed as causally related to the study drug.

The incidences of adverse events with LDV/SOF in IFN-ineligible and IFN-intolerant patients were 100% (4 of 4 subjects) and 80.0% (12 of 15 subjects), respectively, and all events were non-serious. One IFN-ineligible patient in the LDV/SOF+RBV group died due to cardiac arrest, which was assessed as causally related to study drug.[94)]

In foreign phase III studies (Studies GS-US-337-0102, GS-US-337-0108, and GS-US-337-0109), the incidence of adverse events in the LDV/SOF 12-week treatment group was 72.4% (390 of 539 subjects). The incidence of Grade ≥3[93)] adverse events was 2.4% (13 of 539 subjects), the incidence of serious adverse events was 1.1% (6 of 539 subjects), the incidence of adverse events leading to LDV/SOF interruption was 0.4% (2 of 539 subjects), the incidence of adverse events leading to treatment discontinuation was 0.4% (2 of 539 subjects), and no deaths were reported.

Adverse events (including abnormal changes in laboratory values) reported by ≥5% of subjects in the LDV/SOF 12-week treatment group were fatigue (21.5% [116 of 539 subjects]), headache (21.0% [113 of 539 subjects]), nausea (11.3% [61 of 539 subjects]), insomnia (7.6% [41 of 539 subjects]), diarrhoea (7.4% [40 of 539 subjects]), and arthralgia (5.9% [32 of 539 subjects]).

PMDA's view:

The incidences of Grade ≥3 adverse events and serious adverse events in subjects treated with LDV/SOF alone

93) The severity of adverse events was assessed using the Grading Scale for Severity of Adverse Events and Laboratory Abnormalities established by Gilead Sciences, Inc.

94) The applicant explained as follows: This subject had cirrhosis, sarcoidosis, diabetes, and pulmonary fibrosis and a history of splenectomy and the adverse event was accompanied by pyrexia, nausea, vomiting, and diarrhea, suggesting that a serious infection contributed to cardiac arrest.

in Japanese and foreign clinical studies indicates that LDV/SOF is tolerable. The incidence of hepatic dysfunction, which has been reported with other anti-HCV agents, and safety in elderly patients are described in details in the sections below. Since there is limited clinical experience in Japanese patients who were ineligible for or intolerant of IFN, post-marketing information concerning use in these patients should be collected.

4.(iii).B.(3).2) Hepatic dysfunction

The applicant's explanation on the incidence of hepatic dysfunction with LDV/SOF:

Hepatic function-related adverse events[95] occurred in 1 subject (varices oesophageal and oesophageal varices haemorrhage) in the LDV/SOF group of a Japanese study. Oesophageal varices haemorrhage was reported as a serious adverse event and led to LDV/SOF interruption, but its causal relationship to LDV/SOF wasruled out. Grade ≥3 liver function test abnormal occurred in 1 subject (aspartate aminotransferase [AST] increased, Grade 3) and the proportions of subjects who experienced a grade increase from baseline in the events of blood alanine aminotransferase (ALT) increased,[96] blood AST increased,[97] blood alkaline phosphatase (ALP) increased,[98] and blood total bilirubin increased[99] were 2.5% (4 of 157 subjects), 5.1% (8 of 157 subjects), 0.6% (1 of 157 subjects), and 1.3% (2 of 157 subjects), respectively. None of these events required study drug discontinuation or dose adjustment. The outcome was reported as resolved.

PMDA's view:

Since no LDV/SOF-related, clinically relevant hepatic dysfunction was reported in the LDV/SOF group of the Japanese study, the risk of hepatic dysfunction associated with LDV/SOF is tolerable, but it is necessary to collect post-marketing information on the occurrence of hepatic dysfunction.

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

The applicant's explanation on the safety of LDV/SOF in elderly patients:

A Japanese study of LDV/SOF included 107 patients aged ≥65 years (elderly patients) (57 subjects in the LDV/SOF group, 50 subjects in the LDV/SOF+RBV group).[100] A summary of safety in elderly patients and patients aged <65 years (non-elderly patients) in the LDV/SOF group is as shown in Table 33.

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95) Hepatic function-related adverse events were identified by all MedDRA preferred terms considered related to abnormal hepatic function under the MedDRA System Organ Classes of "Hepatobiliary disorders", "Gastrointestinal disorders", and "Investigations".

96) Grade 1, blood ALT (IU/L) >1.25 to 2.50×upper limit of laboratory normal range (ULN); Grade 2, blood ALT >2.50 to 5.00×ULN; Grade 3, blood ALT >5.00 to 10.00×ULN; Grade 4, blood ALT >10.00×ULN

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

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

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

100) The intended study population was patients aged ≥20 years and subjects aged between 28 and 80 years (age at baseline) were enrolled in the study.

Table 33. Summary of safety of LDV/SOF in elderly and non-elderly patients (Japanese phase III study)

	<65 years	≥65 years
	N = 100	N = 57
Any adverse event experienced by patients	62 (62.0)	42 (73.7)
Grade ≥3 adverse events	1 (1.0)	2 (3.5)
Serious adverse events	0	2 (3.5)
Adverse events leading to LDV/SOF interruption	0	1 (1.8)

n (%)

Adverse events reported in ≥5% of elderly patients were nasopharyngitis (29.8% [17 of 57elderly patients] vs. 28.0% [28 of 100 non-elderly patients]), malaise (10.5% [6 of 57 elderly patients] vs. 3.0% [3 of 100 non-elderly patients]), headache (8.8% [5 of 57 elderly patients] vs. 6.0% [6 of 100 non-elderly patients]), stomatitis (7.0% [4 of 57 elderly patients] vs. 2.0% [2 of 100 non-elderly patients]), nausea (7.0% [4 of 57 elderly patients] vs. 1.0% [1 of 100 non-elderly patients]), and anaemia (5.3% [3 of 57 elderly patients] vs. 0% of non-elderly patients). Adverse events reported at a ≥5% higher incidence in elderly patients than in non-elderly patients (anaemia, malaise, nausea, and stomatitis) were all non-serious. None of these events led to LDV/SOF discontinuation.

PMDA's view:

Some adverse events occurred more frequently in elderly patients than in non-elderly patients in the Japanese study of LDV/SOF, which were all non-serious and none of these events led to LDV/SOF discontinuation. Thus, there is no particular problem with the safety of LDV/SOF in elderly patients compared to non-elderly patients. However, clinical experience is limited in elderly patients, who often have reduced physiological function. For this reason, among others, the possibility of occurrence of adverse events in elderly patients cannot be ruled out It is necessary to collect post-marketing information on the safety of LDV/SOF in elderly patients.

4.(iii).B.(3).4) Foreign safety information regarding cardiac arrhythmic events including bradycardia

According to foreign post-marketing safety information, cardiac arrhythmic events including bradycardia have been reported with SOF-containing regimens. PMDA asked the applicant to explain an overview of safety information on cardiac arrhythmic events and the need for a precautionary statement in the package insert in Japan.

The applicant's explanation:

Investigations were made on the occurrence of cardiac arrhythmic events which were experienced by patients treated with SOF-containing regimens and which cannot be attributed to other factors besides SOF (sepsis, gastrointestinal haemorrhage, etc.). Reports submitted by March 4, 2015 revealed 3 post-marketing cases of cardiac arrhythmic events (bradycardia and syncope [2 patients]; and cardiac arrest [fatal outcome] [1 patient]) occurring in non-Japanese patients treated with LDV/SOF. These patients were concomitantly taking amiodarone with β blockers. Cardiac arrhythmic events (bradycardia [3 patients], bradycardia and syncope [2 patients], syncope and sinus node dysfunction [1 patient], cardiac arrest and syncope [1 patient], and sinoatrial block and QT prolongation [1 patient]) were reported in 8 patients taking SOF in combination with another direct acting antiviral (DAA). Of these 8 patients, 6 used amiodarone (4 of the 6 patients used amiodarone with β blockers).

In thorough QTc studies (Studies P7977-0613 and GS-US-344-0109) that evaluated PR and RR interval changes following administration of SOF or LDV alone, no findings of concern were observed. Bradycardia is a known event related to the pharmacologic action of amiodarone and cardiac arrhythmic events occurred in patients taking amiodarone following initiation of treatment with SOF in combination with another DAA. These findings indicate that cardiac arrhythmic events occurred with coadministration of amiodarone with SOF in combination with another DAA. Since the mechanism for this effect is unknown at present, the investigation will be continued. Currently, there is no evidence for a relationship between SOF/RBV or SOF+ PegIFN/RBV and cardiac arrhythmic events.

Given that the LDV/SOF labeling approved in the US states that coadministration of amiodarone is not recommended and that cardiac monitoring should be performed if coadministration is required, a similar precautionary statement in the package insert is also needed in Japan. In addition, patients will continue to be closely watched for the occurrence of these events in the ongoing clinical studies and in the post-marketing experience. If new non-clinical and clinical data become available, the information will promptly be provided to healthcare professionals.

In Japanese and foreign clinical studies of SOF-containing regimens, no events of concern occurred in 6 patients taking amiodarone.[101)] In a Japanese study of LDV/SOF, 1 subject in the LDV/SOF group had clinically relevant 12-lead ECG abnormality (Grade 1 ventricular extrasystoles). The event was assessed as causally related to study drug, but treatment with LDV/SOF was continued and the outcome was reported as resolved.

PMDA's view:
According to foreign post-marketing safety information, cardiac arrhythmic events including bradycardia have been reported in patients taking amiodarone (including a fatal case). Thus, a precautionary statement in the LDV/SOF package insert is needed. It is necessary to collect post-marketing information on cardiac toxicity. If new safety information becomes available, the information should be provided to healthcare professionals promptly and appropriately.

4.(iii).B.(4) Indications
Given that Japanese and foreign clinical studies have demonstrated the efficacy and safety of LDV/SOF in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) [see "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety"] and taking account of the indications for similar drugs and the following considerations [4.(iii).B.(4).1) to 4.(iii).B.(4).4)], PMDA considers that the indications for LDV/SOF should be as shown below.

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

101) Of a total of 9740 subjects, 6 (all non-Japanese) took amiodarone for >1 day during treatment with an SOF-containing regimen. These 6 subjects were examined in details.

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

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

The applicant's explanation on the efficacy of LDV/SOF by subtype of genotype 1:

In vitro studies showed that LDV and SOF[81)] have activity against genotype 1a and 1b viruses [see "3.(i).A.(1).1) *In vitro* antiviral activity"].

In a Japanese study, the SVR12 rates following treatment with LDV/SOF in genotype 1a and 1b patients were both 100% (genotype 1a, 6 of 6 subjects; genotype 1b, 151 of 151 subjects). Based on a pooled analysis of foreign phase III studies (Studies GS-US-337-0102, GS-US-337-0109, and GS-US-337-0108), the SVR12 rates following 12 weeks of treatment with LDV/SOF were 95.6% (302 of 316 subjects) for genotype 1a and 99.1% (109 of 110 subjects) for genotype 1b in treatment-naïve patients and 95.3% (82 of 86 subjects) for genotype 1a and 87.0% (20 of 23 subjects) for genotype 1b in treatment-experienced patients.

The above results indicate that there are no differences in the efficacy of LDV/SOF between different subtypes of genotype 1.

PMDA's view:

In vitro studies showed that LDV and SOF[81)] have activity against genotype 1a and 1b viruses [see "3.(i).A.(1).1) *In vitro* antiviral activity"]. Although the data on the efficacy of LDV/SOF in genotype 1a patients in a Japanese study are limited, the efficacy of LDV/SOF in Japanese genotype 1a patients has been demonstrated and there were no major differences in the efficacy of LDV/SOF between genotype 1a and 1b also in foreign phase III studies.

Based on the above, the efficacy of LDV/SOF in genotype 1a and 1b patients can be expected.

4.(iii).B.(4).2) Cirrhotic patients

The applicant's explanation on the efficacy and safety of LDV/SOF in compensated cirrhotic patients:

Table 34 shows the SVR12 rates following 12 weeks of treatment with LDV/SOF in compensated cirrhotic and non-cirrhotic patients with chronic hepatitis (genotype 1) in Japanese and foreign clinical studies.

Table 34. SVR12 rates in compensated cirrhotic and non-cirrhotic patients with chronic hepatitis (12 weeks of treatment with LDV/SOF)

		Prior treatment experience	Overall	Compensated cirrhotic patients	Non-cirrhotic patients
Japan	GS-US-337-0113	Treatment-naïve and treatment-experienced	100 (157/157)	100 (40/40) [a)]	100 (117/117) [b)]
Overseas	GS-US-337-0102	Treatment-naïve	97.7 (209/214)	94.1 (32/34)	98.3 (177/180)
	GS-US-337-0108	Treatment-naïve	95.4 (206/216)	—	95.4 (206/216)
	GS-US-337-0109	Treatment-experienced	93.6 (102/109)	86.4 (19/22)	95.4 (83/87)

% (n/N)
a) The SVR12 rate in treatment-naïve patients was 100% (13 of 13 subjects) and the SVR12 rate in treatment-experienced patients was 100% (27 of 27 subjects).
b) The SVR12 rate in treatment-naïve patients was 100% (65 of 65 subjects) and the SVR12 rate in treatment-experienced patients was 100% (52 of 52 subjects).

Table 35 shows a summary of safety in compensated cirrhotic and non-cirrhotic patients with chronic hepatitis in the LDV/SOF group of the Japanese study.

Table 35. Summary of safety of LDV/SOF in compensated cirrhotic and non-cirrhotic patients with chronic hepatitis (Japanese phase III study)

	Compensated cirrhotic patients (N = 40)	Non-cirrhotic patients (N = 117)
Any adverse event experienced by patients	25 (62.5)	79 (67.5)
Grade 3 or higher adverse events	2 (5.0)	1 (0.9)
Serious adverse events	1 (2.5)	1 (0.9)
Fatal adverse events	0	0
Adverse events leading to study drug interruption	0	1 (0.9)
Adverse events leading to study drug discontinuation	0	0

n (%)

Adverse events reported at a ≥5% higher incidence in compensated cirrhotic patients than in non-cirrhotic patients were back pain (7.5% [3 of 40 compensated cirrhotic patients] vs. 1.7% [2 of 117 non-cirrhotic patients]) and hyperlipidaemia (5.0% [2 of 40 compensated cirrhotic patients] vs. 0 non-cirrhotic patient). Although the reason for higher incidences of these adverse events in compensated cirrhotic patients is unknown, all events were of Grade 1. Considering the incidences of Grade ≥3 adverse events and serious adverse events, LDV/SOF seems well tolerated in compensated cirrhotic patients.

Based on the above, the efficacy of LDV/SOF is expected and its safety is acceptable in chronic hepatitis C patients with compensated cirrhosis.

PMDA's view:
The SVR12 rate following 12 weeks of treatment with LDV/SOF tended to be lower in treatment-experienced compensated cirrhotic patients than in treatment-naïve compensated cirrhotic patients and non-cirrhotic patients in foreign clinical studies. Meanwhile, in a Japanese study, the SVR12 rate was comparable between compensated cirrhotic and non-cirrhotic patients, regardless of prior treatment experience, and there were no safety concerns. Thus, there have so far been no particular concerns about the use of LDV/SOF in chronic hepatitis C patients with compensated cirrhosis. However, since there is limited clinical experience with LDV/SOF in Japanese chronic hepatitis C patients with compensated cirrhosis, post-marketing surveillance should be used to collect safety and efficacy information from compensated cirrhotic patients. If new information becomes available, the information should be provided to healthcare professionals promptly and

appropriately.

4.(iii).B.(4).3) Use in patients with prior exposure to NS5A inhibitors

PMDA asked the applicant to explain the use of LDV/SOF in patients with prior exposure to NS5A inhibitors.

The applicant's explanation:

Presently, the only NS5A inhibitor approved for chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) in Japan is Daclatasvir Hydrochloride (DCV). According to resistance analyses of patients previously treated with DCV-containing regimens, the major NS5A resistance-associated variants detected were Q30E/R, L31M/V, and Y93C/N[102] in genotype 1a and L31I/M/V and Y93H[103] in genotype 1b. The antiviral activities of LDV against these mutant replicons were determined in non-clinical studies. As a result, all mutant replicons were found to have reduced susceptibility to LDV [see "3.(i).A.(1).2) *In vitro* resistance selection"]. On the other hand, the susceptibility of genotype 1a NS5A mutant replicons to SOF was not reduced.[81]

Although patients with baseline NS5A resistance-associated polymorphisms achieved a certain level of SVR12 rate following treatment with LDV/SOF in Japanese and foreign clinical studies [see "4.(iii).B.(2).2) Viral resistance mutations"], the use of LDV/SOF is not recommended in patients who have failed therapy containing an NS5A inhibitor because (1) no clinical studies have been conducted to evaluate the efficacy of LDV/SOF in patients previously treated with an NS5A inhibitor-containing regimen and (2) there is cross-resistance between LDV and DCV.

PMDA's view:

Given that the efficacy and safety of LDV/SOF have not been studied in patients previously treated with an NS5A inhibitor-containing regimen and that there is cross-resistance between LDV and DCV, the use of LDV/SOF is not recommended in patients who have failed an NS5A inhibitor-containing regimen. However, for patients who discontinued treatment with another NS5A inhibitor-containing regimen due to intolerance to the NS5A inhibitor or other reasons, the use of LDV/SOF may be considered after fully examining the NS5A gene for resistance-associated polymorphisms.

As described above, it is important that physicians with knowledge of and experience in the treatment of viral liver disease carefully determine whether LDV/SOF should be used in patients with prior exposure to NS5A inhibitors, taking account of the presence or absence of resistance-associated variants and the patient's condition. The currently available information on resistance mutations should be provided to healthcare professionals and then post-marketing surveillance should be used to collect information on resistance mutations following treatment with LDV/SOF in patients with prior exposure to NS5A inhibitors and the efficacy of LDV/SOF. The obtained results should be provided to healthcare professionals appropriately.

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[102] McPhee F, et al., *Hepatology*. 2013;58(3):902-911.
[103] Karino Y, et al., *J Hepatol*. 2013;58(4):646-654.

4.(iii).B.(4).4) Use in patients with prior exposure to NS3/4A protease inhibitors

PMDA asked the applicant to explain the use of LDV/SOF in patients with prior exposure to NS3/4A protease inhibitors.

The applicant's explanation:

The results of non-clinical studies showed that NS3/4A protease inhibitor resistance-associated substitutions were not cross-resistant to SOF or LDV [see "3.(i).A.(1).3) Cross-resistance with other anti-HCV agents"].

In a Japanese study, all of 36 patients previously treated with a triple regimen of NS3/4A protease inhibitor+PegIFN+RBV achieved SVR12 (NS3/4A protease inhibitors used in 14 subjects in the LDV/SOF group: TVR [4 subjects], simeprevir sodium [SMV] [6 subjects], vaniprevir [3 subjects], faldaprevir [1 subject]; NS3/4A protease inhibitors used in 22 subjects in the LDV/SOF+RBV group: TVR [10 subjects], SMV [6 subjects], vaniprevir [4 subjects], faldaprevir [2 subjects]). In a foreign phase III study (Study GS-US-337-0109), the SVR12 rates in patients previously treated with a triple regimen of HCV NS3/4A protease inhibitor+PegIFN+RBV were 93.9% (62 of 66 subjects) in the LDV/SOF 12-week treatment group and 96.9% (62 of 64 subjects) in the LDV/SOF+RBV 12-week treatment group.

According to resistance analyses in the foreign phase III study (Study GS-US-337-0109), the SVR12 rates among patients with HCV NS3/4A resistance-associated variants[104)] at baseline were 94.4% (34 of 36 subjects) in the LDV/SOF 12-week treatment group and 97.6% (40 of 41 subjects) in the LDV/SOF+RBV 12-week treatment group. No association between the presence of NS3/4A mutations at baseline and achievement of SVR12 was observed.

Based on the above, the use of LDV/SOF is recommended in patients previously treated with a triple regimen of NS3/4A protease inhibitor+PegIFN+RBV.

PMDA's view:

Based on the absence of cross-resistance between SOF or LDV and NS3/4A protease inhibitors and the results from Japanese and foreign clinical studies, the efficacy of LDV/SOF in patients previously treated with a triple regimen of NS3/4A protease inhibitor+PegIFN+RBV can be expected. However, as the number of Japanese patients previously treated with these triple regimens who received LDV/SOF is limited, post-marketing surveillance should be used to continue collection of information on emergence of resistance mutations, following treatment with LDV/SOF in these patients, the efficacy of LDV/SOF, etc. The obtained results should be provided to healthcare professionals appropriately.

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

On the basis of the following considerations, PMDA concluded that the dosage and administration statement for LDV/SOF should be as shown below.

[104)] NS3/4A resistance-associated variants were defined as V36A/G/M/L/M, F43S, T54A/C/G/S, V55A/I, Q80K/R/L, S122R, R155C/G/K/M/T/Q/S, A156F/G/N/T/V/S, D168A/E/F/G/H/I/N/K/L/P/V/T/Y, I/V170A/T/L, and M175L.

The usual adult dosage is one tablet (90 mg of Ledipasvir and 400 mg of Sofosbuvir), administered orally once daily for 12 weeks.

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

Dosage and administration of LDV/SOF

The applicant's explanation on the rationale for the dosage and administration of LDV/SOF:

The doses of the active substances (LDV and SOF) of the proposed product were selected based on dose selection for LDV or SOF alone.

The data from a foreign phase I study in treatment-naïve patients with chronic hepatitis C (genotype 1) (Study GS-US-256-0102) were analyzed by a sigmoid maximal effect (E_{max}) model to evaluate the relationship between LDV AUC_{tau} and change from baseline in HCV RNA levels. The analysis predicted that >95% of the maximal effect would be achieved at the LDV exposure after administration of ≥30 mg of LDV in genotype 1a patients. The plasma pharmacokinetics of LDV were similar between genotype 1a and 1b patients [see "4.(ii).A.(2).1) Foreign phase I study"]. For these reasons, LDV 30 or 90 mg once daily was selected for phase II studies. A foreign phase II study (Study GS-US-248-0120) evaluated the efficacy and safety of LDV 30 or 90 mg-containing combination regimens[105)] (12 or 24 weeks of treatment) in treatment-naïve patients with chronic hepatitis C (genotype 1). As a result, the SVR24 rate was comparable between the LDV 30 mg group (47.8% [22 of 46 subjects]) and the LDV 90 mg group (58.5% [55 of 94 subjects]) and there were no differences in safety or tolerability. However, since the proportions of patients who experienced breakthrough[106)] were 19.6% (9 of 46 subjects) in the LDV 30 mg group and 10.6% (10 of 94 subjects) in the LDV 90 mg group, and the dose of LDV 90 mg was therefore selected.

The dose of SOF 400 mg was selected based on the results of exposure-response analyses in patients with chronic hepatitis C (genotype 1) and the results from dose-finding studies of SOF in combination with PegIFN+RBV (P7977-0422 and P7977-0221).[81)]

A phase I drug interaction study between LDV and SOF (Study GS-US-334-0101) showed that SOF exposure was increased by LDV, but the increase in exposure remained within the bounds of safety as demonstrated in a previous clinical study. The formulation of a fixed-dose combination tablet containing 90 mg of LDV and 400 mg of SOF was considered of no safety concern [see "4.(ii).A.(1).2).(c) Interaction between LDV and SOF"]. Thus, combining of LDV 90 mg and SOF 400 mg into a single tablet has been decided. A foreign phase I study (Study GS-US-334-0111) evaluated ethnic differences in pharmacokinetics in healthy adults and its results showed no apparent differences in the pharmacokinetics of LDV or SOF after administration of LDV/SOF between Japanese and Caucasian subjects [see "4.(ii).A.(1).1) Phase I study in Japanese and Caucasian

105) LDV was to be combined with vedroprevir (an NS3/4A protease inhibitor), tegobuvir (a non-nucleoside NS5B polymerase inhibitor), and RBV.
106) HCV RNA level once dropped to < LLOQ, and then returned to ≥ LLOQ during the treatment.

subjects"].

According to the results from a foreign phase II study (Study GS-US-337-0118),[107] which had been available at the time of planning a Japanese study, 19 of 19 treatment-naïve patients (100%) and 18 of 19 treatment-experienced patients (94.7%) achieved sustained virologic response 4 weeks after the end of 12-week treatment with once-daily LDV/SOF. Thus, the applicant considered that the efficacy of 12-week treatment with LDV/SOF can be expected regardless of prior treatment experience. Based on these study results, LDV/SOF (LDV 90 mg and SOF 400 mg) was administered once daily for 12 weeks in the Japanese study, in which a high SVR12 rate was achieved. The study raised no particular safety concern.

Table 36 shows the results of subgroup analyses for the SVR12 rate in the LDV/SOF group and LDV/SOF+RBV group in the Japanese study. In all subgroups, the SVR12 rate was similar between the LDV/SOF+RBV group and LDV/SOF group.

Table 36. SVR12 rates in subgroups (Japanese phase III study)

Patient characteristics		Treatment-naïve		Treatment-experienced	
		LDV/SOF (N = 78)	LDV/SOF+RBV (N = 81)	LDV/SOF (N = 79)	LDV/SOF+RBV (N = 80)
Overall		78/78 (100)	78/81 (96.3)	79/79 (100)	80/80 (100)
Age	<65 years	56/56 (100)	52/54 (96.3)	44/44 (100)	57/57 (100)
	≥65 years	22/22 (100)	26/27 (96.3)	35/35 (100)	23/23 (100)
Gender	Male	31/31 (100)	32/33 (97.0)	29/29 (100)	33/33 (100)
	Female	47/47 (100)	46/48 (95.8)	50/50 (100)	47/47 (100)
Cirrhosis	No	65/65 (100)	68/70 (97.1)	52/52 (100)	59/59 (100)
	Yes	13/13 (100)	10/11 (90.9)	27/27 (100)	21/21 (100)
IFN eligibility	IFN-eligible	74/74 (100)	69/71 (97.2)	—	—
	IFN-ineligible	4/4 (100)	9/10 (90.0)	—	—
Response to prior treatment	Nonresponder [a)]	—	—	25/25 (100)	26/26 (100)
	Relapse/Breakthrough [b)]	—	—	39/39 (100)	39/39 (100)
	IFN-intolerant [c)]	—	—	15/15 (100)	15/15 (100)
HCV RNA level	<800,000 IU/ml	6/6 (100)	8/8 (100)	9/9 (100)	13/13 (100)
	≥800,000 IU/ml	72/72 (100)	70/73 (95.9)	70/70 (100)	67/67 (100)
IL28B	CC	50/50 (100)	44/45 (97.8)	31/31 (100)	29/29 (100)
	Non CC	28/28 (100)	34/36 (94.4)	48/48 (100)	51/51 (100)

n/N (%), —: Not applicable

a) Patient who did not achieve undetectable HCV RNA levels on treatment with IFN.

b) Patient who achieved undetectable HCV RNA levels during treatment with IFN or within 4 weeks after the end of treatment, but did not achieve SVR.

c) Patient who discontinued IFN treatment due to adverse drug reactions, etc.

A summary of safety in the Japanese study are as shown in Table 37. Since the incidences of overall adverse events and adverse events leading to RBV dose adjustment or interruption were higher in the LDV/SOF+RBV group than in the LDV/SOF group, administration of LDV/SOF alone was considered preferable from the safety and tolerability standpoints.

[107] The study was intended to assess the safety, tolerability, and antiviral efficacy of LDV/SOF or LDV/SOF + RBV administered for 8 or 12 weeks in treatment-naïve chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) (CTD5.3.5.1.5).

Table 37. Summary of safety (Japanese phase III study)

	Japanese phase III study	
	LDV/SOF	LDV/SOF+RBV
	N = 157	N = 161
Any adverse event experienced by subjects	104 (66.2)	123 (76.4)
Grade ≥3 adverse events	3 (1.9)	2 (1.2)
Serious adverse events	2 (1.3)	2 (1.2)
Fatal adverse events	0	1 (0.6)
Adverse events leading to LDV/SOF interruption	1 (0.6)	1 (0.6)
Adverse events leading to LDV/SOF discontinuation	0	2 (1.2)
Adverse events leading to dose adjustment or interruption of study drug	1 (0.6)	20 (12.4)
Adverse events leading to study drug discontinuation	0	3 (1.9)

n (%)

Based on the above, the proposed dosage and administration of LDV/SOF is 90 mg/400 mg, administered orally once daily for 12 weeks for the treatment of chronic hepatitis C patients with or without compensated cirrhosis (genotype 1).

PMDA concluded that LDV/SOF FDC once daily for 12 weeks for chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) is acceptable.

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

The applicant's explanation on the clinical positioning of LDV/SOF for chronic hepatitis C patients with or without compensated cirrhosis (genotype 1):

The Japanese Hepatitis Management Guidelines[74)] include the following recommendations: a triple regimen of SMV or vaniprevir+PegIFN+RBV is recommended for IFN-eligible, treatment-naïve chronic hepatitis C patients with high viral load and IFN-eligible patients with prior relapse; a triple regimen of SMV or vaniprevir+PegIFN+RBV or the DCV+ASV regimen for IFN-eligible patients with prior nonresponse; and the DCV+ASV regimen for IFN-eligible patients with prior nonresponse and IFN-ineligible-naïve/intolerant patients.[108)] On the other hand, there is currently no therapy recommended for patients previously treated with a triple regimen of NS3/4A protease inhibitor+PegIFN+RBV. The PegIFN+RBV regimen or the DCV+ASV regimen is recommended for compensated cirrhotic patients, based on history of prior treatment and IFN eligibility.

Patients treated with a triple regimen of NS3/4A protease inhibitor+PegIFN+RBV may have adverse reactions to IFN and/or RBV or tolerability problems. A combination of DCV and ASV is an IFN- and RBV-free regimen and the SVR24 rate was as high as 84.7% (188 of 222 subjects),[109)] whereas the SVR24 rate was low in patients with genotype 1a infection and patients with baseline NS5A resistance-associated polymorphisms[110)] and adverse events such as hepatic dysfunction have been reported.

LDV/SOF is used as an IFN- and RBV-free regimen of 12-week duration. The study results demonstrated the efficacy of LDV/SOF was high and its safety was acceptable in chronic hepatitis C patients with or without

108) Watchful waiting is also recommended, depending on IFN eligibility and the degree of cancer risk, for some patient groups.
109) Kumada H, et al., *Hepatology*. 2014;59:2083-2091.
110) A Japanese clinical study evaluated the efficacy and safety of the DCV+ASV regimen in IFN-ineligible-naïve/intolerant and nonresponder chronic hepatitis C patients with or without compensated cirrhosis (genotype 1). As a result, the SVR24 rates in patients with the NS5A substituion Y93H or L31M/V were 43.3% (13 of 30 subjects) or 25.0% (2 of 8 subjects), respectively (Daklinza Tablets 60 mg package insert, 2nd edition).

compensated cirrhosis (genotype 1), regardless of baseline patient characteristics and viral factors [see "4.(iii).B.(2) Efficacy," "4.(iii).B.(3) Safety," and "4.(iii).B.(4) Indications"].

Based on the above, LDV/SOF can become a first-line drug for chronic hepatitis C patients with or without compensated cirrhosis (genotype 1).

PMDA's view:
Since none of the Japanese and foreign studies included an active control group, rigorous comparison with existing therapies is difficult, but the efficacy of LDV/SOF in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) can be expected to a certain extent [see "4.(iii).B.(2) Efficacy"]. No particular tolerability problems were found. These results indicate that LDV/SOF can become a new treatment option for chronic hepatitis C patients with or without compensated cirrhosis (genotype 1).

4.(iii).B.(7) Post-marketing investigations
The applicant is planning the following post-marketing surveillance study of LDV/SOF.
[Drug use-results survey]
- Objectives: To collect information about and evaluate safety and efficacy in routine clinical settings.
- Planned sample size: 3000 patients (including 1000 chronic hepatitis C patients with compensated cirrhosis)
  Basis for sample size determination
  The planned sample size of 3000 patients provides a 95% probability of detecting at least one case of an adverse drug reaction with an incidence of 0.1%. According to the available information including the results of an investigation by the applicant and published literature, approximately 30% of chronic hepatitis C patients enrolled in this drug use-results survey are expected to have compensated cirrhosis. Thus, the survey is intended to enroll 3000 chronic hepatitis C patients including approximately 1000 compensated cirrhotic patients.
- Observation period: The observation period for safety will be from the start of treatment with LDV/SOF up to 4 weeks after its completion (or its discontinuation) and the observation period for efficacy will be for 36 weeks from the start of treatment with LDV/SOF (including a 24-week post-treatment follow-up period).
- Survey period: 3 years (including a 2-year patient enrollment period)

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

In addition to the investigations proposed by the applicant, PMDA considers that it is necessary to collect the followingpost-marketing information
- Safety and efficacy in IFN-ineligible or -intolerant patients
- Safety and efficacy in elderly patients and compensated cirrhotic patients
- The occurrence of cardiotoxic events
- The emergence of resistance mutations following treatment with LDV/SOF in patients with prior exposure to another NS5A inhibitor or NS3/4A protease inhibitors and the efficacy of LDV/SOF

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

4.(iii).B.(8) Others

The applicant reported failure to comply with the following obligations (some of the foreign post-marketing safety information was not reported or notified appropriately) during a Japanese study (Study GS-US-337-0113): reporting to the Minister of Health, Labour and Welfare in accordance with Article 273 of the Ordinance for Enforcement of the Pharmaceutical Affairs Act ([also with the relevant provisions of the revised ordinance, which is the Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics] the Ordinance of the Ministry of Health and Welare (MHW) No.1 of 1961; hereinafter referred to as the "Enforcement Ordinance"); and notifying the investigators and the heads of the medical institutions in accordance with Article 20 of the Ministerial Ordinance on Good Clinical Practice (MHW Ordinance No. 28 of 1997; hereinafter referred to as the "GCP Ministerial Ordinance").[111)] The unreported safety information was reported to the Minister of Health, Labour and Welfare, notified to the investigators and the heads of the medical institutions, and reported to the institutional review boards after this issue was revealed.

PMDA assessed the safety of LDV/SOF, including whether there was any unknown adverse reaction, among the unreported events, and then concluded that there are no new safety concerns other than those examined in "4.(iii).B.(3) Safety."

Some of the LDV/SOF safety information was not appropriately reported or notified during the drug development in Japan and such failure to comply with the statutory obligations should be corrected, also in terms of ensuring the safety of subjects in a clinical trial. Although the corrective actions and preventive measures proposed by the applicant[81)] are acceptable at present, the applicant must appropriately implement the corrective actions and preventive measures and promptly improve the internal system or take other measures to prevent similar situations from recurring.

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

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

IV. Overall Evaluation

Based on the submitted data, the efficacy of LDV/SOF in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) has been demonstrated and its safety is acceptable in view of its observed

111) See Sovaldi Tablets 400 mg Review Report (Sovaldi Tablets 400 mg/Copegus Tablet 200 mg Review Report, February 23, 2015) for the cause for failure to appropriately report the safety information etc., and future intended improvements.

benefits. However, it is necessary to collect the following post-marketing information:

- Safety and efficacy in IFN-ineligible or -intolerant patients
- Safety and efficacy in elderly patients and compensated cirrhotic patients
- The occurrence of cardiotoxic events
- The emergence of resistance mutations following treatment with LDV/SOF in patients with prior exposure to another NS5A inhibitor or NS3/4A protease inhibitors and the efficacy of LDV/SOF

PMDA considers that LDV/SOF may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

May 14, 2015

I. Product Submitted for Registration

[Brand name]	Harvoni Combination Tablets
[Non-proprietary name]	Ledipasvir Acetonate/Sofosbuvir
[Applicant]	Gilead Sciences K.K.
[Date of application]	September 24, 2014

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

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

(1) Safety

PMDA's conclusions on safety [see "4.(iii).B.(3) Safety" of Review Report (1)] were supported by the expert advisors. The following comments on the precautionary statement about coadministration of amiodarone with Harvoni Combination Tablets (LDV/SOF) were raised.

- Fatal cases have been reported overseas when LDV/SOF was coadministered with amiodarone. In order to confirm the post-marketing safety of LDV/SOF more carefully, appropriate contraindication or warning statements or other precautions should be included in the package insert.
- Since the elimination half-life of amiodarone is very long, it is more appropriate to include the elimination half-life of amiodarone in the Precautions for Use section of the package insert.

PMDA concluded that some precautionary statements about coadministration of amiodarone with LDV/SOF should be included in the Important Precautions section of the LDV/SOF package insert, taking into account the expert advisors' comments as well as the following points: (1) The US and EU labelings state that coadministration of amiodarone is not recommended and that if coadministration is required, cardiac monitoring should be performed; (2) amiodarone is intended for use only in patients with life-threatening arrhythmias who have not responded to other available antiarrhythmics or when alternative agents could not be tolerated; and (3) while amiodarone is known to affect cardiac conduction, Sofosbuvir and Ledipasvir have no direct effects on cardiac conduction, etc. The precautionary statements about coadministration of amiodarone with LDV/SOF are as follows:

- Coadministration of amiodarone with LDV/SOF should be avoided wherever possible.
- Prior to coadministering amiodarone with LDV/SOF, the patient or his/her family should be fully informed of the risk of serious arrhythmic events such as bradycardia and advised to contact his/her attending physician immediately if signs or symptoms of arrhythmia develop.
- When initiating concomitant use of LDV/SOF and amiodarone, the patient should undergo appropriate cardiac monitoring in an in-patient setting for at least the first 3 days of coadministration. Monitoring of the heart rate should be continued by the patient or his/her family etc., on a daily basis for at least the first 2 weeks after discharge from the hospital, with close attention paid to the possible development of signs of arrhythmia etc. If abnormalities occur, appropriate measures should be taken.
- Since the plasma elimination half-life with chronic use of amiodarone is very long, ranging from 19 to 53 days, the above measures should be taken also for patients discontinuing amiodarone prior to starting LDV/SOF.

PMDA instructed the applicant to appropriately provide the above information and the details of the occurrence of arrhythmia reported overseas to date, such as bradycardia, and precaution information concerning coadministration of amiodarone with LDV/SOF to patients or their families, using information materials designed both for healthcare professionals and for patients. The applicant agreed to the instructon.

(2) Draft risk management plan

PMDA's conclusions on post-marketing surveillance [see "4.(iii).B.(7) Post-marketing investigations" of Review Report (1)] were supported by the expert advisors.

PMDA considers that post-marketing surveillance should be used to collect the following information and the obtained information should be provided to healthcare professionals as soon as the information is accumulated.

- Safety and efficacy in interferon (IFN)-ineligible or -intolerant patients
- Safety and efficacy in elderly patients and compensated cirrhotic patients
- The occurrence of cardiotoxic events
- The emergence of resistance mutations following treatment with LDV/SOF in patients with prior exposure to another NS5A inhibitor or NS3/4A protease inhibitors and the efficacy of LDV/SOF

Post-marketing information on resistance mutations should be collected from literature, etc. It is necessary to collect information on resistance mutations in patients who have failed to achieve sustained HCV RNA response after treatment with LDV/SOF, whenever possible. Such information should include the patients' clinical course after the end of treatment. The obtained findings should be provided to healthcare professionals promptly.

PMDA requested the applicant to address the above points and the applicant agreed to the request.

Taking account of the above discussion, PMDA concluded that the safety specification and efficacy concerns as shown in Table 38 should be included in the current draft risk management plan and that additional

pharmacovigilance activities and risk minimization activities as shown in Table 39 should be conducted. Table 40 shows an outline of the draft drug use-results survey plan submitted.

Table 38. Safety specification and efficacy concerns of the draft risk management plan

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

Table 39. Summary of additional pharmacovigilance activities and risk minimization activities in the draft risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
· Early Post-marketing Phase Vigilance (EPPV) · Drug use-results survey	· EPPV · Develop and provide materials designed for healthcare professionals on coadministration of amiodarone. · Develop and provide materials designed for patients on coadministration of amiodarone

Table 40. Outline of the draft drug use-results survey plan

Objectives	To evaluate safety and efficacy in routine clinical settings.
Survey method	Central registry system
Patients to be included in the survey	Chronic hepatitis C patients with or without compensated cirrhosis
Survey period (Observation period)	3 years (up to 24 weeks after the end of treatment)
Planned sample size	3000 patients (including 1000 chronic hepatitis C patients with compensated cirrhosis)
Main information to be collected	Safety and efficacy in IFN-ineligible or -intolerant patients, safety and efficacy in elderly patients and compensated cirrhotic patients, the occurrence of cardiotoxic events (including coadministration of amiodarone), the emergence of resistance mutations following treatment with LDV/SOF in patients with prior exposure to another NS5A inhibitor or NS3/4A protease inhibitors and the efficacy of LDV/SOF

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

1. PMDA's conclusion on the results of document-based GLP/GCP inspection and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.1).

Due to noncompliance with the GCP for Drugs during a Japanese clinical study for the registration of Sovaldi Tablets 400 mg (the same applicant), PMDA requested the applicant to perform a pre-inspection self-audit of a clinical study of LDV/SOF (5.3.5.1.1) that was conducted during the same period under a similar system. As a result, as is the case with the Japanese clinical study of Sovaldi Tablets 400 mg, noncompliance with the GCP

for Drugs by the monitor at a trial site were found: delays in the submission of the investigator's brochure (revised version) and the reporting of some of the safety information to the investigators and the head of the medical institution (trial site), and forged entries in the monitoring reports. PMDA asked the applicant how to handle the relevant data. The applicant responded that the data from all subjects enrolled at this trial site would be excluded.

As a result of the inspection, the clinical studies as a whole were carried out in accordance with GCP. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the application documents as long as the data in question are excluded from the analysis by the applicant. There were findings requiring improvement for some trial sites and the sponsor (Clinical Trial In-Country Representative) as shown below, though not significantly affecting the overall assessment of the study. The findings were notified to the heads of the relevant medical institutions, the applicant, and the sponsor (Clinical Trial In-Country Representative).

[Findings requiring improvement]

Trial sites

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

Sponsor (Clinical Trial In-Country Representative)

- Some of serious, unexpected adverse drug reactions and other information reported from outside Japan were not immediately notified to the investigators or the heads of the medical institutions.

The details of this finding were as described below:

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

events identified no new safety concerns about LDV/SOF.

- During the clinical study, some of serious, unexpected adverse drug reactions and other information collected from foreign clinical studies were not notified immediately to some of the heads of the medical institutions because the relevant monitor failed to do so.
- Inconsistencies between the source documents and the CRF (inconsistencies in the time of blood collection, the date and time of the last dose taken before blood collection, etc., and inconsistencies in the results of causality assessment of adverse events) failed to be detected during monitoring visits.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that approval may be granted after modifying the indication and dosage and administration statements as shown below, with the following condition. Since LDV/SOF is a drug with a new active ingredient and a new combination drug, the re-examination period is 8 years. Neither Ledipasvir Acetonate drug substance nor the drug product is classified as a poisonous drug or a powerful drug. The product is not classified as a biological product or a specified biological product.

[Indications]	Suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis.
[Dosage and administration]	The usual adult dosage is one tablet (90 mg of Ledipasvir and 400 mg of Sofosbuvir), administered orally once daily for 12 weeks.
[Condition for approval]	The applicant is required to develop and appropriately implement a risk management plan.