Report on the Deliberation Results

November 16, 2016

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Ximency Combination Tablets
Non-proprietary Name	Daclatasvir Hydrochloride/Asunaprevir/Beclabuvir Hydrochloride (JAN*)
Applicant	Bristol-Myers Squibb K.K.
Date of Application	December 21, 2015

Results of Deliberation

In its meeting held on November 11, 2016, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. Beclabuvir Hydrochloride, a drug substance, is not classified as a poisonous drug or a powerful drug, but the drug product is classified as a powerful drug.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until the data from the planned number of patients have been accumulated, thereby identifying the characteristics of treated patients, collecting data on the safety and efficacy of the product, and taking necessary measures to ensure its proper use.

**Japanese Accepted Name (modified INN)*

Review Report

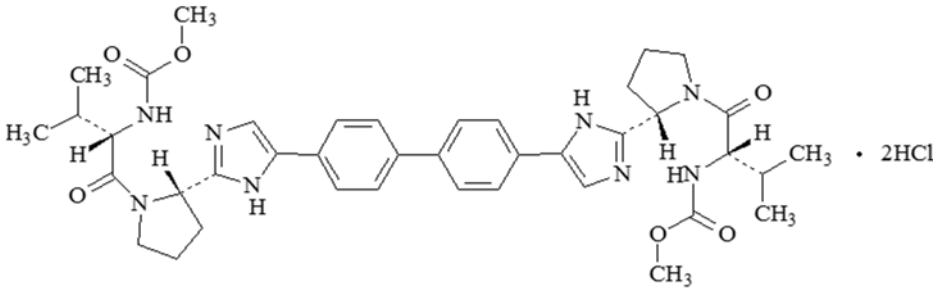
October 11, 2016
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Ximency Combination Tablets
Non-proprietary Name	Daclatasvir Hydrochloride/Asunaprevir/Beclabuvir Hydrochloride
Applicant	Bristol-Myers Squibb K.K. (application submitted by Bristol-Myers K.K., whose name was changed later)
Date of Application	December 21, 2015
Dosage Form/Strength	Each tablet contains 16.5 mg of Daclatasvir Hydrochloride (15 mg of Daclatasvir), 100 mg of Asunaprevir, and 39.6 mg of Beclabuvir Hydrochloride (37.5 mg of Beclabuvir)
Application Classification	Prescription drug, (1) Drug with a new active ingredient and (2) New prescription combination drug

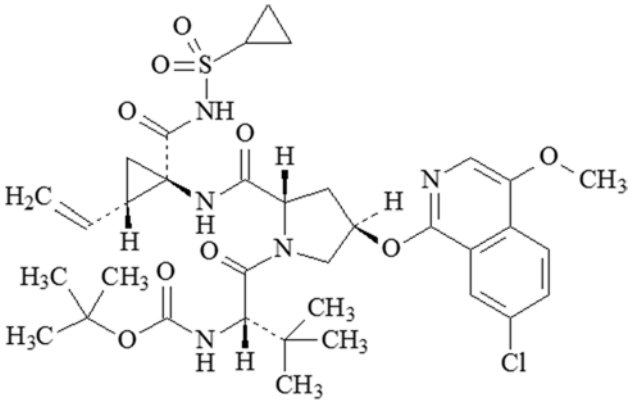
Chemical Structure

Daclatasvir Hydrochloride



Molecular formula:	$C_{40}H_{50}N_8O_6 \cdot 2HCl$
Molecular weight:	811.80
Chemical name:	Dimethyl *N*,*N*'-([1,1'-biphenyl]-4,4'-diylbis{1*H*-imidazole-5,2-diyl-[(2*S*)-pyrrolidine-2,1-diyl][(1*S*)-3-methy-1-oxobutane-1,2-diyl]})dicarbamate dihydrochloride

Asunaprevir

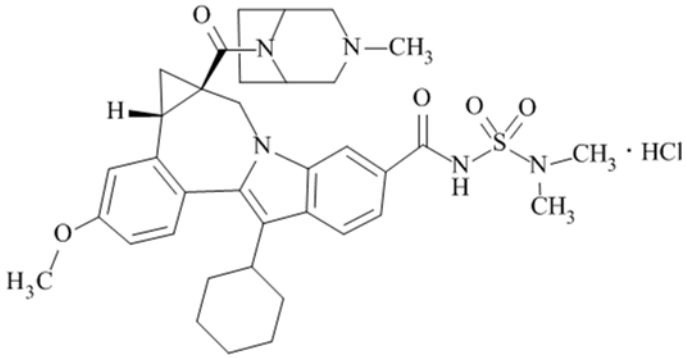


Molecular formula: $C_{35}H_{46}ClN_5O_9S$

Molecular weight: 748.29

Chemical name: 1,1-Dimethylethyl{(2*S*)-1-[(2*S*,4*R*)-4-({7-chloro-4-methoxyisoquinolin-1-yl}oxy)-2-({(1*R*,2*S)*-1-[(cyclopropanesulfonyl) carbamoyl]-2-ethenylcyclopropyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

Beclabuvir Hydrochloride



Molecular formula: $C_{36}H_{45}N_5O_5S{\cdot}HCl$

Molecular weight: 696.30

Chemical name: (4b*S*,5a*R*)-12-Cyclohexyl-*N*-(dimethylsulfamoyl)-3-methoxy-5a-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-4b,5,5a,6-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-9-carboxamide monohydrochloride

Items Warranting Special Mention None

Reviewing Office Office of New Drug IV

Results of Review

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that Ximency Combination Tablets has efficacy in the suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients without cirrhosis or with compensated cirrhosis and that its safety is acceptable in view of its observed benefits. Given that hepatic function disorders, including bilirubin elevation-related adverse events, increased alanine aminotransferase, and increased aspartate aminotransferase, were reported in patients treated with Ximency Combination Tablets, the applicant should ensure that close monitoring of patients for such events is carried out and that measures for safety management are taken in the post-marketing setting, while collecting relevant post-marketing information.

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

Indication	Suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients without cirrhosis or with compensated cirrhosis
Dosage and Administration	The usual adult dosage is 2 tablets, administered orally twice daily after meals for 12 weeks.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until the data from the planned number of patients have been accumulated, thereby identifying the characteristics of treated patients, collecting data on the safety and efficacy of the product, and taking necessary measures to ensure its proper use.

Appendix

Review Report (1)

August 25, 2016

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

Product Submitted for Approval

Brand Name	Ximency Combination Tablets
Non-proprietary Name	Daclatasvir Hydrochloride/Asunaprevir/Beclabuvir Hydrochloride
Applicant	Bristol-Myers Squibb K.K. (application submitted by Bristol-Myers K.K., whose name was changed later)
Date of Application	December 21, 2015
Dosage Form/Strength	Each Tablet contains 16.5 mg of Daclatasvir Hydrochloride (15 mg of Daclatasvir), 100 mg of Asunaprevir, and 39.6 mg of Beclabuvir Hydrochloride (37.5 mg of Beclabuvir)
Proposed Indication	Suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients without cirrhosis or with compensated cirrhosis
Proposed Dosage and Administration	The usual adult dosage is 2 tablets, administered orally twice daily after meals for 12 weeks.

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List of Abbreviations

ASV	Asunaprevir
AUC	Area under the plasma concentration versus time curve
AUC_{inf}	Area under the plasma concentration versus time curve extrapolated to infinite time
AUC_{tau}	Area under the plasma concentration versus time curve over the dosing interval
BCRP	Breast cancer resistance protein
BCV	Beclabuvir hydrochloride
BID	Bis in die
BSEP	Bile salt export pump
CC_{50}	50% cytotoxic concentration
CL	Clearance
CL_{cr}	Creatinine clearance
C_{max}	Maximum plasma concentration
C_{trough}	Trough plasma concentration
CYP	Cytochrome P450
DCV	Daclatasvir hydrochloride
EC_{50}, EC_{75}, EC_{90}	50%, 75% or 90% effective concentration
Efflux ratio	Basal-to-apical versus apical-to-basal ratio
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
IC_{50}	50% inhibitory concentration
IFN	Interferon
INR	International normalized ratio
MDCK	Madin-Darby canine kidney
pDILI	Potential drug-induced liver injury
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPK	Population pharmacokinetics
QD	Quaque die (once daily)
RBV	Ribavirin
SVR X	Sustained virologic response at X weeks (after the end of treatment)
T_{max}	Time to maximum plasma concentration
Guidelines for the Management of Hepatitis C Virus Infection, Version 5	The Japan Society of Hepatology Drafting Committee for Hepatitis Management. JSH Guidelines for the Management of Hepatitis C Virus Infection Version 5. May 2016
DCV/ASV/BCV FDC	Ximency Combination Tablets

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

Ximency Combination Tablets were developed by Bristol-Myers Squibb K.K. as a fixed-dose combination formulation containing the following 3 active ingredients: beclabuvir hydrochloride (BCV), which inhibits viral protein NS5B polymerase that plays an important role in hepatitis C virus (HCV) replication; asunaprevir (ASV, whose brand name is Sunvepra Capsules 100 mg), an HCV NS3/4A protease inhibitor; and daclatasvir hydrochloride (DCV, whose brand name is Daklinza Tablets 60 mg), an HCV NS5A inhibitor. ASV and DCV are already approved in Japan.

An estimated 1.5 to 2 million people have been infected with HCV in Japan, and approximately 70% of the HCV-infected persons have genotype 1 infection (Guidelines for the Management of Hepatitis C Virus Infection, Version 5). Currently, the following agents are available for the treatment of patients with chronic hepatitis C (genotype 1) in Japan.

Table 1. Therapeutic drugs for patients with chronic hepatitis C (genotype 1) in Japan

Agent	Abbreviated name	Route of administration	Main characteristics	Remarks
Interferons (including peg-interferons)	IFN	Injection	–	–
Ribavirin	RBV	Oral	Purine nucleoside derivative	Combination regimen consisting of IFN and RBV
Telaprevir	–	Oral	NS3/4A protease inhibitor	Combination regimen consisting of IFN, RBV, and telaprevir
Simeprevir sodium	–	Oral	NS3/4A protease inhibitor	Combination regimen consisting of IFN, RBV and simeprevir sodium
Vaniprevir	–	Oral	NS3/4A protease inhibitor	Combination regimen consisting of IFN, RBV, and vaniprevir
Asunaprevir	ASV	Oral	NS3/4A protease inhibitor	Combination regimen consisting of DCV and ASV (IFN-free)
Daclatasvir hydrochloride	DCV	Oral	NS5A inhibitor	Combination regimen consisting of ASV and DCV
Sofosbuvir	–	Oral	NS5B polymerase inhibitor	Fixed-dose combination drug containing ledipasvir acetone solvate and sofosbuvir (IFN-free)
Ledipasvir acetone solvate	–	Oral	NS5A inhibitor	Fixed-dose combination drug containing sofosbuvir and ledipasvir acetone solvate
Paritaprevir hydrate	–	Oral	NS3/4A protease inhibitor	Fixed-dose combination drug containing ombitasvir hydrate, low-dose ritonavir, and paritaprevir hydrate (IFN-free)
Ombitasvir hydrate	–	Oral	NS5A inhibitor	Fixed-dose combination drug containing paritaprevir hydrate, low-dose ritonavir, and ombitasvir hydrate

The DCV + ASV combination regimen improved the treatment outcomes of chronic hepatitis C patients without cirrhosis or with compensated cirrhosis by reducing various interferon (IFN)-related events including pyrexia and depression, which occur frequently in patients receiving IFN-containing therapy. However, an analysis of the effect of baseline NS5A- or NS3-resistance-associated variants on sustained virologic responses with the DCV + ASV regimen showed that 35.4% (17 of 48) of subjects harboring the NS5A Y93H mutations and 42.9% (6 of 14) of subjects harboring the NS5A L31I/M/V mutations

had achieved sustained virologic response 24 weeks after the end of treatment (SVR24 rate).[1)] In a foreign phase II study, the SVR24 rate in subjects with HCV genotype 1a infection was 22.2% (2 of 9 subjects) (Package Insert for Daklinza Tablets 60 mg, version 10). Bristol-Myers Squibb K.K. developed a fixed-dose combination (FDC) drug containing DCV, ASV, and BCV (DCV/ASV/BCV FDC), which is expected to be more effective than the DCV + ASV regimen, regardless of the baseline status of resistance-associated variants or HCV genotype.

Since the results from Japanese clinical studies of DCV/ASV/BCV FDC in genotype 1 chronic hepatitis C patients without cirrhosis or with compensated cirrhosis became available, the applicant has filed a marketing application for DCV/ASV/BCV FDC (i.e., Ximency Combination Tablets).

As of August 2016, DCV/ASV/BCV FDC has not been approved in any foreign countries or regions.

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

DCV, ASV, and BCV are used as the drug substances. DCV is identical to the drug substance of Daklinza Tablets 60 mg which has received marketing authorization.

2.1 Drug substance (Asunaprevir, ASV)

The characterization and manufacturing process of ASV are the same as those of Sunvepra Capsules 100 mg which has received marketing authorization.

The proposed specifications for ASV are the same as the specifications for the drug substance of Sunvepra Capsules 100 mg; that is, content, description, identification (infrared spectroscopy and high performance liquid chromatography [HPLC]), purity (heavy metals, related substances [HPLC], and residual solvents [gas chromatography]), and assay (HPLC). In addition, [redacted] has been newly included in the proposed specifications for ASV.

Based on the results of the stability studies shown in Table 2, and in accordance with "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003), a re-test period of [redacted] months has been proposed for the drug substance when stored in double polyethylene bags (with a desiccant) inside a high-density polyethylene drum at room temperature, protected from light. The long-term testing will be continued for [redacted] months.

1) The proportion of subjects with undetectable HCV RNA levels at 24 weeks after the end of treatment

Table 2. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches (drug substance manufactured with the optimized Process X)	25°C	60%RH	Double polyethylene bags (with a desiccant) + a high-density polyethylene drum	24 months
	3 pilot-scale batches (drug substance manufactured with Process Y)			Double polyethylene bags (without a desiccant) + a high-density polyethylene drum	24 months
Accelerated	3 commercial-scale batches (drug substance manufactured with the optimized Process X)	40°C	75%RH	Double polyethylene bags (with a desiccant) + a high-density polyethylene drum	6 months
	3 pilot-scale batches (drug substance manufactured with Process Y)			Double polyethylene bags (without a desiccant) + a high-density polyethylene drum	6 months

2.2 Drug substance (Beclabuvir Hydrochloride, BCV)

2.2.1 Characterization

The drug substance is a white to pale yellowish white powder and has been characterized by powder X-ray diffraction, Fourier transform near-infrared spectroscopy, thermal analysis, melting point, hygroscopicity, particle size, optical rotation, solubility, pH, dissociation constant (sulfonamide group, tertiary amine), distribution coefficient, crystalline polymorphism, and forced degradation. At least 2 crystalline forms of the drug substance ([redacted], [redacted]) have been identified. Only [redacted] is produced in the commercial manufacturing process. This crystalline form has been confirmed to be stable at room temperature.

The chemical structure of the drug substance has been elucidated by ultraviolet-visible absorption spectroscopy, infrared spectroscopy, hydrogen nuclear magnetic resonance spectroscopy (^{1}H-NMR), carbon nuclear magnetic resonance spectroscopy (^{13}C-NMR), mass spectrometry, and single-crystal X-ray crystallography. The drug substance has 2 chiral centers

2.2.2 Manufacturing process

The drug substance is synthesized using [redacted] and [redacted] as starting materials.

The Quality by Design approach was utilized mainly for the following activities:

- Identification of [redacted] as critical quality attributes
- Identification of critical process parameters through a quality risk assessment

The following have been identified as critical steps: [redacted], and [redacted] for [redacted]; [redacted], and [redacted] for

[redacted]; and [redacted], [redacted], [redacted], and [redacted] for [redacted]. [redacted] and [redacted] have been identified as the critical intermediates, for which control parameters and control values have been specified.

2.2.3 Control of drug substance

The proposed drug substance specifications include content, description, identification (infrared spectroscopy and HPLC), purity (related substances [HPLC], residual solvents [gas chromatography], [redacted]), [redacted], [redacted], [redacted], and assay (HPLC).

2.2.4 Stability of drug substance

The results of the main stability studies of the drug substance are summarized in Table 3. Photostability testing demonstrated that the drug substance is not photostable.

Table 3. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage packaging	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	Double polyethylene bags (with a desiccant) + a high-density polyethylene drum	18 months
	3 pilot-scale batches	25°C	60% RH	Double polyethylene bags (without a desiccant) + a high-density polyethylene drum	30 months
Accelerated	3 pilot-scale batches	40°C	75% RH		6 months

Based on the above and in accordance with "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003), a re-test period of [redacted] months has been proposed for the drug substance when stored in double polyethylene bags (with a desiccant) inside a high-density polyethylene drum at room temperature, protected from light. The long-term testing will be continued for [redacted] months.

2.3 Drug product

2.3.1 Description and composition of drug product and formulation development

The drug product is a tablet containing 16.48 mg of daclatasvir hydrochloride (15 mg of daclatasvir), 100 mg of ASV, and 39.57 mg of BCV (37.5 mg of beclabuvir). The drug product also contains the following excipients: lactose hydrate, microcrystalline cellulose, silicon dioxide, croscarmellose sodium, magnesium stearate, and [redacted].

2.3.2 Manufacturing process

The drug product is produced through the manufacturing process comprising the following steps: [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], tableting, coating suspension preparation, coating, testing and storage, packaging, labeling, and testing and storage. Of them, [redacted], [redacted], [redacted], and [redacted] are identified as critical steps. For [redacted] and [redacted] out of these critical steps, control parameters and control values have been specified.

The Quality by Design approach was utilized mainly for the following activities:

- Identification of [redacted], [redacted], [redacted], and [redacted] as critical quality attributes
- Determination of drug product formulation and the ranges of process parameters based on the results of evaluations including quality risk assessment and design of experiments.

2.3.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (HPLC, [redacted]), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), dissolution (HPLC), and assay (HPLC).

2.3.4 Stability of drug product

The results of the stability studies of the drug product are summarized in Table 4. Photostability testing demonstrated that the drug product is photostable.

Table 4. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage packaging	Storage period
Long-term	3 pilot-scale batches	25°C	60% RH	Blister pack	24 months
Accelerated	3 pilot-scale batches	40°C	75% RH		6 months

Based on the above and in accordance with "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003), a re-test period of 36 months has been proposed for the drug product when stored in a blister pack (polyvinyl chloride/double polychlorotrifluoroethylene films/aluminum foil) at room temperature. The long-term testing will be continued for [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA considers that the quality of the drug substances and drug product is adequately controlled.

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

The pharmacological effects of a new active ingredient BCV were investigated in primary pharmacodynamic studies and safety pharmacology studies. Doses and concentrations of BCV are expressed as free base.

3.1 Primary pharmacodynamics

3.1.1 Mechanism of action (CTD 4.2.1.1-1, 4.2.1.1-4)

The results of a co-crystallization study demonstrated that BCV binds to the HCV NS5B polymerase thumb site 1. The inhibitory activities of BCV against human or viral polymerases and other enzymes were studied in polymerase assays. The results are shown in Table 5. In the tests for inhibition of ligand binding using nucleic-acid binding probes, the 50% inhibitory concentration (IC_{50}) of BCV against DNA- and RNA-binding was 60 and >20 μmol/L, respectively.

Table 5. Inhibitory activities of BCV against human and viral polymerases and other enzymes

Enzyme	IC_{50} (μmol/L)[a)]
HCV genotype 1b (Con1) NS5B polymerase	0.011
Bovine polymerase α	>80
Human polymerase β	>100
Human polymerase γ	>100
BVDV polymerase	>93
HIV reverse transcriptase	>100
Klenow polymerase	>11, 99
HIV integrase	>40

Mean
a) Results of ≥2 measurements

3.1.2 *In vitro* antiviral activity

3.1.2.1 Antiviral activity of BCV against HCV replicon cells (CTD 4.2.1.1-1, 4.2.1.1-2)

In HCV replicon assays (luciferase assays), the antiviral activity of BCV against replicon cells from different genotypes was determined based on the number of HCV replicon copies. In addition, the inhibitory activity of BCV against polymerases of different genotypes was determined in polymerase assays. The results are shown in Table 6. In the presence of 40% human serum, the antiviral activity of BCV against genotype 1b replicon cells was decreased by 0.23-fold.

Table 6. Antiviral activity of BCV against various genotypes and inhibitory activity of BCV against polymerases

HCV genotype (strain)	EC_{50} (nmol/L) against replicon	IC_{50} (nmol/L) against polymerase
1a (H77c)	3.2	3.3
1a (clinical isolate)	1.6-5.3[a)]	–
1b (Con1)	6	4.2
1b (clinical isolate)	3.5-9.5[b)]	–
2a (JFH-1)	87	165
2a (HC-J6)	498	228
2b (patient consensus)[e)]	–	164
2b (clinical isolate)[f)]	480->1000[b)]	–
3a (patient consensus)[g)]	–	1.8
3a (clinical isolate)[f)]	3.5-9.5[c)]	–
4a (database consensus)[h)]	–	19.9
4a (clinical isolate)[f)]	3-18[d)]	7.6-27.1[b)]
5a (database consensus)[i)]	–	4.8
5a (clinical isolate)[f)]	0.8-4.3[a)]	–
6a (patient consensus)	–	61.6
6a (clinical isolate)[j)]	8.6-79.5[d)]	–

Mean; –, Not evaluated

a) Range of EC_{50} values against 4 strains
b) Range of EC_{50} values against 2 strains
c) Range of EC_{50} values against 5 strains
d) Range of EC_{50} values against 3 strains
e) Common sequence of HCV from chimpanzees infected with HCV genotype 2b (HC-J8) (a 97.4% match with the genotype 2b sequence of European Hepatitis C Virus Database)
f) Evaluated as hybrid replicons constructed using HCV genotype 1a (H77c) or genotype 1b (Con1) replicons encoding NS5B from genotype 2b, 3a, 4a, or 5a chronic hepatitis C patients.
g) Common sequence of HCV from chimpanzees infected with HCV genotype 3a (S52) (a 97.8% match with the genotype 3a sequence of European Hepatitis C Virus Database)
h) Base sequence synthesized based on 11 types of base sequences from Genbank (base sequence database by the National Center for Biotechnology Information in the US) (a 99.8% match with the genotype 4a sequence of European Hepatitis C Virus Database)
i) Base sequence synthesized based on 5 types of base sequences from Genbank (a 98.3% match with the genotype 4a sequence of European Hepatitis C Virus Database)
j) Common sequence of HCV from clinical isolates (a 97.2% match with the genotype 6a sequence of European Hepatitis C Virus Database)

3.1.2.2 Antiviral activity of metabolites (CTD 4.2.1.1-3)

In HCV and bovine viral diarrhea virus replicon assays (luciferase assays), the antiviral activity (50% effective concentration [EC_{50}]) of metabolites of BCV was determined based on the number of replicon copies of each virus. In addition, the inhibitory activity (IC_{50}) of metabolites of BCV against virus polymerase was determined in polymerase assays. Furthermore, the cytotoxicity of metabolites of BCV against HCV and bovine viral diarrhea virus replicon cells was investigated by calculating the 50% cytotoxic concentration (CC_{50}). The results are shown in Table 7.

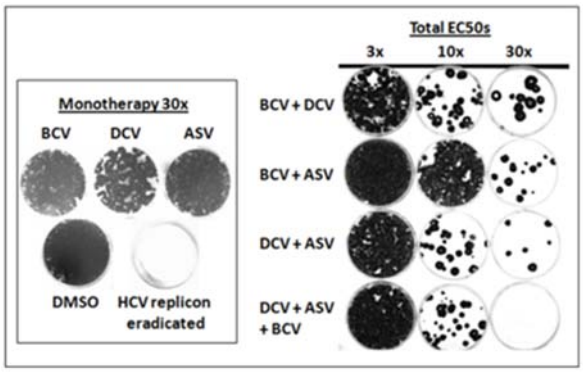
Table 7. Antiviral activity, polymerase inhibitory activity, and cytotoxicity of metabolites of BCV

	IC_{50}, EC_{50}, or CC_{50} (μmol/L)				
	BMS-794712 (M1)	BMT-171207 (M6)	BMT-110547 (M3)	BMT-142478 (M7)	BMS-948158 (M17)
Genotype 1b NS5B polymerase	0.001	0.0015	0.001	0.001	0.066
Bovine viral diarrhea virus polymerase	>10	–	–	–	> 10
Genotype 1a replicon (H77c)	0.002	0.004	0.013	0.031	8.1
Genotype 1b replicon (Con1)	0.004	0.010	0.021	0.050	14.1
Bovine viral diarrhea virus replicon	17	20	15	12	–
CC_{50}	14	36	>100	47	>100[a)]

Mean; –, Not evaluated
a) Results of one calculation

3.1.2.3 Effects of the combination of DCV, ASV, and BCV (CTD 4.2.1.1-1, 4.2.1.1-7)

The effects of the combination of DCV, ASV, and BCV were evaluated in HCV genotypes 1a (H77c) replicon cells. The results are shown in Figure 1. While surviving HCV colonies were observed when cells were co-treated with any 2 of DCV, ASV, and BCV at a concentration that was 15-fold the EC_{50} (0.3, 60, and 48 nmol/L, respectively), there were no surviving HCV colonies when cells were co-treated with DCV, ASV, and BCV at a concentration that was 10-fold the EC_{50} (0.2, 40, and 32 nmol/L, respectively).



	Concentration (nmol/L)		
	3×[a)]	10×[a)]	30×[a)]
BCV			96
DCV			0.6
ASV			120
BCV+DCV	4.8/0.03	16/0.1	48/0.3
BCV+ASV	4.8/6	16/20	48/60
DCV+ASV	0.03/6	0.1/20	0.3/60
DCV+ASV+BCV	0.02/4.0/3.2	0.067/13.3/10.7	0.2/40/32

a) Expressed as total EC_{50}. For example, when the total EC_{50} was 30×, the concentrations of 2 drugs used in combination were 15-fold their respective EC_{50} values, and the concentrations of 3 drugs used in combination were 10-fold their respective EC_{50} values.

Figure 1. Effects of the combination of DCV, ASV, and BCV against genotype 1a replicon cells

The antiviral activity of the combination of DCV, ASV, and BCV was evaluated in HCV genotype 1b (Con1) replicon cells and variants containing D168V, the main NS3 resistance variant, and L31M and Y93H, the main NS5A resistance variants. The results are shown in Figure 2. There was no apparent decrease in the number of colonies until 7 days of treatment with DCV and ASV at a concentration of 5- and 0.1-fold[2)] their respective EC_{50} values (250 and 40 nmol/L, respectively) to the variants. Meanwhile, a decrease in the number of colonies was observed, regardless of the use of ribavirin (RBV), within 7 days of treatment with DCV, ASV, and BCV at a concentration of 5-, 0.1-, and 125-fold[2)] their respective EC_{50} values (250, 40, and 500 nmol/L, respectively).

2) Calculated based on the EC_{50} value against each variant.

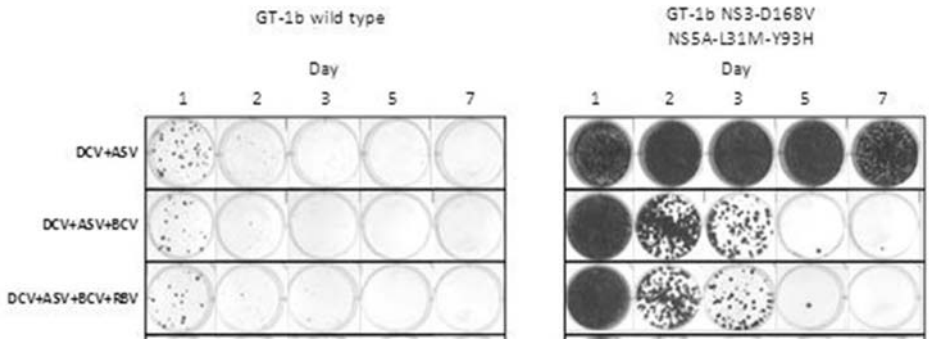


Figure 2. Antiviral activity of DCV, ASV, and BCV against wild-type and mutant replicons

In addition, HCV replicon cells were used to evaluate the antiviral effects of BCV in combination with DCV, ASV, BMS-790453 (a nucleoside NS5B polymerase inhibitor), BMS-762407 (a non-nucleoside NS5B polymerase inhibitor), or DCV + ASV.[3)] The results are shown in Table 8.

Table 8. Effects of BCV in combination with other agents on HCV replicon cells

	DCV	ASV	DCV + ASV	BMS-790453	BMS-762407
Combination index (minimum) [95% CI]	0.65 [0.59, 0.72]	0.86 [0.71, 1.01]	0.93 [0.79, 1.07]	0.43 [0.37, 0.49]	0.61 [0.49, 0.72]
Combination index (maximum) [95% CI]	1.02 [0.88, 1.16]	1.07 [1.00, 1.14]	1.11 [0.91, 1.30]	0.95 [0.85, 1.05]	0.90 [0.82, 0.97]
Effect	Additive or synergistic	Additive	Additive	Additive or synergistic	Synergistic

CI, confidence interval

3.1.2.4 Antiviral activity of BCV against viruses other than HCV (CTD 4.2.1.1-1)

The antiviral activity of BCV against viruses other than HCV (bovine viral diarrhea virus, human immunodeficiency virus [HIV], herpes simplex virus type 1 and type 2, influenza virus, canine parainfluenza virus, human rhinovirus, coxsackievirus, poliovirus, and human coronavirus) was determined. The EC_{50} was >4 μmol/L against any of these viruses tested.

3.1.3 Cytotoxicity against various cells (CTD 4.2.1.1-1)

Various types of cells were cultured in the presence of BCV for 3 to 5 days to evaluate cytotoxicity (CC_{50}). The CC_{50} of BCV[4)] against liver-derived Huh-7 cells, kidney-derived Vero cells, kidney-derived MDBK cells, MRC5 cells (human lung embryonic fibroblasts), and MT2 cells (human T-lymphocytic leukemia cells) was 20, 29, 30, 16, and 14 μmol/L, respectively.

3) The EC_{50}, EC_{75}, and EC_{90} values of BCV alone and in combination with other drugs were calculated. The combination index and its 95% CI were calculated for each combination by the isobologram method. The effect of each combination was assessed as "inhibitory effect" if the lower bound of the CI was >1, "synergetic effect" if the upper bound of the CI was ≤1, and "additional effect" if the CI includes 1 (Pharmacological Reviews 2006;58:621-681).

4) CC_{50} values of BCV against the respective cell types were calculated twice, and the lower concentrations were shown.

3.1.4 Resistance profiles

3.1.4.1 Resistance selection and antiviral activity of BCV against variants (CTD 4.2.1.1-1, 4.2.1.1-4, 4.2.1.1-5)

Multiple amino acid substitutions were observed after culturing HCV replicon cells of different genotypes in the presence of 300 nmol/L BCV for 5 to 10 days. In HCV replicon assays (luciferase assays), the antiviral activity of BCV against HCV replicon cells containing these amino acid substitutions was determined based on the number of HCV replicon copies. The results are shown in Table 9.

Table 9. Antiviral activity of BCV against variants (NS5B region)

Genotype (viral strain)	Amino acid substitution	EC_{50} (nmol/L)	Fold resistance[b)]	Replication efficiency of variant/ replication efficiency of wild-type[c)]
1a (H77c)	Wild type	4	1	1
	P495A	58	15	0.6-0.8
	P495S	253	64	0.16-0.18
	P495L	133	32	0.25-0.3
	P495T	142	36	0.07-0.14
1b (Con1)	Wild type	7	1	1
	P495A	144	20	0.38-0.45
	P495S	378	54	0.06-0.07
	P495L	368	53	0.08-0.14
	V499A	11.5	1.6	0.42-0.55
3a (H77c)[a)]	Wild type	5	1	1
	C494S	170	34	–[d)]
	P495S	–	–	Not replicated
4a (Con1)[a)]	Wild type	4.5	1	1
	V494A	15.5	3.4	0.33-0.46
	P495A	111	25	0.3-0.34
	P495L	–	–	Not replicated
5a (Con1)[a)]	Wild type	4	1	1
	V494A	–	–	Not replicated
	P495H	670	167	–[d)]
	P495L	–	–	Not replicated
	P495S	–	–	Not replicated
6a (Con1)[a)]	Wild type	10.6	1	1
	V494A	179	17	–[d)]

EC_{50} is expressed as mean value.
–, Not evaluated
a) Evaluated as hybrid replicons constructed using HCV genotype 1a (H77c) or genotype 1b (Con1) replicons encoding NS5B from genotype 3a, 4a, 5a or 6a chronic hepatitis C patients.
b) Mutant EC_{50}/wild-type EC_{50}
c) Results of transient replication assays
d) Not applicable because of the result from stable cells.

In addition, amino acid substitutions identified in HCV genotype 1were selected based on the reports of *in vitro* resistance selection studies of the combination of DCV, ASV, and BCV (*Antimicrobial Agents and Chemotherapy*. 2012;56:5230-5239), a single-dose study of BCV in genotype 1 chronic hepatitis C patients (CTD 4.2.1.1-5), and studies on other HCV NS5B inhibitors targeting the thumb site 1 (*Antimicrob Agents and Chemother*. 2013;57:4727-4735). The resistance of these variants to BCV[5)] was

5) Mutant EC_{50}/wild-type EC_{50}

evaluated in HCV replicon assays (luciferase assays) based on the number of HCV replicon copies. The results are shown in Table 10.

Table 10. Resistance of variants (NS5B region) to BCV

Genotype (viral strain)	Amino acid substitution	Fold resistance [a)]	Replication efficiency of variant/ replication efficiency of wild-type
1a (H77c)	T389I	1	1.1-2.6
	L392I	5-7	0.1-0.4
	L392F	1	1.2
	A421V	1-3	0.3-0.9
	V494A	2	0.1
	L497M	1	0.1
	A499V	1	0.5
	T389I + A421V	3-5	0.5-1.2
1b (Con1)	L392I	7	0.2
	V499A	2	0.5

a) Mutant EC_{50}/wild-type EC_{50}

3.1.4.2 Cross-resistance

3.1.4.2.1 Antiviral activity of BCV against resistance variants (CTD 4.2.1.1-1, 4.2.1.1-4)

The antiviral activity of BCV against genotype 1b (Con1) replicon variants was determined in HCV replicon assays (luciferase assays) based on the number of HCV replicon copies. The results are shown in Table 11.

Table 11. Antiviral activity of BCV against resistance variants

	Amino acid substitution	EC_{50} (nmol/L)	Fold resistance[a)]
	Wild type	5.0	1
Resistance-associated variant in NS5B thumb site 1	P495S	192	38
	P495L	316	63
Resistance-associated variant in NS5B catalytic site	S282T	4	0.8
Resistance-associated variant in NS5B thumb site 2	M423T	5.0	1
Resistance-associated variant in NS5B palm site 1	M414T	7.0	1.4
Resistance-associated variant in NS5B palm site 2	C316Y	2.0	0.4
Resistance-associated variant in NS3	R155Q	5.3	1
	A156V	2.4	0.5
	D168V	3.0	0.6
Resistance-associated variant in NS5A	Y93H	3.8	0.8
	L31V + Y93H	2.9	0.6

EC_{50} is expressed as mean value.
a) Mutant EC_{50}/wild-type EC_{50}

3.1.4.2.2 Antiviral activity of DCV and ASV against BCV-resistant variants (CTD 4.2.1.1-6)

The antiviral activity of DCV and ASV against BCV-resistant variants was determined in HCV replicon assays (luciferase assays) based on the number of HCV replicon copies. The results are shown in Table 12.

Table 12. Antiviral activity of DCV and ASV against BCV-resistant variants

Genotype	Amino acid substitution	EC_{50} (nmol/L)			
		BCV	DCV	ASV	BMS-929075 (NS5B palm site 2 inhibitor)
1a (H77c)	Wild type	4	0.008	1	10
	P495A	57	0.009	1	6
	P495S	186	0.009	1	4
	P495L	130	0.008	2	6
1b (Con1)	Wild type	6	0.002	2	2
	P495A	82	0.002	1	1
	P495S	195	0.002	2	1
	P495L	316	0.002	2	1

Mean

3.2 Secondary pharmacodynamics

No secondary pharmacodynamic data were submitted in the current application.

3.3 Safety pharmacology (CTD 4.2.3.1-1, 4.2.3.2-3, 4.2.3.2-4, 4.2.3.2-5; reference data CTD 4.2.1.3-1, 4.2.1.3-2, 4.2.1.3-3, 4.2.1.3-4, 4.2.1.3-5, 4.2.1.3-6, 4.2.1.3-7)

Studies were conducted to evaluate the effects of BCV on receptors, channels, etc., as well as on the central nervous, cardiovascular, and respiratory systems (Table 13).

Table 13. Summary of safety pharmacology studies

Organ system evaluated	Test system	Endpoint/ evaluation method	Dose or concentration	Route of administration	Noteworthy findings
Effects on receptors/ channels, etc.	Binding and enzymatic assays (2 samples each)[a)]	Binding inhibition rate, enzyme inhibitory activity	BCV 6.6 μg/mL BMS-794712 6.5 μg/mL	*in vitro*	BCV, 57% inhibition of phosphodiesterase 4 BMS-794712, 71% inhibition of phosphodiesterase 4
	U937 cell (2 samples each)[a)]	Phosphodiesterase 4 inhibitory activity	BCV 4.2×10^{-4} to 6.6 μg/mL	*in vitro*	IC_{50}, 1.3 μg/mL
Central nervous system	CD1 mouse (5/sex/group)	Single oral dose toxicity study	BCV 0, 125, 375, or 1250 mg/kg	Oral	No findings at 125 mg/kg, Tremor, clonic convulsion, etc. (including fatal cases) at >375 mg/kg
	SD rat (20/sex/group)	Repeated oral dose toxicity study (6 months)	BCV 0, 5, 20, or 80 mg/kg	Oral	None
	Beagle dog (6/sex/group)	Repeated oral dose toxicity study (9 months)	BCV 0, 1, 5, or 25 mg/kg	Oral	None

Organ system evaluated	Test system	Endpoint/ evaluation method	Dose or concentration	Route of administration	Noteworthy findings
Cardiovascular system	HEK-293 cell (2-3 samples for each concentration)[a)]	hERG current	BCV 1.98, 6.6, or 19.8 μg/mL	*in vitro*	IC_{50}, 8.2 μg/mL
		Sodium current	BCV 6.6 μg/mL		66.3% inhibition at 6.6 μg/mL
	Isolated rabbit Purkinje fiber (3 samples for each concentration)[a)]	Purkinje fiber action potential	BCV 1.98, 6.6, or 19.8 μg/mL	*in vitro*	No findings at 1.98 μg/mL An increase in the action potential duration at 50% repolarization (APD_{50}) by 10.1% at 6.6 μg/mL An increase in APD_{50} by 14.4% at 19.8 μg/mL
	Isolated rabbit heart (3-4 samples for each concentration)[a)]	Atrial electrogram, electrocardiogram, coronary perfusion rate	BCV 0.7, 1.98, 6.6, or 19.8 μg/mL	*in vitro*	A decrease in heart rate by 4% to 18%, and a prolongation of sinus node recovery time by 7% to 22% at ≥0.7 μg/mL
	Anesthetized rabbit (3 males/group)[a)]	Blood pressure, heart rate, electrocardiogram	BCV 0, 1, 3, 10, or 15 mg/kg	Intravenous (cumulative dose)	No findings at ≤1 mg/kg A transient increase in arterial blood pressure by 9% to 19%, and a decrease in heart rate by 7% to 20% at ≥3 mg/kg
	Beagle dog (3/sex/group)[a)]	Telemetry	0 or 53 mg/kg	Oral	Vomiting, but no effects on blood pressure, heart rate, or ECG parameters at 53 mg/kg
	Beagle dog (5/sex/group)	Repeated oral dose toxicity study (1 month)	BCV 0, 1, 5, or 25 mg/kg	Oral	None
Respiratory system	CD1 mouse (5/sex/group)	Single oral dose toxicity study	BCV 0, 125, 375, or 1250 mg/kg	Oral	No findings at 125 mg/kg Labored respiration, etc. (including fatal cases) at >375 mg/kg
	SD rat (25/sex/group)	Repeated oral dose toxicity study (6 months)	BCV 0, 5, 20, or 80 mg/kg	Oral	None
	Beagle dog (5/sex/group)	Repeated oral dose toxicity study (1 month)	BCV 0, 1, 5, or 25 mg/kg	Oral	None

a) Performed as non-GLP studies

The applicant's explanation about the summary of safety pharmacology studies:

No effects were observed on the central nervous and respiratory systems in rats at 80 mg/kg, and the C_{max} in the treated animals was approximately 47-fold the human exposure (C_{max}).[6)] As to findings on the cardiovascular system, abnormalities including a slight decrease in heart rate were observed at 0.7 μg/mL in *in vitro* studies, and the concentration was approximately 39-fold the human exposure (C_{max}). In addition, no effects were observed in dogs at 25 mg/kg, and the C_{max} in the treated animals was approximately 43-fold the human exposure (C_{max}).[7)] The effects of BMS-794712, the major metabolite

6) The exposure ratio in *in vivo* studies was calculated based on the human steady-state exposure to BCV following repeated administration at the recommended clinical dose (75 mg/dose twice daily) in a foreign phase II study (AI443014); that is, C_{max} of 1.49 μg/mL or AUC of 17.4 μg·h/mL [see "6.2.3.2 Study in subjects with hepatic impairment"]. The exposure ratio in *in vitro* studies was calculated using the C_{max} of BCV in the unbound form in humans (0.018 μg/mL) taking account of the plasma protein binding rate of BCV being 98.8%. In a 6-month oral toxicity study in rats, the mean C_{max} in male rats after administration at 80 mg/kg was 69.3 μg/mL [see "4.1.3 Repeated-dose studies"].

7) Calculated using the mean C_{max} (63.7 μg/mL) in male and female dogs at 25 mg/mL in a 9-month oral toxicity study in dogs (CTD 4.2.3.2-5).

of BCV, were evaluated in a 9-month oral toxicity study in dogs, in which dogs were exposed to the metabolite at a dose that was approximately 63-fold the human AUC. Based on the above, BCV is unlikely to affect the central nervous, cardiovascular, or respiratory system in humans.

3.R Outline of the review conducted by PMDA

3.R.1 Antiviral activity of BCV

PMDA asked the applicant to explain whether BMS-794712, the major metabolite of BCV, contributes to the efficacy of DCV/ASV/BCV FDC.

The applicant's explanation:

In genotype 1a and 1b HCV replicon assays, the antiviral activity of BMS-794712 (EC_{50}, approximately 2-4 nmol/L) was similar to that of BCV (EC_{50}, approximately 3-6 nmol/L) [see Sections 3.1.2.1 and 3.1.2.2]. Given that the minimum concentration (C_{min}) and the AUC of BMS-794712 accounted for approximately 23% and 27%, respectively, of those of BCV after co-administration of 75 mg BCV, 30 mg DCV, and 200 mg ASV twice daily for 14 days [see Section 6.2.3.2], the antiviral activity of BMS-794712 also contributes to the efficacy of DCV/ASV/BCV FDC.

PMDA's view:

The applicant's explanation is acceptable. Based on the submitted data, the antiviral activity of BCV and BMS-794712 against HCV is considered promising. The antiviral activity of DCV and ASV was evaluated at the time of the initial applications for Daklinza Tablets 60 mg and Sunvepra Capsules 100 mg (Review Reports on Daklinza Tablets 60 mg and Sunvepra Capsules 100 mg, dated June 6, 2014), and the results of evaluation of the antiviral activity of the combination of DCV, ASV, and BCV against HCV replicon cells clearly demonstrated the pharmacodynamic effects of the combination. The efficacy of the co-administration of DCV, ASV, and BCV in patients with chronic hepatitis C without cirrhosis or with compensated cirrhosis is described in Section 7.R.1.

3.R.2 Resistance to BCV

The applicant's explanation about the resistance profile of BCV:

In *in vitro* resistance selection studies, the BCV-resistant variants identified in genotype 1a and 1b HCV replicon cells were mutations at position 495 in the NS5B region, and the EC_{50} values of BCV against these variants were 15- to 64-fold the EC_{50} of BCV against the wild-type [see Section 3.1.4.1]. No reduction in the antiviral activity of DCV or ASV was observed against BCV-resistant variants, and no reduction in the antiviral activity of BCV was observed against DCV- or ASV-resistant variants [see Section 3.1.4.2]. No reduction in the antiviral activity of BCV was observed against variants at position 282, which are resistant to sofosbuvir, an approved NS5B polymerase inhibitor [see Section 3.1.4.2].

PMDA's view:

The results of *in vitro* studies [see Section "3.1.4 Resistance profiles"] demonstrated that the antiviral activity of BCV was decreased by mutations at position 495 in the NS5B region and that no cross-

resistance was identified between BCV and DCV, ASV, or sofosbuvir. The relationship between resistance mutations and the efficacy of the co-administration of DCV, ASV, and BCV in clinical studies is described in Section 7.R.1.2. However, given the limited information available from clinical studies, and because the emergence of any resistance mutations is potentially important information in terms of the efficacy of the DCV + ASV + BCV combination regimen, post-marketing information on resistance to these agents should be collected by literature review and other measures. Any new findings should be communicated to healthcare professionals in an expedited manner.

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

The pharmacokinetics (PK) of BCV and its major metabolite, BMS-794712, after administration of BCV (radiolabeled or non-radiolabeled form) were studied in mice, rats, rabbits, dogs, and monkeys. Liquid chromatography/tandem mass spectrometry was utilized for determining concentrations of BCV and BMS-794712 in plasma and biological samples (lower limit of quantitation [LLOQ], 0.1-0.5 ng/mL for BCV and 0.1-1.0 ng/mL for BMS-794712). Radioactivity distribution in tissue from animals treated with ^{14}C-BCV was determined using quantitative whole-body autoradiography, and total radioactivity levels in samples including bile, urine, and feces were determined using liquid scintillation counting.

Doses and concentrations of BCV are expressed as free base. A description of the results of PK studies of DCV and ASV was omitted in this section because the data were submitted and evaluated at the time of the initial applications for Daklinza Tablets 60 mg and Sunvepra Capsules 100 mg.

4.1 Absorption

4.1.1 *In vitro* studies (CTD 4.2.2.2-1, 4.2.2.2-3, 4.2.2.2-4)

The basal-to-apical versus apical-to-basal ratio (efflux ratio) of 3 μmol/L BCV in Caco-2 cell monolayers at a pH of 5.5, 6.5, and 7.4 was 2.2, 1.3, and 8.3, respectively.

4.1.2 Single-dose studies (CTD 4.2.2.2-1, 4.2.2.2-2)

Table 14 shows the PK parameters of unchanged BCV and BMS-794712 (a metabolite of BCV) in mice, rats, dogs, and monkeys after a single dose of BCV. The absolute bioavailability of oral BCV in mice, rats, dogs, and monkeys was >100%, 42% to 47%, 86%, and 15%, respectively.

Table 14. PK parameters of BCV and BMS-794712 after a single dose of BCV

BCV									
Species	Route	Dose (mg/kg)	n	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	T_{max} [a] (h)	$t_{1/2}$ [a] (h)	CL (mL/min/kg)	Vss (L/kg)
Mouse	IV	2 [b]	3 males/time point	2.16	10.4	0.05	3.4	3.2	1.1
		5 [c]	3 males/time point	3.92	17.7	0.5	3.2	4.7	1.3
	Oral	5 [b]	3 males/time point	3.99	46.5	8.0	3.6	–	–
		20 [c]	3 males/time point	12.8	96.9	1.0	3.3	–	–
P-gp knockout mouse	IV	2	3 males/time point	3.04	12.6	0.05	4.2	2.6	0.9
	Oral	5	3 males/time point	4.54	45.5	8.0	4.2	–	–
Rat	IV	5	3 males	10.2 ± 2.22	36.1 ± 6.74	0.17 [0.17, 0.17]	8.1 [7.4, 9.8]	2.4 ± 0.5	1.5 ± 0.4
	Oral	10	3 males	2.19 ± 0.34	31.1 ± 15.97	6 [6, 8]	6.4 [5.0, 11.1]	–	–
Dog	IV	1	3 males	10.4 ± 4.62	48.5 ± 25.9	0.08 [0.08, 0.08]	15.1 [9.3, 17.0]	0.34 ± 0.23	0.4 ± 0.1
	Oral	3	3 males	5.98 ± 2.28	123 ± 72.3	6 [4, 6]	12.2 [7.7, 13.9]	–	–
Monkey	IV	1	3 males	23.8 ± 1.92	2.40 ± 0.45	0.08 [0.08, 0.08]	1.4 [1.3, 1.4]	4.7 ± 1.0	0.1 ± 0.0
		2	3 males	6.10 ± 2.22	2.92 ± 1.19	0.25 [0.25, 0.25]	1.5 [1.4, 3.5]	8.5 ± 3.7	0.6 ± 0.2
	Oral	3	3 males	0.34 ± 0.25	1.14 ± 0.67	1 [1, 2]	3.3 [3.0, 3.8]	–	–
BMS-794712									
Species	Route	Dose (mg/kg)	n	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	T_{max} [a] (h)	$t_{1/2}$ [a] (h)	CL (mL/min/kg)	Vss (L/kg)
Mouse	IV	2 [b]	3 males/time point	0.028	0.14	3.0	–	–	–
		5 [c]	3 males/time point	0.16	0.88	1.0	4.0	–	–
	Oral	5 [b]	3 males/time point	0.15	1.53	3.0	–	–	–
		20 [c]	3 males/time point	0.73	4.99	3.0	3.7	–	–
P-gp knockout mouse	IV	2	3 males/time point	0.069	0.84	3.0	–	–	–
	Oral	5	3 males/time point	0.22	3.18	6.0	–	–	–
Rat	IV	5	3 males	0.014 ± 0.003	0.287 ± 0.24	2 [2, 4]	4.0, 6.6 [d]	–	–
	Oral	10	3 males	0.023 ± 0.003	0.23 ± 0.18	6 [6, 8]	13.4 [e]	–	–
Dog	IV	1	3 males	0.048 ± 0.034	1.86 ± 1.79	6 [0.5, 24]	8.9 [f]	–	–
	Oral	3	3 males	0.366 ± 0.13	6.17 ± 4.81	4 [4, 6]	12.6 [7.2, 14.8]	–	–
Monkey	IV	1	3 males	0.034 ± 0.007	0.088 ± 0.034	0.5 [0.5, 0.75]	1.7 [1.7, 2.0]	–	–
		2	3 males	0.099 ± 0.061	0.259 ± 0.138	0.75 [0.5, 0.75]	1.8 [1.7, 1.9]	–	–
	Oral	3	3 males	0.107 ± 0.057	0.450 ± 0.271	2 [2, 2]	2.7 [1.7, 4.5]	–	–

Mean ± standard deviation
–: Not evaluated or not calculable
a) Median [range]
b) FV-BETA mouse
c) Balb/c mouse
d) Results from 2 animals
e) Result from 1 animal
f) Result from 1 animal

4.1.3 Repeated-dose studies (CTD 4.2.3.2-1, 4.2.3.2-2, 4.2.3.2-3, 4.2.3.2-4, 4.2.3.2-5)

Table 15 shows the PK parameters of unchanged BCV and BMS-794712 in rats and dogs after repeated oral administration of BCV. In rats and dogs, there were no clear gender-related differences in the C_{max} or AUC_{0-24} of unchanged BCV or BMS-794712, while the data showed accumulation of BCV and BMS-794712 associated with repeated administration. In rats, more than dose-proportional increases in the plasma concentration of BCV were observed.

Table 15. PK parameters of BCV and BMS-794712 after repeated administration of BCV

BCV									
Species (treatment duration)	Daily dose (mg/kg)	n	Sampling time point	C_{max} (μg/mL)		AUC_{0-24} (μg·h/mL)		T_{max} (h)	
				Male	Female	Male	Female	Male	Female
Rat (2 weeks)	30	6/sex/ time point	Day 1	11.4	12.5	133	128	–	–
			Day 8	13.7	19.1	193	170	–	–
	100	6/sex/ time point	Day 1	43.0	33.4	673	531	–	–
			Day 8	52.3	84.5	930	1419	–	–
	300	6/sex/ time point	Day 1	95.0	89.7	1947	1584	–	–
			Day 8	84.5	112	1735	2283	–	–
Rat (6 months)	5	3/sex/ time point	Day 1	1.12	1.14	10.1	6.91	4.0	2.0
			Day 176	1.75	1.30	19.6	22.4	4.0	6.0
	20	3/sex/ time point	Day 1	5.48	6.67	75.5	70.9	4.0	2.0
			Day 176	15.2	14.6	187	162	6.0	6.0
	80	3/sex/ time point	Day 1	37.5	27.6	551	302	6.0	6.0
			Day 176	69.3	70.1	1500	1260	8.0	4.0
Dog (9 months)	1	6/sex	Day 1	1.86 ± 0.27	1.85 ± 0.20	23.9 ± 3.79	23.2 ± 4.5	2.7 ± 1.0	2.7 ± 1.0
			Week 39	2.70 ± 0.47	3.18 ± 0.75	38.0 ± 7.0	44.8 ± 16.2	2.0 ± 1.1	2.0 ± 0.0
	5	6/sex	Day 1	7.54 ± 0.99	7.48 ± 1.55	98.0 ± 13.7	113 ± 27.9	2.7 ± 1.0	3.3 ± 1.0
			Week 39	12.9 ± 2.19	16.2 ± 5.35	182 ± 39.9	254 ± 99.4	3.0 ± 1.1	2.2 ± 0.98
	25	6/sex	Day 1	33.1 ± 7.58	31.9 ± 10.5	596 ± 159	501 ± 150	4.0 ± 1.3	3.7 ± 0.82
			Week 39	63.4 ± 12.2	64.0 ± 14.5	1170 ± 316	1100 ± 281	3.3 ± 2.1	2.7 ± 1.0
BMS-794712									
Species (treatment duration)	Daily dose (mg/kg)	n	Sampling time point	C_{max} (μg/mL)		AUC_{0-24} (μg·h/mL)		T_{max} (h)	
				Male	Female	Male	Female	Male	Female
Rat (2 weeks)	30	6/sex/ time point	Day 1	0.12	0.11	0.62	0.55	–	–
			Day 8	0.14	0.16	0.92	0.76	–	–
	100	6/sex/ time point	Day 1	1.03	0.29	13.8	5.41	–	–
			Day 8	2.25	2.36	32.0	38.5	–	–
	300	6/sex/ time point	Day 1	5.30	3.06	73.0	34.9	–	–
			Day 8	4.59	10.2	90.4	181	–	–
Rat (6 months)	5	3/sex/ time point	Day 1	0.008	0.006	0.041	0.028	4.0	2.0
			Day 176	0.018	0.029[a)]	0.194	0.309	4.0	24
	20	3/sex/ time point	Day 1	0.058	0.045	0.669	0.245	4.0	2.0
			Day 176	0.177	0.115	2.38	1.14	6.0	4.0
	80	3/sex/ time point	Day 1	0.907	0.346	10.5	2.72	6.0	6.0
			Day 176	5.30	1.54	98.2	32.7	8.0	6.0
Dog (9 months)	1	6/sex	Day 1	0.132 ± 0.025	0.123 ± 0.035	1.31 ± 0.44	1.28 ± 0.18	2.3 ± 0.82	2.7 ± 1.0
			Week 39	0.191 ± 0.049	0.237 ± 0.072	2.15 ± 0.59	2.92 ± 1.11	2.5 ± 1.2	3.7 ± 0.82
	5	6/sex	Day 1	0.748 ± 0.273	0.607 ± 0.186	7.30 ± 2.54	8.28 ± 3.47	2.7 ± 1.0	3.0 ± 1.1
			Week 39	1.35 ± 0.28	1.70 ± 0.70	16.0 ± 5.05	24.4 ± 11.2	3.7 ± 0.82	3.3 ± 1.0
	25	6/sex	Day 1	3.13 ± 1.15	2.45 ± 1.23	64.0 ± 25.8	45.6 ± 23.7	12 ± 9.7	4.7 ± 1.0
			Week 39	15.4 ± 4.01	11.7 ± 2.58	302 ± 90.2	225 ± 48.9	4.7 ± 2.4	4.7 ± 1.0

–: Not evaluated
a) Result from only 1 animal because the results from the other 2 animals were below the LLOQ.

4.2 Distribution

4.2.1 Plasma protein binding and distribution in blood cells (CTD 4.2.2.2-1, 4.2.2.3-1, 4.2.2.3-3)

In *in vitro* studies, the serum protein bound fraction of BCV (10 μmol/L) in mouse, rat, dog, monkey and human serum was 98.8%, 98.7%, 97.8%, 97.9%, and 98.8%, respectively; and the serum protein bound fraction of BMS-794712 (10 μmol/L) in rat, dog, monkey and human serum was 98.7%, 98.9%, 97.2%, and 98.8%, respectively. Plasma protein bound fractions of BCV or BMS-794712 in human plasma showed no concentration-dependent changes within a concentration range from 0.1 to 10 μmol/L.

In *in vitro* studies, the blood-to-plasma ratio of BCV (1 μmol/L) in rats, dogs, monkeys, and humans was 0.61 to 0.78, 1.48 to 1.70, 0.99 to 1.25, and 0.67 to 0.73, respectively.

4.2.2 Tissue distribution (CTD 4.2.2.3-4, 4.2.2.3-5)

Tissue distribution of radioactivity was examined in albino and pigmented male rats (n = 1 each/time point) after a single oral dose of ^{14}C-BCV at 10 mg/kg. In pigmented rats, the highest levels of radioactivity were detected in most tissues at 4 hours post-dose, and radioactivity levels were high in the adrenal gland, liver, stomach, small intestine, and cecum (11.5, 39,1, 14.8, 297, and 33.6 μg eq./g, respectively). In albino rats, radioactivity levels in tissues were the highest at 1 hour post-dose, but the tissue distribution of radioactivity was similar to that in pigmented rats. Radioactivity levels in the uvea and skin in both pigmented and albino rats were low or below the LLOQ, indicating that BCV is unlikely to bind specifically to melanin-containing tissues.

Radioactivity levels in tissues in albino rats (n = 1/sex for a single dose, n = 1 male for repeated doses) were determined after a single or repeated oral doses of ^{14}C-BCV at 20 mg/kg.

After a single dose, tissue distribution of radioactivity was similar in both sexes. The tissue-to-plasma ratio of radioactivity exceeded 1 in the adrenal gland, diaphragm, exorbital lacrimal gland, brown fat, Harderian gland, intraorbital lacrimal gland, kidneys, renal cortex, renal medulla, large intestine, lungs, myocardium, pancreas, pituitary gland, salivary gland, small intestine, gastric mucosa, and thyroid, and was particularly high in the liver and preputial gland. Radioactivity was eliminated from all tissues excluding the preputial gland in rats of both sexes by 48 hours post-dose. Radioactivity levels were below the LLOQ at any time point in bile, the ocular lens, and the central nervous system tissues excluding paraventricular tissue.

After repeated doses, the tissue-to-plasma ratio of radioactivity exceeded 1 in the adrenal gland, bulbourethral gland, diaphragm, epididymis, exorbital lacrimal gland, brown fat, intraorbital lacrimal gland, kidneys, renal cortex, renal medulla, large intestine, lungs, myocardium, pancreas, pituitary gland, prostate gland, salivary gland, small intestine, stomach, gastric mucosa, thymus, and thyroid, and was particularly high in the Harderian gland, liver, preputial gland, and cecum. The results were nearly consistent with the results after a single dose. Radioactivity levels fell below the LLOQ in all tissues except for the preputial gland by 72 hours after the last dose and in the preputial gland at 168 hours after the last dose.

4.2.3 Distribution in the liver (CTD 4.2.2.2-1)

Following oral or intravenous administration of BCV to mice, rats, dogs, and monkeys,[8)] the liver to serum or plasma ratio of BCV[9)] was 5.7 to 10.7 (intravenous administration) and 3.1 to 5.1 (oral

8) BCV was administered orally at 20 mg/kg or intravenously at 5 mg/kg to mice, orally at 10 mg/kg or intravenously at 5 mg/kg to rats, orally at 3 mg/kg to dogs, and orally at 3 mg/kg to monkeys.

9) Concentration ratio for mice and AUC ratio for rats, dogs, and monkeys

administration) in mice, 11.2 (intravenous administration) and 15.0 (oral administration) in rats, 2.0 (oral administration) in dogs, and 24.0 (oral administration) in monkeys. The liver to serum or plasma ratio of BMS-794712[9)] in mice, rats, dogs, and monkeys was 8.4 to 12.6, 26.1, 3.9, and 114, respectively.

4.2.4 Placental transfer (CTD 4.2.2.3-5)

The radioactivity levels in tissues in dams and fetuses were determined after a single oral dose of ^{14}C-BCV at 20 mg/kg to pregnant rats on gestation day 18. In fetuses, radioactivity was detected in all tissues evaluated[10)] at 2 to 8 hours post-dose, and the highest levels of radioactivity were detected at 4 hours post-dose. The radioactivity levels in the amniotic sac at 0.5 to 24 hours post-dose were higher than those in maternal blood at 12 or 24 hours post-dose. Radioactivity was not detected in the amniotic sac at 48 or 72 hours post-dose. Radioactivity levels in the amniotic fluid were below the LLOQ at all time points excluding 4 hours post-dose.

4.3 Metabolism

4.3.1 Possible metabolic pathway (CTD 4.2.2.4-1, 4.2.2.4-2)

Based on the study results presented in Sections 4.3.2 and 4.3.3, the possible metabolic pathways of BCV were estimated (Figure 3). BCV metabolites were primarily formed via N-demethylation, O-demethylation, and hydroxylation. No metabolites unique to humans were identified.

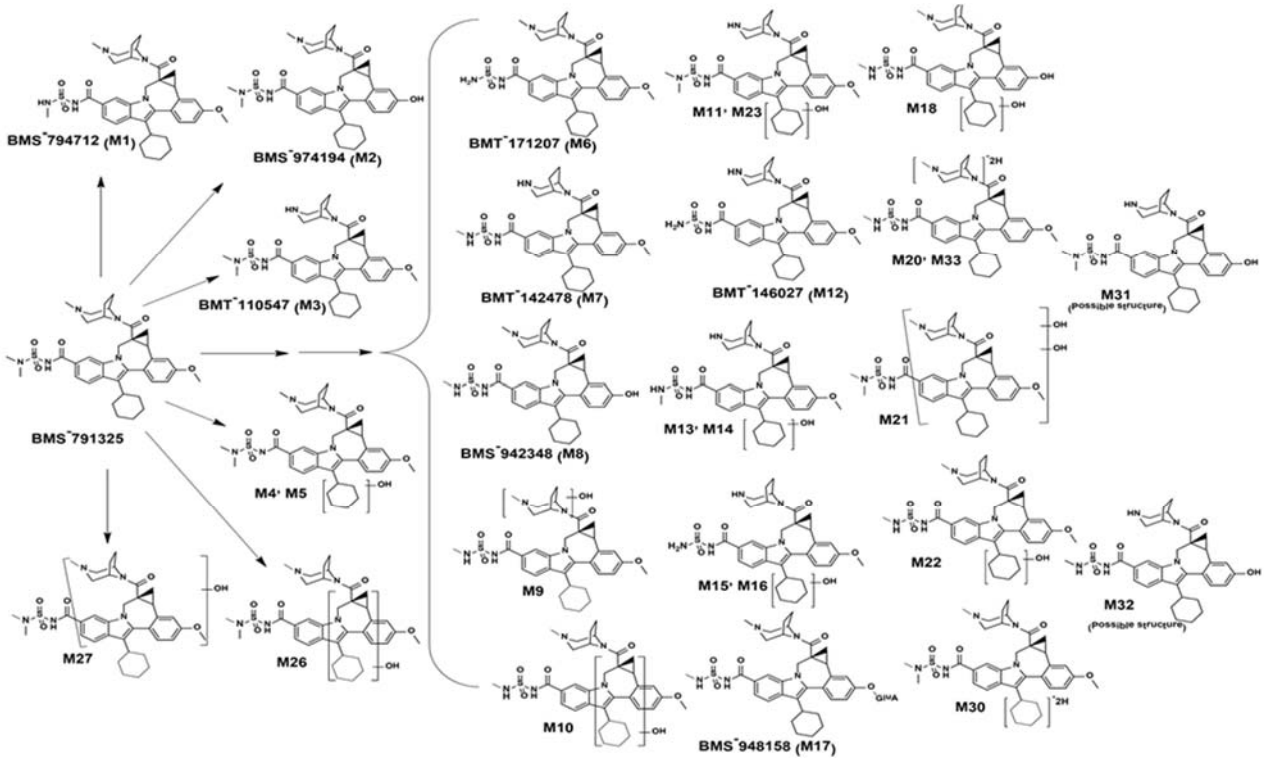


Figure 3. Possible metabolic pathways of BCV

10) The adrenal gland, blood, brain, brown fat, eyes, gastrointestinal tract, kidneys, liver, lungs, muscle, myocardium, and spinal cord

4.3.2 *In vitro* metabolism (CTD 4.2.2.2-1, 4.2.2.4-1, 4.2.2.4-8)

When ^{14}C-BCV (10 μmol/L) was added to mouse, rat, rabbit, dog, monkey, and human liver microsomes in the presence of NADPH and glutathione, to mouse, rat,[11] dog, monkey, and human liver S9 fractions in the presence of NADPH, and to mouse, rat, dog, monkey, and human hepatocytes, 28 metabolites[12] were detected. Major metabolites were BMS-794712, BMT-110547, and M4. There were no unique human BCV metabolites detected.

Metabolism of BCV was studied by incubating BCV with human liver microsomes (with or without human cytochrome P450 [CYP] specific inhibitors) or with recombinant human CYP isoforms. The metabolism of BCV by human liver microsomes was inhibited by approximately 57% in the presence of ketoconazole (1 μmol/L), a CYP3A4 inhibitor, and by approximately 72% in the presence of troleandomycin (50 μmol/L), a CYP3A4 inhibitor. When BCV (1 μmol/L) was incubated with recombinant human CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C91, CYP2C19, CYP2D6, or CYP3A4), BCV was shown to be metabolized mainly by CYP3A4. When BCV (2 μmol/L) was incubated with recombinant human CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP3A5), BCV was shown to be metabolized mainly by CYP3A4 and CYP3A5. When BMS-794712 (3 and 30 μmol/L) was incubated with recombinant human CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP3A5), BMS-794712 was shown to be metabolized mainly by CYP3A4 and CYP3A5, which contributed to the metabolism of the metabolite to a greater extent than CYP2E1, CYP2C8, or CYP2C9.

4.3.3 *In vivo* metabolism (CTD 4.2.2.4-2, 4.2.2.4-4)[13]

Following a single oral dose of ^{14}C-BCV at 30 mg/kg in mice (n = 5/time point), unchanged BCV represented 93.4% to 96.1% of total plasma radioactivity, and BMS-794712 and BMT-110547 were identified as BCV metabolites in plasma. Following a single oral dose of ^{14}C-BCV at 30 mg/kg in mice (n = 9), unchanged BCV, BMS-794712, and BMT-110547 (accounting for 30.3%, 20.5%, and 16.4%, respectively, of the dose administered) were identified in feces. BMS-974194, M4, and BMT-142478 were also detected in feces.

Following a single oral dose of ^{14}C-BCV at 20 mg/kg in bile duct-cannulated male rats and untreated male rats (n = 3 each), unchanged BCV represented 96.2% to 97.8% of total plasma radioactivity and BMS-794712, BMS-974194, and BMT-110547 were identified as BCV metabolites in plasma in untreated rats. Unchanged BCV, BMS-794712, BMS-974194, BMT-110547, and M4 (accounting for 20.3%, 17.9%, 8.8%, 11.2%, and 12.9%, respectively, of the dose administered) were detected in feces in untreated rats. In bile duct-cannulated rats, unchanged BCV in bile and feces accounted for 35.3% and 10.7%, respectively, of the dose administered. BMS-794712, BMS-974194, BMT-110547, and M4

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11) Pretreated with Aroclor 1254

12) Demethylated metabolites: BMS-794712, BMS-974194, BMT-171207, BMT-110547, BMT-142478, BMS-942348, and BMT-146027; Oxidized metabolites: M4, M5, M9, M10, M11, M13, M14, M15, M16, M18, M20, M21, M22, M23, M26, M27, M30, M31, M32, and M33; Glucuronide-conjugated metabolite: BMS-948158

13) Metabolites presented in this section are as follows:
[Demethylated metabolites] BMS-794712, BMS-974194, BMT-110547, BMT-171207, BMT-142478, BMS-942348, and BMT-146027; [Oxidized metabolites] M4, M9, M10, M11, M13, M14, M15, and M16; [Glucuronide-conjugated metabolite] BMS-948158

(accounting for 9.2%, 4.3%, 9.6%, and 2.4%, respectively, of the dose administered) were detected in bile.

Following a single oral dose of ^{14}C-BCV at 60 mg/kg in rabbits (n = 3), unchanged BCV represented 73.3% to 89.0% of total plasma radioactivity, and BMT-110547, BMS-794712, BMT-142478, and M21 were identified in plasma.

Following a single oral dose of ^{14}C-BCV at 5 mg/kg in male dogs (n = 3), unchanged BCV represented 87.1% to 91.0% of total plasma radioactivity, and BMS-794712 and BMT-110547 were identified in plasma. Unchanged BCV, BMS-794712, BMT-110547, M4, and BMT-142478 (accounting for 31.1%, 35.0%, 9.9%, 4.8%, and 2.3%, respectively, of the dose administered) were identified in feces.

Following a single oral dose of ^{14}C-BCV at 125 mg/kg in bile duct-cannulated male monkeys (n = 3), unchanged BCV and BMS-794712 represented 66.4% to 80.3% and 19.7% to 31.8%, respectively, of total plasma radioactivity. In bile, unchanged BCV, BMS-794712, BMT-110547, BMT-142478, M9, M13, and M14 (accounting for 0.7%, 3.1%, 3.2%, 7.6%, 3.8%, 3.4%, and 4.3%, respectively, of the dose administered) were detected. Other metabolites recovered included M4, BMT-171207, BMS-942348, M10, M11, BMT-146027, and M15.

In a clinical study (AI443005), unchanged BCV and BMS-794712 accounted for 67.9% to 86.1% and 10.3% to 24.6%, respectively, of total plasma radioactivity in subjects. In healthy subjects (n = 6) from whom no bile samples were collected, unchanged BCV and BMS-794712 found in feces accounted for 6.9% and 11.7%, respectively, of the dose administered. In healthy subjects (n = 3) from whom bile samples were collected, unchanged BCV and BMS-794712 found in bile accounted for 6.8% and 1.3%, respectively, of the dose administered, and unchanged BCV and metabolites of BCV found in feces accounted for 5.4% and 46.4%, respectively, of the dose administered [see Section 6.2.1.1.4].

4.4 Excretion

4.4.1 Excretion in urine, feces, and bile (CTD 4.2.2.4-2, 4.2.2.5-1 to -5)

Following a single oral dose of ^{14}C-BCV in male mice (n = 9 at 30 mg/kg), male rats (n = 3 at 20 mg/kg), and male dogs (n = 3 at 5 mg/kg), urinary and fecal excretion over 168 hours was evaluated. The mean urinary and fecal excretion of radioactivity was 0.20% and 94.6%, respectively, of the dose in mice, 0.05% and 92.1% of the dose in rats, and 0.20% and 91.9% of the dose in dogs.

Following a single oral dose of ^{14}C-BCV in bile duct-cannulated male rats (n = 3, at 20 mg/kg) and male monkeys (n = 3, at 125 mg/kg), mean urinary, biliary, and fecal excretion of radioactivity was evaluated. The mean urinary, biliary, and fecal excretion of radioactivity was 0.56%, 67.2%, and 23.2%, respectively, of the dose in rats and 10.2%, 41.9%, and 21.7%, respectively, of the dose in monkeys.

4.4.2 Excretion in milk (CTD 4.2.2.3-5)

Following a single oral dose of ^{14}C-BCV at 20 mg/kg in postpartum rats (day 9 to 11 postpartum, n = 3 /time point), the milk-to-plasma ratios of radioactivity were 0.277 and 0.258 based on C_{max} and AUC, respectively.

4.5 Pharmacokinetic drug interactions

4.5.1 Enzyme inhibition and induction (CTD 4.2.2.2-1, 4.2.2.4-6, 4.2.2.4-7, 4.2.2.4-3, 4.2.2.4-5, 4.2.2.6-8)

The inhibitory effects of BCV and BMS-794712 on CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) were evaluated using human liver microsomes. When midazolam and testosterone were used as CYP3A4 substrates, BCV inhibited CYP3A4 with IC_{50} values of 24.3 μmol/L and 37.1 μmol/L, respectively. BCV also inhibited CYP2C8 with an IC_{50} value of 23.7 μmol/L. BCV did not show any inhibitory effects on other CYP isoforms (IC_{50} >40 μmol/L). BMS-794712 inhibited the activity of CYP3A4 with an IC_{50} value of 33.4 μmol/L when midazolam was used as a substrate, and had no inhibitory effects on other CYP isoforms (IC_{50} >40 μmol/L). The time-dependency of the inhibitory effects of BCV and BMS-794712 was evaluated. The IC_{50} values against CYP3A4 (midazolam and testosterone as substrates) were 9.6 and 8.3 μmol/L, respectively, for BCV and 12.1 and 7.0 μmol/L, respectively, for BMS-794712, indicating that BCV and BMS-794712 are time-dependent inhibitors of CYP3A4.

The inhibitory effect of BCV on UGT1A1 was evaluated in human liver microsomes. The IC_{50} value of BCV was 12.6 μmol/L.

The CYP (CYP1A2, CYP2B6, CYP3A4) induction potential of BCV and BMS-794712 was evaluated in human hepatocytes. BCV and BMS-794712 did not induce CYP1A2 or CYP2B6 while increasing CYP3A4 mRNA expression and enzymatic activity.

Cells expressing the human pregnane X receptor were used to evaluate the potential of BCV (0.0025-50 μmol/L) to promote active human pregnane X receptor-mediated induction of CYP3A4 gene transcription. With an EC_{50} value of >50 μmol/L, BCV did not show the potential to activate the human pregnane X receptor.

4.5.2 Substrate for drug transporters and inhibitory effects (CTD 4.2.2.2-1, 4.2.2.2-3, 4.2.2.2-4, 4.2.2.3-6, 4.2.2.3-7, 4.2.2.4-8, 4.2.2.6-1 to -7)

In Caco-2 cell monolayers, the efflux ratio of BCV (3 μmol/L) was 8.3, which was reduced to 1.1 and 0.9 in the presence of ketoconazole and cyclosporine A (both P-glycoprotein [P-gp] inhibitors), respectively, suggesting that BCV is a substrate for P-gp. In wild-type Madin-Darby canine kidney (MDCK) cells and MDCK cells expressing human breast cancer resistance protein (BCRP), the efflux ratios of ^{3}H-BCV (1 μmol/L) were 1.8 and 3.8, respectively, suggesting that BCV is a substrate for BCRP. Furthermore, the ratio of the uptake of BCV into HEK293 cells expressing OATP1B1 or

OATP1B3 to the uptake of BCV into wild-type HEK293 cells was 0.94 to 0.96 and 0.79 to 0.83, respectively, and the uptake of BCV was not inhibited by rifampicin, a substrate for OATP1B1 and OATP1B3. These findings suggest that BCV is not a substrate for OATP1B1 or OATP1B3.

The inhibitory effects of BCV and BMS-794712 on P-gp, BCRP, OATP1B1, OATP1B3, NTCP, OAT1, OAT3, OCT2, MRP2, and BSEP were evaluated using Caco-2 cell monolayers, MDCK cells expressing BCRP, HEK293 cells expressing OATP1B1, OATP1B3, NTCP, OAT1, OAT3, or OCT2, and membrane vesicles expressing multidrug resistance protein (MRP2) and bile salt export pump (BSEP). The IC_{50} values of BCV against P-gp, BCRP, OATP1B1, OATP1B3, NTCP, BSEP, and OAT1 were 10.3, 2.3, 3.8, 1.6, 5.0, 3.8, and 42.9 μmol/L, respectively. The IC_{50} values of BCV were >50 μmol/L against MRP2 and >100 μmol/L against both OAT3 and OCT2. The IC_{50} values of BMS-794712 against BCRP, OATP1B1, OATP1B3, NTCP, BSEP, and OAT1 were 6.5, 1.4, 1.9, 11.0, 4.1, and 79.6 μmol/L, respectively. The IC_{50} values of BMS-794712 were >50 μmol/L against both P-gp and MRP2, and >100 μmol/L against both OAT3 and OCT2. The inhibitory effects of BMS-948158 on BCRP, OATP1B1, OATP1B3, NTCP, MRP2, and BSEP were evaluated using HEK293 cells expressing OATP1B1, OATP1B3, or NTCP and membrane vesicles expressing MRP2 and BSEP. The IC_{50} values of BMS-948158 against MRP2, OATP1B1, and OATP1B3 were 17.1, 10.2, and 30.0 μmol/L, respectively, while the IC_{50} value against BSEP was >50 μmol/L. Given that the inhibition constant (Ki) values[14] of BCV against P-gp and BCRP were estimated to be 3.75 and 1.15 μmol/L, respectively, and that the concentration of BCV in the gastrointestinal tract[15] after administration at the clinical dose (75 mg) was estimated to be 456 μmol/L, BCV is likely to inhibit P-gp and BCRP when administered at the clinical dose. The estimated Ki values of BCV against OATP1B1, OATP1B3, and NTCP were 1.9, 0.8, and 2.5 μmol/L, respectively. The estimated maximum concentration[16] of unbound BCV in the portal vein after administration of BCV at the clinical dose (75 mg) was 0.0985 μmol/L based on the unbound fraction of BCV (1%) [see Section 4.2.1] and C_{max} (2.25 μmol/L) [see Section 6.2.3.2]. These findings suggest that BCV may inhibit OATP1B1, OATP1B3, and NTCP when administered at the clinical dose. The estimated IC_{50} values of BCV against OAT1, OAT3, and OCT2 were 42.9, >100, and >100 μmol/L, respectively, and the estimated IC_{50} values of BMS-794712 against OAT1, OAT3, and OCT2 were 79.6, >100, and >100 μmol/L, respectively. The C_{max} of unbound BCV and BMS-794712 was 2.25 and 0.95 μmol/L, respectively [see Section 6.2.3.2]. These findings suggest that BCV does not inhibit OAT1, OAT3, or OCT2 when administered at the clinical dose.

4.R Outline of the review conducted by PMDA

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

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14) Ki value = $IC_{50}/2$

15) Concentration in the gastrointestinal tract (μmol/L) = dose (mg) × 1000/molecular weight (g/mol)/0.25 (L)

16) Maximum unbound drug concentration in the portal vein = C_{max} + [absorption rate constant (min^{-1}) × dose (μmol) × bioavailability in the gastrointestinal tract/hepatic blood flow rate (L/min)]

5. Toxicity and Outline of the Review Conducted by PMDA

Toxicity studies of BCV consisted of the following studies: single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, phototoxicity, and other toxicity studies (mechanistic studies). Doses and concentrations of BCV are expressed as free base. Unless otherwise specified, 0.1 mol/L Tris hydrochloride buffer (pH 8.5) was used as vehicle for *in vivo* studies.

5.1 Single-dose toxicity

5.1.1 Single oral dose toxicity study in mice (CTD 4.2.3.1-1)

CD1 mice (n = 5/sex/group) were given a single oral dose of BCV at 0 (vehicle), 125, 375, or 1250 mg/kg. Deaths or moribund sacrifice occurred in 4 of 10 mice in the 375 mg/kg group and in all 10 mice in the 1250 mg/kg group. Abnormalities observed in the animals that died or were sacrificed moribund included tremor, clonic convulsion, labored respiration, hunched posture, recumbency, and decreased activity. In surviving animals, unformed stools were observed at ≥125 mg/kg and decreased activity, perigenital soiling, and liquid or mucous stools were observed at ≥375 mg/kg.

Based on the above, the approximate lethal dose was determined to be 125 to 375 mg/kg.

5.2 Repeated-dose toxicity

Oral administration studies were conducted in rats (for 2 weeks, 1 month, or 6 months) and dogs (for 1 month or 9 months). The no observed adverse effect levels (NOAELs) determined in the 6-month repeated oral dose toxicity study in rats and the 9-month repeated oral dose toxicity study in dogs were 20 and 25 mg/kg, respectively. The $AUC_{0\text{-}24}$ (175 and 1135 μg·h/mL) at these NOAELs was 10.2- and 65.2-fold the $AUC_{0\text{-}24}$[17] (17.4 μg·h/mL) in chronic hepatitis C patients without cirrhosis or with compensated cirrhosis receiving BCV 75 mg.

The main toxic changes observed in rats after repeated doses of BCV were intestinal symptoms including mixed inflammatory cell infiltration and degeneration at the base of the gastric mucosa, shortening or adhesion of intestinal villus epithelial cells, lymphoplasmacytic infiltration of the lamina propria, and regenerative changes of the gastrointestinal epithelia. Although increased liver weight and hepatocellular hypertrophy were observed in repeated oral dose studies in rats, the applicant explained that these findings were adaptive changes related to CYP induction in the liver and were not toxicologically significant (*Food Chem Toxicol*. 1998;36:831-839).

5.2.1 Two-week oral toxicity study in rats (Reference data CTD 4.2.3.2-1)

SD rats (n = 6/sex/group) were given BCV orally at 0 (vehicle),[18] 30, 100, or 300 mg/kg for 2 weeks.

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17) Calculated based on the $AUC_{0\text{-}12}$ (8.72 μg·h/mL) of BCV after administration of DCV + ASV + BCV in a phase II study in treatment-naïve non-Japanese patients with genotype 1 or 4 chronic hepatitis C without cirrhosis or with compensated cirrhosis (AI443014, CTD 5.3.5.1-2)

18) A mixture of 0.1 mol/L sodium phosphate buffer, hydroxypropylcellulose-SL, and D-α-tocopherol polyethylene glycol succinate

All 12 animals in the 300 mg/kg group died or were sacrificed moribund. In these animals, the following abnormalities were observed: decreased body weight, distention of the stomach and small intestine, multifocal white plaques in the forestomach, gelatinous thickening of the small intestine, mixed inflammatory cell infiltration and degeneration at the base of the gastric mucosa, blunting or fusion of villi of the small intestines, lymphoplasmacytic infiltration of the lamina propria, regenerative changes of the gastrointestinal epithelia, degeneration of the seminiferous tubular epithelium, cytoplasmic alteration of bone marrow megakaryocytes, and single-cell necrosis of lymphocytes in the thymus and spleen. The applicant explained that these deaths were attributable to the gastrointestinal toxicity of BCV.

The following abnormalities were observed at ≥30 mg/kg: decreased body weight, decreased erythrocyte count, decreased number of goblet cells and epithelial regenerative changes in the large intestine, and single-cell necrosis of lymphocytes in the mantle of the Peyer's patches. The following abnormalities were observed at ≥100 mg/kg: decreased food consumption; increased neutrophil count and increased reticulocyte count suggestive of regenerative reaction; increases in platelet count, red cell distribution width, and mean corpuscular volume (MCV); decreases in hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) suggestive of increased erythrocyte metabolism; anisocytosis and diminished size of red blood cells as peripheral blood smear test findings; increases in alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin in serum; decreases in total protein and albumin in serum; and single-cell necrosis of lymphocytes in the mesenteric lymph node.

Based on the above, the NOAEL in this study could not be determined.

5.2.2 One-month oral toxicity study in rats (CTD 4.2.3.2-2)

SD rats (n = 15/sex/group) were given BCV orally at 0 (vehicle), 5, 15, or 50 mg/kg for 1 month (including a 2-week recovery period for reversibility assessment). Examinations performed in this study included a neurological test.

No BCV-related death or moribund sacrifice occurred. Increased liver weight was observed at 50 mg/kg. After a 2-week recovery period, the increased liver weight was reversible.

Based on the above, the NOAEL in this study was determined to be 50 mg/kg.

5.2.3 Six-month oral toxicity study in rats (CTD 4.2.3.2-3)

SD rats (n = 25/sex/group) were given BCV orally at 0 (vehicle), 5, 20, or 80 mg/kg for 6 months (including a 1-month recovery period for reversibility assessment).

Deaths that were possibly related to BCV occurred in 5 of 50 animals in the 80 mg/kg group. In 3 of the 5 fatal cases, the following abnormalities were detected: dilation of the gastrointestinal tract, fluid

accumulation, crypt epithelial apoptosis in the stomach and small intestine, mixed inflammatory cell infiltration at the base of the gastric mucosa, hyperplasia and necrosis of the crypt epithelium of the gastrointestinal tract, and degeneration of intestinal villus epithelial cells with lymphoplasmacytic infiltration of the lamina propria. These deaths were considered attributable to gastrointestinal toxicity. The causes of deaths in other 2 animals were unknown. Increased liver weight and hypertrophy of hepatocytes were observed at ≥5 mg/kg. The following abnormalities were observed at 80 mg/kg: an increase in platelet count; decreases in lymphocyte count, leukocyte count, reticulocyte count, MCV, and MCH; increases in total bilirubin and ALP in serum; decreases in total cholesterol and triglyceride in serum; crypt epithelial apoptosis and hyperplasia in the small intestine; and crypt epithelial apoptosis at the base of the gastric mucosa. After a 1-month recovery period, decreased lymphocyte and leukocyte counts were reversible in animals treated at ≤20 mg/kg, though not at 80 mg/kg. Other findings were reversible.

Based on the above, the NOAEL in this study was determined to be 20 mg/kg.

5.2.4 One-month oral toxicity study in dogs (CTD 4.2.3.2-4)

Beagle dogs (n = 5/sex/group) were given BCV orally at 0 (vehicle), 1, 5, or 25 mg/kg for 1 month (including a 2-week recovery period for reversibility assessment).

No death or moribund sacrifice occurred. Erosion of the prepuce and scrotum was observed at ≥5 mg/kg. Transient skin flushing in the neck, abdomen, muzzle, or auricle that was consistent with the T_{max} of BCV was observed at 25 mg/kg. The erosion of the prepuce and scrotum changed to scabs or red discoloration over time. The applicant explained that the above cutaneous findings were of little toxicological significance because (i) there were no abnormal changes in clinical signs and (ii) none of these findings were reported in a 9-month oral toxicity study in dogs [see Section 5.2.5]. During the treatment period or after a 2-week recovery period, all the findings were reversible.

Based on the above, the NOAEL in this study was determined to be 25 mg/kg.

5.2.5 Nine-month oral toxicity study in dogs (CTD 4.2.3.2-5)

Beagle dogs (n = 6/sex/group) were given BCV orally at 0 (vehicle), 1, 5, or 25 mg/kg for 9 months (including a 2-month recovery period for reversibility assessment).

No death or moribund sacrifice occurred. Coldness of the auricle, soft stools, mucous stools, and vomiting were observed at 25 mg/kg. The applicant explained that the soft stools, mucous stools, and vomiting were of little toxicological significance because they did not affect the clinical signs. All the findings were reversible after a 2-month recovery period.

Based on the above, the NOAEL in this study was determined to be 25 mg/kg.

5.2.6 One-week oral combination toxicity study in rats (CTD 4.2.3.2-7)

SD rats (n = 10/sex/group) were given a combination of BCV, DCV, and ASV orally at 0/0/0 (vehicle[19)]), 1/10/15, 11/30/60, or 0/30/60 mg/kg for 1 week.

No death or moribund sacrifice occurred. Adrenal cortex hyperplasia and multifocal cytoplasmic vacuolation were observed at 11/30/60 and 0/30/60 mg/kg. Both findings were mild and the same as the abnormal changes reported in toxicity studies of DCV alone.

As shown above, the combination of BCV, DCV, and ASV did not cause new toxicity or aggravation of toxicological findings reported after administration of the individual drugs as a single agent.

5.2.7 One-month oral combination toxicity study in rats (CTD 4.2.3.2-8)

SD rats (n = 10/sex/group) were given a combination of BCV and ASV orally at 0/0 (vehicle),[19)] 15/30, or 30/60 mg/kg for 1 month.

No death or moribund sacrifice occurred. Increases in total protein and globulin in serum, a decrease in AST in serum, and liver weight increase were observed in all the groups excluding the control group, and increases in ALP, total cholesterol, and total bilirubin in serum were observed in the 30/60 mg/kg group. The increases in ALP and total bilirubin in serum were the same as the changes reported in a toxicity study of BCV alone [see Section 5.2.3] or ASV alone. The applicant explained that the increases in total protein, globulin, and total cholesterol in serum and a decrease in AST were all mild in severity and thus of little toxicological significance.

As shown above, the combination of BCV and ASV did not cause new toxicity or aggravation of toxicological findings reported after administration of the individual drugs as a single agent.

5.2.8 One-month oral combination dose range-finding study in dogs (CTD 4.2.3.2-9)

Beagle dogs (n = 4/sex/group) were given a combination of BCV and DCV orally at 0/0 (vehicle),[20)] 1.5/3, or 3/15 mg/kg for 1 month.

There were no deaths, moribund sacrifices, or changes in clinical signs.

As shown above, the combination of BCV and DCV did not cause any toxicity.

5.2.9 One-month oral combination dose toxicity study in dogs (CTD 4.2.3.2-10)

Beagle dogs (n = 4/sex/group) were given a combination of BCV, DCV, and ASV orally at 0/0/0 (vehicle[19)]), 1.5/3/7.5, or 3/15/15 mg/kg for 1 month.

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19) 50% 0.1 mol/L phosphate buffer (pH 3), 30% polyethylene glycol 400, 20% vitamin E d-α-tocopheryl polyethylene glycol 1000 succinate

20) 75% 0.1 mol/L phosphate buffer (pH 3), 15% polyethylene glycol 400, 5% polyvinylpyrrolidone, 25% vitamin E d-α-tocopheryl polyethylene glycol 1000 succinate

No death or moribund sacrifice occurred. Hypertrophy and hyperplasia of hepatic Kupffer cells were observed in all the groups excluding the control group, and subacute inflammation of the liver was observed in the 3/15/15 mg/kg group. The hepatic findings, which were also reported in toxicity studies of DCV alone, occurred at an exposure level that was lower than both the concentration of DCV in the liver and the NOAEL (15 mg/kg) in the repeated dose toxicity studies of DCV alone. According to the applicant's explanation, the hepatic findings at a lower dose of DCV may be associated with the co-administration of BCV, DCV, and ASV.

The exposure to BCV after co-administration of BCV + DCV + ASV, BCV + ASV, or BCV + DCV was similar to that after administration of BCV alone.

5.3 Genotoxicity (CTD 4.2.3.3.1-1, 4.2.3.3.1-2, 4.2.3.3.2-1)

Genotoxicity studies consisted of a bacterial reverse mutation assay using bacterial cells exposed to BCV (CTD 4.2.3.3.1-1), a chromosomal aberration assay in Chinese hamster ovary cells (CTD 4.2.3.3.1-2), and a rat bone marrow micronucleus assay (CTD 4.2.3.3.2-1). None of these studies revealed evidence of genotoxicity.

5.4 Carcinogenicity

Oral carcinogenicity studies were conducted in mice and rats. In the carcinogenicity studies in mice and rats, the non-carcinogenic dose was estimated to be 25 mg/kg for both species. The $AUC_{0\text{-}24}$ (125 and 236 μg·h/mL, respectively) at this dose was 7.2- and 13.5-fold the $AUC_{0\text{-}24}$ (17.4 μg·h/mL)[17] in chronic hepatitis C patients without cirrhosis or with compensated cirrhosis receiving 75 mg of BCV.

5.4.1 Five-day range-finding study and 28-day oral toxicity study in mice (CTD 4.2.3.4.2-1)

A 5-day and 28-day range-finding studies were conducted to select doses for a 26-week carcinogenicity study in Tg rasH2 mice. CByB6F1/non-Tg rasH2 mice (n = 5/sex/group) were given BCV orally at 0 (vehicle), 50, 100, 150, 200, or 300 mg/kg for 5 days. Death occurred in 1 of 10 mice in the 200 mg/kg group and in 3 of 10 mice in the 300 mg/kg group. Decreased activity, hunched posture, labored respiration, and panting were observed at ≥200 mg/kg. Taking into account deaths occurring at ≥200 mg/kg, the maximum tolerance dose (MTD) in the 28-day oral study was determined to be 150 mg/kg.

CByB6F1/non-Tg rasH2 mice (n = 10/sex/group) were given BCV orally at 0 (vehicle), 25, 50, 100, or 150 mg/kg for 28 days. No death or moribund sacrifice occurred. Labored respiration or panting, decreased activity, and nasal inflammation were observed at ≥50 mg/kg. Hunched posture, decreased body weight, decreased food consumption, decreases in MCH, leukocyte count, and lymphocyte count, decreased glycogen in the liver, and inflammation and necrosis in the airway were observed at ≥100 mg/kg. Although the nasal inflammation observed at ≥50 mg/kg was related to BCV, similar lesions were not observed in long-term treatment studies. The applicant therefore considered that it was of little toxicological significance. The labored respiration or panting and decreased activity observed at 50

mg/kg were also considered to be of little toxicological significance because the former occurred less frequently and the latter was a transient event.

Based on the above, the NOAEL in the study was determined to be 50 mg/kg.

5.4.2 Twenty-six-week oral carcinogenicity study in Tg rasH2 mice (CTD 4.2.3.4.2-2)

Tg rasH2 mice (n = 25/sex/group) were given BCV orally at 0 (water), 0 (vehicle), 1, 5, or 25 mg/kg for 26 weeks. No BCV-related reduced body weight gain, non-neoplastic lesions, or neoplastic lesions were observed.

5.4.3 Two-year oral carcinogenicity study in rats (CTD 4.2.3.4.1-1)

SD rats (n = 65/sex/group) were given BCV orally for 2 years. BCV was administered to males at 0 (water), 0 (vehicle), 5, 10, or 25 mg/kg and to females at 0 (water), 0 (vehicle), 10, 25, or 80/50 mg/kg. Females in the 80/50 mg/kg group received BCV at 80 mg/kg from Day 1 through Day 365. However, because reduced body weight gain, decreased food consumption, and BCV-related gastrointestinal tract toxicity were observed during this period, the dose was decreased to 50 mg/kg from Day 366 onward. Non-neoplastic changes observed were lipofuscin pigmentation in hepatocytes at ≥25 mg/kg and the darkening of the liver and increased incidence and severity of focal basophilic hepatocytes at 80/50 mg/kg. Increased incidence of benign hepatocellular adenoma at 80/50 mg/kg was reported as a neoplastic change.

5.5 Reproductive and developmental toxicity

Studies of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits, and study for effects on pre- and postnatal development, including maternal function in rats, were conducted. The NOAEL for embryo-fetal development was determined to be 30 and 60 mg/kg in rats and rabbits, respectively. The $AUC_{0\text{-}24}$ and C_{max} at the NOAEL in rats were 223 and 15.4 μg·h/mL, respectively. The $AUC_{0\text{-}24}$ and C_{max} at the NOAEL in rabbits were 203 and 18.7μg·h/mL, respectively. These values were compared with exposure data from chronic hepatitis C patients without cirrhosis or with compensated cirrhosis receiving 75 mg of BCV. The $AUC_{0\text{-}24}$ values in rats and rabbits were 13.0- and 10.3-fold, respectively, the human exposure ($AUC_{0\text{-}t}$ [17.4 μg·h/mL][17]) and the C_{max} values in rats and rabbits were 12.0- and 12.6-fold, respectively, the human exposure (C_{max} [1.49 μg·h/mL]). Placental transfer of BCV and excretion of BCV in milk were confirmed in rats [see Sections 4.2.4 and 4.4.2].

5.5.1 Oral study of fertility and early embryonic development to implantation in male rats (CTD 4.2.3.5.1-1)

Male SD rats (n = 25/group) were given BCV orally at 0 (vehicle), 20, 60, 100, or 150/100 mg/kg from 28 days prior to mating until 1 week after the end of the mating period while being housed in cages with untreated female rats.

In the 100 mg/kg group, 1 of 25 males was sacrificed moribund. Abnormalities including decreased activity, hunched posture, labored respiration, and respiratory sound were observed in the 150 mg/kg group on Day 4. Therefore, the dose in this group was decreased to 100 mg/kg on Days 5 to 7. Despite the suspension of dosing from Days 8 to 14, these abnormalities were not reversible. Consequently, all 25 males in the group were sacrificed moribund on Day 15. Necrosis of the gastric crypt epithelium and other abnormalities were observed in these animals. In paternal animals, decreased body weight and dark stools were observed at ≥60 mg/kg and abnormalities including decreased food consumption at ≥100 mg/kg. There were no effects on fertility or early embryonic development.

Based on the above, the NOAEL in this study was determined to be 20 mg/kg for paternal toxicity and 100 mg/kg for fertility and early embryonic development.

5.5.2 Oral study of fertility and early embryonic development to implantation in female rats (CTD 4.2.3.5.1-2)

Female SD rats (n = 25/group) were given BCV orally at 0 (vehicle), 15, 40, or 100 mg/kg from 2 weeks prior to mating until gestation day 7 while being housed in cages with untreated male rats.

No BCV-related death or moribund sacrifice occurred. In maternal animals, decreased body weight and decreased food consumption were observed at 100 mg/kg. There were no effects on fertility or early embryonic development.

Based on the above, the NOAEL in this study was determined to be 40 mg/kg for maternal toxicity and 100 mg/kg for fertility and early embryonic development.

5.5.3 Embryo-fetal development study in rats(CTD 4.2.3.5.2-3)

Pregnant SD rats (n = 22/group) were given BCV orally at 0 (vehicle), 10, 30, or 100 mg/kg from gestation day 6 to gestation day 15.

No death or moribund sacrifice occurred. Decreased food consumption, decreased body weight, and low pregnant uterus weight were observed in dams at 100 mg/kg. Embryo/fetal abnormalities observed at 100 mg/kg included no live fetuses in 2 of 22 dams, an increase in percent post-implantation loss, decreased fetal weight, malformations (e.g., agnathia, cleft palate, aglossia), and variations (e.g., aplasia of maxilla, squamosal bone, and supraoccipital bone). According to the applicant's explanation, the increased percent post-implantation loss and decreased fetal weight were attributed to the deterioration of clinical signs in dams. The applicant also explained that the fetal malformations and variations were not BCV-related changes because their incidences were within the range of historical control data from the laboratory.[21)]

[21)] The historical data collected from 21 to 27 studies conducted at the testing laboratory between 20[redacted] and 20[redacted]

Based on the above, the NOAEL in this study was determined to be 30 mg/kg for both maternal general toxicity and embryo-fetal developmental toxicity.

5.5.4 Embryo-fetal development study in rabbits (CTD 4.2.3.5.2-4)

Pregnant New Zealand White rabbits (n = 22/group) were given BCV orally at 0 (vehicle), 30, 60, or 100 mg/kg from gestation day 7 to gestation day 19.

No BCV-related death or moribund sacrifice occurred. Abnormalities including abortion, decreased food consumption, and reduced body weight gain were observed in dams at 100 mg/kg. Embryo/fetal abnormalities observed at 100 mg/kg were decreased fetal weight and delayed ossification of hyoid bone and metacarpal.

Based on the above, the NOAEL in this study was determined to be 60 mg/kg for both maternal general toxicity and embryo-fetal developmental toxicity.

5.5.5 Study for effects on pre- and postnatal development, including maternal function in rats (CTD 4.2.3.5.3-1)

Pregnant SD rats (n = 25/group) were given BCV orally at 0 (vehicle), 10, 30, or 75 mg/kg from gestation day 6 to lactation day 20. In the F_1 offspring, memory and learning performance were evaluated based on water maze test results.

No toxicological abnormalities were found in dams. In the F_1 offspring, low body weight was observed from birth to weaning at 75 mg/kg.

Based on the above, the NOAEL in this study was determined to be 75 mg/kg for maternal general toxicity and 30 mg/kg for F_1 offspring developmental toxicity.

Since DCV, an active ingredient of DCV/ASV/BCV FDC, is known to have embryocidal and teratogenic effects, the applicant plans to take the following measures: (i) DCV/ASV/BCV FDC is to be contraindicated in pregnant women or women who may possibly be pregnant and (ii) the package insert and other relevant documents will contain information on the necessity of the use of contraception in women of childbearing potential to ensure that such information is appropriately communicated to healthcare professionals.

5.6 Other toxicity studies

5.6.1 Phototoxicity studies (CTD 4.2.3.7.7-1, 4.2.3.7.7-2)

Given that the absorption bands of BCV are located at [redacted] and [redacted] nm within the solar wavelength range (290-700 nm) and that the molar extinction coefficients at these absorption bands are [redacted] and [redacted] $Lmol^{-1}$ cm^{-1}, respectively, phototoxicity studies (a neutral red uptake study in Balb/c 3T3 mouse fibroblasts and a phototoxicity study in Long Evans pigmented rats) were performed.

Phototoxicity was investigated in an *in vitro* study in mouse 3T3 fibroblasts, and the results showed that BCV has phototoxic potential. In another study, Long Evans rats were given a single oral dose of BCV at 0 (vehicle), 50, 100, or 200 mg/kg and were irradiated with ultraviolet A (UVA) (6.5 kw, 30 minutes) at 4 hours post-dose. The results showed no phototoxicity.

Based on the above results and the fact that no BCV-related phototoxicity was reported in any clinical studies, the applicant explained that phototoxicity is unlikely to pose a safety concern for the clinical use of BCV.

5.6.2 Three-month oral study to investigate effects on monkey gallbladder (Reference data, CTD 4.2.3.7.3-1)

In an exploratory toxicity study (CTD 4.2.3.2-6) of BCV administered orally to cynomolgus monkeys for a week, an increase in mitosis of the epithelium of the gallbladder was observed at 125 mg/kg (the highest dose). The mechanism of the increase in mitosis and its time course and reversibility were investigated in a new study. Male cynomolgus monkeys (n = 16/group) were given BCV orally at 0 (vehicle) or 125 mg/kg for 3 months (including a 4-week recovery period for reversibility assessment). In this study, the following examinations were performed to evaluate time courses: bile test; measurements of the weights of the gallbladder and liver; macroscopic and histopathological examinations of gallbladder, liver, and duodenum; and immunohistochemistry test of the gallbladder based on Ki67 (nucleosis marker).

Reduced feeding behavior and increased total bile acid were observed at 125 mg/kg. There were no abnormalities in the weight of the liver or gallbladder, nor were there any particular macroscopic and histopathological findings. The increased total bile acid was considered to be of little toxicological significance because it was only a slight increase. After a 4-week recovery period, all the findings were reversible. The applicant explained that the mitosis of the epithelium of the gallbladder observed in the 1-week exploratory toxicity study in monkeys was not reproducible and therefore unrelated to BCV.

5.6.3 Toxicity study of metabolite

BMS-794712 was identified as the major metabolite found in humans receiving BCV [see Section 4.3.3]. According to the applicant's explanation, the metabolite was evaluated in the following investigations, which demonstrated its safety.

5.6.3.1 General toxicity study of metabolite

The $AUC_{0\text{-}24}$ of BMS-794712 (263.5 μg·h/mL) at the NOAEL in the 9-month oral toxicity study in dogs (CTD 4.2.3.2-5) was approximately 63-fold the human exposure[22)] to BMS-794712.

22) In Study AI443014, the daily exposure ($AUC_{0\text{-}t}$) to BMS-794712 after multiple oral administration of DCV 60 mg QD, ASV 200 mg BID, and BCV 75 mg BID for 14 days in treatment naïve or IFN-experienced, non-Japanese patients with genotype 1 or 4 chronic hepatitis C without cirrhosis or with compensated cirrhosis was 4.16 μg·h/mL [see 6.2.3.2].

5.6.3.2 Genotoxicity of metabolite

The $AUC_{0\text{-}24}$ (45.2 μg·h/mL) and C_{max} (3.53 μg/mL) of BMS-794712 at the highest dose in the rat micronucleus assay (CTD 4.2.3.3.2-1) were 11-fold and approximately 11-fold, respectively, the human exposure to BMS-794712 ($AUC^{22)}$ and C_{max} [0.314 μg/mL]).

5.6.3.3 Reproductive and developmental toxicity of metabolite

The $AUC_{0\text{-}24}$ (6.67 μg·h/mL) and C_{max} (0.499 μg/mL) of BMS-794712 at the NOAEL in the rabbit embryo-fetal development study (CTD 4.2.3.5.2-4) were 1.6-fold and 1.6-fold, respectively, the human exposure ($AUC^{22)}$ and C_{max} [0.314 μg/mL]).

5.6.3.4 Carcinogenicity of metabolite

The exposure to BMS-794712 in the 2-year oral carcinogenicity study in rats (CTD 4.2.3.4.1-1) was equivalent to or higher than the human AUC. The $AUC_{0\text{-}24}$ (1.78 μg·h/mL) of BMS-794712 at the non-carcinogenic dose was 0.43-fold the human AUC.[22)]

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following reviews, PMDA concluded that there are no particular toxicological concerns with the clinical use of DCV/ASV/BCV FDC.

5.R.1 Relevance of hepatocellular adenoma observed in rats to humans

Considering the increased incidence of hepatocellular adenoma observed in the carcinogenicity study in rats, PMDA asked the applicant to explain the onset of hepatocellular adenoma and its relevance to humans.

The applicant's explanation:

Hepatocellular adenoma is unlikely to pose a safety concern for the clinical use of BCV, for the following reasons:

- Hepatocellular adenoma is known to be caused by induction of CYPs in rodents. Given that abnormalities suggestive of CYP induction caused by BCV were observed in the repeated dose toxicity study in rats [see Section 5.2], BCV was considered to be involved in the onset of hepatocellular adenoma observed in the carcinogenicity study in rats. However, since there have been no reports of hepatocellular adenoma caused by this mechanism in humans, the abnormalities in rats are unlikely to be relevant to humans (*Toxicol Pathol*. 2010;38:487-501; *Toxicol Sci*. 2006;89:51-6).
- The plasma exposure to BCV in rats treated at a dose at which hepatocellular adenoma did not occur was 13.5-fold the human exposure to BCV at the clinical dose [see Section 5.4].
- No precancerous lesions or neoplastic changes were observed in the 6-month repeated dose study in rats, in which BCV was administered for a period of time exceeding the duration of clinical use [see Section 5.2.3].

PMDA accepted the applicant's explanation.

5.R.2 Appropriateness of doses used in the 26-week oral carcinogenicity study in Tg rasH2 mice

No BCV-related reduced body weight gain, non-neoplastic lesions, or neoplastic lesions occurred in the 26-week oral carcinogenicity study in Tg rasH2 mice [see Section 5.4.2]. PMDA asked the applicant to explain the rationale for the doses selected for the 26-week oral carcinogenicity study in Tg rasH2 mice.

The applicant's explanation:

Because labored respiration or panting, decreased activity, and histological changes in the nasal cavity were observed at 50 mg/kg in the 28-day oral toxicity study in CByB6F1/non-Tg rasH2 mice [see Section 5.4.1], the dose level of 50 mg/kg was considered too high for a 26-week administration. For this reason, the applicant decided to select a dose level of 25 mg/kg as the highest dose in the 26-week oral carcinogenicity study in Tg rasH2 mice. Given that the exposure to BCV at 25 mg/kg in this study was 7.2-fold the human plasma exposure to BCV at the clinical dose [see Section 5.4], the carcinogenicity of BCV can be evaluated based on the results of the study.

PMDA accepted the applicant's explanation.

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

6.1 Biopharmaceutic studies and associated analytical methods

Three different oral formulations of BCV (Formulations 1 to 3)[23] and an injection formulation of BCV (Formulation 4)[24] were used for studies. In clinical studies using DCV/ASV/BCV fixed-dose combination (FDC) tablets, 3 types of oral FDC tablets (Formulations 5 to 7)[25] were used. The to-be-marketed formulation is a DCV/ASV/BCV FDC tablet (Formulation 8), which is a smaller tablet containing half the quantity of each of 3 active ingredients contained in Formulation 7 (BCV 37.5 mg, DCV 15 mg, and ASV 100 mg). Studies were conducted to evaluate the bioequivalence between [redacted] tablet of Formulation 7 and [redacted] tablets of Formulation 8, and the results demonstrated the bioequivalence of the 2 formulations. This section summarizes the results of the main biopharmaceutic studies (an absolute bioavailability study and a food effect study). Liquid chromatography/tandem mass spectrometry was utilized for determining concentrations of BCV and BMS-794712 in human plasma and urine (LLOQs for BCV and BMS-794712, 0.1-2.0 ng/mL in plasma and 1.0-5.0 ng/mL in urine).

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23) Formulation 1: an immediate-release capsule used at the early stage of development
Formulation 2: a single-component tablet of BCV 75 mg (an unbound form of BCV) used in phase I and II studies
Formulation 3: a single-component tablet of BCV 400 mg (an unbound form of BCV) used in phase I studies

24) Formulation 4: an intravenous injection of ^{13}C-BCV

25) Formulation 5: a non-film-coated FDC tablet containing 30 mg of DCV, 200 mg of ASV Drug Substance B, and 75 mg of BCV, used in phase I studies
Formulation 6: a non-film-coated FDC tablet containing 30 mg of DCV, 200 mg of ASV Drug Substance A, and 75 mg of BCV, used in phase I studies
Formulation 7: a film-coated FDC tablet that was equivalent to Formulation 5 in terms of formula, used in phase III studies (AI443102, AI443113, and AI443117)

A description of the results of the biopharmaceutic studies of DCV and ASV is omitted in this section because the data were submitted and evaluated at the time of the initial applications for Daklinza Tablets 60 mg and Sunvepra Capsules 100 mg.

6.1.1 Absolute bioavailability study (BCV) (reference data, CTD 5.3.1.1-2, Study AI443109 [April 2014 to May 2014])

The geometric mean [90% confidence interval (CI)] of the absolute bioavailability of BCV was 66.1% [63.0%, 69.3%] in non-Japanese healthy subjects (PK evaluation population, n = 8) who received a single dose of BCV 150 mg (2 tablets of Formulation 2) orally in the fasted state, followed 1.75 hours later by ^{13}C-BCV 100 μg intravenously.

6.1.2 Food effect study (DCV/ASV/BCV FDC tablet) (reference data, CTD 5.3.1.1-3, Study AI443111 [April 2014 to May 2014])

A single oral dose of a DCV/ASV/BCV FDC tablet (Formulation 7) was administered to non-Japanese healthy subjects (PK evaluation population, n = 24) to evaluate the effect of food. The PK parameters for each component are shown in Table 16. The C_{max} and AUC_{inf} of DCV, BCV, and BMS-794712 were similar irrespective of prandial status or the content of a meal. The C_{max} and AUC_{inf} of ASV were high after a high-fat or low-fat meal compared to those in the fasted state.

Table 16. PK parameters for DCV, ASV, and BCV administered in the fasted state or after a high- or low-fat meal

	Fasted state (n = 23)	After a high-fat meal (n = 24)	After a low-fat meal (n = 23)
DCV			
C_{max} (ng/mL)	839 (30)	702 (45)	834 (27)
AUC_{inf} (ng·h/mL)	8666 (36)	7309 (38)	8970 (35)
ASV			
C_{max} (ng/mL)	102 (108)	445 (97)	272 (66)
AUC_{inf} (ng·h/mL)	559 (67)	1703 (57)	1075 (42)
BCV			
C_{max} (ng/mL)	1383 (28)	1750 (36)	1579 (24)
AUC_{inf} (ng·h/mL)	9914 (42)	11,071 (37)	10,464 (38)
BMS-794712			
C_{max} (ng/mL)	249 (39)	245 (33)	267 (29)
AUC_{inf} (ng·h/mL)	2228 (34)	2227 (34)	2301 (31)

Geometric mean (CV%)

6.2 Clinical pharmacology studies

The results from 2 studies on the drug interactions with DCV and the results from 1 study on the drug interactions with ASV were newly submitted for the current application. In addition, the results from 6 foreign phase I studies (including 2 drug interaction studies) on the PK of BCV alone were submitted. The submitted data on the PKs of DCV in combination with ASV and BCV or of a DCV/ASV/BCV FDC tablet were the results from 8 foreign phase I studies (including 5 drug interaction studies) and 1 foreign phase II study, as well as the results from PPK analysis and an exposure-response analysis conducted in the Japanese phase III study, foreign phase II studies, and foreign phase III studies. A description of the results of PK studies of DCV and ASV is omitted in this section because the data were

submitted and evaluated at the time of the initial applications for Daklinza Tablets 60 mg and Sunvepra Capsules 100 mg.

6.2.1 Studies in healthy subjects

6.2.1.1 Administration of BCV alone

6.2.1.1.1 Phase I study (CTD 5.3.3.4-4, Study AI443006 [May 2013 to September 2013])

The PK was investigated after administration of multiple oral doses of BCV at 75 mg twice daily (BID) for 15 days to Japanese and non-Japanese healthy subjects (PK evaluation population, n = 16). In Japanese and non-Japanese healthy subjects, the C_{max} [geometric mean (CV%)] of BCV on Day 15 was 1073 ng/mL (26) and 796 ng/mL (33), respectively, and the AUC [geometric mean (CV%)] of BCV was 5753 ng·h/mL (20) and 4458 ng·h/mL (26), respectively. The C_{max} [geometric mean (CV%)] of BMS-794712 on Day 15 was 248 ng/mL (24) and 184 ng/mL (24), respectively, and the AUC [geometric mean (CV%)] of BMS-794712 was 1609 ng·h/mL (19) and 1225 ng·h/mL (24), respectively.

6.2.1.1.2 Phase I study (reference data, CTD 5.3.3.1-1, Study AI443001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK was investigated after administration of a single oral dose of BCV at 10 to 900 mg to non-Japanese healthy subjects (PK evaluation population, n = 36) in the fasted state. The PK parameters are shown in Table 17.

Table 17. PK parameters of BCV and BMS-794712 following a single dose of BCV

	Dose	n	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	T_{max} (h)	$t_{1/2}$ (h)
BCV	10 mg	6	86.8 (22)	904 (29)	3.68 (34)	5.94 (18)
	30 mg	6	278 (14)	2600 (26)	3.33 (20)	5.64 (17)
	100 mg	6	994 (25)	8172 (22)	2.09 (28)	6.22 (10)
	300 mg	6	3917 (33)	34,447 (42)	2.98 (50)	5.47 (19)
	600 mg	6	6891 (38)	58,475 (46)	3.41 (22)	4.46 (7)
	900 mg	6	8749 (30)	103,591 (17)	4.22 (31)	4.58 (14)
BMS-794712	10 mg	6	14.0 (28)	208 (33)	5.26 (43)	7.04 (29)
	30 mg	6	47.4 (23)	597 (31)	4.56 (23)	6.85 (17)
	100 mg	6	187 (36)	1979 (41)	3.77 (31)	6.81 (7)
	300 mg	6	751 (29)	8533 (37)	4.10 (40)	6.46 (17)
	600 mg	6	1386 (39)	14,490 (46)	3.94 (28)	5.22 (4)
	900 mg	6	2142 (42)	27,949 (28)	4.97 (45)	4.97 (15)

Geometric mean (CV%)

6.2.1.1.3 Phase I study (reference data, CTD 5.3.3.1-2, Study AI443003 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK was investigated after administration of multiple oral doses of BCV at 10 to 300 mg BID or at 900 mg once daily (QD) to non-Japanese healthy subjects (PK evaluation population, n = 30). The PK parameters are shown in Table 18. The accumulation ratio of AUC was 1.5 after administration of BCV at 10 mg BID and 0.8 after administration of BCV at 300 mg BID.

Table 18. PK parameters of BCV and BMS-794712 following multiple doses of BCV

	Dose	Time point (day)	n	C_{max} (μg/mL)	AUC_{tau} (μg·h/mL)	T_{max} (h)	$t_{1/2}$ (h)
BCV	10 mg BID	1	6	0.09 (28)	0.71 (22)	3.46 (56)	–
		14	6	0.14 (43)	1.07 (45)	3.85 (41)	9.47 (34)
	30 mg BID	1	6	0.23 (25)	1.71 (16)	4.70 (63)	–
		14	4	0.29 (32)	1.97 (30)	2.63 (35)	7.47 (30)
	100 mg BID	1	6	1.27 (22)	7.59 (18)	2.75 (52)	–
		14	6	0.95 (40)	5.90 (22)	3.09 (65)	10.11 (36)
	300 mg BID	1	6	3.75 (44)	25.15 (33)	3.20 (31)	–
		14	6	3.38 (15)	18.89 (23)	2.57 (31)	10.70 (21)
	900 mg QD	1	–	–	–	–	–
		14	5	5.58 (44)	38.29 (45)	3.07 (35)	11.01 (68)
BMS-794712	10 mg BID	1	6	0.01 (25)	0.11 (25)	6.40 (42)	–
		14	6	0.03 (42)	0.23 (52)	5.43 (15)	10.29 (25)
	30 mg BID	1	6	0.03 (25)	0.25 (23)	6.51 (42)	–
		14	4	0.05 (42)	0.41 (37)	3.66 (26)	7.79 (17)
	100 mg BID	1	6	0.20 (24)	1.41 (23)	4.44 (19)	–
		14	6	0.20 (41)	1.54 (28)	2.49 (53)	10.38 (23)
	300 mg BID	1	6	0.68 (38)	5.05 (32)	4.16 (77)	–
		14	6	0.87 (20)	5.51 (26)	3.27 (24)	10.33 (20)
	900 mg QD	1	–	–	–	–	–
		14	5	1.21 (49)	9.48 (46)	3.91 (25)	9.26 (68)

Geometric mean (CV%)
–: Not evaluated

6.2.1.1.4 Mass balance study (reference data, CTD 5.3.3.1-3, Study AI443005 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Mass balance was investigated after administration of a single oral dose of ^{14}C-BCV at 800 mg to non-Japanese healthy subjects (PK evaluation population, n = 9). In 6 subjects without bile collection, a mean of 89.4% of radioactivity was recovered over 168 hours post-dose, and 0.25% and 89.2% of radioactivity were recovered in urine and feces, respectively. Unchanged BCV and metabolites accounted for 7.8% and 84.1%, respectively, of the total radioactivity in feces. In 3 subjects with bile collection, a mean of 89.2% of radioactivity was recovered over 168 hours post-dose, and 0.24%, 18.5%, and 70.5% of radioactivity were recovered in urine, bile, and feces, respectively. Unchanged BCV and metabolites accounted for 7.6% and 65.7%, respectively, of the total radioactivity in feces. Unchanged BCV and metabolites accounted for 36.7% and 52.5%, respectively, of the total radioactivity in bile.

6.2.2 Studies in patients

6.2.2.1 Administration of BCV alone

6.2.2.1.1 Phase I study (reference data, CTD 5.3.3.2-1, Study AI443002 [May 2008 to June 2009])

The PK was investigated after administration of a single oral dose of BCV at 100 to 900 mg to non-Japanese patients with genotype 1 chronic hepatitis C (PK evaluation population, n = 24). The results are shown in Table 19. The mean maximum decrease from baseline in HCV RNA after administration of BCV at 100, 300, 600, or 900 mg was 1.3, 2.5, 2.8, and 2.6 $\log_{10}$ IU/mL, respectively.

Table 19. PK parameters of BCV and BMS-794712 following a single dose of BCV

	Dose	n	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	T_{max} (h)	$t_{1/2}$ (h)
BCV	100 mg	5	1.43 (23)	17.17 (42)	2.61 (60)	8.36 (26)
	300 mg	5	4.78 (22)	69.36 (23)	3.03 (34)	9.19 (21)
	600 mg	5	10.20 (20)	112.03 (27)	2.99 (36)	6.76 (13)
	900 mg	3	16.55 (31)	290.25 (27)	3.30 (17)	7.78 (4)
BMS-794712	100 mg	5	0.24 (17)	3.65 (40)	5.03 (55)	9.93 (27)
	300 mg	5	0.69 (47)	13.20 (38)	5.28 (39)	10.04 (21)
	600 mg	5	1.83 (40)	25.55 (45)	3.31 (24)	7.21 (14)
	900 mg	3	2.55 (41)	65.64 (31)	7.83 (25)	8.95 (3)

Geometric mean (CV%)

6.2.2.2 PPK analysis (CTD 5.3.3.5-2, 5.3.3.5-3, 5.3.3.5-4, 5.3.3.5-5)

Population pharmacokinetic (PPK) analysis was performed (NONMEM ver.7.2) using plasma concentration data (1228 subjects; 11,382 sampling points for DCV, 11,300 sampling points for ASV, 10,728 sampling points for BCV) obtained from a foreign phase II study (AI443014), foreign phase III studies (AI443102 and AI443113), and a Japanese phase III study (AI443117) in chronic hepatitis C patients without cirrhosis or with compensated cirrhosis. As the final structural model, PK was described by a one-compartment model with zero-order release, first-order absorption, and first-order elimination for DCV; a two-compartment model with zero-order release, first-order absorption, and first-order elimination for ASV; and a one-compartment model with first-order absorption, first-order elimination, and absorption lag time for BCV.

Sex, race, and ALT change ratio[26)] were identified as covariates affecting apparent oral clearance (CL/F) of DCV; and sex, race, baseline body weight, and ALT change ratio were identified as covariates affecting V/F.[27)] Sex, age, cirrhosis status, race, baseline ALT, and ALT change ratio were identified as covariates affecting CL/F of ASV; age, sex, race, and ALT change ratio were identified as covariates affecting Vc/F; and formulation administered was identified as covariates affecting ka and F.[28)] Age, baseline body weight, race, baseline ALT, ALT change ratio, and concomitant proton pump inhibitor were identified as covariates affecting CL/F of BCV; and sex, baseline body weight, cirrhosis status, and ALT change ratio were identified as covariates affecting V/F.[29)] The estimated steady-state PK parameters of DCV, ASV, and BCV are shown in Table 20.

26) The on-treatment ALT level divided by the baseline ALT level

27) Candidate covariates included age, body weight, sex, race, baseline CL_{cr}, baseline ALT, baseline AST, baseline viral load, previous treatment, viral genotype, host genotype, cirrhosis status, use of RBV, dose of DCV, dose of ASV, dose of BCV, concomitant proton pump inhibitor, concomitant histamine H2 receptor antagonist, concomitant CYP3A4 inducer, concomitant CYP3A4 inhibitor, concomitant P-gp inhibitor, concomitant Ca channel inhibitor, concomitant beta-blocker, formulation administered, ALT change ratio, and AST change ratio.

28) Candidate covariates included age, body weight, sex, race, baseline CL_{cr}, baseline ALT, baseline AST, baseline viral load, previous treatment, viral genotype, host genotype, cirrhosis status, use of RBV, dose of DCV, dose of ASV, dose of BCV, concomitant proton pump inhibitor, concomitant histamine H2 receptor antagonist, concomitant CYP3A4 inducer, concomitant CYP3A4 inhibitor, concomitant P-gp inhibitor, concomitant Ca channel inhibitor, concomitant beta-blocker, formulation administered, ALT change ratio, and AST change ratio.

29) Candidate covariates included age, body weight, sex, race, baseline CL_{cr}, baseline ALT, baseline AST, baseline viral load, previous treatment, viral genotype, host genotype, cirrhosis status, use of RBV, dose of DCV, dose of ASV, dose of BCV, concomitant proton pump inhibitor, concomitant histamine H2 receptor antagonist, concomitant CYP3A4 inducer, concomitant CYP3A4 inhibitor, concomitant P-gp inhibitor, concomitant Ca channel inhibitor, concomitant beta-blocker, formulation administered, ALT change ratio, and AST change ratio.

Table 20. Steady-state PK parameters of DCV, ASV, and BCV estimated by simulation using the final model

	Dose	C_{max} (μg/mL)	C_{min} (μg/mL)	AUC for 24 hours (μg·h/mL)
DCV	30 mg BID	0.73 [0.48, 1.36]	0.37 [0.22, 0.84]	13.04 [8.49, 25.97]
ASV	200 mg BID	0.28 [0.13, 1.02]	0.05 [0.02, 0.33]	3.54 [1.83, 14.69]
BCV	75 mg BID	1.14 [0.72, 2.35]	0.40 [0.17, 1.08]	18.10 [10.84, 40.75]

Median [5 percentile, 95 percentile]

6.2.2.3 Exposure-response analysis (CTD 5.3.3.5-6, 5.3.3.5-7)

Analyses were performed using data from a foreign phase II study (AI443014), foreign phase III studies (AI443102 and AI443113), and a Japanese phase III study (AI443117) conducted in chronic hepatitis C patients without cirrhosis or with compensated cirrhosis receiving DCV, ASV, and BCV (efficacy analysis population, n = 1150; safety analysis population, n = 1153) to investigate relationships between mean steady-state plasma concentrations of DCV, ASV, and BCV and efficacy (SVR12) and between those concentrations and safety; that is, adverse events (Grade 3 or 4 abnormalities in ALT, AST, or total bilirubin; pyrexia, and eosinophilia) reported after co-administration of DCV, ASV, and BCV.

Relationships between efficacy (SVR12) and mean steady-state plasma concentrations of DCV, ASV, and BCV as well as the effects of covariates were analyzed using a logistic regression model. The covariates selected were as follows: HCV genotype 1a, resistance-associated mutation at Q30 in NS5A in patients with HCV genotype 1a, baseline HCV RNA, prior null response to IFN unrelated to adverse events, and interactions with BCV.

Known safety data suggested that Grade 3 or 4 abnormalities in ALT, AST, or total bilirubin was unlikely to be related to DCV exposure (Review Reports on Daklinza Tablets 60 mg and Sunvepra Capsules 100 mg dated June 6, 2014). The exposure-response relationships between steady-state plasma concentrations of ASV or BCV and Grade 3 or 4 abnormalities in ALT, AST, or total bilirubin and the effects of covariates were analyzed using a logistic regression model. ASV concentrations, race, and body weight of non-Asian patients were identified as covariates for the exposure-response model for Grade 3 or 4 abnormalities in ALT; race was identified as a covariate for the exposure-response model for Grade 3 or 4 abnormalities in AST; and ASV concentrations, race, and fibrosis score F4 were identified as covariates for Grade 3 or 4 abnormalities in total bilirubin. Results suggested that the incidence of Grade 3 or 4 abnormalities in ALT or total bilirubin increased with an increase in the plasma concentration of ASV.

Furthermore, steady-state plasma concentrations of DCV, ASV, and BCV were investigated based on the presence or absence of pyrexia and eosinophilia. The steady-state plasma concentrations of DCV, ASV, and BCV in subjects with pyrexia or eosinophilia were similar to those in subjects without pyrexia or eosinophilia.

6.2.3 Intrinsic factor pharmacokinetic studies

6.2.3.1 Study in subjects with renal impairment (Reference data, CTD 5.3.3.3-1, Study AI443110 [April 2014 to June 2014])

The PK of each component was studied in non-Japanese subjects with normal renal function[30] (n = 8) and non-Japanese subjects with renal impairment (8 subjects with mild renal impairment,[31] 7 subjects with moderate renal impairment,[32] 8 subjects with severe renal impairment,[33] and 8 subjects with renal failure requiring hemodialysis) after administration of multiple oral doses of DCV 30 mg, ASV 200 mg, and BCV 150 mg BID (a DCV/ASV/BCV [30/200/75 mg] FDC tablet + BCV 75 mg). The results are shown in Table 21.

30) Subjects with CL_{cr} ≥90 mL/min
31) Subjects with CL_{cr} 60 to <90 mL/min
32) Subjects with CL_{cr} 30 to <60 mL/min
33) Subjects with CL_{cr} <30 mL/min without receiving hemodialysis

Table 21. PK parameters of each component following multiple doses of DCV + ASV + BCV

	n	Ratio of least squares geometric means[a] [90% CI]			
		C_{max}	AUC_{tau}	C_{max} (unbound form)	AUC_{tau} (unbound form)
DCV					
Mild renal impairment[b]	8	1.16 [1.03, 1.31]	1.22 [1.09, 1.37]	1.13 [0.97, 1.33]	1.20 [1.02, 1.40]
Moderate renal impairment[b]	6	1.35 [1.19, 1.52]	1.50 [1.33, 1.68]	1.29 [1.10, 1.51]	1.44 [1.23, 1.68]
Severe renal impairment[b]	8	1.45 [1.29, 1.63]	1.65 [1.47, 1.86]	1.37 [1.17, 1.61]	1.57 [1.34, 1.84]
Renal failure (immediately after hemodialysis)[c]	8	0.95 [0.72, 1.25]	1.00 [0.76, 1.33]	0.55 [0.40, 0.75]	0.58 [0.41, 0.80]
Renal failure (2 days after hemodialysis)[c]	8	0.90 [0.69, 1.19]	1.00 [0.76, 1.32]	0.55 [0.40, 0.75]	0.61 [0.44, 0.85]
ASV					
Mild renal impairment[b]	8	1.29 [0.98, 1.69]	1.33 [1.11, 1.59]	1.37 [1.05, 1.79]	1.41 [1.18, 1.69]
Moderate renal impairment[b]	7	1.65 [1.26, 2.17]	1.76 [1.47, 2.11]	1.87 [1.43, 2.45]	1.99 [1.66, 2.39]
Severe renal impairment[b]	8	1.88 [1.43, 2.47]	2.03 [1.69, 2.43]	2.19 [1.67, 2.87]	2.37 [1.97, 2.85]
Renal failure (immediately after hemodialysis)[c]	8	0.89 [0.45, 1.73]	0.84 [0.52, 1.35]	0.98 [0.51, 1.90]	0.94 [0.58, 1.50]
Renal failure (2 days after hemodialysis)[c]	8	0.50 [0.26, 0.98]	0.67 [0.42, 1.08]	0.69 [0.36, 1.33]	0.92 [0.57, 1.48]
BCV					
Mild renal impairment[b]	8	1.15 [1.02, 1.29]	1.28 [1.14, 1.45]	1.19 [1.04, 1.35]	1.32 [1.15, 1.52]
Moderate renal impairment[b]	7	1.32 [1.17, 1.49]	1.65 [1.45, 1.86]	1.41 [1.24, 1.61]	1.75 [1.53, 2.01]
Severe renal impairment[b]	8	1.42 [1.26, 1.60]	1.86 [1.65, 2.11]	1.54 [1.35, 1.75]	2.02 [1.76, 2.32]
Renal failure (immediately after hemodialysis)[c]	8	0.93 [0.70, 1.23]	1.03 [0.75, 1.40]	1.01 [0.75, 1.37]	1.12 [0.81, 1.56]
Renal failure (2 days after hemodialysis)[c]	8	0.75 [0.57, 1.00]	1.01 [0.75, 1.38]	0.92 [0.68, 1.24]	1.23 [0.89, 1.72]
BMS-794712					
Mild renal impairment[b]	8	1.20 [1.06, 1.36]	1.33 [1.18, 1.51]	1.23 [1.08, 1.40]	1.36 [1.19, 1.55]
Moderate renal impairment[b]	7	1.45 [1.28, 1.64]	1.77 [1.57, 2.01]	1.51 [1.32, 1.72]	1.85 [1.62, 2.11]
Severe renal impairment[b]	8	1.59 [1.40, 1.80]	2.05 [1.81, 2.32]	1.67 [1.46, 1.91]	2.15 [1.89, 2.46]
Renal failure (immediately after hemodialysis)[c]	8	0.87 [0.63, 1.19]	0.92 [0.66, 1.27]	0.97 [0.70, 1.34]	1.02 [0.73, 1.43]
Renal failure (2 days after hemodialysis)[c]	8	0.78 [0.57, 1.08]	1.00 [0.72, 1.39]	0.97 [0.70, 1.34]	1.24 [0.89, 1.73]

a) Ratio relative to subjects with normal renal function.
b) Estimated by regression analysis based on the results obtained from subjects with normal renal function and those with mild, moderate, or severe renal impairment.
c) Ratio of geometric least-squares means of PK parameters in subjects with renal failure requiring hemodialysis to those in subjects with normal renal function.

6.2.3.2 Study in subjects with hepatic impairment (5.3.5.1-2, Study AI443014 [November 2011 to July 2015])

The PK of each component was studied in non-Japanese subjects with chronic hepatitis C without cirrhosis or with compensated cirrhosis (Child-Pugh A) (treatment-naïve or IFN-experienced subjects [genotype 1] and treatment-naïve subjects [genotype 4]) (PK evaluation population, n = 26) after administration of multiple oral doses of DCV 30 mg, ASV 200 mg, and BCV 75 mg BID for 14 days. The results are shown in Table 22. The PK of DCV, BCV, and BMS-794712 was similar between chronic hepatitis C subjects with compensated cirrhosis and those without cirrhosis. Meanwhile, ASV exposure was higher in subjects with compensated cirrhosis than in those without cirrhosis. The PK of each component was studied in non-Japanese subjects with chronic hepatitis C without cirrhosis or with compensated cirrhosis (Child-Pugh A) (treatment-naïve or IFN-experienced subjects [genotype 1] and

treatment-naïve subjects [genotype 4]) (PK evaluation population, n = 17) after administration of multiple oral doses of DCV 60 mg QD and ASV 200 mg and BCV 75 mg BID for 14 days. The C_{max} of DCV, ASV, BCV, and BMS-794712 was 1.37, 0.25, 1.49, and 0.31 μg/mL, respectively; and the AUC_{tau} was 14.37, 1.15, 8.72, and 2.08 μg·h/mL, respectively.

Table 22. PK parameters of DCV, ASV, BCV, and BMS-794712 following multiple doses of DCV + ASV + BCV

	Chronic hepatitis C with compensated cirrhosis (n = 8)	Chronic hepatitis C without cirrhosis (n = 18)	Total (n = 26)	Chronic hepatitis C with compensated cirrhosis (n = 8)	Chronic hepatitis C without cirrhosis (n = 18)	Total (n = 26)
	C_{max} (μg/mL)			AUC_{tau} (μg·h/mL)		
DCV	0.66 (41)	0.87 (33)	0.80 (36)	5.16 (54)	6.76 (34)	6.22 (40)
ASV	0.66 (107)	0.28 (92)	0.36 (121)	2.90 (110)	1.17 (69)	1.55 (130)
BCV	1.38 (25)	1.38 (35)	1.38 (32)	9.71 (44)	8.30 (38)	8.71 (40)
BMS-794712	0.33 (37)	0.32 (42)	0.32 (40)	2.78 (50)	2.15 (42)	2.32 (46)

Geometric mean (CV%)

6.2.4 Pharmacokinetic drug interactions

6.2.4.1 Drug interactions between DCV and co-administered drugs (reference data, CTD 5.3.3.4-1, Study AI444064 [[redacted] 20[redacted] to [redacted] 20[redacted]; reference data, CTD 5.3.3.4-2, Study AI444273 [March 2014 to May 2014])

The data submitted for the current application included the results of 2 studies evaluating drug interactions between DCV and co-administered drugs. The ratios of the geometric least-squares means (co-administration/alone) [90% CIs] of C_{max}, AUC_{tau}, and C_{24} of co-administered drugs are shown in Table 23. The ratios of the geometric least-squares means [90% CIs] of PK parameters of DCV co-administered with dolutegravir to those of DCV alone were 1.03 [0.84, 1.25] for C_{max}, 0.98 [0.83, 1.15] for AUC_{tau}, and 1.06 [0.88, 1.29] for C_{24}.

Table 23. Effects of DCV on PK parameters of co-administered drugs

Drug	Dosage regimen		n	Ratio of geometric least-squares means [90% CI]		
	Co-administered drug	DCV		C_{max}	AUC_{tau}	C_{24}
Buprenorphine	Buprenorphine/naloxone 8-24 mg QD/ 2-6 mg QD[a)]	60 mg QD	11/9[a)]	1.40 [1.03, 1.64]	1.37 [1.24, 1.52]	1.17 [1.03, 1.32]
Norbuprenorphine			11/9[a)]	1.65 [1.38, 1.99]	1.62 [1.30, 2.02]	1.46 [1.12, 1.89]
Dolutegravir	50 mg QD	60 mg QD	12	1.29 [1.07, 1.57]	1.33 [1.11, 1.59]	1.45 [1.25, 1.68]

a) C_{max} was the mean of the results from 11 subjects; C_{24} and AUC_{tau} were the means of the results from 9 subjects.

6.2.4.2 Drug interactions between ASV and co-administered drugs (reference data, CTD 5.3.3.4-3, Study AI447038 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The data submitted for the current application included the results of a study evaluating drug interactions between ASV and co-administered drugs. Among subjects enrolled in this study, subjects receiving ASV plus buprenorphine/naloxone underwent analysis. The ratios of the geometric least-squares means [90% CIs] of C_{max}, AUC_{0-24}, and C_{24} of buprenorphine/naloxone co-administered with ASV to those of buprenorphine/naloxone alone were 0.85 [0.71, 1.01], 0.97 [0.73, 1.30], and 1.01 [0.71, 1.43],

respectively, for buprenorphine, and 1.17 [0.96, 1.42], 1.10 [0.72, 1.68], and 1.13 [0.75, 1.71], respectively, for norbuprenorphine.

6.2.4.3 Drug interactions between BCV and co-administered drugs (reference data, CTD 5.3.3.1-1, Study AI443001 [[redacted] 20[redacted] to [redacted] 20[redacted]; CTD 5.3.3.4-4, Study AI443006 [May 2013 to September 2013])

A study was conducted to evaluate drug interactions between BCV and co-administered drugs. The ratios of the geometric least-squares means [90% CIs] of PK parameters of BCV co-administered with other drugs to those of BCV alone and vice versa are shown in Table 24 andTable 25, respectively.

Table 24. Effects of co-administered drugs on PK parameters of BCV

Drug	Dosage regimen		n	Substance measured	Ratio of geometric least-squares means [90% CI]		
	Co-administered drug	BCV			C_{max}	AUC_{inf}	C_{24}
Famo-tidine	40 mg single dose	100 mg single dose	6	BCV	1.13 [0.93, 1.36]	1.16 [1.01, 1.33]	1.16 [0.92, 1.48]
				BMS-794712	1.00 [0.80, 1.26]	1.04 [0.89, 1.20]	1.03 [0.86, 1.23]
Rito-navir	200 mg BID	30 mg single dose	6	BCV	2.03 [1.68, 2.46]	12.07 [9.03, 16.13]	21.86 [13.92, 34.35]
				BMS-794712	0.06 [0.04, 0.09]	NA	0.14 [0.10, 0.21]

Table 25. Effects of BCV on PK parameters of co-administered drugs

Drug	Dosage regimen		n	Ratio of geometric least-squares means [90% CI]	
	Co-administered drug	BCV		C_{max}	AUC_{inf}
Midazolam	Midazolam 5 mg	150 mg BID	8	0.66 [0.57, 0.76]	0.50 [0.45, 0.57]
1'-hydroxymidazolam				1.16 [0.96, 1.40]	1.10 [0.97, 1.25]

6.2.4.4 Drug interactions between DCV + ASV + BCV and co-administered drugs[34)]

A study was conducted to evaluate drug interactions between DCV + ASV + BCV and co-administered drugs. The ratios of the geometric least-squares means [90% CIs] of PK parameters of DCV + ASV + BCV co-administered with other drugs to those of DCV + ASV + BCV alone and vice versa are shown in Table 26 and Table 27, respectively. Effects of the combination of DCV and ASV on the PK of BCV were evaluated based on the PK data of BCV from Studies AI443012 and AI443014 (reference data, CTD 5.3.5.4-1; CTD 5.3.5.1-2).

34) Reference data, CTD 5.3.5.4-1, Study AI443012 [October 2010 to November 2012]; CTD 5.3.5.1-2, Study AI443014 [November 2011 to July 2015]; reference data, CTD 5.3.3.4-9, Study AI443116 [June 2014 to [redacted] 20[redacted]]; reference data, CTD 5.3.3.4-8, Study AI443016 [April 2014 to July 2014]; reference data, CTD 5.3.3.4-5, Study AI443021 [February 2014 to April 2014]; reference data, CTD 5.3.3.4-6, Study AI443108 [February 2014 to April 2014]; reference data, CTD 5.3.3.4-7, Study AI443115 [April 2014 to May 2014]

Table 26. Effects of co-administered drugs on PK parameters of BCV

Drugs	Dosage regimen		n	Substance measured	Ratio of geometric least-squares means [90% CI]		
	Co-administered drug	DCV/ASV/BCV			C_{max}	AUC_{tau}	C_{12}
Escitalo-pram	10 mg QD	DCV/ASV/BCV 30/200/150 mg BID	18	DCV	1.08 [0.99, 1.17]	1.00 [0.93, 1.09]	0.98 [0.89, 1.07]
				ASV	0.96 [0.79, 1.17]	0.92 [0.85, 1.00]	0.84 [0.76, 0.94]
				BCV	1.02 [0.94, 1.11]	0.96 [0.91, 1.02]	0.85 [0.76, 0.94]
				BMS-794712	0.97 [0.90, 1.03]	0.93 [0.89, 0.98]	0.87 [0.80, 0.95]
Sertraline	50 mg QD	DCV/ASV/BCV 30/200/150 mg BID	23	DCV	1.06 [1.02, 1.11]	0.96 [0.93, 0.98]	0.93 [0.89, 0.98]
				ASV	1.11 [0.92, 1.34]	1.02 [0.92, 1.13]	0.86 [0.79, 0.93]
				BCV	1.08 [1.01, 1.16]	0.94 [0.92, 0.97]	0.82 [0.76, 0.87]
				BMS-794712	1.00 [0.94, 1.07]	0.92 [0.89, 0.95]	0.85 [0.80, 0.90]
DCV, ASV	DCV 30 mg ASV 200 mg	BCV 75 mg BID[a)]	11/17[b)]	BCV	1.00 [0.79, 1.25]	0.96 [0.73, 1.27]	1.02 [0.63, 1.67]
				BMS-794712	1.16 [0.91, 1.48]	0.98 [0.74, 1.29]	1.01 [0.67, 1.52]

a) Co-administered with pegIFNα-2a/RBV
b) (Number of subjects receiving BCV/pegIFNα/RBV)/(Number of subjects receiving DCV/ASV/BCV)

Table 27. Effects of DCV/ASV/BCV on PK parameters of concomitant drugs

Drug	Dosage regimen		n	Ratio of geometric least-squares means [90% CI]	
	Co-administered drug	DCV/ASV/BCV		C_{max}	AUC
Ethinylestradiol	Ethinylestradiol/ norethisterone 1 mg QD/20 μg QD	30/200/150 mg BID	22	1.09 [1.01, 1.18]	0.85 [0.79, 0.90]
Norethisterone			22	0.79 [0.71, 0.88]	0.94 [0.83, 1.05]
Caffeine	200 mg single dose[a)]	30/200/75 mg BID	20	0.97 [0.93, 1.02]	0.96 [0.90, 1.01]
Metoprolol	Metoprolol 50 mg single dose[a)]	30/200/75 mg BID	20	1.40 [1.20, 1.64]	1.71 [1.49, 1.97]
α-hydroxymetoprolol			20	0.74 [0.68, 0.81]	0.88 [0.83, 0.94]
Montelukast	Montelukast 10 mg single dose[a)]	30/200/75 mg BID	20	1.01 [0.95, 1.08]	0.92 [0.88, 0.97]
36-hydroxymontelukast			20	1.29 [1.15, 1.44]	1.01 [0.90, 1.12]
Flurbiprofen	50 mg single dose[a)]	30/200/75 mg BID	20	0.94 [0.88, 0.99]	0.90 [0.87, 0.93]
Omeprazole	Omeprazole 40 mg single dose[a)]	30/200/75 mg BID	18[e)]	0.57 [0.42, 0.78]	0.51 [0.35, 0.73]
5-hydroxyomeprazole			18[f)]	0.92 [0.75, 1.12]	0.83 [0.75, 0.92]
Midazolam	Midazolam 5 mg single dose[a)]	30/200/75 mg BID	20	0.57 [0.50, 0.65]	0.53 [0.47, 0.60]
1'-hydroxymidazolam			20	0.89 [0.78, 1.02]	0.87 [0.80, 0.95]
Digoxin	0.25 mg single dose[a)]	30/200/75 mg BID	20[g)]	1.23 [1.12, 1.35]	1.23 [1.17, 1.29]
Pravastatin	Pravastatin 40 mg single dose[a)]	30/200/75 mg BID	20	2.01 [1.63, 2.47]	1.68 [1.43, 1.97]
Pravastatin lactone			20[h)]	0.99 [0.78, 1.26]	0.84 [0.69, 1.02]
Methadone[b)]	40-120 mg QD	30/200/150 mg BID	16	0.66 [0.53, 0.81]	0.75 [0.64, 0.87]
Buprenorphine[c)]	Buprenorphine/naloxone 8-24 mg QD/2-6 mg QD	30/200/150 mg BID	16	0.76 [0.65, 0.90]	0.92 [0.81, 1.05]
Norbuprenorphine[c)]			16	0.98 [0.81, 1.18]	0.98 [0.83, 1.17]
Naloxone[d)]			16	0.77 [0.43, 1.35]	1.38 [0.82, 2.32]
Rosuvastatin	10 mg single dose	30/200/150 mg BID	18	9.13 [7.60, 10.98]	3.24 [2.78, 3.77]
Escitalopram	10 mg QD	30/200/150 mg BID	18	0.68 [0.64, 0.73]	0.65 [0.61, 0.69]
Sertraline	50 mg QD	30/200/150 mg BID	23	0.68 [0.65, 0.71]	0.62 [0.60, 0.65]

a) Administered as a cocktail formulation consisting of caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin.
b) Normalized by the dose of 40 mg.
c) Normalized by the dose of 8 mg.
d) Normalized by the dose of 2 mg.
e) The number of subjects for AUC evaluation was 14.
f) The number of subjects for AUC evaluation was 17.
g) The number of subjects for AUC evaluation was 18.
h) The number of subjects for AUC evaluation was 19.

6.2.5 QT/QTc study (CTD 5.3.4.1-1, Study AI443112 [April 2014 to May 2014])

A 3-treatment, 3-period, crossover study[35)] was conducted in 58 non-Japanese healthy subjects to evaluate the effects of BCV on the QT/QTc interval. Subjects received multiple oral doses of placebo or BCV at 600 mg QD for 2 days and then at 900 mg once, or a single oral dose of moxifloxacin 400 mg as a positive control. The largest difference in change from baseline in the QTc interval corrected for heart rate using the Fridericia formula between BCV and placebo [90% CI] was 4.47 [2.38, 6.57] msec at 8 hours post-dose on Day 3, and the upper bound of the 90% confidence interval was below 10

35) There was a washout period of ≥7 days between treatments.

msec. On the basis of this result, the applicant explained that BCV has no effects on the QT/QTc interval.[36)] The C_{max} and AUC_{tau} of BCV were 13.87 μg/mL and 120.28 μg·h/mL, respectively.

6.R Outline of the review conducted by PMDA

6.R.1 PK in Japanese patients with renal impairment

The exposure to BCV and BMS-794712 was higher in subjects with moderate to severe renal impairment than in subjects with normal renal function, while the exposure in subjects with renal failure after receiving hemodialysis was similar to that in subjects with normal renal function [see Section 6.2.3.1].

PMDA asked the applicant to explain the factors contributing to the above results and the effects of renal impairment on the exposure to each active ingredient contained in DCV/ASV/BCV FDC.

The applicant's explanation:

After administration of ^{14}C-BCV to healthy subjects, the radioactivity recovered in urine was <1% of the dose administered, indicating that renal excretion makes a negligible contribution to the elimination of BCV or its metabolite [see Section 6.2.1.1.4]. Decreases in the expression and activity of all the major CYP isoforms including CYP3A4 were observed in rat hepatocytes incubated in the presence of serum containing uremic toxins, which had been collected from patients with renal failure requiring hemodialysis before receiving hemodialysis. However, no decreases in the expression or activity of any of the major CYP isoforms were observed in serum samples collected after hemodialysis (*Br J Pharmacol*. 2005;144:1067-1077; *J Pharmacol Sci*. 2008;108:157-163). The mechanism by which the exposure to BCV and BMS-794712 increased in subjects with moderate to severe renal impairment is unknown. However, given that BCV and BMS-794712 were shown to be metabolized mainly by CYP3A4 and CYP3A5 [see Section 4.3], uremic toxins accumulated in subjects with moderate to severe renal impairment may have inhibited the clearance of BCV and BMS-794712, resulting in an increase in the exposure to BCV and BMS-794712. This may have explained why no increase was observed in the exposure to BCV or BMS-794712 in post-dialysis subjects with renal failure.

The effects of renal impairment on the exposure to each active ingredient contained in DCV/ASV/BCV were evaluated based on the ratios of the geometric least-squares means of AUC_{tau} of DCV, ASV, and BCV in subjects with each degree of renal impairment to those in subjects with normal renal function (CL_{cr} ≥90 mL/min), and the ratios were 1.22, 1.33, and 1.28, respectively, for mild renal impairment (CL_{cr} ≥60 and <90 mL/min) vs. normal renal function; 1.5, 1.76, and 1.65, respectively, for moderate renal impairment (CL_{cr} ≥30 and <60 mL/min) vs. normal renal function; and 1.65, 2.03, and 1.86, respectively, for severe renal impairment (CL_{cr} of <15 mL/min) vs. normal renal function. These results showed that the level of AUC_{tau} of each component increases with the increasing severity of renal impairment [see Section 6.2.3.1].

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36) The largest difference in change from baseline in the QTc interval corrected for heart rate using the Fridericia formula between moxifloxacin and placebo [90% CI] was 12.4 [10.31, 14.49] msec at 4 hours post-dose.

Taking into account that the increased exposure of DCV, ASV, and BCV is associated with renal impairment, the safety of DCV/ASV/BCV FDC in Japanese patients with chronic hepatitis C without cirrhosis or with compensated cirrhosis is discussed in Section 7.R.2.5.

6.R.2 PK in chronic hepatitis C patients with compensated cirrhosis

The applicant's explanation about the PK after co-administration of DCV, ASV, and BCV in chronic hepatitis C patients with compensated cirrhosis:

The model for PPK analysis [see Section 6.2.2.2] was used to estimate the median daily steady-state AUC [5 percentile, 95 percentile] of ASV in Japanese patients without cirrhosis and those with compensated cirrhosis, and the resulting estimates were 5.76 [3.31, 15.6] and 12.4 [6.60, 28.9] μg·h/mL, respectively. ASV exposure was higher in patients with compensated cirrhosis than in non-cirrhotic patients. As the result of the exposure-response analysis of adverse events (Grade 3 or 4 abnormalities in ALT, AST, and total bilirubin, pyrexia, and eosinophilia), ASV exposure was shown to be a significant covariate for Grade 3 or 4 abnormalities in ALT or total bilirubin [see Section 6.2.2.3]. However, the effect of ASV exposure on Grade 3 or 4 abnormalities in ALT was small, and abnormalities in total bilirubin was associated more strongly with the severity of hepatic fibrosis than with ASV exposure.

PMDA's view:

An increase in ASV exposure associated with compensated cirrhosis may increase the risk of hepatic impairment. The necessity of precautions regarding the use of DCV/ASV/BCV FDC in chronic hepatitis C patients with compensated cirrhosis is discussed in Section 7.R.4.1.

6.R.3 Dosage regimen in Japanese phase III study

The applicant's explanation of the rationale for the dosage regimen employed in the Japanese phase III study (AI443117):

DCV:

The dosage regimen of DCV (30 mg BID) in the Japanese phase III study (AI443117) was selected based on the following:

- The C_{max} and AUC_{tau} of DCV after administration of DCV 60 mg QD in combination with ASV softgel capsule 100 mg BID were 1.12 μg/mL and 11.88 μg·h/mL, respectively (Review Reports on Daklinza Tablets 60 mg and Sunvepra Capsules 100 mg dated June 6, 2014). The C_{max} and AUC_{tau} of DCV after administration of DCV 60 mg QD in combination with ASV 200 mg BID and BCV 75 mg BID were 1.37 μg/mL and 14.37 μg·h/mL, respectively [see Section 6.2.3.2]. The C_{max} and AUC_{tau} of DCV after co-administration of DCV 30 mg + ASV 200 mg + BCV 75 mg BID were 0.80 μg/mL and 6.22 μg·h/mL, respectively [see Section 6.2.3.2]. As described above, the C_{max} and daily AUC_{tau} of DCV after administration of DCV 60 mg QD in combination with ASV softgel capsule 100 mg BID were not markedly different from those after administration of DCV 60 mg

QD in combination with ASV 200 mg BID and BCV 75 mg BID, and the daily AUC_{tau} of DCV after administration of DCV 60 mg QD was not markedly different from that after administration of DCV 30 mg BID.

- In the phase I study in patients with chronic hepatitis C (AI444004), the changes from baseline in HCV RNA at Day 7 were 3.86 and 3.14 log_{10} IU/mL after administration of multiple doses of DCV 30 mg BID and 60 mg QD, respectively (CTD 5.3.3.2.2 of the initial application document for Daklinza Tablets 60 mg), showing similarity between these 2 dosage regimens.

The C_{max} of DCV administered at 30 mg BID was approximately 50% of the C_{max} of DCV administered at 60 mg QD. However, since the foreign phase II study (AI443014) demonstrated that the efficacy and safety of DCV 30 mg BID are equivalent to those of DCV 60 mg QD [see Section 7.1], the decrease in C_{max} of DCV was considered to have no effects on the efficacy and safety of the study treatment.

ASV:

The dosage regimen of ASV (200 mg BID) in the Japanese phase III study (AI443117) was selected taking account of the following:

- In the Japanese phase II study of ASV (AI1447017) and the Japanese phase III study (AI447026), the C_{max} and AUC_{tau} of ASV after administration of DCV 60 mg QD in combination with ASV 200 mg BID were 0.71 μg/mL and 2.95 μg·h/mL, respectively, and the C_{max} and AUC_{tau} of ASV after co-administration of DCV 60 mg QD and ASV softgel capsule 100 mg BID were 0.65 μg/mL and 2.16 μg·h/mL, respectively (Review Reports on Daklinza Tablets 60 mg and Sunvepra Capsules 100 mg dated June 6, 2014).
- The effects of BCV on the PK parameters of DCV and ASV were evaluated. The ratios of geometric least-squares means [90% CI] of the C_{max} and AUC of ASV co-administered with BCV to those of ASV administered alone were 0.79 [0.45, 1.40] and 0.62 [0.39, 1.00], respectively, indicating that ASV exposure decreased when ASV was co-administered with BCV. However, given that ASV exposure varied greatly from subject to subject and that the efficacy of treatment was demonstrated in the foreign phase II study (AI443014), concomitant BCV is unlikely to have any clinically significant effects on ASV exposure.

The C_{max} and AUC_{tau} of ASV (median [5 percentile, 95 percentile]) after administration of a DCV/ASV/BCV FDC tablet (Formulation 7) in the Japanese phase III study (AI443117) were estimated to be 0.55 [0.30, 1.45] μg/mL and 3.51 [1.72, 10.76] μg·h/mL, respectively, based on the PPK model [see Section 6.2.2.2]. The C_{max} and AUC_{tau} of ASV (median [5 percentile, 95 percentile]) after administration of DCV 60 mg QD in combination with ASV softgel capsule 100 mg BID were estimated to be 0.35 [0.20, 0.82] μg/mL and 1.95 [1.10, 5.48] μg·h/mL, respectively, based on the PPK model. Although the C_{max} and AUC_{tau} of ASV after administration of Formulation 7 were higher than those after administration of ASV softgel capsule, their distributions were almost the same, indicating that there were no marked differences in the C_{max} and AUC_{tau} of ASV between the 2 different formulations.

BCV:

The dosage regimen of BCV (75 mg BID) in the Japanese phase III study (AI443117) were selected taking account of the following:

- In the phase I study (AI443002), the mean maximum decrease from baseline in HCV RNA after administration of a single dose of BCV at 100, 300, 600, or 900 mg was 1.3, 2.5, 2.8, or 2.6 $\log_{10}$ IU/mL, respectively [see Section 6.2.2.1.1].
- Based on the results of the phase I multiple dose study (AI443003) [see Section 6.2.1.1.3], the lowest total daily dose of BCV needed to have an antiviral activity similar to that of a single dose of 100 mg was considered to be 150 mg.
- Because serious intrahepatic cholestasis was observed in 1 subject in the 900 mg QD group in Study AI443003, twice-daily (BID) administration was selected. BID administration allows for sustained AUC and trough concentrations, although C_{max} is decreased.
- In the foreign phase II study (AI443012) in which BCV was administered at 75 or 150 mg BID in combination with pegIFNα-2a and RBV, the SVR12 rates in the BCV 75 mg group and 150 mg group were 69.2% (9 of 13 subjects) and 46.2% (6 of 13 subjects), respectively, showing no differences in the safety profile of BCV between the 2 dose levels (75 mg and 150 mg).
- In the foreign phase II study (A1443014), doses of BCV were investigated for co-administration of DCV, ASV, and BCV. Results showed no marked difference in the efficacy and safety of the combination regimen between the 2 dose levels of BCV (75 and 150 mg BID) [see Section 7.1].
- In the phase I study in healthy subjects including Japanese healthy adults (AI443006), the steady-state AUC_{tau} values of BCV and BMS-794712 in Japanese subjects were approximately 30% higher than those in Caucasian subjects. This difference was unlikely to be clinically significant; therefore, the change of the BCV dose for use in Japanese patients was considered unnecessary.

When DCV, ASV, and BCV were co-administered for either 12 or 24 weeks in the foreign phase II study (AI443014), there were no clear differences in the efficacy and safety of the treatment between the 2 treatment durations. Based on the results, a duration of 12 weeks was selected for the co-administration of DCV, ASV, and BCV.

PMDA's view:

The applicant's explanation of the rationale for the dosage regimen employed in the Japanese phase III study (AI443117) is acceptable.

6.R.4 Food effect

PMDA asked the applicant to explain why the proposed regimen for DCV/ASV/BCV FDC requires administration in the fed state while there are no food-related conditions in the approved regimen for DCV + ASV.

The applicant's explanation of the rationale for administration of DCV/ASV/BCV FDC in the fed state:
The effect of food on the dose of DCV 60 mg was investigated in the foreign phase I study (AI444039). While the ratios of the geometric least-squares means of C_{max} and AUC_{inf} [90% CI] of DCV administered after a high-fat meal to those of DCV administered in the fasted state were 0.72 [0.66, 0.79] and 0.77 [0.73, 0.80], respectively, the DCV exposure after a low-fat meal was similar to that in the fasted state. The effect of food on the dose of ASV softgel capsule 200 mg was investigated in the foreign phase I study (AI447024). The ratios of the geometric least-squares means of C_{max} and AUC_{inf} [90% CI] of ASV administered after a standard meal to those of ASV administered in the fasted state were 1.31 [0.95, 1.82] and 1.17 [0.95, 1.44], respectively, showing that the effect of a high-fat meal was similar to that of a standard meal (Review Reports on Daklinza Tablets 60 mg and Sunvepra Capsules 100 mg dated June 6, 2014). Based on the above, no food-related conditions were set for the approved dosage and administration for DCV + ASV.

The effect of food on the treatment with a DCV/ASV/BCV FDC tablet was investigated in the foreign phase I study (AI443111). The C_{max} and AUC_{inf} of DCV, BCV, and BMS-794712 were similar irrespective of prandial status or the content of a meal taken. Meanwhile, the C_{max} and AUC_{inf} of ASV administered after a high-fat or low-fat meal were higher than those of ASV administered in the fasted state [see Section 6.1.2]. Based on the above, DCV/ASV/BCV FDC was administered after a meal to increase the bioavailability of ASV in the Japanese phase III study (AI443117).

PMDA's view:
The applicant's explanation is acceptable. The dosage and administration of DCV/ASV/BCV FDC is discussed in Section 7.R.5.

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

The results from 1 foreign phase II study and 1 Japanese phase III study were submitted for the current application as the evaluation data on the efficacy and safety of DCV/ASV/BCV FDC. The results from 2 foreign phase III studies were submitted as the reference data. The results of the clinical studies submitted are summarized in Table 28.

Table 28. Summary of main clinical studies on the efficacy and safety of DCV/ASV/BCV

	Phase	Study identifier	Subjects		n	Dosage regimen
Foreign	II	AI443014 (Evaluation)	Genotype 1 or 4 chronic hepatitis C patients without cirrhosis or with compensated cirrhosis	Part 1: Treatment-naïve (genotype 1a/1b)	66	DCV 60 mg QD + ASV 200 mg BID + BCV 75 mg or 150 mg BID
				Part 2: Treatment-naïve (genotype 1a/1b, 4), IFN-experienced (genotype 1a/1b)	233	DCV 30 mg BID + ASV 200 mg BID + BCV 75 mg or 150 mg BID
				Part 3: Treatment-naïve (genotype 1a/1b)	21	DCV 30 mg BID + ASV 200 mg BID + BCV 75mg BID + RBV
Japanese	III	AI443117 (Evaluation)	Genotype 1 chronic hepatitis C patients without cirrhosis or with compensated cirrhosis	Treatment-naïve (genotype 1b)	224	12 weeks of the DCV/ASV/BCV FDC tablet[a)] BID, or 24 weeks of DCV 60 mg QD + ASV 100 mg BID
				Treatment-naïve (genotype 1a)	3	12 weeks of the DCV/ASV/BCV FDC tablet[a)] BID
				IFN-experienced (genotype 1a/1b)	65	12 weeks of the DCV/ASV/BCV FDC tablet[a)] BID
Foreign	III	AI443102 (Reference)	Patients with genotype 1 chronic hepatitis C without cirrhosis	Treatment naïve	312	12 weeks of the DCV/ASV/BCV FDC tablet[a)] BID
				IFN-experienced	103	
Foreign	III	AI443113 (Reference)	Genotype 1 chronic hepatitis C patients with compensated cirrhosis	Treatment-naïve	112	12 weeks of the DCV/ASV/BCV FDC tablet[a)] BID + RBV or placebo
				IFN-experienced	90	

a) A film-coated tablet containing DCV 30 mg, ASV 200 mg, and BCV 75 mg

7.1 Foreign phase II study (CTD 5.3.5.1-2, Study AI443014 [November 2011 to July 2015])

A randomized, open-label study was conducted at 31 sites in foreign countries (26 sites in the US and 5 sites in France) to investigate the efficacy and safety of the DCV + ASV + BCV combination regimen in treatment-naïve[37)] or IFN-experienced[38)] (genotype 1) or treatment-naïve (genotype 4) chronic hepatitis C patients without cirrhosis or with compensated cirrhosis (target sample size, 316 subjects).

The dosage regimen and target sample size defined for each treatment group are shown in Table 29. The protocol specified that subjects who experienced virologic breakthrough[39)] during the study were to receive additional treatment with pegIFN + RBV (for groups 1 through 12) or pegIFN (for group 13) and were allowed to be treated for 48 weeks.

37) Patients who had not received any IFN-based treatment or treatment with a direct-acting antiviral

38) Patients who were null responders to a prior treatment with pegIFN + RBV (patients who did not achieve ≥2 $\log_{10}$ IU/mL decline in their HCV RNA after a ≥12-week treatment with pegIFN + RBV)

39) Cases where ≥1 $\log_{10}$ IU/mL rise in HCV RNA from the lowest level was achieved for 2 consecutive measurements, or where the HCV RNA level fell below the LLOQ (detectable or undetectable) for 2 consecutive measurements and then was at or above the LLOQ for 2 consecutive measurements.

Table 29. Dosage regimen and sample size for each group in the foreign phase II study (AI443014)

Group	DCV[a)]	ASV[a)]	BCV[a)]	RBV	IFN-experienced	Genotype	Duration of treatment (weeks)	n[b)]
1	60 mg QD	200 mg BID	75 mg BID	No	No	1a/1b	24	16
2	60 mg QD	200 mg BID	75 mg BID	No	No	1a/1b	12	16
3	60 mg QD	200 mg BID	150 mg BID	No	No	1a/1b	24	16
4	60 mg QD	200 mg BID	150 mg BID	No	No	1a/1b	12	18
5	30 mg BID	200 mg BID	75 mg BID	No	No	1a/1b	12	80
6	30 mg BID	200 mg BID	150 mg BID	No	No	1a/1b	12	86
7	30 mg BID	200 mg BID	75 mg BID	No	No	4	12	11
8	30 mg BID	200 mg BID	150 mg BID	No	No	4	12	10
9	30 mg BID	200 mg BID	75 mg BID	No	Yes	1a/1b	12	11
10	30 mg BID	200 mg BID	150 mg BID	No	Yes	1a/1b	12	11
11	30 mg BID	200 mg BID	75 mg BID	No	Yes	1a/1b	24	12
12	30 mg BID	200 mg BID	150 mg BID	No	Yes	1a/1b	24	12
13	30 mg BID	200 mg BID	75 mg BID	Yes[c)]	No	1a/1b	12	21

a) DCV, ASV, and BCV were to be administered after a meal.
b) The planned and actual number of subjects treated with the study drug
c) RBV was administered at 1000 to 1200 mg BID based on the body weight of each subject.

A total of 320 randomized subjects who received ≥1 dose of the study drug were included in the efficacy and safety analysis populations.

Efficacy analysis showed that the SVR12 rates[40)] in groups 1 through 13 were 93.8% (15 of 16 subjects), 93.8% (15 of 16 subjects), 93.8% (15 of 16 subjects), 88.9% (16 of 18 subjects), 88.8% (71 of 80 subjects), 89.5% (77 of 86 subjects), 90.9% (10 of 11 subjects), 90.0% (9 of 10 subjects), 81.8% (9 of 11 subjects), 100% (11 of 11 subjects), 83.3% (10 of 12 subjects), 100% (12 of 12 subjects), and 85.7% (18 of 21 subjects), respectively.

Adverse events (including abnormal laboratory values) occurred in 92 of 118 subjects (78.0%) treated with BCV 75 mg BID for 12 weeks (groups 2, 5, 7, and 9), in 101 of 125 subjects (80.8%) treated with BCV 150 mg BID for 12 weeks (groups 4, 6, 8, and 10), in 26 of 28 subjects (92.9%) treated with BCV 75 mg BID for 24 weeks (groups 1 and 11), and in 25 of 28 subjects (89.3%) treated with BCV 150 mg BID for 24 weeks (groups 3 and 12) when BCV doses were co-administered with DCV and ASV; and adverse events occurred in 14 of 21 subjects (66.7%) treated with BCV 75 mg BID in combination with DCV, ASV, and RBV for 12 weeks (group 13). Among the above adverse events, study drug-related adverse events, i.e., adverse drug reactions (including abnormal laboratory values)[41)] occurred in 59 of 118 subjects (50.0%) treated with BCV 75 mg BID for 12 weeks, in 69 of 125 subjects (55.2%) treated with BCV 150 mg BID for 12 weeks, in 18 of 28 subjects (64.3%) treated with BCV 75 mg BID for 24 weeks, and in 17 of 28 subjects (60.7%) treated with BCV 150 mg BID for 24 weeks, as well as in 11 of 21 subjects (52.4%) treated with BCV 75 mg BID plus RBV for 12 weeks (group 13). The adverse events and adverse drug reactions occurring in ≥5% of subjects in any combined group are summarized in Table 30 and Table 31, respectively.

40) The proportion of subjects with undetectable HCV RNA 12 weeks after the end of treatment. Since consistency between SVR12 and SVR24 was reported (*Hepatology*. 2010;51:1122-6), the SVR12 rate was chosen as the primary endpoint.
41) Adverse events assessed by the investigator (sub-investigator) as related to the study drug.

Table 30. Adverse events occurring in ≥5% of subjects in any combined group (12- or 24-week regimen)

	Genotypes 1 or 4				Genotype 1
	Treatment-naïve or IFN-experienced				Treatment-naïve
	12 weeks		24 weeks		12 weeks
Dosage regimen of BCV	75 mg BID	150 mg BID	75 mg BID	150 mg BID	75 mg BID + RBV
Combined group	2, 5, 7, 9	4, 6, 8, 10	1, 11	3, 12	13
N	118	125	28	28	21
Any adverse event	92 (78.0)	101 (80.8)	26 (92.9)	25 (89.3)	14 (66.7)
Diarrhoea	20 (16.9)	15 (12.0)	4 (14.3)	3 (10.7)	3 (14.3)
Nausea	14 (11.9)	14 (11.2)	2 (7.1)	2 (7.1)	2 (9.5)
Abdominal distension	4 (3.4)	1 (0.8)	0	2 (7.1)	0
Abdominal pain	4 (3.4)	5 (4.0)	0	4 (14.3)	0
Toothache	4 (3.4)	2 (1.6)	0	3 (10.7)	0
Abdominal pain upper	3 (2.5)	7 (5.6)	2 (7.1)	3 (10.7)	0
Flatulence	2 (1.7)	7 (5.6)	1 (3.6)	0	0
Abdominal pain lower	0	1 (0.8)	2 (7.1)	0	0
Fatigue	15 (12.7)	11 (8.8)	6 (21.4)	4 (14.3)	4 (19.0)
Pain	6 (5.1)	5 (4.0)	0	0	0
Asthenia	5 (4.2)	6 (4.8)	3 (10.7)	3 (10.7)	0
Influenza-like illness	1 (0.8)	1 (0.8)	2 (7.1)	0	1 (4.8)
Headache	28 (23.7)	35 (28.0)	10 (35.7)	7 (25.0)	3 (14.3)
Dizziness	3 (2.5)	5 (4.0)	0	2 (7.1)	2 (9.5)
Disturbance in attention	1 (0.8)	2 (1.6)	1 (3.6)	2 (7.1)	1 (4.8)
Upper respiratory tract infection	11 (9.3)	4 (3.2)	3 (10.7)	2 (7.1)	1 (4.8)
Nasopharyngitis	9 (7.6)	7 (5.6)	1 (3.6)	1 (3.6)	0
Tooth abscess	2 (1.7)	0	2 (7.1)	0	0
Sinusitis	1 (0.8)	5 (4.0)	1 (3.6)	0	2 (9.5)
Arthralgia	7 (5.9)	6 (4.8)	3 (10.7)	2 (7.1)	0
Myalgia	4 (3.4)	6 (4.8)	1 (3.6)	2 (7.1)	0
Back pain	2 (1.7)	4 (3.2)	3 (10.7)	3 (10.7)	0
Pain in extremity	2 (1.7)	6 (4.8)	0	3 (10.7)	0
Muscle spasms	1 (0.8)	1 (0.8)	2 (7.1)	1 (3.6)	0
Musculoskeletal pain	0	0	2 (7.1)	1 (3.6)	0
Insomnia	9 (7.6)	9 (7.2)	2 (7.1)	1 (3.6)	2 (9.5)
Anxiety	3 (2.5)	3 (2.4)	1 (3.6)	2 (7.1)	0
Depression	1 (0.8)	4 (3.2)	3 (10.7)	1 (3.6)	1 (4.8)
Pruritus	4 (3.4)	12 (9.6)	3 (10.7)	3 (10.7)	0
Alopecia	2 (1.7)	1 (0.8)	1 (3.6)	3 (10.7)	3 (14.3)
Rash	2 (1.7)	4 (3.2)	2 (7.1)	2 (7.1)	0
Dry skin	1 (0.8)	3 (2.4)	2 (7.1)	0	0
Dermatitis contact	0	1 (0.8)	0	2 (7.1)	1 (4.8)
Cough	7 (5.9)	11 (8.8)	1 (3.6)	0	1 (4.8)
Dyspnoea	2 (1.7)	1 (0.8)	0	0	3 (14.3)
Decreased appetite	3 (2.5)	4 (3.2)	0	1 (3.6)	3 (14.3)
Hot flush	0	1 (0.8)	2 (7.1)	1 (3.6)	0
Hypertension	0	3 (2.4)	1 (3.6)	2 (7.1)	0
Palpitations	0	0	0	2 (7.1)	0

n (%)

Table 31. Adverse drug reactions occurring in ≥5% of subjects in any combined group (12- or 24-week regimen)

	Genotypes 1 or 4				Genotype 1
	Treatment-naïve or IFN-experienced				Treatment-naïve
	12 weeks		24 weeks		12 weeks
Dosage regimen of BCV	75 mg BID	150 mg BID	75 mg BID	150 mg BID	75 mg BID + RBV
Combined group	2, 5, 7, 9	4, 6, 8, 10	1, 11	3, 12	13
N	118	125	28	28	21
Any adverse drug reaction	59 (50.0)	69 (55.2)	18 (64.3)	17 (60.7)	11 (52.4)
Diarrhoea	14 (11.9)	11 (8.8)	3 (10.7)	3 (10.7)	3 (14.3)
Nausea	12 (10.2)	11 (8.8)	2 (7.1)	2 (7.1)	2 (9.5)
Abdominal distension	2 (1.7)	1 (0.8)	0	2 (7.1)	0
Abdominal pain	2 (1.7)	0	0	3 (10.7)	0
Toothache	0	1 (0.8)	0	1 (3.6)	0
Abdominal pain upper	3 (2.5)	3 (2.4)	0	2 (7.1)	0
Flatulence	2 (1.7)	5 (4.0)	1 (3.6)	0	0
Abdominal pain lower	0	1 (0.8)	1 (3.6)	0	0
Fatigue	11 (9.3)	7 (5.6)	5 (17.9)	2 (7.1)	4 (19.0)
Pain	5 (4.2)	4 (3.2)	0	0	0
Asthenia	4 (3.4)	6 (4.8)	2 (7.1)	3 (10.7)	0
Influenza-like illness	0	1 (0.8)	0	0	0
Headache	18 (15.3)	27 (21.6)	5 (17.9)	5 (17.9)	3 (14.3)
Dizziness	2 (1.7)	2 (1.6)	0	0	2 (9.5)
Disturbance in attention	0	2 (1.6)	0	0	1 (4.8)
Upper respiratory tract infection	0	0	0	0	0
Nasopharyngitis	1 (0.8)	0	0	0	0
Tooth abscess	0	0	0	0	0
Sinusitis	1 (0.8)	1 (0.8)	0	0	0
Arthralgia	3 (2.5)	1 (0.8)	2 (7.1)	0	0
Myalgia	3 (2.5)	1 (0.8)	1 (3.6)	1 (3.6)	0
Back pain	1 (0.8)	0	0	1 (3.6)	0
Pain in extremity	1 (0.8)	0	0	0	0
Muscle spasms	1 (0.8)	1 (0.8)	0	1 (3.6)	0
Musculoskeletal pain	0	0	0	0	0
Insomnia	7 (5.9)	5 (4.0)	1 (3.6)	1 (3.6)	2 (9.5)
Anxiety	2 (1.7)	1 (0.8)	0	1 (3.6)	0
Depression	0	2 (1.6)	1 (3.6)	0	1 (4.8)
Pruritus	4 (3.4)	7 (5.6)	1 (3.6)	3 (10.7)	0
Alopecia	2 (1.7)	0	1 (3.6)	1 (3.6)	1 (4.8)
Rash	1 (0.8)	2 (1.6)	1 (3.6)	1 (3.6)	0
Dry skin	0	2 (1.6)	2 (7.1)	0	0
Dermatitis contact	0	0	0	0	0
Cough	4 (3.4)	3 (2.4)	0	0	0
Dyspnoea	1 (0.8)	0	0	0	3 (14.3)
Decreased appetite	2 (1.7)	3 (2.4)	0	1 (3.6)	3 (14.3)
Hot flush	0	1 (0.8)	0	1 (3.6)	0
Hypertension	0	0	0	0	0
Palpitations	0	0	0	1 (3.6)	0

n (%)

No deaths were reported. Serious adverse events occurred in 2 subjects (calculus ureteric and oesophageal adenocarcinoma in 1 subject each) in the 12-week BCV 75 mg group, 2 subjects (pleurisy and chest pain in 1 subject, and abdominal wall abscess in 1 subject) in the 12-week BCV 150 mg BID

group, 1 subject (radiculopathy) in the 24-week BCV 75 mg BID group, and 2 subjects (psychotic disorder and syncope in 1 subject each) in the 24-week BCV 150 mg BID group. None of these serious adverse events were related to the study drug, and their outcomes were all reported as resolved.

Adverse events leading to discontinuation occurred in 1 subject (oesophageal adenocarcinoma) in the 12-week BCV 75 mg BID group and 2 subjects (abdominal wall abscess and throat tightness in 1 subject each) in the 12-week BCV 150 mg BID group. All these events, excluding throat tightness in 1 subject, were considered unrelated to the study drug, and their outcomes were all reported as resolved.

7.2 Japanese phase III study (CTD 5.3.5.1-1, Study AI443117 [May 2014 to August 2015])

A randomized, double-blind, parallel-group study (treatment-naïve[37)] patients [genotype 1b]) using the DCV + ASV combination regimen as control and an open-label, uncontrolled study (treatment-naïve or IFN-experienced patients[42)] [genotype 1a]) were conducted at 35 sites in Japan to investigate the efficacy and safety of the co-administration of DCV, ASV, and BCV in genotype 1 chronic hepatitis C patients without cirrhosis or with compensated cirrhosis[43)] (target sample size, 276 subjects).[44)]

Treatment-naïve (genotype 1b) patients received an FDC tablet containing DCV 30 mg, ASV 200 mg, and BCV 75 mg (DCV/ASV/BCV FDC tablet) orally BID after meals for 12 weeks[45)] (DCV/ASV/BCV group) or DCV 60 mg QD + ASV 100 mg BID orally for 24 weeks (DCV + ASV group). Treatment-naïve or IFN-experienced (genotype 1a) patients received the DCV/ASV/BCV FDC tablet BID orally after meals for 12 weeks (Figure 4).

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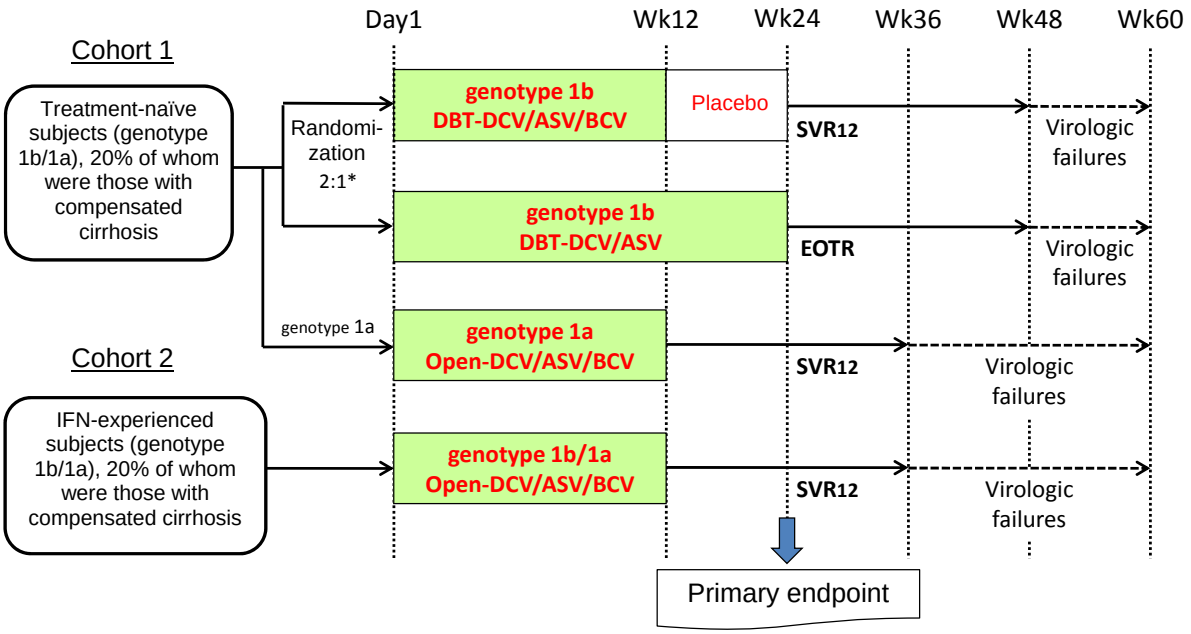
42) Null responders or partial responders to IFN-based treatment, relapsed patients after previous treatment, and patients intolerant to IFN were defined as follows. The study excluded patients previously treated with IFN in combination with direct-acting antivirals including telaprevir and simeprevir sodium.
   (a) Null responder: Patients with <2 $\log_{10}$ IU/mL decline from baseline in HCV RNA following ≥12 weeks of treatment with pegIFNα/RBV or IFNβ/RBV
   (b) Partial responder: Patients who achieved ≥2 $\log_{10}$ IU/mL decline from baseline in HCV RNA following ≥12 weeks of treatment with pegIFNα/RBV or IFNβ/RBV but had HCV RNA above the LLOQ
   (c) Patients experiencing a relapse after previous treatment: Patients who achieved an HCV RNA level below the LLOQ at the end of the previous treatment and then had an HCV RNA level above the LLOQ during the follow-up period
   (d) Patients intolerant to IFN: Patients who previously received IFN-based treatment for <12 weeks and then discontinued treatment due to toxicities associated with IFN and/or RBV.

43) The study included chronic hepatitis C patients with cirrhosis meeting any of the following criteria:
   (a) Patients with a METAVIR score of F4, or a score of F4 under the new Inuyama classification system, based on a liver biopsy performed before the start of study treatment
   (b) The severity of cirrhosis assessed by Fibroscan within 12 months before the start of study treatment was >14.6 kPa.
   (c) At screening, the discriminant score for diagnosing cirrhosis in chronic hepatitis patients was >0:
   Discriminant score calculated by the following: γ-globulin (%) × 0.124 + hyaluronic acid (ng/mL) × 0.001 + sex (male, 1; female, 2) × (–0.413) + platelet count ($10{,}000/mm^3$) × (–0.075) – 2.005

44) The protocol required that approximately 20% of subjects should be chronic hepatitis C patients with compensated cirrhosis.

45) Treatment-naïve genotype 1b patients in the DCV/ASV/BCV group orally received the DCV/ASV/BCV FDC tablet for 12 weeks and then placebo for another 12 weeks.



* Subjects (genotype 1a) were assigned to the DCV/ASV/BCV group in the open-label study without being randomized.
Subjects (genotype 1b) were stratified according to the presence or absence of compensated cirrhosis.

DBT, Double-blind setting
Open, Open-label setting

Figure 4. Study design of the Japanese phase III study (AI443117)

The efficacy and safety analysis populations consisted of 224 randomized, treatment-naïve (genotype 1b) subjects who received ≥1 dose of the study drug (149 subjects in the DCV/ASV/BCV group [123 subjects without cirrhosis and 26 subjects with compensated cirrhosis] and 75 subjects in the DCV/ASV group [61 subjects without cirrhosis and 14 subjects with compensated cirrhosis]), 3 treatment-naïve (genotype 1a) subjects who received ≥1 dose of the study drug in the open-label setting, 64 IFN-experienced (genotype 1b) subjects (44 subjects without cirrhosis and 20 subjects with compensated cirrhosis), and 1 IFN-experienced (genotype 1a) subject without cirrhosis.

Efficacy data were analyzed. The SVR12 rate[46)] [95% CI] in treatment-naïve (genotype 1b) subjects without cirrhosis in the DCV/ASV/BCV group was the primary endpoint, and the result was 95.9% [90.8%, 98.7%] (118 of 123 subjects), showing that the lower bound of the 95% CI exceeded the pre-defined SVR12 threshold (79%[47)]). The SVR12 rates [95% CIs] in treatment-naïve (genotype 1b) subjects with compensated cirrhosis, IFN-experienced (genotype 1a or 1b) subjects without cirrhosis, and IFN-experienced (genotype 1a or 1b) subjects with compensated cirrhosis in the DCV/ASV/BCV group were 96.2% [80.4%, 99.9%] (25 of 26 subjects), 95.6% [84.9%, 99.5%] (43 of 45 subjects), and 95.0% [75.1%, 99.9%] (19 of 20 subjects), respectively. The SVR12 rate in treatment-naïve (genotype 1a) subjects without cirrhosis was 100% (3 of 3 subjects), and the 1 IFN-experienced (genotype 1a) subject without cirrhosis did not achieve SVR. The SVR12 rates [95% CIs] in treatment-naïve (genotype

46) The proportion of subjects with undetectable HCV RNA 12 weeks after the end of treatment. For subjects with no available HCV RNA data at 12 weeks after the end of treatment, data on SVR 12 achievement status were imputed by the Next Value Carried Backwards method using the first HCV RNA level obtained at the post-treatment week 12 visit.

47) In the Japanese phase III study of simeprevir sodium, the SVR12 rate in treatment-naïve non-cirrhotic patients with chronic hepatitis C was 89.1%, and the upper bound of its 95% CI was 94.2%. In the Japanese phase III study of DCV/ASV/BCV FDC, taking into account the absence of IFN and ribavirin, the SVR 12 threshold was determined to be 79% by subtracting 15% from 94.2%.

1b) subjects without cirrhosis and those with compensated cirrhosis in the DCV/ASV group were 85.2% [76.3%, 94.1%] (52 of 61 subjects) and 92.9% [66.1%, 99.8%] (13 of 14 subjects), respectively.

Among treatment-naïve (genotype 1b) chronic hepatitis C subjects without cirrhosis or with compensated cirrhosis, the incidence of adverse events (including abnormal laboratory values) was 73.2% (109 of 149 subjects) in the DCV/ASV/BCV group and 84.0% (63 of 75 subjects) in the DCV/ASV group. Among IFN-experienced (genotype 1b) chronic hepatitis C subjects without cirrhosis or with compensated cirrhosis, the incidence of adverse events (including abnormal laboratory values) was 84.4% (54 of 64 subjects) in the DCV/ASV/BCV group. Among treatment-naïve (genotype 1b) chronic hepatitis C subjects without cirrhosis or with compensated cirrhosis, the incidence of adverse drug reactions was 56.4% (84 of 149 subjects) in the DCV/ASV/BCV group and 52.0% (39 of 75 subjects) in the DCV/ASV group. Among IFN-experienced (genotype 1b) chronic hepatitis C subjects without cirrhosis or with compensated cirrhosis, the incidence of adverse drug reactions was 57.8% (37 of 64 subjects) in the DCV/ASV/BCV group. The adverse events and adverse drug reactions occurring in ≥5% of subjects in any treatment group are summarized in Table 32.

Table 32. Adverse events and adverse drug reactions (including abnormal laboratory values) occurring in ≥5% of subjects in any treatment group

Name of event	Adverse event				Adverse drug reaction			
	Genotype 1b			Genotype 1a/1b	Genotype 1b			Genotype 1a/1b
	Treatment-naïve		IFN-experienced	Treatment-naïve or treatment-experienced	Treatment-naïve		IFN-experienced	Treatment-naïve or IFN-experienced
	DCV/ASV/BCV	DCV/ASV	DCV/ASV/BCV	DCV/ASV/BCV	DCV/ASV/BCV	DCV/ASV	DCV/ASV/BCV	DCV/ASV/BCV
N	149	75	64	217	149	75	64	217
Any event	109 (73.2)	63 (84.0)	54 (84.4)	166 (76.5)	84 (56.4)	39 (52.0)	37 (57.8)	123 (56.7)
ALT increased	40 (26.8)	20 (26.7)	8 (12.5)	50 (23.0)	40 (26.8)	19 (25.3)	8 (12.5)	50 (23.0)
AST increased	33 (22.1)	18 (24.0)	8 (12.5)	42 (19.4)	33 (22.1)	18 (24.0)	8 (12.5)	42 (19.4)
Lipase increased	1 (0.7)	4 (5.3)	3 (4.7)	4 (1.8)	1 (0.7)	4 (5.3)	2 (3.1)	3 (1.4)
Diarrhoea	12 (8.1)	10 (13.3)	7 (10.9)	19 (8.8)	8 (5.4)	8 (10.7)	3 (4.7)	11 (5.1)
Abdominal pain upper	7 (4.7)	1 (1.3)	4 (6.3)	11 (5.1)	3 (2.0)	1 (1.3)	4 (6.3)	7 (3.2)
Nausea	7 (4.7)	6 (8.0)	4 (6.3)	11 (5.1)	4 (2.7)	2 (2.7)	2 (3.1)	6 (2.8)
Stomatitis	3 (2.0)	6 (8.0)	1 (1.6)	5 (2.3)	1 (0.7)	0	1 (1.6)	2 (0.9)
Pyrexia	29 (19.5)	10 (13.3)	14 (21.9)	44 (20.3)	24 (16.1)	6 (8.0)	11 (17.2)	36 (16.6)
Malaise	10 (6.7)	3 (4.0)	4 (6.3)	14 (6.5)	10 (6.7)	2 (2.7)	3 (4.7)	13 (6.0)
Eosinophilia	28 (18.8)	8 (10.7)	8 (12.5)	37 (17.1)	28 (18.8)	8 (10.7)	8 (12.5)	37 (17.1)
Lymphopenia	9 (6.0)	3 (4.0)	4 (6.3)	14 (6.5)	8 (5.4)	1 (1.3)	4 (6.3)	13 (6.0)
Pruritus	7 (4.7)	2 (2.7)	7 (10.9)	14 (6.5)	6 (4.0)	2 (2.7)	5 (7.8)	11 (5.1)
Rash	7 (4.7)	6 (8.0)	4 (6.3)	11 (5.1)	6 (4.0)	3 (4.0)	4 (6.3)	10 (4.6)
Nasopharyngitis	11 (7.4)	15 (20.0)	10 (15.6)	21 (9.7)	0	1 (1.3)	0	0
Hyperbilirubinaemia	22 (14.8)	5 (6.7)	9 (14.1)	32 (14.7)	22 (14.8)	5 (6.7)	9 (14.1)	32 (14.7)
Headache	13 (8.7)	7 (9.3)	10 (15.6)	24 (11.1)	9 (6.0)	5 (6.7)	7 (10.9)	17 (7.8)
Back pain	3 (2.0)	4 (5.3)	1 (1.6)	4 (1.8)	0	0	0	0
Decreased appetite	9 (6.0)	2 (2.7)	5 (7.8)	14 (6.5)	8 (5.4)	2 (2.7)	4 (6.3)	12 (5.5)

n (%)

No deaths were reported. Among treatment-naïve or IFN-experienced chronic hepatitis C subjects without cirrhosis or with compensated cirrhosis, serious adverse events occurred in 13 of 217 subjects treated with the DCV/ASV/BCV FDC tablet (gallbladder disorder in 4 subjects; hyperbilirubinaemia, pyrexia, and pyelonephritis in 2 subjects each; and hepatomegaly, ALT increased, AST increased, C-reactive protein increased, international normalized ratio [INR] increased, gastric varices haemorrhage, ileus, sepsis, disseminated intravascular coagulation, vertigo positional, and erythema multiforme in 1 subject each [some subjects experienced more than one event]) and in 8 of 75 subjects treated with DCV/ASV (bile duct stone, duodenal ulcer perforation, haemorrhoids, gastroenteritis, deafness, erythema nodosum, sick sinus syndrome, overdose, and prostate cancer in 1 subject each [some subjects experienced more than one event]). The following serious adverse events in 8 subjects in the DCV/ASV/BCV group were considered related to the study drug: gallbladder disorder in 4 subjects, hyperbilirubinaemia and pyrexia in 2 subjects each, and hepatomegaly, ALT increased, AST increased, C-reactive protein increased, INR increased, and erythema multiforme in 1 subject each (some subjects experienced more than one event). The following serious adverse events in 2 subjects in the DCV/ASV group were considered related to the study drug: deafness and duodenal ulcer perforation in 1 subject each. The outcomes of all these events were reported as "resolved," except for prostate cancer in the DCV/ASV group, which was reported as "not resolved."

Adverse events leading to discontinuation occurred in 21 subjects in the DCV/ASV/BCV group (ALT increased in 11 subjects, hyperbilirubinaemia in 10 subjects, AST increased in 5 subjects, gallbladder disorder in 2 subjects, and INR increased, prothrombin level decreased, pyrexia, ileus, and erythema multiforme in 1 subject each [some subjects experienced more than one event]) and in 7 subjects in the DCV/ASV group (ALT increased in 3 subjects, AST increased and hyperbilirubinaemia in 2 subjects each, and bile duct stone, pyrexia, malaise, and sick sinus syndrome in 1 subject each [some subjects experienced more than one event]). Except for ileus in 1 subject in the DCV/ASV/BCV group and bile duct stone and sick sinus syndrome in 1 subject each in the DCV/ASV group, all these adverse events were considered related to the study drug. The outcomes of all the adverse events leading to discontinuation were reported as resolved.

Outline of the review

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy and study plan

In view of the following review, PMDA concluded that DCV/ASV/BCV FDC is expected to be effective for treating Japanese patients with genotype 1 chronic hepatitis C without cirrhosis or with compensated cirrhosis.

However, given the limited information available from clinical studies, post-marketing information on the relationship between baseline resistance mutations and the efficacy of the DCV/ASV/BCV FDC tablet and on the status of resistance mutations in patients failing to achieve SVR despite treatment with

DCV/ASV/BCV FDC should be collected by literature review and other measures. Any new findings should be communicated to healthcare professionals in an expedited manner.

The above conclusion by PMDA will be finalized, taking into account the comments made in the Expert Discussion.

7.R.1.1 Efficacy and study plan

The applicant's explanation about the efficacy of DCV/ASV/BCV FDC:

At the time of starting the Japanese phase III study (AI443117), DCV and ASV had not been approved in Japan, but the applicant had obtained information that the SVR12 rate in patients with chronic hepatitis C (genotype 1b) was 90.1%[48)] in a Japanese clinical study of the DCV + ASV combination regimen (Package Insert of Daklinza Tablets 60 mg, version 10). Meanwhile, the SVR12 rate in patients with chronic hepatitis C (genotype 1a) was 22.2%[49)] in a foreign clinical study of the DCV + ASV combination regimen (CTD 5.3.5.2.3 of the initial application for Daklinza Tablets 60 mg), indicating the necessity for more effective treatment options for patients with chronic hepatitis C (genotype 1a). In a foreign phase II study (AI443014) conducted to investigate the efficacy and safety of the DCV + ASV + BCV combination regimen, the SVR12 rates in treatment-naïve (genotype 1b) patients and treatment-naïve (genotype 1a) patients after treatment with the DCV + ASV + BCV combination regimen [groups 1 through 6; see Section 7.1] were 95.7% and 90.3%, respectively, suggesting that the efficacy of this regimen was sufficient regardless of HCV genotype. Under these circumstances, the applicant considered it necessary to clarify the clinical positioning of the DCV + ASV + BCV combination regimen relative to the DCV + ASV combination regimen in Japan. Therefore, the DCV + ASV combination regimen was selected as the control regimen in the Japanese phase III study (AI443117). However, the DCV + ASV combination regimen was not approved in Japan at the time of planning this study and therefore its clinical positioning was unclear. For this reason, the study was not designed to verify the superiority or non-inferiority of the DCV + ASV + BCV combination regimen to the DCV + ASV combination regimen. Instead, by referring to the results of Japanese studies of simeprevir sodium in treatment-naïve (genotype 1b) chronic hepatitis C patients, the clinically significant SVR12 threshold was pre-defined as 79% and the study was designed so that the efficacy of the DCV + ASV + BCV combination regimen would be demonstrated if the lower bound of the 95% CI of SVR12 rate exceeded the threshold.

The SVR12 rate [95% CI] in treatment-naïve (genotype 1b) chronic hepatitis C subjects without cirrhosis in the DCV/ASV/BCV FDC group, which was the primary endpoint, was 95.9% [90.8%, 98.7%] (118 of 123 subjects). Since the lower bound of the 95% CI exceeded the pre-defined SVR12 threshold (79%), the efficacy of the regimen was demonstrated [see Section 7.2]. The results of subgroup analyses of (genotype 1b) chronic hepatitis C subjects without cirrhosis or with compensated cirrhosis

48) Results in treatment-naïve chronic hepatitis C subjects who were eligible for IFN-based treatment and chronic hepatitis C subjects who relapsed after previous therapy

49) Results of subjects with chronic hepatitis C with <2 $\log_{10}$ IU/mL decline from baseline in HCV RNA after $\geq$12 weeks of treatment with PegIFNα + RBN

are summarized in Table 33, which show that the efficacy of the DCV/ASV/BCV FDC tablet in subjects was similar irrespective of cirrhosis status. The SVR24 rates in treatment-naïve and IFN-experienced (genotype 1b) subjects without cirrhosis in the DCV/ASV/BCV FDC group were 95.1% (117 of 123 subjects) and 97.7% (43 of 44 subjects), respectively, which were similar to the SVR12 rates in these subject populations. The SVR24 rates in treatment-naïve and IFN-experienced chronic hepatitis C subjects with compensated cirrhosis in the DCV/ASV/BCV FDC group were 96.2% (25 of 26 subjects) and 95.0% (19 of 20 subjects), respectively.

Table 33. SVR12 rates by subgroup in the Japanese phase III study (AI443117)

		Treatment-naïve (genotype 1b)		IFN-experienced (genotype 1b)
		DCV/ASV/BCV	DCV/ASV	DCV/ASV/BCV
N		149	75	64
Overall		143/149 (96.0)	65/75 (86.7)	62/64 (96.9)
Degree of liver fibrosis	Chronic hepatitis C without cirrhosis	118/123 (95.9)	52/61 (85.2)	43/44 (97.7)
	Chronic hepatitis C with compensated cirrhosis	25/26 (96.2)	13/14 (92.9)	19/20 (95.0)
Age	<65 years	74/78 (94.9)	43/46 (93.5)	34/35 (97.1)
	≥65 years	69/71 (97.2)	22/29 (75.9)	28/29 (96.6)
Response to previous treatment	Null responder	–	–	5/5 (100)
	Partial responder	–	–	16/17 (94.1)
	Relapsed	–	–	21/21 (100.0)
	Intolerant to IFN	–	–	20/21 (95.2)
HCV RNA	<10 million IU/mL	104/106 (98.1)	40/46 (87.0)	50/51 (98.0)
	≥10 million IU/mL	39/43 (90.7)	25/29 (86.2)	12/13 (92.3)
IL28B polymorphism (RS12979860)	CC	91/96 (94.8)	44/51 (86.3)	31/32 (96.9)
	Non-CC	51/51 (100.0)	21/24 (87.5)	31/32 (96.9)
IL28B polymorphism (RS8099917)	TT	92/97 (94.8)	44/51 (86.3)	31/32 (96.9)
	Non-TT	50/50 (100.0)	21/24 (87.5)	31/32 (96.9)

n/N (%)

The SVR12 rate in treatment-naïve or IFN-experienced (genotype 1a) subjects without cirrhosis was 75.0% (3 of 4 subjects) after treatment with the DCV/ASV/BCV FDC tablet. Although the available data from subjects with genotype 1a infection were limited, the SVR12 rates in treatment-naïve and IFN-experienced (genotype 1a) subjects without cirrhosis were 90.4% (207 of 229 subjects) and 85.3% (64 of 75 subjects), respectively, and the SVR12 rates in treatment-naïve and IFN-experienced (genotype 1a) subjects with compensated cirrhosis were 90.0% (36 of 40 subjects) and 85.7% (30 of 35 subjects), respectively, in foreign phase III studies of DCV/ASV/BCV FDC tablet (AI443102 and AI443113). In these foreign studies, the SVR12 rates in treatment-naïve and IFN-experienced (genotype 1b) subjects without cirrhosis were 97.6% (81 of 83 subjects) and 100% (28 of 28 subjects), respectively, and the SVR12 rates in treatment-naïve and IFN-experienced (genotype 1b) subjects with compensated cirrhosis were 100% (17 of 17 subjects) and 90.0% (9 of 10 subjects), respectively, showing that the results in subjects with genotype 1a infection were similar to those in subjects with genotype 1b infection. Therefore, DCV/ASV/BCV FDC is expected to be effective for treating treatment-naïve or IFN-

experienced Japanese patients with chronic hepatitis C (genotype 1a) without cirrhosis or with compensated cirrhosis.

Based on the above, the efficacy of DCV/ASV/BCV FDC is considered to be promising in Japanese patients with chronic hepatitis C (genotype 1) without cirrhosis or with compensated cirrhosis.

PMDA's view:
Considering the approval status of relevant drugs at the time of starting the Japanese phase III study (AI443117) and the then available data from other clinical studies, it is understandable that the applicant did not design the study to verify the superiority or non-inferiority of DCV/ASV/BCV FDC to the DCV + ASV regimen or other therapies as the control at study sites in Japan. In the Japanese phase III study (AI443117), the lower bound of the 95% CI of the SVR12 rate in treatment-naïve (genotype 1b) chronic hepatitis C subjects without cirrhosis in the DCV/ASV/BCV group exceeded the pre-defined SVR12 threshold (79%). Moreover, the SVR12 rates in IFN-experienced (genotype 1b) subjects without cirrhosis, treatment-naïve (genotype 1b) subjects with compensated cirrhosis, and IFN-experienced (genotype 1b) subjects with compensated cirrhosis in the DCV/ASV/BCV group were 97.7% (43 of 44 subjects), 96.2% (25 of 26 subjects), and 95.0% (19 of 20 subjects), respectively. Taking into account the above results in subjects with genotype 1b infection and the results of Japanese and foreign studies in patients with chronic hepatitis C (genotype 1a), PMDA concluded that the efficacy of DCV/ASV/BCV FDC is promising in treatment-naïve or IFN-experienced (genotype 1) chronic hepatitis C patients without cirrhosis or with compensated cirrhosis. However, the applicant should provide healthcare professionals appropriately with information advising that the efficacy of the DCV/ASV/BCV FDC tablet may be decreased in HCV genotype 1a infected patients with baseline resistance mutations in the NS5A region [see Section 7.R.1.2].

7.R.1.2 Viral resistance mutations

The applicant's explanation about the emergence of viruses resistant to the DCV/ASV/BCV FDC tablet and the effects of resistant viruses on the efficacy of the DCV/ASV/BCV FDC tablet:
In the resistance analysis population[50)] in the Japanese phase III study (AI443117), the SVR12 rates in HCV genotype 1b-injected subjects by the status of baseline resistance mutation in the NS5A region are shown in Table 34. One subject was excluded from the analysis because the subject could not achieve SVR12 due to being lost to follow-up after achievement of SVR4.

50) All subjects were included in the analysis for resistance mutations in the NS5A region. For the NS3 and NS5B regions, resistance mutation tests were performed in all subjects with virologic failure and randomly selected subjects achieving SVR in an approximate ratio of 1:2. Resistance mutation tests were performed by the population sequence method (direct sequence method; detection sensitivity, 20% to 25%) and all the amino acid substitutions in target regions were investigated. The main mutations to be analyzed were as follows: positions 36, 54, 55, 77, 80, 122, 155, 156, 168, 169, and 170 in the NS3 region; 24, 28, 29, 30, 31, 32, 58, 62, 92, and 93 (genotype 1a) and 28, 30, 31, and 93 (genotype 1b) in the NS5A region; and 389, 392, 421, 494, 495, 496, and 499 in the NS5B region.

Table 34. SVR12 rates in HCV genotype 1b-infected subjects by baseline resistance mutation in Japanese phase III study (AI443117)

		DCV/ASV/BCV				DCV/ASV	
		Treatment-naïve		IFN-experienced		Treatment-naïve	
Region	Resistance mutation	Mutation positive	Mutation negative	Mutation positive	Mutation negative	Mutation positive	Mutation negative
NS5A	L28, R30, L31, P58, Q62, A92, or Y93	93.8 (60/64)	98.8 (83/84)	96.8 (30/31)	97.0 (32/33)	73.7 (28/38)	100 (37/37)
	L28M, R30Q, L31, or Y93H	90.5 (38/42)	99.1 (105/106)	92.9 (13/14)	98.0 (49/50)	59.1 (13/22)	98.1 (52/53)
	L31 or Y93	88.9 (24/27)	98.3 (119/121)	100 (12/12)	96.2 (50/52)	43.8 (7/16)	98.3 (58/59)
	L31 or Y93H	88.9 (24/27)	98.3 (119/121)	100 (11/11)	96.2 (51/53)	43.8 (7/16)	98.3 (58/59)
	L28	90.0 (9/10)	97.1 (134/138)	75.0 (3/4)	98.3 (59/60)	100 (3/3)	86.1 (62/72)
	R30	93.8 (15/16)	97.0 (128/132)	75.0 (3/4)	98.3 (59/60)	83.3 (5/6)	87.0 (60/69)
	L31	100 (3/3)	96.6 (140/145)	100 (1/1)	96.8 (61/63)	–	86.7 (65/75)
	Y93	87.5 (21/24)	98.4 (122/124)	100 (11/11)	96.2 (51/53)	43.8 (7/16)	98.3 (58/59)
	Y93H	87.5 (21/24)	98.4 (122/124)	100 (10/10)	96.3 (52/54)	43.8 (7/16)	98.3 (58/59)

% (n/N)
–: Not applicable

Baseline resistance mutations at L31 and Y93H in the NS5A region have been reported to affect the efficacy of the DCV + ASV combination regimen (*Adv Ther*. 2015;32:637-649). Also in the DCV/ASV group in Study AI443117, decreased efficacy was observed in subjects who were positive for the L31 or Y93H mutation. On the other hand, there were no marked effects on SVR12 rates in treatment-naïve or IFN-experienced subjects in the DCV/ASV/BCV group. Baseline resistance mutations in the NS3 and NS5B regions were examined in 11 and 9 subjects, respectively, in whom no resistance mutations in these regions were identified.

Among subjects treated with the DCV/ASV/BCV FDC tablet in the Japanese phase III study (AI443117), 8 subjects had virologic failure.[51)] NS3, NS5A, and NS5B resistance mutations identified in the 8 subjects are shown in Table 35. While no NS3 or NS5B resistance mutations were detected in any of 7 subjects with HCV genotype 1b infection at baseline or at the time of virologic failure, NS5A resistance mutations were detected in 5 of the 7 subjects after the end of treatment. Resistance mutations were newly detected in 2 of the 7 subjects after the end of treatment. In 1 subject with HCV genotype 1a infection, no resistance mutations were detected in the NS3, NS5A, or NS5B region at baseline, but resistance mutations were detected at R155K in the NS3 region, Y93N in the NS5A region, and P495S in the NS5B region at the time of virologic failure.

51) Of 9 subjects with virologic treatment failure in the DCV/ASV/BCV group, 1 subject was excluded from the analysis because the subject was lost to follow-up after achieving SVR4.

Table 35. NS3, NS5A, and NS5B resistance mutations in subjects with virologic failure

Subject	Genotype	NS3[a]			NS5A[a]			NS5B[a]		
		Baseline resistance mutation	At the time of virologic failure		Baseline resistance mutation	At the time of virologic failure		Baseline resistance mutation	At the time of virologic failure	
			Resistance mutation	Fold change in susceptibility[b]		Resistance mutation	Fold change in susceptibility[b]		Resistance mutation	Fold change in susceptibility[b]
Treatment-naïve	1b	–	–		Y93H	Q54, Y93H	6.7[c]	–	–	
	1b	–	–		–	L31V	33.3	–	–	
	1b	–	–		Y93Y/H	Y93H	30	–	–	
	1b	–	–		Y93/H	Y93H	30	–	–	
	1b	–	–		–[d]	–[d]		–	–	
IFN-experienced	1b	–	–		–	L31V	33.3	–	–	
	1b	–	–		–[e]	–[e]		–	–	
	1a	–	R155K	18.9	–	Y93N	34833.3	–	P495S	98.4

–, No resistance mutation

a) Genotype 1b: resistance mutations at R155 and D168 in the NS3 region, L31 and Y93 in the NS5A region, and P495 in the NS5B region;
Genotype 1a: resistance mutations at R155 and D168 in the NS3 region, M28, Q30, L31, and Y93 in the NS5A region, and P495 in the NS5B region

b) Mutant EC_{50}/ wild-type EC_{50}

c) In addition to resistance mutations, Q54 variant in the NS5A region affected the change in susceptibility.

d) Although mutations were detected at L28M, R30Q, and A92T (fold change in susceptibility, 1.7) at baseline and at L28M, R30H, and A92T (fold change in susceptibility, 266.7) at the time of virologic failure, their involvement in resistance to DCV was unknown, according to the applicant's explanation.

e) Although mutations were observed at L28M, R30Q, and Q62N (fold change in susceptibility, 1.3) at baseline and at L28M, R30H, and Q62N (fold change in susceptibility, 900) at the time of virologic failure, their involvement in resistance to DCV was unknown, according to the applicant's explanation.

The efficacy of treatment was investigated in subjects with HCV genotype 1a infection. Table 36 shows the SVR12 rates in the resistance analysis populations[50,52)] in Japanese and foreign phase III studies of the DCV/ASV/BCV FDC tablet (Studies AI443117, 443102, and 443113), which are summarized according to the baseline status of NS5A resistance mutations.

Table 36. SVR12 rates in HCV genotype 1a-infected subjects with by baseline status of NS5A resistance mutations (Pooled analysis of Studies AI443117, 443102, and 443113)

		Chronic hepatitis C without cirrhosis		Chronic hepatitis C with compensated cirrhosis	
Region	Resistance mutation	Mutation positive	Mutation negative	Mutation positive	Mutation negative
NS5A	M28, Q30, L31, H58, E62, A92, or Y93	85.5 (53/62)	90.2 (220/244)	77.8 (14/18)	92.9 (52/56)
	M28, Q30, L31, or Y93	77.1 (27/35)	90.8 (246/271)	77.8 (7/9)	90.8 (59/65)
	M28	81.5 (22/27)	90.0 (251/279)	80.0 (4/5)	89.9 (62/69)
	Q30	0 (0/5)	90.7 (273/301)	66.7 (2/3)	90.1 (64/71)
	L31	100 (4/4)	89.1 (269/302)	100 (2/2)	88.9 (64/72)
	Y93	50.0 (1/2)	89.5 (272/304)	0 (0/1)	90.4 (66/73)

% (n/N)
–, Not applicable

The SVR12 rate in chronic hepatitis C subjects without cirrhosis or with compensated cirrhosis with a baseline Q30 variant in the NS5A region was 25.0% (2 of 8 subjects), suggesting that the Q30 variant

52) A total of 3 subjects (2 subjects who had difficulty in undergoing resistance mutation tests at baseline and 1 subject who died after the end of treatment) were excluded from this analysis.

may affect the efficacy of the DCV/ASV/BCV FDC tablet. Among 42 subjects[53] with virologic failure, 30 subjects were found to harbor the Q30 variant at the time of virologic failure. However, since the proportion of subjects with the Q30 variant at baseline was small, the variant had little effect on the overall SVR12 rate. Analysis was performed on baseline resistance mutations in the NS3 or NS5B regions. While mutations at positions 155 and 168, which caused a decrease in ASV activity in *in vitro* studies, were detected in 1 subject each among 148 subjects undergoing resistance mutation tests, a mutation at position 495, which caused a decrease in BCV activity, was not detected in any subjects. Although there were few subjects with baseline resistance mutations in the NS3 or NS5B region, it was difficult to draw a conclusion about the effects of baseline resistance mutations in the NS3 or NS5B region on the efficacy of the DCV/ASV/BCV FDC tablet due to the limited number of subjects tested for resistance mutations. Some of 42 subjects with virologic failure were found to harbor certain resistance mutations; mutations at R155 and D168 in the NS3 region were detected in 35 and 6 (some subjects had more than one mutation), respectively, and mutations at P495 in the NS5B region were detected in 12 subjects. These resistance mutations may be associated with virologic failure.

PMDA's view:

Baseline NS5A resistance mutations (e.g., L31, Y93), which have been reported to affect the efficacy of the DCV + ASV combination regimen, had no clear impact on the efficacy of the DCV/ASV/BCV FDC tablet in subjects with HCV genotype 1b infection and therefore, its efficacy in this patient population is promising. Meanwhile, the results of foreign clinical studies suggested that baseline NS5A resistance mutations may decrease the efficacy of the DCV/ASV/BCV FDC tablet in patients with HCV genotype 1a infection. This information should be communicated to healthcare professionals appropriately. Given that resistance mutations in the NS3 and NS5B regions were detected in HCV genotype 1a infected subjects with virologic failure in foreign clinical studies and that there are limited data available from clinical studies on the relationship between resistance mutations and the efficacy of the DCV/ASV/BCV FDC tablet, post-marketing information on resistance mutations at baseline and resistance mutations in patients who fail to achieve SVR despite the treatment with DCV/ASV/BCV FDC should be collected by literature review or other measures. Any new findings should be communicated to healthcare professionals in an expedited manner.

7.R.2 Safety

On the basis of the review of the safety of DCV/ASV/BCV FDC in Sections 7.R.2.1 through 7.R.2.5," PMDA concluded that the safety of DCV/ASV/BCV FDC in Japanese patients with chronic hepatitis C (genotype 1) without cirrhosis or with compensated cirrhosis is acceptable.

However, given that hepatic function disorders, including bilirubin elevation-related events,[54] ALT increased, and AST increased, were reported in patients treated with the DCV/ASV/BCV FDC tablet, the applicant should advise physicians to perform periodic liver function tests for early detection of

53) One subject who had difficulty in receiving resistance mutation tests at baseline and who did not achieve SVR12 was included.

54) Adverse events coded to MedDRA (v 17.1) PTs "blood bilirubin increased," "hyperbilirubinaemia," "bilirubin conjugated increased," "blood bilirubin unconjugated increased," "gallbladder disorder," "cholecystitis," and "hepatomegaly"

hepatic function disorder and to take appropriate measures including discontinuation of DCV/ASV/BCV FDC based on the patient's condition. At the same time, post-marketing information on those events should be collected to take new measures as needed. Because of limited clinical experience with the use of the DCV/ASV/BCV FDC tablet in elderly patients, the collection of post-marketing information on this patient population is necessary.

The above conclusion by PMDA will be finalized, taking into account the comments made in the Expert Discussion.

7.R.2.1 Difference in safety profile between the DCV/ASV/BCV FDC tablet and the DCV + ASV combination regimen

The applicant's explanation about the safety profiles of the DCV/ASV/BCV FDC tablet and the DCV + ASV combination regimen:

Table 37 summarizes the safety results in subjects treated with the DCV/ASV/BCV FDC tablet and those treated with DCV + ASV in the Japanese phase III study (AI443117). No deaths were reported in subjects treated with the DCV/ASV/BCV FDC tablet. Analyses of data from treatment-naïve (genotype 1b) chronic hepatitis C subjects without cirrhosis or with compensated cirrhosis showed no clear differences in the incidences of overall adverse events, Grade 3 or 4 adverse events, serious adverse events, or adverse events leading to discontinuation between the DCV/ASV/BCV group and the DCV/ASV group.

Table 37. Safety summary of the Japanese phase III study (AI443117) (safety analysis population)

	Treatment-naïve		IFN-experienced	Treatment-naïve or IFN-experienced
	Genotype 1b		Genotype 1b	Genotype 1a/1b
	DCV/ASV/BCV	DCV/ASV	DCV/ASV/BCV	DCV/ASV/BCV
N	149	75	64	217
Any adverse event	109 (73.2)	63 (84.0)	54 (84.4)	166 (76.5)
Grade 3 or 4 adverse events	44 (29.5)	17 (22.7)	16 (25.0)	62 (28.6)
Serious adverse events	10 (6.7)	8 (10.7)	2 (3.1)	13 (6.0)
Adverse events leading to discontinuation	17 (11.4)	7 (9.3)	4 (6.3)	21 (9.7)
Death	0	0	0	0

n (%)

According to the analyses of data from treatment-naïve (genotype 1b) chronic hepatitis C subjects, the adverse events reported with an incidence ≥5% higher in the DCV/ASV/BCV group than in the DCV/ASV group were eosinophilia, pyrexia, and hyperbilirubinaemia, which occurred in 28 of 149 subjects (18.8%), 29 of 149 subjects (19.5%), and 22 of 149 subjects (14.8%), respectively, in the DCV/ASV/BCV group, and in 8 of 75 subjects (10.7%), 10 of 75 subjects (13.3%), and 5 of 75 subjects (6.7%), respectively, in the DCV/ASV group [see Section 7.2]. According to analyses of data from treatment-naïve (genotype 1b) chronic hepatitis C subjects, the Grade 3 or 4 adverse events reported with an incidence ≥3% higher in the DCV/ASV/BCV group than in the DCV/ASV group were ALT increased, AST increased, and hyperbilirubinaemia, which occurred in 24 of 149 subjects (16.1%), 16

of 149 subjects (10.7%), and 8 of 149 subjects (5.4%), respectively, in the DCV/ASV/BCV group, and in 9 of 75 subjects (12.0%), 5 of 75 subjects (6.7%), and 1 of 75 subjects (1.3%), respectively, in the DCV/ASV group.

PMDA's view:

Based on the incidences of Grade 3 or 4 adverse events, serious adverse events, and other significant adverse events in the DCV/ASV/BCV group in the Japanese phase III study (AI443117), the safety of DCV/ASV/BCV FDC is acceptable if used under the supervision of a physician with adequate knowledge and experience in the treatment of viral liver disease. The sections below present a detailed review of data on adverse events reported with a higher incidence in the DCV/ASV/BCV group than in the DCV/ASV group; that is, hepatic function disorders including hyperbilirubinaemia, ALT increased, and AST increased, pyrexia, and eosinophil count increased, as well as safety in elderly patients. The safety of DCV/ASV/BCV FDC in chronic hepatitis C patients with compensated cirrhosis is described in Section 7.R.4.2.

7.R 2.2 Hepatic function disorder

The applicant's explanation about hepatic adverse events in subjects treated with the DCV/ASV/BCV FDC tablet:

Table 38 summarizes the incidences of bilirubin elevation-related adverse events,[54)] ALT increased, and AST increased reported in the Japanese phase III study (AI443117). Table 39 shows time to onset of Grade 3 or 4 hepatic adverse events in the DCV/ASV/BCV group.

Table 38. Summary of hepatic adverse events (Study AI443117)

	Bilirubin elevation-related adverse events		ALT increased		AST increased	
	DCV/ASV/BCV[a)]	DCV/ASV	DCV/ASV/BCV[a)]	DCV/ASV	DCV/ASV/BCV[a)]	DCV/ASV
N	217	75	217	75	217	75
Any adverse event	34 (15.7)	6 (8.0)	50 (23.0)	20 (26.7)	42 (19.4)	18 (24.0)
Grade 3 or 4 adverse events	13 (6.0)	1 (1.3)	30 (13.8)	9 (12.0)	20 (9.2)	5 (6.7)
Serious adverse events	5 (2.3)	0	1 (0.5)	0	1 (0.5)	0
Adverse events leading to discontinuation	10 (4.6)	2 (2.7)	11 (5.1)	3 (4.0)	5 (2.3)	2 (2.7)

n (%)

a) All subjects (treatment-naïve or IFN-experienced, genotype 1a or 1b) receiving the DCV/ASV/BCV FDC tablet

Table 39. Time to first onset of Grade 3 or 4 hepatic adverse events after treatment with the DCV/ASV/BCV FDC tablet[a)] (Study AI443117)

N	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13
ALT increased													
30	0	1	1	2	0	9	2	1	1	4	2	7	0
AST increased													
20	0	0	1	1	0	8	1	1	2	2	1	3	0
Blood bilirubin increased													
12	0	8	3	0	0	1	0	0	0	0	0	0	0
Cholecystitis or adverse events related to gallbladder disorder													
3	1	2	0	0	0	0	0	0	0	0	0	0	0
Cholangitis, cholangitis acute, bile duct stenosis, bile duct obstruction, biliary dilatation, or hepatomegaly													
0	0	0	0	0	0	0	0	0	0	0	0	0	0

n

a) Week 1 (Days 1-11), Week 2 (Days 12-18), Week 3 (Days 19-25), Week 4 (Days 26-32), Week 5 (Days 33-39), Week 6 (Days 40-46), Week 7 (Days 47-53), Week 8 (Days 54-60), Week 9 (Days 61-67), Week 10 (Days 68-74), Week 11 (Days 75-81), Week 12 (Days 82-88), Week 13 (Day ≥89)

When the incidence of bilirubin elevation-related adverse events was analyzed, the incidences of overall adverse events, Grade 3 or 4 adverse events, serious adverse events, and adverse events leading to discontinuation were higher in the DCV/ASV/BCV group than in the DCV/ASV group. When the incidence of ALT or AST increased was analyzed, the incidence of Grade 3 or 4 adverse events was higher in the DCV/ASV/BCV group than in the DCV/ASV group. According to the analysis of time-to-onset of Grade 3 or 4 ALT or AST increased, the highest number of events occurred in the DCV/ASV/BCV group at Week 6, but no specific tendency was observed. Meanwhile, the median time to onset (range) of Grade 3 or 4 bilirubin elevation-related adverse events (e.g., Grade 3 or 4 blood bilirubin increased, cholecystitis, and adverse events related to gallbladder disorder) was 16.0 days (11-43 days), and all the cases occurred no later than Week 6. These results suggest that patients should be carefully monitored for bilirubin elevation-related adverse events in the early stage of treatment with DCV/ASV/BCV FDC.

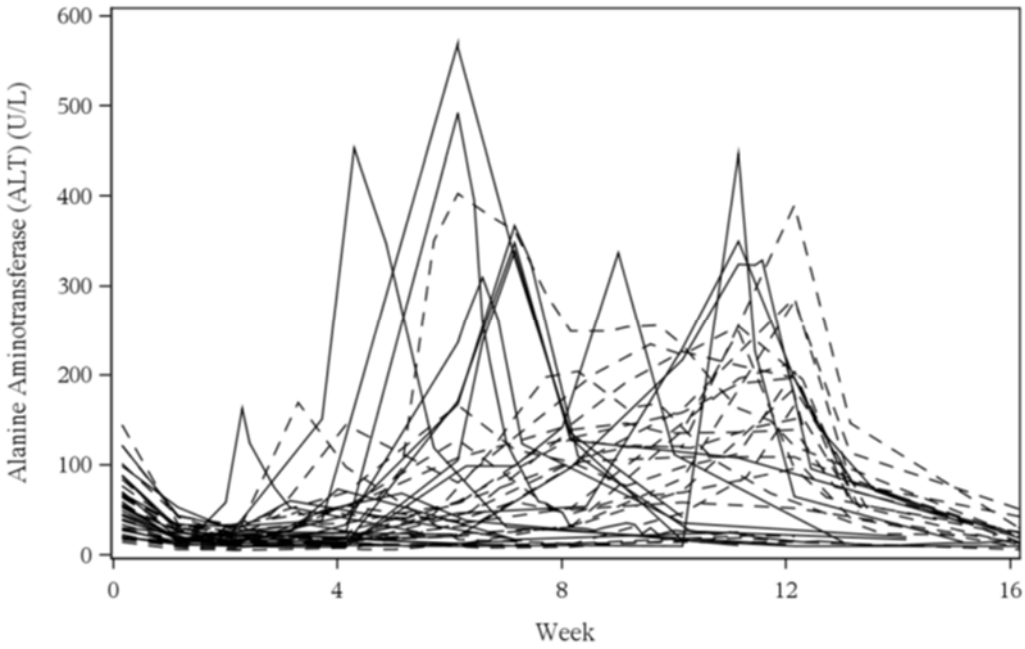
Grade 3 or 4 bilirubin elevation-related adverse events were reported by 13 subjects treated with the DCV/ASV/BCV FDC tablet, and all the events resolved. Of the 13 subjects, 9 discontinued study treatment. In 1 subject who continued to receive the DCV/ASV/BCV FDC tablet and 3 subjects who resumed study treatment after an interruption, no aggravation or new onset of bilirubin elevation-related adverse events was reported in association with the use of the DCV/ASV/BCV FDC tablet. Table 40 summarizes the demographic data, time of discontinuation, liver function test values at the time of discontinuation, and measures taken in 19 subjects who discontinued study treatment due to abnormal liver function test values in the Japanese phase III study (AI443117). Abnormal liver function test values resolved in all subjects after discontinuation of study treatment.

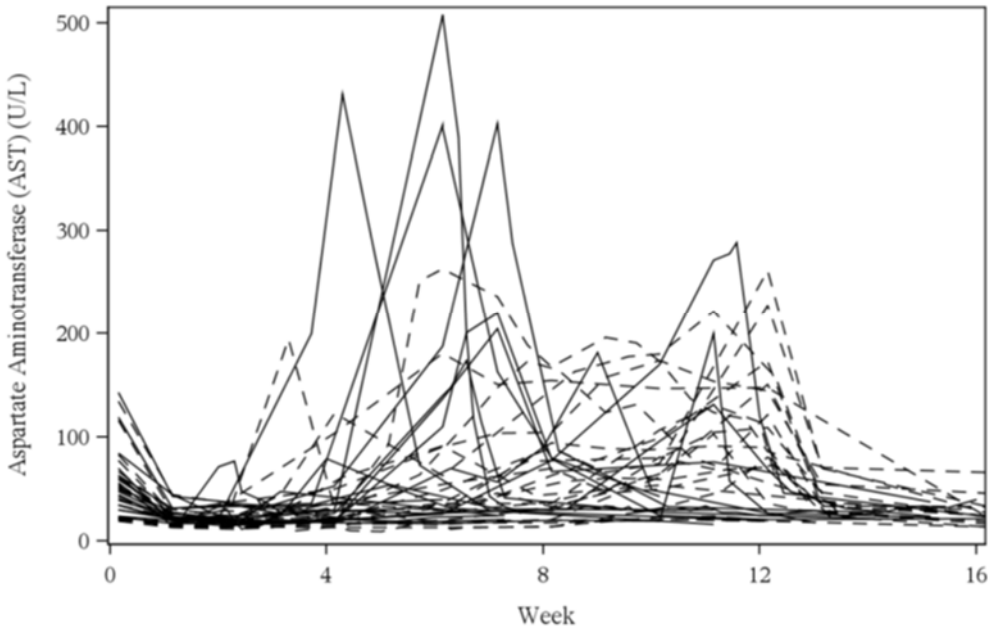
Table 40. Summary of subjects who discontinued treatment with the DCV/ASV/BCV FDC tablet due to abnormal liver function test values

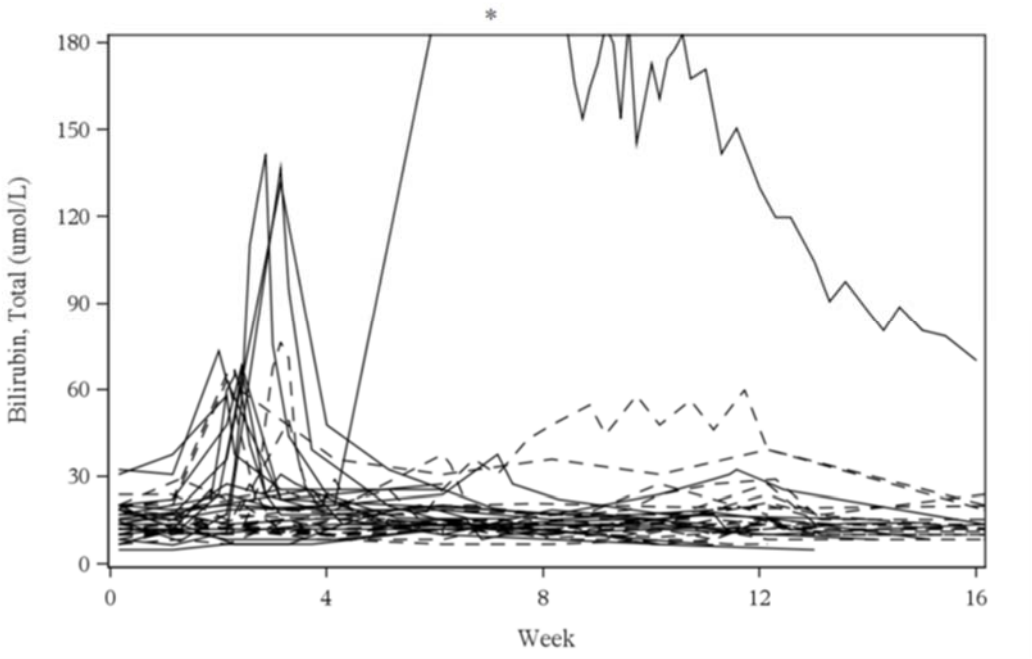
Age	Sex	Adverse event	Time to onset (days)[a)]	Time to discontinu-ation (days)[a)]	Duration of adverse event (days)	Liver function test value at discontinuation			Liver function test value at resolution			Measure[b)]
						ALT (U/L)	AST (U/L)	Total bilirubin (μmol/L)	ALT (U/L)	AST (U/L)	Total bilirubin (μmol/L)	
69	F	ALT increased	46	46	54	310	174	15.4	20	22	8.6	No
60	F	ALT increased	63	63	29	337	182	10.3	15	18	5.1	No
53	F	ALT increased	78	78	57	350	132	17.8	20	22	13	No
57	M	Hyperbilirubinaemia	22	22	15	32	26	136.8	69	54	20.2	No
71	F	Hyperbilirubinaemia	14	15	9	18	35	63.3	22	31	22.2	No
77	M	Hyperbilirubinaemia, ALT increased, AST increased, PT decreased	43	43	176	492	508	203.5	13	24	22.2	Yes
64	F	Hyperbilirubinaemia	16	22	7	53	28	17.1	53	28	17.1	No
67	F	ALT increased, AST increased	50	50	23	367	403	37.6	27	33	17.1	No
50	M	ALT increased	78	78	8	447	200	17.4	65	27	16.1	No
74	F	Hyperbilirubinaemia	22	22	29	26	25	131.7	18	31	18.8	No
57	F	ALT increased, AST increased/ hyperbilirubinaemia	71/ 78	81	43/36	329	289	32.5	19	24	13.7	No
66	F	Hyperbilirubinaemia	18	20	20	19	17	141.6	10	19	16.1	No
63	F	ALT increased, AST increased	30	30	20	453	432	13.7	31	29	13.7	No
65	F	ALT increased	50	50	85	348	205	17.1	15	38	18.8	No
78	M	ALT increased	50	50	22	339	220	12	17	25	13.7	No
64	M	Hyperbilirubinaemia /INR increased	13	16	24/8	32	20	66.7	16	18	13.7	No
72	F	ALT increased, AST increased	43	43	29	565	399	10.3	42	43	6.8	No
63	M	Hyperbilirubinaemia	17	17	6	36	20	68.4	61	48	22.2	No
52	F	Hyperbilirubinaemia	15	15	8	30	38	58.1	26	33	25.7	No

a) Number of days elapsed from the start day of study treatment
b) Treatment for adverse events

Meanwhile, treatment with the DCV/ASV/BCV FDC tablet was not discontinued but interrupted or continued in 21 subjects who had Grade 3 or 4 adverse events related to abnormal liver function test values (interrupted in 3 subjects and continued in 18 subjects). Figure 5 shows the time courses of ALT, AST, and total bilirubin levels in subjects who discontinued treatment with the DCV/ASV/BCV FDC tablet due to adverse events related to abnormal liver function test values and subjects who experienced dose interruption or who continued treatment with the DCV/ASV/BCV FDC tablet after having adverse events related to abnormal liver function test values.


Alanine Aminotransferase (ALT) (U/L)
600
500
400
300
200
100
0
0
4
8
12
16
Week


Aspartate Aminotransferase (AST) (U/L)
500
400
300
200
100
0
0
4
8
12
16
Week



* The maximum total bilirubin level in this subject was 312.9 μmol/L (Day 56).

Figure 5. Time courses of ALT, AST, and total bilirubin levels
(vertical axis, U/L or μmol/L; horizontal axis, weeks after treatment)
Solid line, subjects who discontinued study treatment; dashed line, subjects who experienced dose interruption or who continued study treatment

A decrease in albumin and an increase in international normalized ratio (INR) were observed in 12 of 13 subjects treated with the DCV/ASV/BCV FDC tablet who had Grade 3 or 4 adverse events related to increased bilirubin, suggesting that the treatment may affect hepatic reserve. In 3 subjects, Grade 3 or 4 ALT increased and bilirubin elevation-related events occurred within 30 days of the onset of an abnormality in the ALT or bilirubin level. Of these 3 subjects, 1 chronic hepatitis C subject with compensated cirrhosis met the criteria for potential drug-induced liver injury (pDILI)[55] and developed severe hepatic function disorder.[56] The treatment is unlikely to cause concurrent, marked elevations in bilirubin and ALT levels, which may result in severe hepatic function disorder such as seen in this case; therefore, liver function tests need to be performed once a week in the early stage of treatment in which adverse events related to increased blood bilirubin may be observed. Meanwhile, Grade 3 or 4 ALT increased, though occurring over a wide time range from Week 2 to Week 12, was considered to have little effect on hepatic reserve because neither a decrease in albumin nor a change in INR was observed. Therefore, patient safety can be managed by performing liver function tests including ALT and AST every 2 weeks during treatment as in the DCV + ASV combination regimen. As shown above,

55) Potential drug-induced liver injury (pDILI) was defined as a condition meeting all of the following criteria:
(a) ALT ≥5-fold the baseline or the lowest ALT, whichever is lower, and ≥10-fold the upper limit of normal (ULN)
(b) Total bilirubin ≥2-fold the ULN
(c) ALT increased or hyperbilirubinaemia that occurs with no other direct and obvious causes (for example, in the case of the presence of acute viral hepatitis, cholestasis, concurrent hepatic disorder other than hepatitis C infection, or a history of treatment with any hepatotoxic drugs, the possibility of pDILI is ruled out)

56) A male subject aged 77 years with chronic hepatitis C with compensated cirrhosis. On Day 43 of treatment with the DCV/ASV/BCV FDC tablet, the subject experienced ALP of 694 U/L (Grade 1), ALT of 492 U/L (Grade 4), AST of 508 U/L (Grade 4), total bilirubin of 203.5 μmol/L (Grade 4), direct bilirubin of 145.4 μmol/L, INR of 1.29 (Grade 1), albumin of 34 g/L (Grade 1), PT of 58.1% (Grade 3), gallbladder stone, and swelling of the gallbladder, and then had a diagnosis of pDILI. These events were considered related to the study drug. Study treatment was discontinued, and measures, such as prednisolone therapy, bilirubin absorption therapy, and plasma exchange therapy, were initiated. The subject eventually recovered from the events.

DCV/ASV/BCV FDC has the potential to cause severe liver injury in chronic hepatitis C subjects with compensated cirrhosis. Therefore, liver function tests should be performed every week during treatment in this patient population.

Based on the above, liver function tests should be performed every week at least during the first 6 weeks of treatment to monitor the risk of hyperbilirubinaemia and every 2 weeks after Week 6 to monitor the risk of an increase in ALT levels. Chronic hepatitis C patients with compensated cirrhosis should undergo liver function tests at least once a week during treatment. However, taking into account that some cases of chronic hepatitis C infection with compensated cirrhosis cannot be distinguished from non-cirrhotic chronic hepatitis C in routine clinical settings, liver function tests should be performed every week during treatment irrespective of the presence or absence of compensated cirrhosis. Liver function tests should be performed more frequently in patients with worsening liver function while adequate measures including discontinuation of treatment should be taken.

PMDA's view:
Although the incidence of Grade 3 or 4 bilirubin elevation-related adverse events was higher in subjects treated with the DCV/ASV/BCV FDC tablet in the Japanese phase III study (AI443117), all the relevant cases resolved after discontinuation of treatment or as a result of other measures taken. However, given that not only Grade 3 or 4 bilirubin elevation-related adverse events but also ALT increased and AST increased occurred in the DCV/ASV/BCV group irrespective of compensated cirrhosis [see Section 7.R.4.2] and that a decrease in albumin and a change in INR were also observed, the treatment may have affected hepatic reserve. Moreover, hyperbilirubinaemia occurred concurrently with ALT increased in 1 chronic hepatitis C subject with compensated cirrhosis, who eventually had severe hepatic dysfunction. Therefore, the applicant should provide cautionary statements that liver function tests should be performed at least once a week during treatment with DCV/ASV/BCV FDC irrespective of compensated cirrhosis and that liver function tests should be performed more frequently in patients with worsening liver function and adequate measures, including discontinuation of treatment, should be taken where necessary. In addition, the applicant should collect post-marketing information on the incidences of hepatic function disorder, including bilirubin elevation-related events, ALT increased, and AST increased.

7.R.2.3 Pyrexia and eosinophil count increased
The applicant's explanation about the incidence of pyrexia and eosinophil count increased reported by subjects treated with the DCV/ASV/BCV FDC tablet:
The incidences of pyrexia and eosinophilia in the Japanese phase III study (AI443117) are summarized in Table 41.

Table 41. Summary of pyrexia and eosinophil count increased (AI443117)

	Pyrexia		Eosinophilia	
	DCV/ASV/BCV[a)]	DCV/ASV	DCV/ASV/BCV[a)]	DCV/ASV
N	217	75	217	75
Any adverse event	44 (20.3)	10 (13.3)	37 (17.1)	8 (10.7)
Grade 3 or 4 adverse events	10 (4.6)	0	3 (1.4)	0
Serious adverse events	2 (0.9)	0	0	0
Adverse events leading to discontinuation	1 (0.5)	1 (1.3)	0	0

n (%)
a) All subjects (treatment-naïve or IFN-experienced, genotype 1a or genotype 1b) treated with the DCV/ASV/BCV FDC tablet

The median time to onset (range) of Grade 3 or 4 pyrexia and eosinophilia was 12.0 days (9-19 days) and 22.0 day (18-26 days), respectively, indicating that all these cases occurred during the first 4 weeks of treatment. Based on the above findings, patients should be monitored for pyrexia and eosinophil count increased particularly in the early stage of treatment. All the cases of Grade 3 or 4 pyrexia and eosinophilia resolved, but 1 subject discontinued treatment with the DCV/ASV/BCV FDC tablet. Four subjects experienced dose interruption due to pyrexia, and one of them discontinued treatment without resuming it after a dose interruption (the subject's request). In other 3 subjects, no disease aggravation was observed even after resumption of treatment. Although a new adverse event (hyperbilirubinaemia) occurred in 1 of the 3 subjects, pyrexia resolved in all the 4 subjects who experienced a dose interruption due to pyrexia. The incidence of eosinophil count increased and liver function test abnormal (Grade 3 or 4 hyperbilirubinaemia and Grade 3 or 4 ALT increased) that occurred concurrently with pyrexia (within 14 days) was 3.2% (7 of 217 subjects); however, these events occurred only in the early stage of treatment and all of them resolved. While hypersensitive reaction[57)] was suspected in 1 of the 7 subjects, pyrexia and eosinophil count increased in the subject were considered to be associated with hepatic function abnormal because no skin symptoms were observed. Based on the above, the package insert will include information on the risk of pyrexia, eosinophil count increased, and liver function test abnormal but not on hypersensitive reaction.

PMDA's view:

In the Japanese phase III study (AI443117), the incidences of pyrexia and eosinophilia were higher in the DCV/ASV/BCV group than in the DCV + ASV group and the incidence of hepatic function disorder occurring concurrently with pyrexia and eosinophilia was 3.2% (7 of 217 subjects). Given that all the cases of pyrexia and eosinophilia reported by subjects treated with the DCV/ASV/BCV FDC tablet occurred during the first 4 weeks of treatment, patients should be monitored closely for these events in the early stage of treatment. If any of these events occur concurrently in patients on treatment, appropriate measures such as discontinuation or suspension of treatment should be taken promptly. Post-marketing information on the incidence of these events should be collected, and any finding should be communicated to healthcare professionals appropriately.

57) Definition of hypersensitive reaction in the Japanese phase III study of the DCV + ASV regimen: subjects meeting all of the following criteria: (a) Grade ≥2 pyrexia (≥38.7°C); (b) an increase in eosinophil count ≥1.5 × 10^9 cells/L; (c) increases in ALT/AST ≥5 × ULN (Review Reports on Daklinza Tablets 60 mg and Sunvepra Capsules 100 mg dated June 6, 2014)

7.R.2.4 Safety in the elderly

The applicant's explanation about the safety of DCV/ASV/BCV FDC in the elderly population:

The safety results in non-elderly (<65 years) and elderly (≥65 years) subjects in the Japanese phase III study (AI443117) are summarized in Table 42.

Table 42. Safety summary in non-elderly (<65 years) and elderly (≥65 years) subjects (Study AI443117)

	DCV/ASV/BCV[a)]		DCV/ASV	
	<65 years	≥65 years	<65 years	≥65 years
N	117	100	46	29
Any adverse event	91 (77.8)	75 (75.5)	38 (82.6)	25 (86.2)
Grade 3 or 4 adverse events	31 (26.5)	31 (31.0)	7 (15.2)	10 (34.5)
Serious adverse events	7 (6.0)	6 (6.0)	3 (6.5)	5 (17.2)
Adverse events leading to discontinuation	12 (10.3)	9 (9.0)	1 (2.2)	6 (20.7)

n (%)

a) All subjects (treatment-naïve or IFN-experiment, genotype 1a or genotype 1b) treated with the DCV/ASV/BCV FDC tablet

When safety data from subjects treated with the DCV/ASV/BCV FDC tablet were analyzed by age group, there were no clear differences in the incidence of Grade 3 or 4 adverse events or serious adverse events between elderly and non-elderly subjects. However, the adverse events that occurred in ≥10% of elderly subjects and with an incidence ≥5% higher in elderly subjects than in non-elderly subjects were ALT increased (24 of 117 non-elderly subjects [20.5%] and 26 of 100 elderly subjects [26.0%]), AST increased (19 of 117 non-elderly subjects [16.2%] and 23 of 100 elderly subjects [23.0%]), and hyperbilirubinaemia (14 of 117 non-elderly subjects [12.0%] and 18 of 100 elderly subjects [18.0%]), showing that there was a tendency toward higher incidence of hepatic adverse events in elderly subjects than in non-elderly subjects.

PMDA's view:

There was a trend toward increased incidence of hepatic adverse events in elderly subjects compared with non-elderly subjects in the Japanese phase III study (AI443117). In general, adverse events may occur in elderly patients due to deteriorated physiological function or other reasons. On the above grounds, post-marketing safety data should be collected in the elderly population.

7.R.2.5 Safety in patients with renal impairment

The applicant's explanation of the safety of DCV/ASV/BCV FDC in chronic hepatitis C patients without cirrhosis or with compensated cirrhosis, who also have renal impairment:

Data from subjects with each degree of renal impairment were compared to those from subjects with normal renal function (CL_{Cr} ≥90 mL/min). The ratios of the geometric least-squares means of AUC_{tau} of DCV, ASV, and BCV were 1.22, 1.33, and 1.28, respectively, for mild renal impairment (CL_{Cr} ≥60 and <90 mL/min) vs. normal renal function; 1.5, 1.76, and 1.65, respectively, for moderate renal impairment (CL_{Cr} ≥30 and <60 mL/min) vs. normal renal function; and 1.65, 2.03, and 1.86, respectively, for severe renal impairment without hemodialysis (CL_{Cr} <30 mL/min) vs. normal renal function. The results show that the AUC_{tau} of each component of DCV/ASV/BCV FDC increases with the increase in

the severity of renal impairment [see Section 6.2.3.1]. The exposure-response analysis of safety showed that a Grade 3-4 elevation in ALT or total bilirubin was not associated with DCV or BCV exposure but was associated with ASV exposure [see Section 6.2.2.3]. The odds ratio of the incidence of a Grade 3-4 elevation in ALT and total bilirubin when plasma ASV concentration increased 2-fold was estimated to be approximately 1.5 and 2.1, respectively. Because the Japanese phase III study (AI443117) excluded patients with CL_{Cr} <50 mL/min, no data were available on the safety of the DCV/ASV/BCV FDC tablet in chronic hepatitis C patients without cirrhosis or with compensated cirrhosis, who also had severe renal impairment. Therefore, patients with severe renal impairment not receiving hemodialysis should be particularly carefully monitored for the risk of hepatic function disorder.

PMDA's view:
Given that an increase in the AUC of each component of DCV/ASV/BCV FDC was associated with renal impairment and that the exposure-response analysis of safety suggested a correlation between Grade 3-4 elevations in ALT or total bilirubin and ASV exposure, the incidence of a Grade 3-4 elevation in total bilirubin is expected to become high in chronic hepatitis C patients without cirrhosis or with compensated cirrhosis, who also have renal impairment, during or after treatment with DCV/ASV/BCV FDC. Therefore, when DCV/ASV/BCV FDC is administered to Japanese patients with chronic hepatitis C without cirrhosis or with compensated cirrhosis who also have renal impairment, liver function tests should be performed in such patients frequently, taking into account the increased risk of abnormal liver function test values. Adequate measures such as discontinuation of treatment should be taken in patients with worsening liver function.

7.R.3 Significance of co-administration

The applicant's explanation about the significance of co-administration:
DCV, ASV, and BCV have different mechanisms of action and resistance profiles. These agents exhibited higher anti-HCV activity when used in combination than when used separately in non-clinical pharmacological studies. Surviving colonies observed after adding the combination of DCV + ASV were eliminated after adding the combination of DCV + ASV + BCV [see Section 3.1.2.3]. Based on the above, the co-administration of DCV + ASV + BCV is expected to suppress the emergence of resistant viruses that cannot be suppressed by the DCV + ASV combination regimen.

Following treatment with the DCV + ASV combination regimen, the SVR24 rates in subjects harboring Y93H and L31I/M/V variants detected as baseline resistance mutations in the NS5A and NS3 regions were 35.4% and 42.9%, respectively (Package Insert for Daklinza Tablets 60 mg, version 10). The Guidelines for the Management of Hepatitis C Virus Infection, version 5, do not recommend the use of the DCV + ASV regimen in patients with these resistance mutations. Meanwhile, following treatment with the DCV/ASV/BCV FDC tablet, the SVR12 rates in subjects harboring mutations at positions Y93 and L31 were 91.4% (32 of 35 subjects) and 100% (4 of 4 subjects), respectively. In subjects with HCV genotype 1a infection, the SVR12 rate after treatment with the DCV + ASV regimen was as low as 22% (2 of 9 subjects) (Package Insert for Daklinza Tablets 60 mg, version 10). In contrast, 3 of 4 subjects

with HCV genotype 1a infection in the DCV/ASV/BCV group in the Japanese phase III study (AI443117) achieved SVR12, and the SVR12 rates in genotype 1a chronic hepatitis C subjects without cirrhosis and those with compensated cirrhosis in a foreign phase III study were 89.1% and 88.0%, respectively. Therefore, DCV/ASV/BCV FDC is expected to exhibit a high therapeutic effect in a consistent manner in patients with HCV genotype 1a infection and those harboring resistance mutations at Y93 or L31, which are considered to affect the antiviral effect of the DCV + ASV regimen.

The DCV + ASV regimen requires DCV to be administered QD and ASV to be administered BID, making the dose frequency of DCV different from that of ASV. On the other hand, DCV/ASV/BCV FDC can be administered BID because it is a fixed-dose combination drug containing 3 active ingredients (DCV, ASV, and BCV). DCV/ASV/BCV FDC is expected to offer patients a simpler regimen and greater convenience and to contribute to the prevention of medication errors or missed doses that may be caused by taking multiple drugs separately. Given that chronic hepatitis C patients without cirrhosis or with compensated cirrhosis are rapidly aging in Japan (*Journal of Hepato-Biliary-Pancreatic Sciences*. 2014;69:603-608) and that, in general, drug compliance can be of clinical concern in elderly patients, convenient medication would be helpful for this patient population. The duration of treatment is 24 weeks for the DCV + ASV regimen whereas it is reduced to 12 weeks for DCV/ASV/BCV FDC. The reduced duration of treatment by half is expected to decrease the medication-related burden on patients.

The safety of DCV/ASV/BCV FDC is generally tolerable. The main safety signals of DCV/ASV/BCV FDC include ALT increased, AST increased, and bilirubin increased, and patients should be carefully monitored for the risk of severe liver disorder. However, these events are considered controllable by weekly liver function tests [see Section 7.R.2.2].

PMDA's view:
The applicant's claim that the co-administration of DCV, ASV, and BCV has pharmacological significance makes sense. Meanwhile, it is not clear whether the combined use of these agents in treating HCV-infected patients can enhance drug compliance or the efficacy of each agent. However, given that combination regimens of fixed-dose combination drugs containing multiple active ingredients with different mechanisms of action have already been approved for the treatment of HCV infection, it is reasonable to offer an FDC drug containing DCV, ASV, and BCV.

7.R.4 Indications

Based on the following review and the results of the Japanese phase III study (AI443117), PMDA considers that DCV/ASV/BCV FDC is expected to be effective in treating genotype 1 chronic hepatitis C patients without cirrhosis or with compensated cirrhosis and that its safety is also acceptable if liver function tests are performed frequently under the supervision of a physician with adequate knowledge and experience in the treatment of viral liver disease [see Sections 7.R.1 and 7.R.2]. Based on the above, PMDA concluded that the proposed indication of DCV/ASV/BCV FDC ("suppression of viremia in

serogroup 1 [genotype 1] chronic hepatitis C patients without cirrhosis or with compensated cirrhosis") is acceptable.

The above conclusion by PMDA will be finalized, taking into account the comments made in the Expert Discussion.

7.R.4.1 Use in chronic hepatitis C patients with compensated cirrhosis

The applicant's explanation about the efficacy and safety of DCV/ASV/BCV FDC in chronic hepatitis C patients with compensated cirrhosis:

The SVR12 rate after administration of the DCV/ASV/BCV FDC tablet in treatment-naïve or IFN-experienced (genotype 1) chronic hepatitis C subjects without cirrhosis and those with compensated cirrhosis in the Japanese phase III study (AI443117) were 95.9% (164 of 171 subjects) and 95.7% (44 of 46 subjects), respectively, showing similarity between the 2 subject populations.

The safety results of the DCV/ASV/BCV FDC tablet in chronic hepatitis C subjects without cirrhosis or with compensated cirrhosis are summarized in Table 43.

Table 43. Summary of safety in the Japanese phase III study (AI443117) (Safety analysis population)

	Chronic hepatitis C without cirrhosis		Chronic hepatitis C with compensated cirrhosis	
	DCV/ASV/BCV[b)]	DCV/ASV	DCV/ASV/BCV[b)]	DCV/ASV
N	171	61	46	14
Any adverse event	130 (76.0)	50 (82.0)	36 (78.3)	13 (92.9)
Grade 3 or 4 adverse events	45 (26.3)	13 (21.3)	17 (37.0)	4 (28.6)
Serious adverse events	9 (5.3)	4 (6.6)	4 (8.7)	4 (28.6)
Adverse events leading to discontinuation	17 (9.9)	5 (8.8)	4 (8.7)	2 (14.3)
Death	0	0	0	0
Adverse events occurring in ≥10% of subjects in any group				
ALT increased	43 (25.1)	19 (31.1)	7 (15.2)	1 (7.1)
AST increased	36 (21.1)	18 (29.5)	6 (13.0)	0
Pyrexia	35 (20.5)	8 (13.1)	9 (19.6)	2 (18.7)
Eosinophilia	29 (17.0)	7 (11.5)	8 (17.4)	1 (7.1)
Hyperbilirubinaemia	19 (11.1)	5 (8.2)	13 (28.3)	0
Headache	20 (11.7)	6 (9.8)	4 (8.7)	1 (7.1)
Grade 3 or 4 hepatic adverse events				
ALT increased	26 (15.2)	9 (14.8)	4 (8.7)	0
AST increased	16 (9.4)	5 (8.2)	4 (8.7)	0
Hyperbilirubinaemia	6 (3.5)	1 (1.6)	6 (13.0)	1 (7.1)
Bilirubin elevation-related adverse events[a)]	7 (4.1)	1 (1.6)	6 (13.0)	1 (7.1)

n (%)

a) Adverse events coded to MedDRA (v. 17.1) PTs "blood bilirubin increased," "hyperbilirubinaemia," "bilirubin conjugated increased," "blood bilirubin unconjugated increased," "gallbladder disorder," "cholecystitis," and "hepatomegaly"

b) All subjects (treatment-naïve or IFN-experienced, genotype 1a or 1b) receiving the DCV/ASV/BCV FDC tablet

While there was no clear difference in the incidence of adverse events leading to discontinuation or serious adverse events between chronic hepatitis C subjects without cirrhosis and those with compensated cirrhosis receiving the DCV/ASV/BCV FDC tablet, the incidence of Grade 3 or 4 adverse

events was 26.3% and 37.0%, respectively, being higher in subjects with compensated cirrhosis than in non-cirrhotic subjects. In chronic hepatitis C subjects without cirrhosis and those with compensated cirrhosis in the DCV/ASV/BCV group, the incidence of hyperbilirubinaemia was 11.1% and 28.3%, respectively, being higher in subjects with compensated cirrhosis than in non-cirrhotic subjects. The incidence of ALT increased was 25.1% and 15.2%, respectively, and the incidence of AST increased was 21.1% and 13.0%, respectively, being higher in non-cirrhotic subjects than in subjects with compensated cirrhosis.

Although there were differences in the incidences of hepatic adverse events between cirrhotic and non-cirrhotic subjects, these events can be monitored by liver function tests and other relevant measures. Therefore, the safety of DCV/ASV/BCV FDC is considered acceptable if liver function tests are performed frequently and if appropriate measures such as discontinuation of treatment are taken in patients with worsening liver function.

PMDA's view:
Based on the results of the Japanese phase III study (AI443117), the efficacy of DCV/ASV/BCV FDC can be promising in the treatment of chronic hepatitis C patients with compensated cirrhosis. Safety data showed a difference in the incidence of hepatic adverse events between chronic hepatitis C subjects with cirrhosis and those with compensated cirrhosis. When DCV/ASV/BCV FDC is used in chronic hepatitis C patients without cirrhosis or with compensated cirrhosis, periodic liver function tests and other methods should be performed for early detection of adverse events, with appropriate measures being taken. The incidence of bilirubin elevation-related adverse events was higher in patients with compensated cirrhosis than in non-cirrhotic patients. Therefore, chronic hepatitis C patients with compensated cirrhosis should be monitored even more carefully during and after treatment with DCV/ASV/BCV FDC.

The safety of DCV/ASV/BCV FDC in chronic hepatitis C patients with compensated cirrhosis is acceptable if appropriate measures, such as monitoring and management of adverse events and the interruption and discontinuation of treatment, are taken under the supervision of a physician who has sufficient knowledge and experience in the treatment of viral liver diseases and who fully understands the safety profile of DCV/ASV/BCV FDC. However, given that there is limited clinical experience with the use of the DCV/ASV/BCV FDC tablet in Japanese patients with chronic hepatitis C with compensated cirrhosis, post-marketing information on the safety and efficacy of DCV/ASV/BCV FDC should be collected in this patient population. Any new findings should be communicated to healthcare professionals appropriately.

7.R.4.2 Use in patients previously treated with NS3/4A protease inhibitor, NS5A inhibitor, or NS5B polymerase inhibitor

Although there is no clinical experience with the use of the DCV/ASV/BCV FDC tablet in genotype 1 chronic hepatitis C patients without cirrhosis or with compensated cirrhosis who failed to achieve SVR

with previous treatment with an NS3/4A protease inhibitor, NS5A inhibitor, or an NS5B polymerase inhibitor, the applicant explained the efficacy of DCV/ASV/BCV in these patient populations (sections below).

7.R.4.2.1 Patients previously treated with NS3/4A protease inhibitor

Resistance mutations detected frequently in subjects who failed to achieve SVR in Japanese clinical studies of NS3/4A protease inhibitors are mutations at V36, T54, Y56, Q80, R155, A156, or D168 in the NS3 region (Package Insert for Vanihep Capsules 150 mg, version 5; Package Insert for Viekirax Combination Tablets, version 4; and others). Of these resistance mutations, only the D168 variant is known as an ASV-resistant mutation detected in HCV genotype 1b-infected patients (Guidelines for the Management of Hepatitis C Virus Infection, Version 5). However, when resistance mutation tests were performed at baseline and at the time of virologic failure in HCV genotype 1b-infected subjects treated with the DCV/ASV/BCV FDC tablet in Japanese and foreign phase III studies (Studies AI443102, AI443113, and AI443117), the D168 variant was not detected in any of 8 subjects who failed to achieve SVR12. As a result, the involvement of the D168 variant in patients failing to achieve SVR could not be confirmed in these studies.

Although there is no clinical experience with the use of the DCV/ASV/BCV FDC tablet in patients previously treated with an NS3/4A protease inhibitor or an NS5A inhibitor, the results of *in vitro* studies demonstrated that the active ingredients of DCV/ASV/BCV FDC; that is, ASV (an NS3/4A protease inhibitor), DCV (an NS5A inhibitor), and BCV (an NS5B polymerase inhibitor), are not cross-resistant to each other (Package Insert for Daklinza Tablets 60 mg, version 10; Package Insert for Sunvepra Capsules 100 mg, version 10) [see also Section 3.1.4.2].

Based on the above, DCV/ASV/BCV FDC is potentially effective in patients previously treated with an NS3/4A protease inhibitor (including co-administration with an NS5A inhibitor) if DCV/ASV/BCV FDC is used by a physician with sufficient knowledge and experience in the treatment of viral liver diseases after a comprehensive assessment of the patient's condition.

7.R.4.2.2 Patients previously treated with an NS5A inhibitor

In subjects who failed to achieve SVR in Japanese clinical studies of NS5A inhibitors, amino acid substitutions at positions 30, 31, 58, or 93 in the NS5A region were frequently detected as resistance mutations (Package Insert for Daklinza Tablets 60 mg, version 10; Package Insert for Harvoni Combination Tablets, version 2; and other relevant documents). Of these resistance mutations, only L31 and Y93 variants are known as DCV-resistant mutations detected in HCV genotype 1b-infected patients (Guidelines for the Management of Hepatitis C Virus Infection, Version 5).

Among HCV genotype 1b-infected subjects[58)] in Japanese and foreign phase III studies of the DCV/ASV/BCV FDC tablet (Studies AI443102, AI443113, and AI443117), the SVR12 rates in subjects with and without baseline mutations (L31 or Y93) in the DCV/ASV/BCV group were 100% (54 of 54 subjects) and 99.7% (285 of 286 subjects), respectively, demonstrating that baseline status of L31 or Y93 mutation has no impact on the efficacy of the DCV/ASV/BCV FDC tablet.

Moreover, the results of *in vitro* studies demonstrated that ASV (an NS3/4A protease inhibitor) and BCV (an NS5B polymerase inhibitor), both of which are active ingredients of DCV/ASV/BCV FDC, are not cross-resistant to various NS5A inhibitor-resistant mutations (Package Insert for Daklinza Tablets 60 mg, version 10; Package Insert for Sunvepra Capsules 100 mg, version 10) [see also Section 3.1.4.2].

Based on the above, DCV/ASV/BCV FDC is potentially effective in patients previously treated with an NS5A inhibitor if DCV/ASV/BCV FDC is used by a physician with sufficient knowledge and experience in the treatment of viral liver diseases after a comprehensive assessment of the patient's condition.

7.R.4.2.3 Patients previously treated with an NS5B inhibitor

Amino acid substitution at position 282 in the NS5B region was detected as resistance mutation in *in vitro* studies of sofosbuvir, an NS5B polymerase inhibitor (Package insert for Harvoni Combination Tablets, version 2). Meanwhile, the only BCV-resistant mutation detected in *in vitro* studies of BCV was the mutation at position 495 in the NS5B region, which was not cross-resistant to sofosbuvir [see Section 3.1.4]. In any of 7 HCV genotype 1b-infected subjects who failed to achieve SVR12, no mutation at 495 was detected either at baseline or at the time of virologic failure.

Based on the above, DCV/ASV/BCV FDC is potentially effective in patients who have previously been treated with an NS5B inhibitor if DCV/ASV/BCV FDC is used by a physician with sufficient knowledge and experience in the treatment of viral liver diseases after a comprehensive assessment of the patient's condition.

PMDA's view:

Because the DCV/ASV/BCV FDC tablet was not administered to any chronic hepatitis C patients without cirrhosis or with compensated cirrhosis, who had failed to respond to an NS3/4A protease inhibitor, NS5A inhibitor, or an NS5B polymerase inhibitor, in any Japanese or foreign clinical studies, there is too little evidence to recommend the use of DCV/ASV/BCV FDC in these patient populations.

58) A total of 11 subjects (1 subject who could not undergo the baseline resistance mutation test but achieved SVR12, 1 subject infected with HCV genotypes 1b and 2 in whom HCV genotype 2 was detected after a relapse, 1 subject infected with HCV genotype 1g, 1 subject who was lost to follow-up after achieving SVR4, and 7 subjects who received the study drug for ≤28 days and discontinued study treatment due to adverse events or based on the subject's request before achieving SVR12) were excluded from this analysis.

However, taking into account the following, the use of DCV/ASV/BCV FDC in patients previously treated with other NS3/4A protease inhibitors, NS5A inhibitors, or NS5B polymerase inhibitors is allowed if resistance mutations in the individual patients are thoroughly evaluated by a physician with sufficient knowledge and experience in the treatment of viral liver diseases:

- Resistance profiles of various NS3/4A protease inhibitors, NS5A inhibitors, or NS5B polymerase inhibitors are not necessarily consistent. In non-clinical studies, ASV and BCV exerted antiviral activity against HCV harboring some mutations in the NS3 and NS5B regions that were resistant to other components (Package Insert for Sunvepra Capsules 100 mg, version 10) [see also Section 3.1.4].
- In the Japanese phase III study (AI443117), some subjects with baseline NS5A mutations achieved SVR12 after treatment with the DCV/ASV/BCV FDC tablet, although no information was available on the relationship between baseline NS3/NS5B resistance mutations and the efficacy of the DCV/ASV/BCV FDC tablet.
- There are very limited treatment options for patients who have previously been treated with an NS3/4A protease inhibitor, NS5A inhibitor, or an NS5B polymerase inhibitor.

As described above, the appropriateness of the use of DCV/ASV/BCV FDC in individual patients previously treated with an NS3/4A protease inhibitor, NS5A inhibitor, or an NS5B polymerase inhibitor should be carefully determined by a physician with sufficient knowledge and experience in the treatment of viral liver diseases, based on the status of resistance mutations and the patient's condition. The applicant should provide healthcare professionals with currently available information on resistance mutations. At the same time, the applicant should collect post-marketing information on resistance mutations and the efficacy of DCV/ASV/BCV FDC in patients who have previously been treated with an NS3/4A protease inhibitor, NS5A inhibitor, or an NS5B polymerase inhibitor, if any. Any findings should be communicated to healthcare professionals.

7.R.5 Dosage and administration

On the basis of the following review, PMDA concluded that it is possible to determine the dosage and administration for DCV/ASV/BCV FDC as shown below:

The usual adult dosage is 2 tablets (30 mg of DCV, 200 mg of ASV, and 75 mg of BCV), administered orally twice daily after meals for 12 weeks.

The above conclusion by PMDA will be finalized, taking into account the comments made in the Expert Discussion.

Dosage and administration of DCV/ASV/BCV FDC

The applicant's explanation about the proposed dosage and administration:

DCV, ASV, and BCV have different mechanisms of action and resistance profiles. These agents exhibited higher anti-HCV activity when co-administered than when used separately in *in vitro* studies, and surviving colonies observed after adding the combination of DCV + ASV were eliminated after adding the combination of DCV + ASV + BCV [see Section 3.1.2.3]. The co-administration of DCV, ASV, and BCV is expected to suppress the emergence of resistant viruses that cannot be suppressed by the DCV + ASV combination regimen. The efficacy and safety of the co-administration of DCV, ASV, and BCV were demonstrated in a foreign phase II study (AI443014), and the results were considered to justify the use of the DCV +ASV + BCV regimen in genotype 1 chronic hepatitis C patients without cirrhosis or with compensated cirrhosis. Thus, the applicant conducted the Japanese phase III study (AI443117) using the combination regimen.

In the Japanese phase III study (AI443117), subjects were to receive DCV 30 mg, ASV 200 mg, and BCV 75 mg BID. This dosage regimen was selected based on the results of Japanese and foreign clinical studies [see Section 6.R.3]. The daily dose was specified as 2 FDC tablets of DCV/ASV/BCV (30/200/75 mg) administered BID in view of the significance of the co-administration of DCV, ASV, and BCV [see Section 7.R.3]. Each dose was to be taken after a meal in order to increase the bioavailability of ASV during treatment with DCV/ASV/BCV FDC [see Section 6.R.4].

The efficacy and tolerability of the DCV/ASV/BCV FDC tablet were demonstrated in genotype 1 chronic hepatitis C subjects without cirrhosis or with compensated cirrhosis in the Japanese phase III study (AI443117). Consequently, the following dosage and administration statement was proposed: 2 tablets of DCV/ASV/BCV (30/200/75 mg) twice daily after meals for 12 weeks.

PMDA's view:
Based on the review presented in Sections 7.R.1, 7.R.2, and 7.R.3, the proposed dosage and administration statement for DCV/ASV/BCV FDC is acceptable.

7.R.6 Clinical positioning

The applicant's explanation about the clinical positioning of DCV/ASV/BCV FDC in the treatment of genotype 1 chronic hepatitis C patients without cirrhosis or with compensated cirrhosis:
Currently in Japan, several oral antivirals have been approved for treating genotype 1 chronic hepatitis C patients without cirrhosis or with compensated cirrhosis [see Section 1]. Among the approved antivirals, ledipasvir/sofosbuvir FDC (an IFN-free combination regimen) is contraindicated in patients with severe renal impairment (epidermal growth factor receptor [eGFR] <30 mL/min/1.73 m^2) and patients with renal failure requiring hemodialysis (Package Insert for Harvoni Combination Tablets, version 2). In principle, the use of the ombitasvir/paritaprevir/ritonavir FDC tablet in combination with a calcium antagonist is not recommended, and co-administration of many other drugs with ombitasvir/paritaprevir/ritonavir FDC is contraindicated or not recommended (Package Insert for Viekirax Combination Tablets, version 4). While the DCV + ASV combination regimen is recommended for the treatment of patients receiving hemodialysis (Guidelines for the Management of

Hepatitis C Virus Infection, Version 5), the regimen has been reported to decrease SVR12 rates in patients with NS5A-L31 or Y93 variants (Package Insert for Sunvepra Capsules 100 mg, version 10; Package Insert for Daklinza Tablets 60 mg, version 10).

The SVR12 rate after treatment with the DCV/ASV/BCV FDC tablet in treatment-naïve or IFN-experienced (genotype 1) chronic hepatitis C patients without cirrhosis or with compensated cirrhosis was 95.9% (208 of 217 subjects). While the efficacy of this regimen may have been decreased in HCV genotype 1a-infected patients with a baseline Q30 mutation, the efficacy of treatment was not affected in patients with other baseline resistance mutations [see Section 7.R.1.2].

Although the main safety signals of DCV/ASV/BCV FDC include risks of hepatic function disorders such as Grade 3 or 4 ALT increased, AST increased, and hyperbilirubinaemia, there is no problem with tolerability. These events are considered controllable by frequent liver function tests. Concomitant calcium antagonists appear to have no clear impact on the treatment, and the use of DCV/ASV/BCV FDC in patients with severe renal impairment or patients with renal failure requiring hemodialysis is also allowed if it is administered carefully after thorough consideration of the increased risk of hepatic function disorder.

Based on the above, DCV/ASV/BCV FDC represents a new treatment option for genotype 1 chronic hepatitis C patients without cirrhosis or with compensated cirrhosis.

PMDA's view:
The results of Japanese clinical studies were reviewed in Sections 7.R.1 and 7.R.2. Based on the review, DCV/ASV/BCV FDC can be a new treatment option for genotype 1 chronic hepatitis C patients without cirrhosis or with compensated cirrhosis, provided that the eligibility of each patient for treatment with DCV/ASV/BCV FDC is determined by a physician who has sufficient knowledge and experience in the treatment of viral liver diseases and who fully understands the safety profile of DCV/ASV/BCV FDC, and that appropriate measures such as monitoring and management of adverse events and interruption and discontinuation of treatment are taken as necessary.

7.R.7 Post-marketing investigations

The applicant plans to conduct the following post-marketing surveillance. Taking into account the incidence of hepatic function disorder in subjects treated with the combination of DCV, ASV, and BCV in the Japanese phase III study (AI443117) and the planned precautionary statements related to liver function tests, a drug use-results survey covering all patients treated with DCV/ASV/BCV FDC will be conducted in order to collect post-marketing information on the safety of DCV/ASV/BCV FDC and the status of proper drug use as soon as possible and to take additional measures to ensure its safety in a prompt manner.

Specified use-results survey (all-case surveillance)

- Objectives: To identify the incidence of hepatic function disorders reported as adverse drug reactions and to investigate background factors that may contribute to the adverse drug reactions.
- Planned sample size: 1000 patients
  A total of 1000 patients will be needed to evaluate adverse drug reactions with a certain degree of accuracy.
- Observation period: from the start of treatment with DCV/ASV/BCV FDC to 24 weeks after the last dose
- Survey period: 33 months following the market launch of DCV/ASV/BCV FDC (patients will be registered for 24 months following the market launch)

PMDA's view:
Taking into account the safety profiles of DCV/ASV/BCV FDC and the content of the planned precautionary statements, information should be collected on the safety of DCV/ASV/BCV FDC and the status of proper drug use as soon as possible and in a comprehensive manner. Therefore, the applicant's plan of a drug use-results survey covering all patients treated with DCV/ASV/BCV FDC is appropriate. The following information should be collected in the post-marketing setting:
- Safety and efficacy in elderly patients, chronic hepatitis C patients with compensated cirrhosis, and patients with renal impairment
- Incidence of hepatic function disorder
- Relationships between the efficacy of DCV/ASV/BCV and resistance mutations at baseline or at the time of virologic failure
- Efficacy of DCV/ASV/BCV FDC in patients who have previously been treated with an NS3/4A protease inhibitor, NS5A inhibitor, or an NS5B polymerase inhibitor, and resistance mutations detected in such patients

The above conclusion by PMDA will be finalized, taking into account the comments made in the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA
The assessments are currently underway. The results and PMDA's conclusion will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)
On the basis of the submitted data, PMDA has concluded that DCV/ASV/BCV FDC has efficacy in the treatment of genotype 1 chronic hepatitis C patients without cirrhosis or with compensated cirrhosis has been demonstrated and its safety is acceptable in view of its observed benefits.

PMDA has concluded that DCV/ASV/BCV FDC may be approved if the product is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

October 11, 2016

Product Submitted for Approval

Brand Name	Ximency Combination Tablets
Non-proprietary Name	Daclatasvir Hydrochloride/Asunaprevir/Beclabuvir Hydrochloride
Applicant	Bristol-Myers Squibb K.K. (application submitted by Bristol-Myers K.K., whose name was changed after submission of the marketing application)
Date of Application	December 21, 2015

1. Content of the Review

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

PMDA's conclusions described in the Review Report (1) (Sections "7.R.1 Efficacy and study plan," "7.R.3 Significance of co-administration," "7.R.4 Indications," and "7.R.5 Dosage and administration") were supported by the expert advisors at the Expert Discussion.

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

1.1 Patients intended for treatment with Ximency Combination Tablets

In view of the efficacy, safety, and clinical positioning of Ximency Combination Tablets (hereinafter referred to as DCV/ASV/BCV FDC), the expert advisors made the following comments on patients intended for treatment with DCV/ASV/BCV FDC:

- Given that patients on DCV/ASV/BCV FDC need to undergo weekly liver function tests in routine clinical settings, patient selection for treatment with the product is likely to be restricted due to the inconvenience of weekly testing.
- DCV/ASV/BCV FDC is expected to be used in patients who have failed to respond to other direct-acting antiviral agents (DAAs) and patients with resistance mutations in the HCV NS3/4A, NS5A, or NS5B region.

In response to the above comments from the expert advisors, PMDA conducted the following review:

In any Japanese or foreign clinical studies, DCV/ASV/BCV FDC was not administered to any chronic hepatitis C patients without cirrhosis or with compensated cirrhosis who had failed to respond to a combination regimen containing an approved NS3/4A protease inhibitor, NS5A inhibitor, or NS5B

polymerase inhibitor. The use of DCV/ASV/BCV FDC in these patient populations should be decided carefully. However, given that currently available treatment options for these patient populations are extremely limited and that the antiviral activities of co-administered DCV, ASV, and BCV against viruses harboring resistance mutations in the NS3 or NS5A region were demonstrated in *in vitro* studies [see Section 3.1.2.3 of Review Report (1)], DCV/ASV/BCV FDC may be selected, according to the patient's condition, by a physician with sufficient knowledge and experience in the treatment of viral liver diseases. Therefore, if information on the efficacy and safety of DCV/ASV/BCV FDC in these patient populations is collected in the post-marketing surveillance, it will offer useful data for treatment selection.

Based on the above review, PMDA instructed the applicant to undertake a post-marketing survey to evaluate the efficacy and safety of DCV/ASV/BCV FDC and the emergence of resistance mutations in chronic hepatitis C patients without cirrhosis or with compensated cirrhosis who have failed to respond to a combination regimen containing an existing NS3/4A protease inhibitor, NS5A inhibitor, or NS5B polymerase inhibitor, and to communicate any new findings to healthcare professionals in a prompt and appropriate manner.

The applicant's response:
In the specified use-results survey, prior treatment (e.g., combination therapy containing an NS3/4A protease inhibitor, NS5A inhibitor, NS5B polymerase inhibitor, or interferon) will be included in the survey items, and the efficacy and safety of DCV/ASV/BCV FDC and the emergence of resistance mutations will be evaluated in patients who have previously been treated with an NS3/4A protease inhibitor, NS5A inhibitor, or NS5B polymerase inhibitor.

1.2 Safety

The expert advisors largely supported PMDA's conclusion on safety [see Section 7.R.2 of Review Report (1)] and additionally provided the following comment on safety in patients with renal impairment:

- Taking into account that patients with renal impairment with creatinine clearance <50 mL/min were excluded from the Japanese phase III study (AI443117), healthcare professionals should be adequately informed of the following: the safety of DCV/ASV/BCV FDC has not been established in patients with renal impairment with creatinine clearance <50 mL/min.

In response to the above comment from the expert advisors, PMDA undertook a further review (as below) and concluded that the risk of hepatic function disorder may be increased even in patients with moderate renal impairment:

- Patients with renal impairment with creatinine clearance <50 mL/min were excluded from the Japanese phase III study (AI443117), resulting in limited information on the safety of DCV/ASV/BCV in patients with renal impairment.

- In the clinical pharmacology study in patients with renal impairment (AI443110), increased ASV exposure was observed not only in patients with severe renal impairment but also in those with moderate renal impairment [see Section 6.2.3.1 of Review Report (1)].
- The results of the exposure-response analysis on safety suggested that a Grade 3-4 elevation in alanine aminotransferase or total bilirubin level was associated with ASV exposure [see Section 6.2.2.3 of Review Report (1)].

On the basis of the above review, PMDA instructed the applicant to provide information in the package insert advising that DCV/ASV/BCV FDC should be carefully administered to patients with moderate renal impairment as well as those with severe renal impairment. The applicant agreed to provide a precautionary statement regarding the use of DCV/ASV/BCV FDC in patients with renal impairment with creatinine clearance <50 mL/min.

1.3 Draft risk management plan

Based on the review presented in Section "7.R.7 Post-marketing investigations" of Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA considers that the following issues should be additionally evaluated in the post-marketing surveillance:

- Safety and efficacy in elderly patients, patients with compensated cirrhosis, and patients with renal impairment
- Incidence of hepatic function disorder
- Relationships between the efficacy of DCV/ASV/BCV FDC and resistance mutations at baseline or at the time of virologic failure
- Efficacy of DCV/ASV/BCV FDC in patients who have previously been treated with an NS3/4A protease inhibitor, NS5A inhibitor, or an NS5B polymerase inhibitor, and resistance mutations detected in such patients

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

Taking account of the above discussion, PMDA concluded that the safety and efficacy specifications as shown in Table 44 should be included in the current draft risk management plan and that additional pharmacovigilance activities and risk minimization activities as shown in Table 45 should be conducted, and accepted an outline of the draft specified use-results survey plan as shown in Table 46.

Table 44. Safety and efficacy specifications in the draft risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hepatic function disorder, decreased hepatic reserve • Erythema multiforme • Decreased platelet count • Interstitial pneumonia • Hepatitis B virus reactivation	• Hematotoxicity • Administration to patients with severe renal impairment	None
Efficacy specification		
• Efficacy in routine clinical settings • Emergence of drug resistance		

Table 45. Summary of additional pharmacovigilance activities and risk minimization activities included under the draft risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance (EPPV) • Specified use-results survey (all-case surveillance)	• EPPV • Development and distribution of materials for healthcare professionals (the Guide to Proper Use)

Table 46. Outline of draft specified use-results survey plan

Objective	To collect information on the safety and efficacy of DCV/ASV/BCV FDC in serogroup 1 (genotype 1) chronic hepatitis C patients without cirrhosis or with compensated cirrhosis in routine clinical settings
Survey method	All-case surveillance
Population	All patients treated with DCV/ASV/BCV FDC during the registration period
Observation period	33 months following the market launch (from the day of the first dose of DCV/ASV/BCV FDC to 24 weeks after the last dose)
Planned sample size	1000 patients (including 300 chronic hepatitis C patients with compensated cirrhosis)
Main survey items	Hepatic function disorder, decreased hepatic reserve, decreased platelet count, interstitial pneumonia, hepatitis B virus reactivation, safety and efficacy in elderly patients, safety and efficacy in patients with renal impairment, emergence of resistance mutations, efficacy, safety, and the emergence of resistance mutations in patients who have failed to respond to previous treatment with a DAA

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

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

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

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing the Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed that, on the whole, clinical studies had been conducted

in accordance with GCP. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. One finding requiring corrective action was found at the sponsor site, as described below, though this finding did not significantly affect the overall assessment of the study. The finding was notified to the applicant (the sponsor).

[Finding requiring corrective action]
Sponsor

- A delay in the provision of an annual report on safety information to the investigator and the head of the medical institution (study site)

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration statements shown below with the following conditions. As Ximency Combination Tablets is a drug with a new active ingredient and a new combination drug, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. Beclabuvir hydrochloride, a drug substance, is not classified as a poisonous drug or a powerful drug, but the drug product is classified as a powerful drug.

Indication

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

Dosage and Administration

The usual adult dosage is 2 tablets, administered orally twice daily after meals for 12 weeks

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until the data from the planned number of patients have been accumulated, thereby identifying the characteristics of treated patients, collecting data on the safety and efficacy of the product, and taking necessary measures to ensure its proper use.