Report on the Deliberation Results

September 14, 2016

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

Brand Name	Grazyna Tablets 50 mg
Non-proprietary Name	Grazoprevir Hydrate (JAN*)
Applicant	MSD K.K.
Date of Application	March 11, 2016

Results of Deliberation

In its meeting held on September 9, 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 re-examination period is 8 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug, and the product is not classified as a biological product or a specified biological product.

Conditions of Approval

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

**Japanese Accepted Name (modified INN)*

Review Report

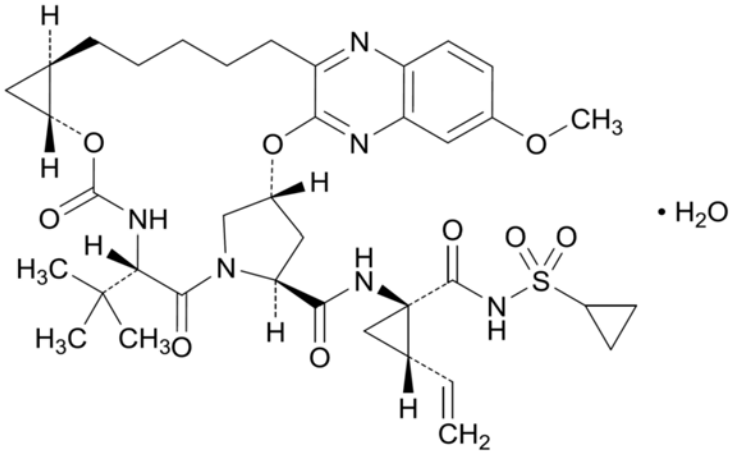
August 29, 2016
Pharmaceuticals and Medical Devices Agency

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

Brand Name	(a)	Grazyna Tablets 50 mg
	(b)	Erelsa Tablets 50 mg
Non-proprietary Name	(a)	Grazoprevir Hydrate
	(b)	Elbasvir
Applicant	MSD K.K.	
Date of Application	March 11, 2016	
Dosage Form/Strength		
	(a)	Each tablet contains 51.15 mg of Grazoprevir Hydrate (50 mg of Grazoprevir).
	(b)	Each tablet contains 50 mg of Elbasvir.

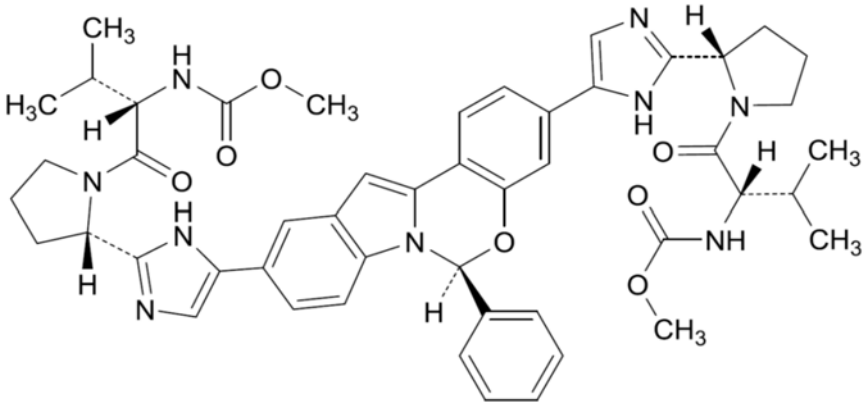
Application Classification Prescription drug, (1) Drugs with a new active ingredient

Chemical Structure (a) Grazoprevir Hydrate



Molecular formula: $C_{38}H_{50}N_6O_9S \cdot H_2O$
Molecular weight: 784.92
Chemical name:
(1a*R*,5*S*,8*S*,10*R*,22a*R*)-*N*-{(1*R*,2*S*)-1-[(Cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-5-(1,1-dimethylethyl)-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide monohydrate

(b) Elbasvir



Molecular formula: $C_{49}H_{55}N_9O_7$
Molecular weight: 882.02
Chemical name:
Dimethyl *N*,*N*‘-([(6*S*)-6-phenyl-6*H*-indolo[1,2-*c*][1,3]benzoxazine-3,10-diyl]bis{1*H*-imidazole-5,2-diyl-(2*S*)-pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Items Warranting Special Mention	Priority review (PSEHB/ELD Notification No.0401-3, dated April 1, 2016)
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the combination regimen of Grazyna Tablets 50 mg and Erelsa Tablets 50 mg has efficacy in the treatment of patients with serogroup 1 (genotype 1) chronic hepatitis C with or without compensated cirrhosis, and that the regimen has acceptable safety in view of their benefits (see Attachment).

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

Indication

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

Dosage and Administration

(a) The usual adult dosage is 100 mg of Grazoprevir, administered orally once daily in combination with Elbasvir for 12 weeks.

(b) The usual adult dosage is 50 mg of Elbasvir, administered orally once daily in combination with Grazoprevir Hydrate for 12 weeks.

Condition of approval

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

Attachment

Review Report (1)

July 7, 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.

Products Submitted for Approval

Brand Name	(a)	Grazyna Tablets 50 mg
	(b)	Erelsa Tablets 50 mg
Non-proprietary Name	(a)	Grazoprevir Hydrate
	(b)	Elbasvir
Applicant	MSD K.K.	
Date of Application	March 11, 2016	
Dosage Form/Strength		
	(a)	Each tablet contains 51.15 mg of Grazoprevir Hydrate (50 mg of Grazoprevir).
	(b)	Each tablet contains 50 mg of Elbasvir.

Proposed Indication

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

Proposed Dosage and Administration

(a) The usual adult dosage is 100 mg of Grazoprevir, administered orally once daily in combination with Elbasvir for 12 weeks.

(b) The usual adult dosage is 50 mg of Elbasvir, administered orally once daily in combination with Grazoprevir Hydrate for 12 weeks.

Table of Contents

List of abbreviations

Abbreviation	
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
AUC_{inf}	Area under the plasma concentration versus time curve extrapolated to infinite time
AUC_{0-t}	Area under the plasma concentration versus time curve from 0 to t hours
AUC_{0-24}	Area under the plasma concentration versus time curve from 0 to 24 hours
BA	Bioavailability
BCRP	Breast cancer resistance protein
BID	bis in die
BMI	Body mass index
BSEP	Bile salt export pump
C_{max}	Maximum plasma concentration
C_t	Plasma concentration at t hours post-dose
C_{trough}	Trough concentration
CL	Clearance
CL/F	Apparent clearance
CYP	Cytochrome P450
CV	Coefficient of variation
DAA	Direct acting antivirals
EBR	Elbasvir
EC_{50}	50% effective concentration
efflux ratio	Basal-to-apical versus apical-to-basal ratio
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
GZR	Grazoprevir hydrate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography

Abbreviation	
ICH Q1E guidelines	"Guidelines for Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004, dated June 3, 2003)
IC_{50}	50% inhibitory concentration
IFN	Interferon
k_a	Primary absorption rate constant
MRP	Multidrug resistance-associated protein
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBPK	Physiologically-based pharmacokinetic(s)
PEG	Polyethylene glycol
PegIFN	Pegylated interferon
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
QD	quaque die
RBV	Ribavirine
SVR12	Sustained viral response 12
t_{max}	Time to maximum plasma concentration
$t_{1/2}$	Estimate of the terminal elimination half-life
UGT	Uridine diphosphate glucuronosyltransferase
V_d	Volume of distribution
V_d/F	Apparent volume of distribution
$V_{d,ss}$	Volume of distribution at steady state

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

Grazoprevir Hydrate (grazoprevir hydrate) and Elbasvir (elbasvir) were developed as therapeutic agents for HCV infection by Merck Sharp & DohmeCorp., a subsidiary of Merck & Co., Inc (the US). Grazoprevir hydrate and elbasvir suppress HCV proliferation by inhibiting the HCV NS3/4A protease and NS5A, respectively, which are involved in HCV replication.

As many as 170 million people are estimated to be infected with HCV worldwide and 1.5 to 2 million people in Japan. Approximately 70% of infections are associated with genotype 1 (Guidelines for the Management of Hepatitis C Virus Infection, 5th edition. Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology; 2016). In Japan, approved treatment options for patients with chronic hepatitis C (genotype 1) are interferon preparations, ribavirin, NS3/4A protease inhibitors (telaprevir, simeprevir sodium, asunaprevir, vaniprevir), an NS5A inhibitor (daclatasvir hydrochloride), an NS5B polymerase inhibitor (sofosbuvir), a combination product of sofosbuvir and ledipasvir acetonate (an NS5A inhibitor) and a combination product of paritaprevir hydrate (an NS3/4A protease inhibitor), ombitasvir hydrate (an NS5A inhibitor), and ritonavir (a CYP3A inhibitor).

After the results from Japanese clinical studies on the combination regimen of grazoprevir hydrate and elbasvir in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) became available, the applicant filed an application for marketing approval for the combination regimen.

Outside Japan, Merck Sharp & DohmeCorp., a subsidiary of Merck & Co., Inc. (the US), developed a fixed-dose combination product containing 102.3 mg of grazoprevir hydrate (100 mg of grazoprevir) and 50 mg of elbasvir. This combination product alone and with ribavirin have been approved in 4 countries including the US and Canada as of June 2016.

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

2.1 Drug substance (grazoprevir hydrate [GZR])

2.1.1 Characterization

The drug substance is a white powder. It is characterized based on thermal analysis, solubility, optical rotation, hygroscopicity, partition coefficient, and dissociation constant (the quinoxaline group and the acylsulfonamide group). Although 6 crystal forms of the drug substance were identified, only Form III (monohydrate) (stable at room temperature) was been confirmed to be produced in the commercial-scale manufacturing process.

The chemical structure of the drug substance were elucidated by ultraviolet absorption spectroscopy, infrared spectroscopy, nuclear magnetic resonance spectrometry (^{1}H- and ^{13}C-NMR), mass spectrometry, and single-crystal x-ray crystallography. The drug substance has 7 chiral centers.

2.1.2 Manufacturing process

The drug substance is synthesized from the following starting materials: [redacted], [redacted], and [redacted]. [redacted] and [redacted] are critical steps with process control items and values specified. The following are the intermediates of the drug substance, each of which has control items and values: [redacted], [redacted], [redacted], and [redacted].

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identity (infrared spectroscopy), optical rotation, purity [heavy metals, [redacted], related substances (HPLC), [redacted] (HPLC), residual solvents (gas chromatography)], water content, and assay (HPLC).

2.1.4 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 1. The photostability studies showed that the drug substance is photosensitive.

Table 1. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	doubled low-density polyethylene bags/a high-density polyethylene drum	24 months
Accelerated	3 commercial-scale batches	40°C	75% RH		6 months

Based on the above, in accordance with the guideline in ICH Q1E, a retest period of [redacted] months was proposed for the drug substance when stored in double low-density polyethylene bags within a high-density polyethylene drum at room temperature. The long-term testing is to be continued up to [redacted] months.

2.2 Drug product (GZR)

2.2.1 Description and composition of the drug product and formulation development

The drug product is a tablet containing 51.15 mg of GZR (50 mg of grazoprevir). Its excipients are sodium lauryl sulfate, copovidone, D-mannitol, croscarmellose sodium, sodium chloride, colloidal silicon dioxide, and magnesium stearate.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of [redacted], lubrication and blending, [redacted], final lubrication and blending, tablet compression, packaging, labeling, testing, and storage. Critical steps are [redacted] and [redacted]. Process control items and values were specified in both steps.

A quality control strategy was developed based on the following identified by a quality-by-design approach.

- [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] or [redacted], and [redacted] as critical quality attributes

- Critical process parameters through quality risk assessment and design of experiments

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identity (HPLC), purity (related substances [HPLC]), uniformity of dosage units (mass variation test), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

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

Table 2. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	aluminum/aluminum blisters	18 months
Accelerated	3 commercial-scale batches	40°C	75% RH		6 months

Based on the above, a shelf-life of 30 months was proposed for the drug product when packaged in an aluminum/aluminum blister and stored at room temperature, in accordance with the guideline in ICH Q1E. The long-term testing is to be continued up to [redacted] months.

2.3 Drug substance (elbasvir [EBR])

2.3.1 Characterization

The drug substance is a white powder. It is characterized based on thermal analysis, solubility, optical rotation, crystalline polymorphism, hygroscopicity, partition coefficient, pH of solution, and dissociation constant (the imidazolium group). The drug substance is an amorphous free base. Although solvation (methanol, ethanol, 1-propanol, and 2-propanol) and hydration products were identified during development, it has been confirmed that the amorphous form only is produced by the commercial-scale manufacturing process.

The chemical structure of the drug substance was elucidated by ultraviolet absorption spectroscopy, infrared spectroscopy, nuclear magnetic resonance spectrometry (^{1}H- and ^{13}C-NMR), mass spectrometry, and single-crystal x-ray crystallography. The drug substance has 5 chiral centers.

2.3.2 Manufacturing process

The drug substance is synthesized using from the following starting materials: [redacted], [redacted], and [redacted].

Critical steps are [redacted] and [redacted]. Process control items and values were specified in both steps. Intermediates are [redacted], [redacted], and [redacted]. Control items and values were specified for each intermediate.

2.3.3 Control of drug substance

The specifications for the drug substance consist of content, description, identity (infrared spectroscopy), optical rotation, purity [heavy metals, [redacted], related substances (HPLC), residual solvents (gas chromatography)], water content, and assay (HPLC).

2.3.4 Stability of drug substance

Table 3 outlines the primary stability studies on the drug substance. The photostability studies showed that the drug substance is photosensitive.

Table 3. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	5°C	—	doubled low-density polyethylene bags/a heat-sealed foil bag ([redacted])/a fiber drum	24 months
Accelerated		25°C	60% RH		12 months

Based on the above, a retest period of [redacted] months was proposed for the drug substance when packaged in double low-density polyethylene bags and placed with [redacted] in a heat-sealed foil bag and stored at 2°C to 8°C in a fiber drum (protected from light). The long-term testing is to be continued up to [redacted] months.

2.4 Drug product (EBR)

2.4.1 Description and composition of the drug product and formulation development

The drug product is a film-coated tablet containing 50 mg of the drug substance. Its excipients are hypromellose, vitamin E polyethylene glycol succinate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, sodium chloride, colloidal silicon dioxide, magnesium stearate, and Opadry II Pink ([redacted]).

2.4.2 Manufacturing process

The manufacturing process of the drug product consists of [redacted], [redacted], [redacted], final lubrication and blending, tablet compression, film coating, packaging, labeling, testing, and storage. Of these steps, [redacted], [redacted], and [redacted] have been defined as critical steps, and process control items and values have been established for all critical steps.

A quality control strategy was developed based on the following identified by a quality-by-design approach.

- [redacted], [redacted], [redacted], [redacted], [redacted] or [redacted], and [redacted] as critical quality attributes
- Critical process parameters through quality risk assessment and design of experiments

2.4.3 Control of drug product

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

2.4.4 Stability of drug product

Table 4 outlines the primary stability studies on the drug product. The photostability studies showed that the drug product is photostable.

Table 4. Stability studies on drug product

Study	Primary batches [a)]	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches ([redacted])	25°C	60% RH	aluminum/aluminum blisters	24 months
	3 commercial-scale batches (beige-colored tablets)				12 months
Accelerated	3 commercial-scale batches ([redacted])	40°C	75% RH		6 months
	3 commercial-scale batches (beige-colored tablets)				6 months

[redacted], formulation used in Japanese clinical studies; pink tablets, final market image formulation

[a)] The equivalence between [redacted] and beige-colored tablets were demonstrated based on the drug product formulation and the results of batch analyses, etc.

Based on the above, a shelf-life of 36 months was proposed for the drug product when packaged in an aluminum/aluminum blister and stored at room temperature, in accordance with the guideline in ICH Q1E. The long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that the quality of the drug substances and drug products of GZR and EBR is adequately controlled.

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

The pharmacological effects of GZR and EBR were assessed in primary pharmacodynamic, secondary pharmacodynamic, and safety pharmacology studies. GZR concentrations are expressed in terms of grazoprevir.

3.1 Primary pharmacodynamics (grazoprevir hydrate [GZR])

3.1.1 Inhibitory activity against NS3/4A protease (CTD 4.2.1.1-6)

The inhibitory activities of GZR against NS3/4A proteases from various genotypes were determined. The results are shown in Table 5.

Table 5. Inhibitory activities of GZR against NS3/4A proteases from various genotypes

Genotype	IC_{50} (nmol/L)
1a	0.007
1b	0.004
2a	0.067
2b	0.135
3a	0.690
4a	0.062
5a	0.067
6a	0.034
Chymotrypsin[a)]	1495

Mean, [a)] human protease

3.1.2 *In vitro* antiviral activity (CTD 4.2.1.1-3, 4.2.1.1-5)

In HCV replicon assays (*Science*. 1999; 285: 110-3) (detection method: real-time PCR), the activity of GZR was evaluated against HCV replicons from different genotypes by measuring HCV RNA levels. The results are shown in Table 6.

Table 6. Activity of GZR against various HCV genotypes/subtypes in cell culture

Genotype (viral strain)	EC_{50} (nmol/L)	EC_{90} (nmol/L)
1a (H77)	0.4	0.9
1b (Con1)	0.5	1.1
1b (Con1) (in the presence of 40% human serum)	1.1	3.1
2a (JFH1)	2.3	7.1
2b (NS3/4A AY232740 [a]) [b]	3.7	7.8
3a (NS3/4A GLA [c]) [b]	7.6	20.5
4a (NS3/4A GU814266 [a]) [b]	0.3	0.8
5a (NS3/4A AF064490 [a]) [b]	1.5	4.5
6a (NS3/4A JN180455.1 [a]) [d]	0.9	2.3

Mean

[a] NS3/4A GenBank accession number

[b] The replicons have NS3/4A sequences from different genotypes in genotype 2a JFH1 background.

[c] NS3 GenBank accession number GU045445.1, NS4A GenBank accession number GU945457.1.

[d] The replicon has the genotype 6a NS3/4A sequence in genotype 1b Con1 background.

The cytotoxicity of GZR to HeLa cells and genotype 1b (Con1) replicon-containing Huh-7 cells was determined. The 50% cytotoxic concentration was 70.4 μmol/L in HeLa cells and 68.9 μmol/L in Huh-7 cells.

3.1.3 Resistance profile

3.1.3.1 Resistance selection studies (CTD 4.2.1.1-2)

Amino acid substitutions listed in Table 7 were identified when genotype 1b (Con1) replicon cells were cultured in the presence of 6 or 30 nmol/L of GZR for 15 days.

Table 7. Summary of resistant colonies selected in genotype 1b (Con1) replicon cells

Concentration (nmol/L)	Amino acid substitutions (colony count)
6	F43S (1), A156T (1), A156S (2), D168A/G/V (3), A156V + D168V (1), A156S + D168A (1)
30	F43S (1), F43F/S (2), A156T (1), A156T/S/A (1), Q41H + A156V (1)

Amino acid substitutions listed in Table 8 were identified when genotype 1a (H77) replicon cells were passaged 10 times in the presence of 0 to 10 nmol/L of GZR.

Table 8. Summary of resistant colonies selected in genotype 1a (H77) replicon cells

Concentration (nmol/L)	Amino acid substitutions (% population[a])
0	Q41R (10)
2.5	Q41R (50), D168E (35)
5	A39V (100), Q41R (90), D168V (90)
10	I48A (40), D168A (30), D168G (30), D168V (40)

[a] Calculated based on peak areas of individual nucleotides on the electropherogram after population sequencing (%)

3.1.3.2 Antiviral activity of GZR against resistance-associated variants (CTD 4.2.1.1-5)

The antiviral activity of GZR was evaluated based on HCV RNA levels measured by HCV replicon assays (method, real-time PCR). Genotype 1a (H77) and 1b (Con1) replicon cells were engineered to encode substitutions reported in *in vitro* resistance selection studies and clinical studies of GZR and EBR, and resistance-associated substitutions to other NS3/4A protease inhibitors (Sovriad Capsules 100 mg package insert 7th edition; Vanihep Capsules 150 mg package insert 5th edition, etc.). The results are shown in Table 9 and Table 10.

Table 9. Antiviral activity of GZR in genotype 1a wild-type and mutant replicon cells

Amino acid substitution in NS3	EC_{50} (nmol/L)	Fold shift [a)]	EC_{90} (nmol/L)	Fold shift [a)]
Wild-type (H77)	0.4	1.0	0.9	1.0
V36A	0.5	1.5	1.1	1.2
V36I	0.4	1.0	0.7	0.8
V36L	0.5	1.4	1.2	1.3
V36M	0.3	1.0	0.9	0.9
A39V	0.1	0.3	0.3	0.3
Q41R	0.8	2.2	1.9	2.1
F43L	0.7	1.9	2.9	3.1
T54A	0.3	0.7	0.5	0.6
T54S	0.3	0.9	1.0	1.1
V55A	0.5	1.4	0.9	0.9
V55I	0.2	0.6	0.6	0.6
Y56H	5.7	16.1	42.6	46.0
Q80K	0.3	0.9	1.0	1.1
Q80R	0.4	1.1	1.7	1.8
V107I	0.2	0.7	0.7	0.7
P146S	0.8	2.4	1.1	1.2
R155K	1.3	3.7	2.8	3.0
R155T	3.4	9.7	7.1	7.7
A156G	1.7	4.8	4.1	4.4
A156L	918 [b)]	2295	1820 [b)]	2022
A156S	0.9	2.5	2.3	2.5
V158I	0.1 [b)]	0.3	0.4 [b)]	0.4
D168A	28.6	80.7	105.8	114.2
D168E	4.9	13.9	11.6	12.5
D168F	8.4	21.0	30	33.3
D168G	9.6	27.2	46.4	50.1
D168H	4.9	12.3	18	20.0
D168I	14.3	40.5	68.5	74.0
D168K	75.1	212.2	280.7	303.1
D168L	4.3	10.8	18	20.0
D168N	0.9	2.5	2.7	2.9
D168S	0.7	2.3	6.4	7.6
D168T	34.7	97.9	85.9	92.7
D168V	10.5	29.7	54.5	58.8
D168Y	6.9	21	24	27
I170T	0.7	2.0	1.8	2.0
I170V	0.1 [b)]	0.3	0.4 [b)]	0.4
V36L + Q80K	0.5	1.4	2.6	2.8
V36L + Q80K + R155S	14.2	40.1	62.2	67.1
V36M + R155K	3.5	9.9	10.1	10.9
V36M + A156T	151	481.0	480	573.0
T54S + R155K	2.0	5.7	5.4	5.8
Y56H + D168N	19.3	61.4	53.2	63.3
R155K + D168N	2.7	7.6	7.5	8.1
R155T + D168N	4.	11.7	10.6	11.4
V36M + V107I + R155K	3.8	10.6	8.0	8.6
WT (Huh 7.5)	0.14	1.0	0.4	1.0
Y56H + D168A	655	4679	2160 [b)]	5400
Y56H + A156T + D168N	2420 [b)]	17,000	> 5000	> 12,500
A156T + D168N	1250 [b)]	8929	2870 [b)]	7175
NS3 Q41R + NS5A M28K [c)]	0.5	1.5	2.4	2.9
NS3 Q41R + NS5A M28T [c)]	0.5	1.6	1.3	1.6

Mean

[a)] Mutant $EC_{50 \text{ or } 90}$/wild-type $EC_{50 \text{ or } 90}$, [b)] N = 1, [c)] amino acid substitutions at NS3 position 41 and NS5A position 28

Table 10. Antiviral activity of GZR in genotype 1b wild-type and mutant replicon cells

Amino acid substitution in NS3	EC_{50} (nmol/L)	Fold shift [a)]	EC_{90} (nmol/L)	Fold shift [a)]
Wild-type (Con1)	0.5	1.0	1.0	1.0
V36A	1.0	2.0	2.2	2.4
V36I	0.2	0.4	0.6	0.6
V36L	0.5	0.9	1.6	1.7
V36M	0.9	1.7	1.8	2.0
Q41L	0.1	0.2	0.3	0.3
Q41R	1.1	2.2	2.2	2.3
F43S	1.3	2.6	4.7	5.0
T54A	0.6	1.2	1.6	1.7
T54C	0.8	1.6	1.6	1.7
T54G	0.8	1.7	2.1	2.2
T54S	0.6	1.2	2.0	2.1
V55A	0.7	1.4	1.4	1.5
V55I	0.7	1.5	1.8	2.0
Y56F	0.7	1.5	2.0	2.2
Y56H	6.3	12.6	18.0	19.4
Q80L	1.1	2.1	2.8	3.0
Q80R	0.9	1.9	2.3	2.5
Q86R	0.1	0.2	0.3	0.3
V107I	0.5	1.0	1.1	1.2
S122A	0.4	0.8	1.1	1.0
S122G	0.3	0.5	1.0	1.0
S122R	0.3	0.5	1.5	1.4
R155E	1.4	2.7	3.8	4.1
R155G	14.2	28.3	29.6	32.0
R155K	1.1	2.2	2.4	2.6
R155N	0.9	1.9	2.3	2.5
R155Q	1.2	2.4	2.9	3.2
R155S	1.7	3.4	5.6	6.0
R155T	6.7	13.3	24.7	26.6
R155W	13.4	26.7	36.1	38.9
A156G	0.7	1.4	1.4	1.5
A156S	1.1	2.1	3.4	3.7
A156T	140.1	279.5	365.3	394.5
A156V	187.7	374.6	578.4	624.6
D168A	6.8	13.6	21.1	22.8
D168E	1.6	3.2	6.1	6.6
D168F	38.0	75.9	102.6	110.8
D168G	5.7	11.3	18.8	20.2
D168H	25.6	51.0	78.2	84.4
D168I	6.6	13.2	37.2	40.1
D168K	60.6	120.9	247.0	266.7
D168L	7.6	15.1	36.3	39.2
D168N	0.4	0.7	1.6	1.8
D168S	2.0	4.1	7.2	6.9
D168T	13.0	26.0	31.2	33.7
D168V	7.2	14.4	25.8	27.8
D168Y	4.2	8.4	13.4	14.5
V170A	0.7	1.4	2.4	2.6
V170I	0.4	0.9	1.5	1.7
V170T	0.5	0.9	1.3	1.4
Y56H + D168A	303	758	847	941
Q80R + D168E	17.1	34.2	74.0	79.9
R155W + A156G	1540 [b)]	3080	> 2000	>2000
R155W + A156G + D168N	278 [b)]	555.0	902 [b)]	974.0
T54S + Q80L + V170I	0.5	0.9	1.9	1.9
A156G + D168N	9.0	18.2	42.5	41.2

Mean, [a)] Mutant $EC_{50 \text{ or } 90}$/wild-type $EC_{50 \text{ or } 90}$, [b)] N = 1

3.1.3.3 Cross-resistance (CTD 4.2.1.1-5)

The antiviral activities of GZR and other NS3/4A protease inhibitors were evaluated based on HCV RNA levels measured by HCV replicon assays (detection method, real-time PCR). Genotype 1a (H77S) or 1b (Con1) replicon cells engineered to encode NS3 or NS5A substitutions reported in clinical studies of GZR and EBR and NS3 or NS5A resistance-associated substitutions to other NS3/4A protease inhibitors or NS5A inhibitors

(Sovriad Capsules 100 mg package insert, 7th edition, Daklinza Tablets 60 mg package insert, 10th edition, etc.). The results are shown in Table 11. Shifts in potency[1)] of GZR, telaprevir, simeprevir, and paritaprevir on genotype 1b (Con1) replicon cells containing NS5A resistance-associated substitutions, namely L31/M/V or Y93H, were 0.6- to 0.8-, 1.0- to 4.0-, 0.2- to 1.6-, and 1.1- to 2.0-fold, respectively.

Table 11. Antiviral activities of GZR and other NS3/4A protease inhibitors against NS3 resistance-associated variants

Genotype	Amino acid substitution	GZR		Telaprevir		Simeprevir		Paritaprevir	
		EC_{50} (nmol/L)	Fold shift [a)]	EC_{50} (nmol/L)	Fold shift [a)]	EC_{50} (nmol/L)	Fold shift [a)]	EC_{50} (nmol/L)	Fold-shift [a)]
1a	Wild-type (H77S)	0.19	1.0	264	1.0	1.5	1.0	1.4	1.0
	V36A	0.3	1.5	373	1.7	2.7	1.9	3.5	2.4
	T54S	0.3	1.5	1330	5.0	4.9	3.4	12.1	8.5
	V55I	0.1	0.7	235	0.9	2.2	1.5	2.9	2.0
	Y56H	3.3	17.7	219.5	0.8	25.1	17.2	16.8	11.8
	Q80K	0.43	2.3	154	0.6	14	9.7	8.7	6.1
	S122R	0.3	1.8	141	0.5	114	77.9	26.4	18.6
	R155K	0.5	2.6	92	0.3	19	13.0	20.0	14.1
	A156S	0.4	2.2	221	0.8	0.07	0.1	0.5	0.3
	D168A	26	138.8	15	0.1	82	56.4	25.8	18.1
	D168E	4.8	25.4	141	0.5	19	13.2	24.0	16.8
	D168N	1.5	8.0	102	0.4	4.5	3.1	8.2	5.7
	D168Y	19	103.8	79	0.3	1658	1,134	128.9	90.6
	I170T	0.5	2.5	515	2.0	10.9	7.5	4.2	2.9
1b	Wild-type (Con1)	0.3	1.0	131	1.0	0.3	1.0	0.4	1.0
	V36A	0.7	2.2	70	0.5	0.3	1.0	0.8	2.2
	T54S	0.4	1.2	65	0.5	0.1	0.5	0.6	1.7
	V55A	0.5	1.6	153	1.2	0.2	0.9	0.5	1.3
	Y56H	15.3	48.1	86	0.7	16	60	2.8	7.9
	Q80R	0.2	0.6	60	0.5	2.5	9	0.7	2.1
	A156T	> 100	> 333	69	0.5	37	139	3.8	10.8
	D168A	37.9	119.3	26	0.2	2033	7646	87	243.5
	D168E	4.3	13.4	50	0.4	23	85	3.1	8.6
	D168N	0.4	1.4	44	0.3	3.2	12	2.0	5.5
	D168V	15	46.4	51	0.4	8280	31,148	113	315.7
	V170A	0.4	1.3	68	0.5	0.06	0.2	0.7	1.8

Mean; [a)] mutant EC_{50}/wild-type EC_{50}

3.1.4 Combined effects of GZR and EBR (CTD 4.2.1.1-7)

Combined effects of GZR (concentration range, 0-5 nmol/L) and EBR (concentration range, 0-6 pmol/L) was evaluated by replicon assays using genotype 1a replicon cells (detection method, real-time PCR). The results are shown in Table 12.

Table 12. Combined effects of GZR and EBR

Test compounds	Synergy volume [a)]	Effect [b)]
GZR + EBR	4.42	Mild
	0.5	Additive
	0.66	Additive

Lower limit of the 95% confidence interval

[a)] Calculated using MacSynergy II program, based on *Antimicrob Agents Chemother*. 1993; 37: 540-5. The test was performed 3 times.

[b)] Synergy volumes: <2, additive; >2 and <5, mild; >5 and <9, moderate; >9, strong; >90, invalid data.

Combined effects of GZR and EBR was studied in genotype 1a replicon cells based on the number of surviving colonies. The results are shown in Table 13.

[1)] Mutant EC_{50}/wild-type EC_{50}

Table 13. Number of surviving colonies in genotype 1a replicon cells treated with combined GZR and EBR

		EBR EC_{90} multiple				
		0	1	3	10	30
GZR EC_{90} multiple	0	(100 [a])	— [b]	293 (0.15)	181 (0.090)	144 (0.072)
	1	— [b]	435 (0.22)	179 (0.090)	82 (0.040)	39 (0.020)
	3	Approx.1000 (0.50)	255 (0.12)	83 (0.042)	9 (0.0045)	1 (0.0020)
	10	120 (0.060)	38 (0.019)	9 (0.0045)	1 (0.00050)	0

The number of surviving colonies (surviving colony count/input [%]); GZR EC_{90}, 1.5 nmol/L; EBR EC_{90} ,6 pmol/L
[a] no drug treatment was set at 100%. [b] too many to count.

3.1.5 *In vivo* study (CTD 4.2.1.1-4)

Chimpanzees were infected with HCV genotype 1a (wild-type or the R155K mutant) or 1b (wild-type) and orally received GZR 1 mg/kg twice daily for 7 days, and plasma HCV RNA levels were measured by real-time PCR. The plasma HCV RNA levels in the genotype 1a wild-type-, 1a R155K mutant-, and 1b wild-type-infected chimpanzees before receiving GZR were approximately 6, 4, and 6 log IU/mL, respectively, and approximately 2.5, 3, and 1.5 log IU/mL, respectively, at the end of GZR dosing.

3.2 Secondary pharmacodynamics (GZR)

3.2.1 Activities against enzymes and receptors (CTD 4.2.1.2-1, 4.2.1.2-4)

The inhibitory activity of GZR against enzymes and receptors was evaluated. Table 14 lists the enzymes and receptors with IC_{50} of <100 μmol/L.

Table 14. Activities of GZR against enzymes or receptors

Enzymes or receptors	IC_{50} (μmol/L)	Selectivity [a]
Matrix metalloproteinase-1	1.47	367,500
Matrix metalloproteinase-12	6.89	1,722,500
5-lipoxygenase	2.84	710,000
Phosphodiesterase 1	31	7,750,000
Phosphodiesterase 4	81.4	20,350,000
Phosphodiesterase 5	94.4	23,600,000
Phosphodiesterase 6	22	5,500,000
MAPK3 (ERK1)	45.7	11,425,000
Protein kinase A	55.6	13,900,000
hERG channel	3.33	682,500
Prostanoid FP receptor	6.49	1,622,500

Mean, [a] IC_{50} of GZR against enzyme or receptor/IC_{50} of GZR against genotype 1b NS3/4A protease

3.2.2 Activities against HIV-1 and HBV (CTD 4.2.1.2-3, 4.2.1.2-5)

Antiviral activity of GZR against HIV-1 was investigated using HIV-infected MT4-GFP cells. The mean EC_{50} values of GZR and positive control (efavirenz, a non-nucleoside reverse transcriptase inhibitor) were ≥8400 and 0.79 nmol/L, respectively.

Antiviral activity of GZR against HBV was investigated by real-time PCR using HBV-infected HepG cells. The mean IC_{50} values of GZR and positive control (lamivudine) were >10,000 and 36.9 nmol/L, respectively.

3.2.3 Activity of combined anti-HIV drugs and GZR (CTD 4.2.1.2-6)

Effects of GZR at concentrations of 0 to 500 nmol/L on the antiviral activities of anti-HIV drugs (tenofovir, emtricitabine, efavirenz, rilpivirine, darunavir, atazanavir, raltegravir, dolutegravir, maraviroc) were studied using MT4-GFP cells infected with HIV-1. GZR did not affect the EC_{50} values of the anti-HIV drugs at any concentration tested.

The effects of anti-HIV drugs (tenofovir, rilpivirine, raltegravir, and maraviroc, 0.3-3 μmol/L each; emtricitabine, efavirenz, darunavir, and dolutegravir, 2.2-20 μmol/L each; and atazanavir, 1-10 μmol/L) on the antiviral activity of GZR were studied using genotype 1a replicon (H77) assays (detection method, real-time PCR). The anti-HIV drugs did not affect the EC_{50} value of GZR.

3.3 Safety pharmacology (GZR) (CTD 4.2.1.3-2 to 4.2.3.2-4, 4.2.3.2-6, Reference data CTD 4.2.1.3-4)

The effects of GZR on the central nervous, cardiovascular, and respiratory systems were assessed (Table 15).

Table 15. Summary of safety pharmacology studies

Organ systems evaluated	Test system	Endpoint, method, etc.	Doses or concentrations	Route of administration	Noteworthy findings
Central nervous	Rats (6 males/group)	FOB	0, 25, 50, 1000 mg/kg	Oral	None
	Rats (6 males/group)	FOB	0, 50, 200, 200 × 2 (6 hours apart) mg/kg	Oral	None
Cardiovascular	Chinese hamster ovary cells (3-4 samples for each concentration)	hERG current	2.5, 7.9, 27, 96 μmol/L	*In vitro*	IC_{50} = 25 μmol/L
	Anesthetized mongrel dogs (3 females)	heart rate (HR), blood pressure, ECG	Consecutive doses of 1, 2, and 2 mg/kg	Intravenous	None
	Beagle dogs (2 dogs/sex/group)	Telemetry	0, 5, 20, 600 mg/kg	Oral	5 mg/kg: none 20 mg/kg: 42% increase in HR, 7% decrease in QT interval 600 mg/kg: 30% increase in HR, 9% decrease in QT interval, 9% decrease in PR interval
Respiratory	Beagle dogs (2 dogs/sex/group)	Telemetry	0, 5, 20, 600 mg/kg	Oral	None

The applicant's explanation about the effects of GZR on the central nervous, cardiovascular, and respiratory systems:

In a single and multiple dose oral toxicokinetic study in rats (reference data CTD 4.2.3.2.5), C_{max} (27.8 μmol/L) after a single 50 mg/kg oral dose of GZR was approximately 45-fold the C_{max} (0.617 μmol/L) in Japanese HCV-infected patients receiving GZR 100 mg, which was estimated from the results of a Japanese study (MK-5172-058) [see Section 6.2.6.1]. A rat FOB study revealed no GZR-related effects on the central nervous system at doses up to 1000 mg/kg. In the cardiovascular and respiratory systems, GZR inhibited hERG current with an IC_{50} of 25 μmol/L, which is >3000-fold the unbound C_{max} (<0.00617 μmol/L) in Japanese HCV-infected patients receiving GZR 100 mg based on GZR's plasma protein binding rate of ≥98%. In conscious dogs, there were no GZR-related effects on QT interval and respiratory function, etc. at doses up to 600 mg/kg, which was approximately 170-fold the C_{max} in Japanese HCV-infected patients receiving GZR 100 mg. [2)] Therefore, GZR should have no effects on the functions of the central nervous, cardiovascular and respiratory systems in its clinical use.

[2)] In a 1-month oral toxicity study in dogs (CTD 4.2.3.2.9), the C_{max} in dogs after a single 600 mg/kg oral dose of GZR was 105 μmol/L.

3.4 Primary pharmacodynamics (elbasvir [EBR])

3.4.1 *In vitro* antiviral activity (CTD 4.2.1.1-9)

In a competitive binding assay using radiolabeled compound, EBR was demonstrated to bind to NS5A protein. The applicant explained that EBR shows antiviral activity by inhibiting NS5A function.

In HCV replicon assays (detection method: real-time PCR), the activity of EBR was evaluated against HCV replicons from different genotypes by measuring HCV RNA levels. The results are shown in Table 16.

Table 16. Activity of EBR against various HCV genotypes/subtypes in cell culture

Genotype (Viral strain)	EC_{50} (nmol/L)	EC_{90} (nmol/L)
1a (H77)	0.004	0.006
1a (H77) (in the presence of 40% human serum)	0.040	0.082
1b (Con1)	0.003	0.006
2a (JFH1)	0.003	0.019
2b (AB030907 [a]) [b]	3.4	11
3a (NC009824 [a]) [c]	0.030	0.12
4a (DQ418782 [a]) [c]	0.003	0.016
5a (SA13_AF064490 [a]) [b]	0.001	0.002
6 (DQ278892 [a]) [b]	0.009	0.017

Mean
a) GenBank accession number
b) The replicons have NS5A sequences from different genotypes in genotype 2a JFH1 background.
c) The replicons have NS5A sequences from different genotypes in genotype 1b Con1 background.

The antiviral activity of EBR in genotype 1a and 1b patient isolates (5 genotype 1a isolates, 4 genotype 1b isolates) in replicon cells was evaluated. The mean EC_{50} ranged[3)] from 0.003 to 0.009 and from 0.003 to 0.01 nmol/L, respectively.

3.4.2 Resistance profile

3.4.2.1 Resistance selection studies (CTD 4.2.1.1-9)

Amino acid substitutions listed in Table 17 were identified when genotype 1a (H77) and 1b (Con1) replicon cells were cultured in the presence of EBR at 1- to 1000-fold multiples of the EC_{90} value.

Table 17. Summary of resistant colonies selected in genotype 1a and 1b replicon cells

Genotype (Viral strain)	EBR[a)]	Number of surviving colonies[b)]	EC_{50} [b)] (nmol/L)	EC_{90} [b)] (nmol/L)	Fold shift in EC_{90}[c)]	Amino acid substitutions
1a (H77)	1000	4	135	526	90,000	Q30D, Q30D + Y93N
	100	56	5	15	3000	Y93N
	10	204	2	11	2000	Not detected
	1	—[d)]	< 2	< 2	< 300	Not detected
	0	—	0.008	0.015	< 3	—
1b (Con1)	1000	3	27	120	20,000	Y93H, L31F + Y93H + V121I
	100	5	—[e)]	—[e)]	—[e)]	—[e)]
	10	38	0.6	12	2000	Y93H, V121I, Y93H + V121I
	1	122	0.2	1	200	Y93H
	0	—	0.008	0.011	< 3	—

—, not tested or not applicable
[a)] EBR EC_{90} multiple used for resistance selection in genotype 1a (H77) or 1b (Con1) replicon cells
[b)] N = 1
[c)] EBR EC_{90} from selected replicon cells/EBR EC_{90} from genotype 1a (H77) or 1b (Con1) replicon cells
[d)] Too many to count
[e)] Not applicable because the cells did not increase.

[3)] The mean was calculated from N = 2 to 3 independent experiments for each clinical isolate.

3.4.2.2 Antiviral activity of EBR against resistance-associated variants (CTD 4.2.1.1-9)

In HCV replicon assays (detection method: real-time PCR), the antiviral activity of EBR was evaluated using genotype 1a (H77) and 1b (Con1) replicon cells engineered to encode NS5A substitutions reported in *in vitro* resistance selection studies and clinical studies of GZR and EBR and NS5A resistance-associated substitutions to other NS5A inhibitors (Daklinza Tablets 60 mg package insert, 10th edition, Harvoni Combination Tablets package insert, second edition, etc.) by measuring HCV RNA levels. The results are shown in Table 18.

In a transient virus transfection assay (detection method, a luciferase reporter gene assay) using genotype 1a (H77) replicon cells, the effect of double substitutions at NS5A positions 31 and 93 on the antiviral activity of EBR was evaluated by quantifying HCV replicon replication. The EC_{50} values against wild-type and the double mutant L31V + Y93H were 0.007 and 272 nmol/L, respectively, and the double substitutions reduced EBR activity by 38,857-fold.

Table 18. Antiviral activity of EBR in genotype 1a and 1b wild-type and mutant replicon cells

Genotype (Viral strain)	Amino acid substitution	EC_{50} (nmol/L)	Fold shift [a)]	EC_{90} (nmol/L)	Fold shift [a)]
1a (H77)	Wild-type (H77)	0.004	1	0.006	1
	M28V	0.008	2	0.013	2.2
	Q30D	3.7	925	8	1333
	Q30E	0.1	25	0.15	25
	Q30H	0.03	7.5	0.2	33.3
	Q30K	0.006	1.5	0.059	9.8
	Q30R	0.5	125	2.5	417
	L31F	0.08	20	0.6	100
	L31M	0.002	0.5	0.009	1.5
	L31V	0.5	125	1.0	167
	Y93C	0.2	50	1.1	183
	Y93H	2.4	600	28	4667
	Y93N	8	2000	18	3000
	Q30D + Y93N	180	45,000	371	61,833
1b (Con1)	Wild-type (Con1)	0.003	1	0.006	1
	L28M	0.006	2	0.02	3.3
	L28V	0.004	1.3	0.01	1.7
	R30Q	0.009	3	0.02	3.3
	L31F	0.05	16.7	0.2	33.3
	L31V	0.01	3.3	0.07	11.7
	Q62E	0.007	2.3	0.012	2
	L31V + Q62E	0.01	3.3	0.03	5
	Y93C	0.005	1.7	0.01	1.7
	Y93H	0.05	16.7	0.4	66.7
	Q62E + Y93H	0.04	13.3	0.2	33.3

Mean, [a)] Mutant $EC_{50 \text{ or } 90}$/wild-type $EC_{50 \text{ or } 90}$

3.4.2.3 Cross-resistance

3.4.2.3.1 Antiviral activity of EBR against NS3 or NS5B resistance-associated variants (CTD 4.2.1.1-10)

The antiviral activity of EBR was evaluated based on HCV RNA levels measured by HCV replicon assays (detection method, real-time PCR). Genotype 1a (H77) or 1b (Con1) replicon cells were engineered to encode NS3 or NS5B substitutions reported in clinical studies of GZR and EBR and NS3 or NS5B resistance-associated substitutions to other NS3/4A protease inhibitors or NS5B polymerase inhibitors (Sovriad capsules 100 mg package insert, 7th edition, Harvoni Combination Tablets package insert, second edition, etc.). The results are shown in Table 19.

Table 19. Antiviral activity of EBR against NS3 or NS5B resistance-associated variants

Genotype (Viral strain)	Class of inhibitor	Amino acid substitution	EC_{50} (nmol/L)
1a (H77)	NS3/4A protease inhibitor	Wild-type	0.001
		T54S	0.0005
		Q80K	0.0007
		R155K	0.0004
		V36M + R155K	0.0009
		D168V	0.0011
	Non-nucleoside NS5B polymerase inhibitor	C316Y	0.0009
		M414I	0.001
		M423T	0.0006
1b (Con1)	NS3/4A protease inhibitor	Wild-type	0.0007
		A156T	0.0015
		A156V	0.0015
		D168Y	0.0009
	Nucleoside NS5B polymerase inhibitor	S282T	0.0003
	Non-nucleoside NS5B polymerase inhibitor	P495L	0.0022

Mean

3.4.2.3.2 Antiviral activities of EBR and other NS5A inhibitors against NS3 or NS5A resistance-associated variants (CTD 4.2.1.1-8, 4.2.1.1-9)

In HCV replicon assays (detection method: real-time PCR), the antiviral activity of EBR was evaluated against genotype 1a (H77) and 1b (Con1) replicons expressing NS3 or NS5A substitutions reported in clinical studies of GZR and EBR and NS3 or NS5A resistance-associated substitutions to other NS3/4A protease inhibitors or NS5A inhibitors (Sovriad capsules 100 mg package insert, 7th edition, Harvoni Combination Tablets package insert, second edition, etc.) by measuring HCV RNA levels. The results are shown in Table 20. In genotype 1b (Con1) replicon cells containing resistance-associated substitutions at NS3 positions 56, 156, or 168, etc., 0.3- to 1.0-, 0.8- to 2.5-, and 1.0- to 2.0-fold shifts[1)] were observed for EBR, ledipasvir, and ombitasvir, respectively.

Table 20. Antiviral activities of EBR and other NS5A inhibitors against NS5A resistance-associated variants

Genotype	Amino acid substitution	EBR		Ledipasvir		Ombitasvir	
		EC_{50} (nmol/L)	Fold shift [a)]	EC_{50} (nmol/L)	Fold shift [a)]	EC_{50} (nmol/L)	Fold shift [a)]
1a [b)]	Wild-type (H77)	0.013	1.0	0.068	1.0	0.12	1.0
	M28A	0.49	38.7	17.4	257.1	40.3	330.3
	M28T	0.21	16.9	2.0	30.2	210.5	1723.8
	M28V	0.019	1.5	0.04	0.6	6.7	55.0
	Q30E	0.52	41.1	65.0	962.2	41.0	335.8
	Q30H	0.05	3.6	6.9	101.9	1.0	7.9
	Q30K	0.47	37.3	32.3	478.1	21.3	178
	Q30L	0.006	0.5	0.7	10.3	0.1 [c)]	0.8 [c)]
	Q30R	0.23	18.2	9.5	140.6	80.5	659.2
	L31M	0.12	9.4	10.1	149.5	0.3	2.1
	L31V	0.82	65.4	18.7	276.3	5.9	48.0
	H58D	0.07	5.8	25.7	379.9	15.1	123.7
	H58P	0.012	1.0	0.1	1.4	0.12	1.0
	Y93C	0.19	14.9	18.0	266.4	76.0	622.4
	Y93N	6.8	538.9	342.3	5067.4	1421	11,637.0
	Y93H	3.3	258.8	98.0	1450.7	1138.0	9319.4
1b	Wild-type (Con1)	0.001	1.0	0.0004	1.0	0.001	1.0
	L31I	0.0011	1.1	0.052	130	0.003	3
	L31M	0.007	7.0	0.03	75	0.006	6
	L31V	0.013	13	0.95	2,375	0.71	710

Mean

[a)] Mutant EC_{50}/wild-type EC_{50}, [b)] Activity was estimated using transient virus transfection assay, [c)] N = 1

3.5 Secondary pharmacodynamics (EBR)

3.5.1 Activities against enzymes and receptors (CTD 4.2.1.2-2 to 4.2.1.2-4)

The inhibitory activity of EBR against enzymes and receptors was evaluated and the results of enzyme and receptor binding displacement assays in which inhibitory activity resulted in an IC_{50} of <10 μmol/L are shown in Table 21.

Table 21. Inhibitory activities of EBR against enzymes or receptors

Enzymes or receptors	IC_{50} (μmol/L)
Serotonin (5-hydroxytryptamine) 5-HT_{2A}	3.91
Adenosine transporter	4.17
Endothelin ET_A	7.8
Protein kinase A	1.65
Protein kinase C	0.877
MAPK3 (ERK1)	2.02

Mean

The cytotoxicity of EBR to different cell lines (Huh7, HepG2, HEK293T, Hep3B, and MT4) was determined. The 50% cytotoxic concentration was >25 μmol/L in all cell lines tested.

3.5.2 Activities against HIV-1 and HBV (CTD 4.2.1.2-3, 4.2.1.2-5)

The potential activity of EBR against HIV-1 was investigated using HIV-infected MT4-GFP cells. The mean EC_{50} values of EBR and positive control (efavirenz, a nonnucleoside reverse transcriptase inhibitor) were ≥8400 and 0.79 nmol/L, respectively.

The potential activity of EBR against HBV was investigated by real-time PCR, using HBV-infected HepG2 cells. The mean IC_{50} values of EBR and positive control (lamivudine) were ≥10,000 and 36.9 nmol/L, respectively.

3.5.3 Activity of combined anti-HIV drugs and EBR (CTD 4.2.1.2-6)

Effects of EBR at concentrations of 0 to 500 nmol/L on the antiviral activities of anti-HIV drugs (tenofovir, emtricitabine, efavirenz, rilpivirine, darunavir, atazanavir, raltegravir, dolutegravir, and maraviroc) were studied using MT4-GFP cells infected with HIV-1. EBR did not affect the EC_{50} values of the anti-HIV drugs at any concentration tested.

The effects of anti-HIV drugs (tenofovir, rilpivirine, raltegravir, and maraviroc, 0.3-3 μmol/L each; emtricitabine, efavirenz, darunavir, and dolutegravir, 2.2-20 μmol/L each; atazanavir, 1-10 μmol/L) on the antiviral activity of EBR were studied using genotype 1a replicon (H77) assays (detection method, real-time PCR). None of the anti-HIV drugs affected the EC_{50} value of EBR.

3.6 Safety pharmacology (EBR) (CTD 4.2.1.3-10 to 4.2.1.3-13, 4.2.3.2-13)

The effects of EBR on the central nervous, cardiovascular, and respiratory systems were assessed (Table 22).

Table 22. Summary of safety pharmacology studies

Organ systems evaluated	Test system	Endpoint, method, etc.	Doses or concentrations	Route of administration	Noteworthy findings
Central nervous	Wistar rats (6 males/group)	FOB	0, 100, 300, 1000 mg/kg BID	Oral	None
Cardiovascular	Chinese hamster ovary cells (4 samples for each concentration)	hERG current	0, 10 μmol/L	*In vitro*	5.2% inhibition at 10 μmol/L
	SD rats (5 females)	Telemetry	Escalating doses of 0, 10, and 40 mg/kg	Oral	None
	Beagle dogs (4 males/group)	Telemetry	0, 0.5, 2, and 50 mg/kg	Oral	None
Respiratory	Beagle dogs (2 dogs/sex/group)	Telemetry	0, 2, 25, and 50 mg/kg	Oral	None

The applicant's explanation about the effects of EBR on the central nervous, cardiovascular, and respiratory systems:

A 7-day tolerability study was conducted in rats. The C_{max} (1.14 μmol/L) after 7 daily doses of EBR 750 mg/kg (reference data CTD 4.2.3.2-12) was 6.4-fold the C_{max} (0.177 μmol/L) in Japanese HCV-infected patients receiving EBR 50 mg, which was estimated from the results of a Japanese study (MK-5172-058) [see Section 6.2.6.2]. In a rat FOB study, there were no EBR-related effects on the central nervous system at even higher doses up to 1000 mg/kg.

In the cardiovascular system, EBR induced a minimal decline in hERG current at 10 μmol/L. Based on EBR's plasma protein binding of ≥99%, 10 μmol/L is >5500-fold the unbound C_{max} (<0.00177 μmol/L) in Japanese HCV-infected patients receiving EBR 50 mg. In a 14-day oral toxicity study in dogs (CTD 4.2.3.2-17), the C_{max} of EBR was 0.59 μmol/L in the respiratory system at 25 mg/kg, and was 3.3-fold the C_{max} in Japanese HCV-infected patients receiving EBR 50 mg. A telemetry study revealed no clear effects of EBR on the respiratory function at even higher doses up to 50 mg/kg. EBR thus has no effects on the central nervous, cardiovascular and respiratory system functions in its clinical use.

3.R Outline of the review conducted by PMDA

3.R.1 Antiviral activities of GZR and EBR

Based on the data submitted, PMDA considers that GZR and EBR demonstrated their anti-HCV activities. Combined antiviral activity of GZR + EBR in HCV replicon cells was evaluated, which demonstrated the pharmacodynamic efficacy of the combined GZR and EBR. The efficacy of the GZR + EBR combination regimen in chronic hepatitis C patients with or without compensated cirrhosis is described in the clinical data section.

3.R.2 Resistance to GZR and EBR

The applicant's explanation about the resistance profiles of HCV genotype 1a and 1b to GZR and EBR:

Critical NS3 substitutions associated with resistance to GZR were observed in subjects who did not respond to the GZR + EBR combination regimen in foreign studies[4)] and caused a ≥5-fold reduction in GZR activity. These substitutions took place at positions 56, 156, and 168 in genotype 1a and at positions 56 and 156 in genotype 1b. No genotype 1b NS3 substitutions at position 156 were observed in patients

[4)] Foreign phase II studies (MK-5172-035, MK-5172-047, and MK-5172-048) and foreign phase III studies (MK-5172-052, MK-5172-060, MK-5172-061, and MK-5172-068)

who experienced virologic failure with approved NS3/4A protease inhibitors (simeprevir, vaniprevir, and paritaprevir), which have a macrocyclic structure similar to that of GZR. Other resistance-associated substitutions in genotype 1a and 1b were observed in patients experiencing virologic failure with any of the approved NS3/4A protease inhibitors (telaprevir, simeprevir, vaniprevir, and paritaprevir) (Vanihep Capsules 150 mg package insert, 5th edition, Viekirax package insert, 4th edition, etc.). On the other hand, the resistance-associated substitutions occurring with approved NS3/4A protease inhibitors at Q80R, S122A/G/R, and R155Q, which were observed in genotype 1b patients experiencing virologic failure with simeprevir, did not reduce GZR activity [see Section 3.1.3.3].

Critical NS5A substitutions associated with resistance to EBR were observed in subjects who did not respond to the GZR + EBR combination regimen in foreign studies[5)] and caused a ≥5-fold reduction in EBR activity. These substitutions took place at positions 28, 30, 31, and 93 in genotype 1a and at positions 31 and 93 in genotype 1b. These resistance-associated substitutions with EBR were observed in patients who did not respond to approved NS5A inhibitors (daclatasvir, ledipasvir, and ombitasvir) (Daklinza Tablets 60 mg package insert, 10th edition, Viekirax package insert, 4th edition, etc.). However, in *in vitro* studies, the substituion-induced EBR activity reduction was less significant than the reduction of ledipasvir or ombitasvir activity. L31I substitution reduced ledipasvir activity but did not reduce EBR activity [see Section 3.4.2.3].

PMDA's view:
Attention is required to resistance-associated substitutions which occurred in subjects who did not respond to the GZR + EBR combination regimen in clinical studies and reduced activity in *in vitro* studies [see Sections 3.1.3 and 3.4.2]. In subjects failing to respond to the treatment, substitutions occurred at positions 56, 156, and 168 in NS3 region of GZR and at positions 30, 31, and 93 in NS5A region of EBR as with similar drugs, and caused reductions in activity in *in vitro* studies. On the other hand, the resistance profiles to various NS3/4A protease inhibitors and NS5A inhibitors are not necessarily the same. GZR and EBR showed anti-HCV activity against some of NS3 and NS5A substitutions conferring resistance to other drugs in *in vitro* studies [see Sections 3.1.3.3 and 3.4.2.3]. The association between the emergence of resistance-associated variants and the efficacy of GZR + EBR in clinical studies is described in the clinical data section. As shown *in vitro* studies, double substitutions at positions 56 and 168, etc. of GZR and at positions 30 and 93 or 31 and 93, etc. of EBR conferred higher levels of resistance than respective single substitutions. Relevant clinical study data are limited while the presence or absence of resistance-associated variants may be important information on the efficacy of GZR + EBR. In light of these facts, post-marketing data including published literature on resistance to GZR + EBR should be collected to communicate new findings to healthcare professionals promptly.

[5)] Foreign phase II studies (MK-5172-035, MK-5172-047, and MK-5172-048) and foreign phase III studies (MK-5172-052, MK-5172-060, MK-5172-061, and MK-5172-068)

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

The pharmacokinetics (PK) following administration of GZR (radiolabeled or unlabeled drug) and EBR (radiolabeled or unlabeled drug) were studied in mice, rats, rabbits, and dogs. GZR or EBR concentrations in biological samples were determined by liquid chromatography/tandem mass spectrometry (Lower limit of quantitation [LLOQ] of GZR: 1-12.7 nmol/L in plasma [12.7 nmol/L in fetal plasma], 12.7 nmol/L in milk, 6.5-102 nmol/L in liver homogenates; LLOQ of EBR: 1-22.7 nmol/L in plasma [2.27 nmol/L in fetal plasma], 22.7 nmol/L in milk, 5-227 nmol/L in liver homogenates). The concentrations of GZR- or EBR- and its metabolite-derived radioactivity in biological samples were determined by liquid scintillation counting. Tissue radioactivity levels were determined by quantitative whole-body autoradiography (LLOQ, 453 ng eq./g for GZR, 99 ng eq./g for EBR). Unless otherwise specified, PK parameters are expressed as the mean, and the doses and concentrations of GZR are expressed in terms of grazoprevir.

4.1 Absorption (grazoprevir hydrate [GZR])

4.1.1 Single-dose studies (CTD 4.2.2.2-1, 4.2.2.3-1)

The plasma PK parameters in rats and dogs (3 males each) following a single oral or intravenous dose of GZR are shown in Table 23. In rats, increases in the C_{max} and AUC_{inf} of oral GZR were more than dose-proportional between 5 and 25 mg/kg and were almost dose-proportional between 25 and 100 mg/kg. In dogs, the C_{max} and AUC_{inf} of oral GZR increased more than dose-proportionally from 1 to 5 mg/kg and were almost dose-proportional over the range of 5 to 30 mg/kg. The liver-to-plasma AUC ratios were approximately 242, 13, and 9 at 5, 25, and 100 mg/kg, respectively, in rats and approximately 36 and 8 at 1 and 5 mg/kg, respectively, in dogs. The applicant explained that the results suggested saturable liver uptake at higher plasma concentrations.

Table 23. PK parameters following a single oral or intravenous dose of GZR

Species	Route of administration	Dose (mg/kg)	No. of animals	C_{max} (μmol/L)	t_{max} (h)	AUC_{inf} (μmol·h/L)	CL (mL/min/kg)	V_d (L/kg)	$t_{1/2}$ (h)
Rat	PO[a)]	5	3	0.3 ± 0.1	4.0 ± 0.0	0.7 ± 0.3	—	—	—
		25	3	12.3 ± 6.1	4.0 ± 2.0	61.0 ± 44.8	—	—	—
		100	3	40.2 ± 9.4	8.0 ± 0.0	258 ± 78.5	—	—	—
	IV[b)]	2	3	—	—	2.3 ± 1.6	27.8 ± 21.9	3.1 ± 2.6	1.4 ± 0.6
Dog	PO[a)]	1	3	0.1 ± 0.1	4.7 ± 1.2	0.4 ± 0.3[c)]	—	—	—
		5	3	7.1 ± 4.1	2.0 ± 0.0	41.3 ± 31.8	—	—	—
		10	3	10.3 ± 11.6	2.3 ± 1.5	66.9 ± 82.7	—	—	—
		20	3	25.6 ± 15.2	2.7± 1.2	237 ± 139	—	—	—
		30	3	42.5 ± 33.4	2.7± 1.2	486 ± 420	—	—	—
	IV[b)]	0.5	3	—	—	2.2 ± 0.9	5.2 ± 1.7	0.7 ± 0.1	3.0 ± 0.8

Mean ± standard deviation (SD); —, not determined; [a)] vehicle, PEG400; [b)] vehicle, PEG200; [c)] AUC_{0-t}

4.1.2 Repeated-dose studies (CTD 4.2.3.2-2, 4.2.3.2-10, Reference data CTD 4.2.3.2-5, 4.2.3.5.2-6, 4.2.3.7.7-3)

The PK parameters in mice, rats, rabbits, dogs and monkeys following repeated oral doses of GZR are shown in Table 24.

Plasma concentrations at all doses in mice showed high inter-animal variability. There were no marked sex-related differences in C_{max} and AUC_{0-24}. Increases in the C_{max} and AUC_{0-24} were more than dose-proportional between 20 and 100 mg/kg/day and almost dose-proportional over the range of 100 to 500 mg/kg/day.

In female rats, C_{max} and AUC_{0-24} were lower at 1000 mg/kg/day as compared to 50 mg/kg/day on Day 1, and there were no marked differences between the doses on Day 14. There was no effect of repeated dosing at 50 mg/kg/day.

In female rabbits, there was no effect of repeated dosing on C_{max} and AUC_{0-24}.

C_{max} and AUC_{0-24} in dogs showed no marked differences by sex or no effect of repeated dosing. Up to Week 12, the C_{max} and AUC_{0-24} were more than dose-proportional between 5 mg/kg/day and 15 mg/kg/day and less than dose-proportional from 15 mg/kg/day to 300 mg/kg/day.

Table 24. PK parameters following repeated oral doses of GZR

Species	Dose (mg/kg/day)	Number of animals	Sampling time point	C_{max} (μmol/L)		t_{max} (h)		AUC_{0-24} (μmol·h/L)	
				Male	Female	Male	Female	Male	Female
Mouse[a)]	20	2-3/sex/time point	Week 13	1.47	1.56	0.50	0.50	6.91	9.02
	100	3/sex/time point	Week 13	38.5	51.6	1.0	0.50	455	448
	200	2 or 3/sex/time point	Week 13	50.9	67.4	1.0	8.0	683	957
	500	2 or 3/sex/time point	Week 13	108	150	2.0	2.0	1390	1550
Rat[b)]	50	6 females	Day 1	—	13.8 ± 1.60	—	3.0 ± 0.45	—	101 ± 11.1
		3 females	Day 14	—	11.4 ± 5.37	—	3.3 ± 0.67	—	70.0 ± 32.8
	1000/300[c)]	6 females	Day 1	—	7.08 ± 1.88	—	1.7 ± 0.49	—	36.5 ± 9.05
		3 females	Day 14	—	24.4 ± 6.24	—	1.0 ± 0.0	—	140 ± 56.6
Rabbit[d)]	200 (BID[e)])	3 females	Day 1	—	88 ± 38	—	9 ± 1	—	902 ± 601
			Day 8	—	92 ± 19	—	7 ± 1	—	902 ± 672
Dog[f)]	5	7/sex	Day 1	11.1 ± 1.12[g)]	10.9 ± 1.13	1.3 ± 0.21[g)]	2.1 ± 0.34	78.3 ± 16.8[g)]	83.7 ± 10.7
			Week 12	10.6 ± 0.917	11.2 ± 1.36	1.7 ± 0.18	1.6 ± 0.20	68.9 ± 8.17	69.8 ± 9.45
	15	4/sex	Day 1	35.0 ± 2.90	44.6 ± 2.63	2.5 ± 0.50	1.8 ± 0.25	352 ± 19.7	472 ± 14.3
			Week 12	26.7 ± 9.34	42.1 ± 6.81	2.6 ± 0.85	2.5 ± 0.50	303 ± 103	431 ± 80.0
	300/100[h)]	4/sex	Day 1	142 ± 58.0	138 ± 15.1	6.0 ± 1.2	7.0 ± 1.0	2470 ± 1,170	2550 ± 376
			Week 12	126 ± 6.11	200 ± 92.8	5.3 ± 1.3	5.3 ± 1.3	1900 ± 142	3340 ± 1,610
		3/sex	Week 26	133 ± 42.8	150 ± 38.9	4.0 ± 0.0	5.3 ± 1.3	2170 ± 893	2420 ± 771
Monkey[i)]	10	1/sex	Day 7	0.23	0.15	2.0	2.0	0.70	0.61

Mean ± standard error (SE); —, not determined; [a)] a spray-dried formulation containing 50% (w/w) GZR (free acid) and 50% (w/w) hydroxypropylmethylcellulose phthalate suspended in 0.5% (w/v) methylcellulose/0.02% (w/v) sodium lauryl sulfate (with 5 mM hydrochloric acid) solution; [b)] dissolved in PEG400 under protection from light; [c)] animals received 1000 mg/kg/day until Day 10 and 300 mg/kg/day from Day 11 onward; [d)] suspended in PEG400; [e)] 4 hours apart; [f)] administered in capsule form; g) n = 6; [h)] animals received 300 mg/kg/day until Day 78 and 100 mg/kg/day from Day 79 onward; [i)] dissolved in PEG400

4.1.3 Repeated-dose study (Co-administration of GZR and EBR) (CTD 4.2.3.7.7-2)

Table 25 shows the PK parameters in dogs (n = 1-3/sex) following repeated oral doses of GZR 5 mg/kg/day and EBR 25 mg/kg/day, alone or in combination. C_{max} and AUC_{0-24} of either drug showed no marked differences by sex or no effect of repeated dosing, indicating no pharmacokinetic interactions following co-administration as compared to either drug alone.

Table 25. PK parameters following repeated oral doses of GZR and EBR, alone or in combination

Method of administration	Number of animals	Sampling time point	C_{max} (μmol/L)		t_{max} (h)		AUC_{0-24} (μmol·h/L)	
			Male	Female	Male	Female	Male	Female
GZR								
Alone	3 females, 1 male	Day 1	6.79	6.14 ± 1.10	2.0	2.7 ± 0.67	34.4	40.4 ± 9.21
	3/sex	Week 5	4.80 ± 0.287	7.54 ± 3.18	2.0 ± 0.0	2.3 ± 0.88	25.2 ± 2.43	35.4 ± 12.2
in combination with EBR	3/sex	Day 1	5.42 ± 2.02	5.82 ± 3.66	5.3 ± 1.3	5.3 ± 1.3	53.3 ± 16.4	63.4 ± 36.8
		Week 5	6.10 ± 2.07	7.14 ± 3.43	4.7 ± 1.8	2.7 ± 0.67	49.3 ± 2.24	71.1 ± 32.7
EBR								
Alone	3/sex	Day 1	0.563 ± 0.0556	0.886 ± 0.356	3.3 ± 0.67	5.3 ± 1.3	7.19 ± 2.76	13.9 ± 4.61
		Week 5	0.522 ± 0.0553	1.36 ± 0.133	2.7 ± 0.67	3.3 ± 0.67	4.48 ± 1.15	14.7 ± 3.67
in combination with GZR	3/sex	Day 1	0.606 ± 0.0659	0.742 ± 0.205	3.3 ± 0.67	5.3 ± 1.3	8.65 ± 0.407	10.7 ± 3.40
		Week 5	0.471 ± 0.0349	0.890 ± 0.289	3.0 ± 1.0	3.3 ± 0.67	5.66 ± 0.566	9.87 ± 3.27

Mean ± SE; GZR, dissolved in PEG400 and administered in capsule form; EBR, dissolved in 10% (w/w) polysorbate 80 solution

4.2 Distribution (GZR)

4.2.1 Tissue distribution (CTD 4.2.2.3-2)

Tissue distribution of radioactivity was evaluated in albino and pigmented rats (1 male each/time point) following a single 50 mg/kg oral dose of ^{14}C-GZR using quantitative whole-body autoradiography. In albino rats, radioactivity levels peaked at 8 hours post-dose in most tissues and decreased to below the LLOQ by 24 hours post-dose.[6)] In albino rats, radioactivity concentrations were high in the liver (207 μg eq./g), and it was estimated that approximately 18% of the dose would be distributed in the liver at 8 hours post-dose. Tissue distribution of radioactivity in pigmented and albino rats was similar.

4.2.2. Plasma protein binding and distribution in blood cells (CTD 4.2.2.2-2, 4.2.2.3-6, 4.2.2.6-1)

The fraction of GZR (0.1-10 μmol/L) unbound to plasma proteins was 1.6%, 1.4%, 0.9%, and 1.2% in rat, rabbit, dog, and human, respectively, and binding was independent of drug concentration. The fraction of GZR 1 and 10 μmol/L unbound to human serum albumin (40 mg/mL) was 2.7% and 2.5%, respectively. The fraction unbound to α1-acid glycoprotein (1 mg/mL) was approximately 11% and 17%, respectively.

Distribution of GZR (0.1-10 μmol/L) in blood cells of rat, dog, and human whole blood was determined. The blood/plasma GZR concentration ratios were 0.60 to 0.62, 0.46 to 0.49, and 0.63 to 0.69, respectively.

4.2.3 Placental transfer (CTD 4.2.2.3-4, 4.2.2.3-5)

Following repeated doses of GZR given to pregnant rats (gestation day 6)[7)] (n = 4/time point) for 15 days and to pregnant rabbits (gestation day 7)[8)] (n = 4/time point) for 14 days, the fetal to maternal plasma concentration ratios were 0.0138 to 0.894 in rats and 0.0128 to 0.0706 in rabbits.

4.3 Metabolism (GZR)

4.3.1 Proposed metabolic pathways

Figure 1 shows the proposed metabolic pathways of GZR based on the results of studies in Sections 4.3.2 and 4.3.3.

[6)] A trace amount of radioactivity (below the LLOQ) was detected in the liver up to 168 hours post-dose.

[7)] GZR 200 mg/kg BID (approximately 6 hours apart) was administered orally from gestation day 6 through 20, and GZR concentrations in maternal and fetal plasma were measured at 2, 8, and 24 hours after the first dose on gestation day 20.

[8)] GZR 100 mg/kg QD was administered intravenously from gestation day 7 through 20, and GZR concentrations in maternal and fetal plasma were measured at 0.5, 2, and 24 hours post-dose on gestation day 20.

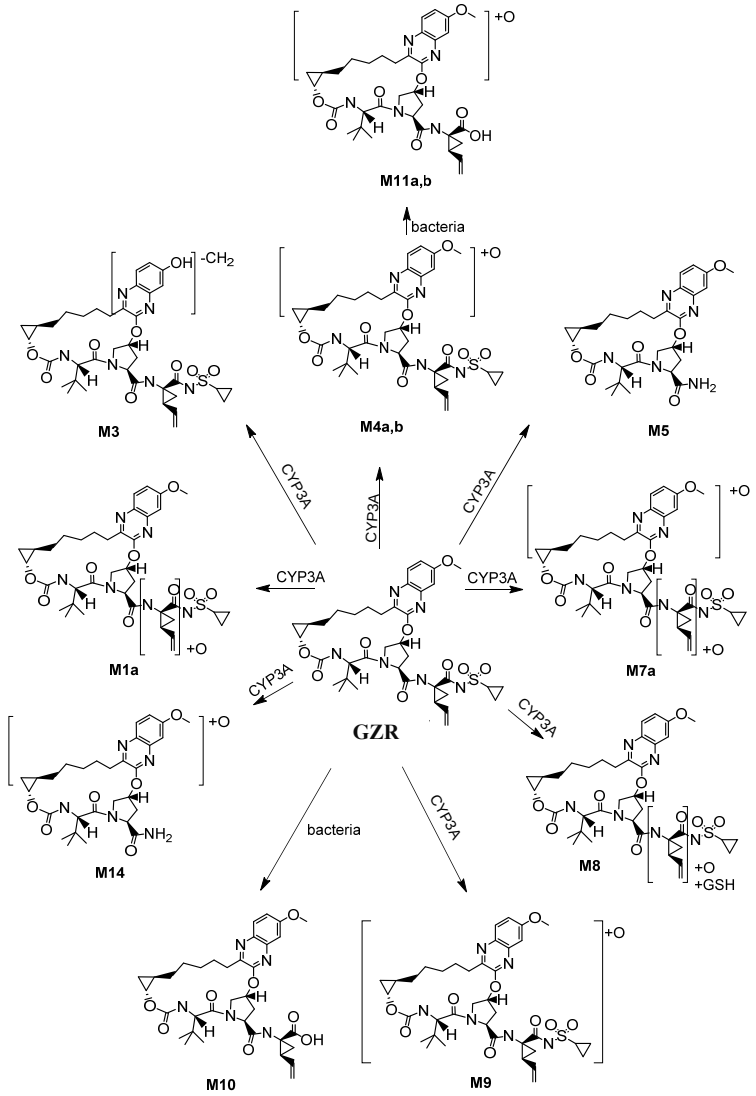


Figure 1. Proposed metabolic pathways of GZR

4.3.2 *In vitro* metabolism (CTD 4.2.2.2-2, 4.2.2.4-2, 4.2.2.4-3, 4.2.2.4-5, 4.2.2.6-1, 4.2.2.6-6)[9)]

The identification of GZR metabolites were performed using hepatic microsomes and hepatocytes from rats, rabbits, dogs and humans and hepatic microsomes from mice. M1a, M3, M4a, M4b, M5, M7a, M8, and M9 were identified in rat, rabbit, dog and human liver microsomal or hepatocyte incubation mixture, and M3, M4a, M4b, and M10 in mouse liver microsomal incubation mixture. After centrifuging human liver microsomes from the incubation mixtures, and the mixture supernatants were incubated with human fecal homogenates. M10 and M11a/b were detected, suggesting that they are produced by gut bacteria.

Using human hepatic microsomes and human CYP expression systems (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), the metabolism of GZR was studied. M1a, M3, M4a, M4b, and M7 were detected in human hepatic microsomes. Addition of anti-CYP2D6 antibody and anti-CYP2C antibody did not inhibit metabolite formation. When anti-CYP3A4 antibody was added, M4a and M4b only were identified. M3 was detected in a CYP2D6 expression system and M1a, M3, M4a, M4b, and M7 in a

[9)] The metabolites listed in this section are as follows: M1a, M3, M4a/b, M5, M7a, M9, and M14 resulting from oxidation; M8 resulting from oxidation and glutathione addition; M10 resulting from hydroxylation; M11a/b resulting from hydroxylation of oxidative metabolite (M4a/b)

CYP3A4 expression system. No metabolites were identified in other CYP expression systems. The formation of M4a and M4b in the CYP3A4 expression system is described by Michaelis-Menten kinetics; the K_m values of M4a and M4b were 3.23 and 3.50 μmol/L, respectively, and the V_{max} values 0.21 and 0.18 pmol/min/pmol P450, respectively.

The above findings and its fecal metabolic profile in humans [see Section 6.2.1.1.2.2] suggested that GZR is metabolized primarily by CYP3A and that GZR and its metabolites are further hydrolyzed by gut bacteria.

4.3.3 *In vivo* metabolism (CTD 4.2.2.2-2, 4.2.2.4-1, 4.2.2.4-4)[9)]

A single 5 mg/kg oral dose of ^{3}H-GZR was administered to bile duct-cannulated rats (3 males). No metabolites were detected in urine, and the unchanged parent drug, M3, M4a, M4b, and M5 were detected in feces (59.3%, 6.2%, 1.7%, 2.7%, and 2.9% of the administered dose, respectively, were recovered). The unchanged parent drug, M1a, M3, M4a, M4b, M5, M7a, M8, and M9 were detected in bile (11.6%, 2.2%, 5.1%, 1.3%, 2.4%, 2.7%, 0.8%, 1.0%, and <0.5% of the administered dose, respectively, were recovered). Following a single 20 mg/kg oral dose of ^{3}H-GZR in rats (3 males), only the unchanged parent drug was detected in plasma and no metabolites were present.

Following a single 200 mg/kg oral dose of ^{3}H-GZR in rabbits (3 females), the unchanged parent drug, M1a, M3, M4a/b, M5, M7a, and M9 were detected in feces (60.2%, 2.0%, 2.6%, 8.2%, 2.6%, 2.0%, and 1.4% of the administered dose, respectively, were recovered). The unchanged parent drug was the major component of radioactivity in plasma, and trace amounts of M3, M4a/b, and M7a were also detected.

The metabolism of GZR was studied in bile duct-cannulated dogs (3 males each). Following a single 0.5 mg/kg intravenous dose of ^{14}C-GZR or a single 1 mg/kg oral dose of ^{14}C-GZR, radioactivity levels in urine and feces were very low. The unchanged parent drug, M3, M4a/b, and M7a were detected in bile (37.1%, 6.3%, 29.1%, and 10.4% of the administered dose, respectively, were recovered), and the unchanged parent drug alone was detected in plasma. After oral administration, the unchanged parent drug and M10 were detected in feces (17.9% and 7.4% of the administered dose, respectively, were recovered), and the unchanged parent drug, M3, M4a/b, and M7a were present in bile (9.4%, 1.5%, 7.1%, and 1.9% of the administered dose, respectively, were recovered).

In a foreign study (MK-5172-007), a single 200 mg oral dose of ^{14}C-GZR was administered. Radioactivity levels in urine were very low, the unchanged parent drug, M4a/b, M7a, M10, M11a/b, and M14 were detected in feces, and the unchanged parent drug alone was detected in plasma [see Section 6.2.1.1.2.2].

4.4 Excretion (GZR)

4.4.1 Urinary and fecal excretion and biliary excretion (CTD 4.2.2.2-2, 4.2.2.4-1, 4.2.2.4-4)

Following a single 200 mg/kg oral dose of ^{3}H-GZR in rabbits (3 females), the urinary and fecal excretion of radioactivity over 72 hours post-dose were 1.4% and 77.3% of the administered dose, respectively. A single

5 mg/kg oral dose of ^{3}H-GZR was administered to bile duct-cannulated rats (3 males) and a single 0.5 mg/kg intravenous dose of ^{14}C-GZR or a single 1.0 mg/kg oral dose of ^{14}C-GZR to dogs (3 males). The urinary, fecal, and biliary excretion of radioactivity over 72 hours post-dose were 0.4%, 72.8%, and 28.1% of the dose, respectively, in rats, 0.5%, 22.0%, and 74.3% of the intravenous dose, respectively, in dogs, and 3.4%, 26.3%, and 27.8% of the oral dose, respectively, in dogs.

4.4.2 Excretion in milk (CTD 4.2.2.3-5)

GZR 25 mg/kg QD, 100 mg/kg QD, or 200 mg/kg BID was administered orally to rats (3-5 females/time point) from gestation day 6 to lactation day 14. Milk concentrations of GZR at 2 and 8 hours post-dose on lactation day 14 were 31.7 and 4.66 µmol/L, respectively, at 100 mg/kg QD and 17.8 and 40.0 µmol/L, respectively, at 200 mg/kg BID. Milk concentration of GZR at 2 hours post-dose at 25 mg/kg QD was 1.70 µmol/L. The radioactivity concentration ratios of milk to maternal plasma at 2 and 8 hours post-dose on lactation day 14 were 0.84 and 0.55, respectively, at 100 mg/kg QD and 0.87 and 0.68, respectively, at 200 mg/kg BID. The radioactivity concentration ratio of milk to maternal plasma at 2 hours post-dose was 0.54 at 25 mg/kg QD.

4.5 Pharmacokinetic interactions (GZR)

4.5.1 Enzyme inhibition and induction (CTD 4.2.2.6-1, 4.2.2.6-4, 4.2.2.6-7, 4.2.2.6-8, 4.2.2.6-14)

An inhibitory effect of GZR on the activities of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A), UGT1A1, carboxyesterases 1 and 2, and cathepsin A in human liver microsomes was assessed. The IC_{50} values of GZR were 66 µmol/L for CYP2B6, 6.1 µmol/L for CYP2C8, >100 µmol/L and 73 µmol/L for CYP3A,[10)] and 54 µmol/L for UGT1A1. GZR did not inhibit the activities of other CYP isoforms, carboxyesterases 1 and 2, or cathepsin A (IC_{50} >100 µmol/L). GZR did not show time-dependent inhibition of CYP2C8 or CYP3A. Based on the C_{max} of GZR (0.617 µmol/L), estimated from the results of a Japanese study (MK-5172-058) [see Section 6.2.6.1] and the unbound fraction (1.2%) [see Section 4.2.2], GZR is unlikely to inhibit metabolizing enzymes other than CYP3A. On the other hand, the maximum concentration of GZR in the intestine in HCV patients[11)] is 522 µmol/L giving no consideration of solubility limitations. The applicant, therefore, explained that GZR has the potential to inhibit intestinal CYP3A.

The potential for GZR to induce CYP isoforms (CYP1A2, CYP2B6, and CYP3A) was studied using human hepatocytes. Induction of CYP isoforms by GZR was <20% of positive control induction (omeprazole, phenobarbital, and rifampicin).

4.5.2 Characterization of GZR as a potential substrate for drug transporters (CTD 4.2.2.6-1, 4.2.2.6-2, 4.2.2.6-15)

Using LLC-PK1 cells and LLC-PK1 cells expressing human and rat P-gp, the membrane permeability of ^{3}H-GZR 1 µmol/L was evaluated. The rate of passive membrane permeability in LLC-PK1 cells was 18.9×10^{-6} cm/s and the efflux ratios in LLC-PK1 cells and LLC-PK1 cells expressing human and rat P-gp were 1.1,

[10)] As CYP3A substrates, testosterone and midazolam were used.
[11)] Maximum concentration in the intestine (µmol/L) = dose (mg) × 1000/molecular weight (g/mol)/0.25 (L)

101.8, and 29.9, respectively. The cellular uptake of ^{3}H-GZR was higher in MDCKII cells expressing human OATP1B1, 1B3, and rat oatp1b2, than in wild-type MDCKII cells. The uptake of GZR into HEK293 cells transiently transfected with human OATP1B1 and 1B3 was studied. The K_m values estimated using a non-linear regression model were 0.43 and 0.18 μmol/L, respectively, and the V_{max} values were 14.3 and 11.5 pmol/min/10^{-6} cells, respectively. In an assay using MDCKII cells expressing human BCRP, a BCRP inhibitor did not inhibit GZR transport completely, allowing endogenous transport in wild-type MDCKII cells. Thus, the characteristics of BCRP as a substrate were not determined. These results indicated that GZR is a substrate of human and rat P-gp, human OATP1B1 and 1B3, and rat oatp1b2.

4.5.3 Inhibition of drug transporters (CTD 4.2.2.6-1, 4.2.2.6-3, 4.2.2.6-5, 4.2.2.6-9, 4.2.2.6-29)

An inhibitory effect of GZR on P-gp, BCRP, OATP1B1, OATP1B3, BSEP, MRP2, MRP3, MRP4, OAT1, OAT3, and OCT2 was assessed. The IC_{50} values against BCRP, OATP1B1, OATP1B3, BSEP, MRP2, MRP3, MRP4, and OAT1 were 12.5, 0.7, 1.1, 0.15, 2.5, 3.8, 1.0, and 15 μmol/L, respectively. The IC_{50} values of GZR against P-gp, OAT3, and OCT2 were all >50 μmol/L. At the clinical dose (100 mg) of GZR, the unbound C_{max} was calculated to be 0.006 μmol/L and the maximum unbound hepatic inlet concentration approximately 0.1 μmol/L[12)] , based on the C_{max} of GZR (0.617 μmol/L) [see Section 6.2.6.1] and the unbound fraction (1.2%) [see Section 4.2.2] estimated from the results of a Japanese study (MK-5172-058). These estimations suggested that GZR at the clinical dose does not inhibit P-gp, OATP1B1, OATP1B3, MRP2, MRP3, MRP4, OAT1, OAT3, or OCT2 and has the potential to inhibit BSEP. The unbound C_{max} (0.006 μmol/L) and the maximum unbound hepatic inlet concentration (approximately 0.1 μmol/L) at the clinical dose (100 mg) indicated no systemic inhibitory effect of GZR on BCRP, whereas the GZR concentration in the intestine (522 μmol/L) [see Section 4.5.1] indicated its potential to inhibit intestinal BCRP.

4.6 Absorption (elbasvir [EBR])

4.6.1 Single-dose studies (CTD 4.2.2.2-3, 4.2.2.2-4)

The plasma PK parameters in rats, rabbits, dogs, and monkeys following a single oral or intravenous dose of EBR or ^{14}C-EBR are shown in Table 26. Following oral administration of EBR 30 mg/kg to rats, the ratios of the liver and brain AUC to plasma AUC were approximately 193 and 0.26, respectively, suggesting a high distribution of EBR into the liver.

Table 26. PK parameters following a single oral or intravenous dose of EBR

Species	Route of administration	Dose (mg/kg)	No. of animals	C_{max} (μmol/L)	t_{max} (h)	AUC_{inf} (μmol·h/L)	CL (mL/min/kg)	V_d (L/kg)	$t_{1/2}$ (h)
Rat	PO[a)]	30	3 males	0.4 ± 0.3	3.3 ± 1.2	2.3 ± 1.0	—	—	—
		300	2 males	0.4, 0.8	4.0, 6.0	5.9, 9.6	—	—	—
	IV[b)]	5	3 males	—	—	4.3 ± 1.6	24 ± 8	5.0 ± 1.1	4.2 ± 1.5
Rabbit	PO[c)]	100	3 females	0.3 ± 0.1	1.3 ± 0.6	1.7 ± 0.5	—	—	—
Dog	PO[d)]	2	3 males	0.29 ± 0.02	3.3 ± 1.2	1.7 ± 0.3	—	—	—
	IV[e)]	1	3 males	—	—	2.4 ± 0.8	8.4 ± 2.3	3.0 ± 0.8	7.7 ± 2.3
Monkey	IV[e)]	1	3 males	—	—	3.6 ± 0.2	5.2 ± 0.3	2.7 ± 0.4	16 ± 4

Mean ± SD; —, not determined; [a)] a 30% EBR spray dried-formulation dissolved or suspended in citric acid buffer containing 0.4% hydroxypropyl methylcellulose (pH4); [b)] dissolved in 3% dimethylacetamide/97% hydroxypropyl-β-cyclodextrin (40%) solution; [c)] ^{14}C-EBR suspended in 10% polysorbate 80 solution; [d)] dissolved in 10% polysorbate 80/90% PEG400 solution; [e)] dissolved in

[12)] Maximum unbound hepatic inlet concentration = C_{max}+ (absorption rate constant (min^{-1}) × dose (μmol) × BA in the gastrointestinal tract/hepatic blood flow rate [L/min])
Calculated assuming that the unbound fraction was 0.01 and that the hepatic blood flow rate was 1.62 L/min.

Species	Route of administration	Dose (mg/kg)	No. of animals	C_{max} (μmol/L)	t_{max} (h)	AUC_{inf} (μmol·h/L)	CL (mL/min/kg)	V_d (L/kg)	$t_{1/2}$ (h)

20% hydroxypropyl-β-cyclodextrin solution

4.6.2 Repeated-dose studies (CTD 4.2.3.2-11, 4.2.3.2-15, 4.2.3.2-19, 4.2.3.5.2-17)

The PK parameters in mice, rats, pregnant rabbits, and dogs following repeated oral doses of EBR are shown in Table 27.

Mice

There were no marked sex differences in C_{max} and AUC_{0-24}. Increases in the C_{max} and AUC_{0-24} were dose-proportional between 10 mg/kg/day and 50 mg/kg/day and less than dose-proportional over the range of 50 to 1000 mg/kg/day. The applicant explained that less than dose-proportional increases in the C_{max} and AUC_{0-24} at ≥50 mg/kg/day are related to low solubility of EBR in the small intestine, which is its major absorption site.

Rats

The AUC_{0-24} at 50 mg/kg/day was higher in males than in females and there were no marked sex differences in the C_{max} and AUC_{0-24} at other doses. Increases in the C_{max} and AUC_{0-24} were less than dose-proportional over the range of 50 to 1000 mg/kg/day. The AUC_{0-24} following repeated doses of EBR 300 mg/kg/day tended to be higher than that following a single dose of EBR 300 mg/kg/day [see Section 4.6.1].

Pregnant rabbits

The C_{max} increased in a less than dose-proportional manner over the range of 30 to 1000 mg/kg/day. The increase in AUC_{0-24} was dose-proportional over the range of 30 to 1000 mg/kg/day.

Dogs

There were no marked sex differences in the C_{max} and AUC_{0-24}. Increases in the C_{max} and AUC_{0-24} were dose-proportional from 5 mg/kg/day to 25 mg/kg/day at each time point and less than dose-proportional from 25 mg/kg/day to 1000 mg/kg/day. At 1000 mg/kg/day, the C_{max} and AUC_{0-24} after repeated dosing tended to be slightly lower than those on Day 1. The C_{max} and AUC_{0-24} were unaffected by repeated dosing at other doses.

Table 27. PK parameters following repeated oral doses of EBR

Species	Dose (mg/kg/day)	Number of animals	Sampling time point	C_{max} (μmol/L)		t_{max} (h)		AUC_{0-24} (μmol·h/L)	
				Male	Female	Male	Female	Male	Female
Mouse	10	3/sex/time point	Week 4	0.59	0.44	1.0	1.0	3.47	2.33
	50	3/sex/time point	Week 4	3.59	3.23	2.0	1.0	21.1	13.6
	300	3/sex/time point	Week 4	7.36	6.76	4.0	2.0	76.0	68.3
	1000	3/sex/time point	Week 4	11.0	9.62	4.0	2.0	182	120
Rat	50	3 or 4/sex/time point	Week 13	0.58	0.42	2.0	2.0	5.96	2.75
	300	2-4/sex/time point	Week 13	0.92	0.97	4.0	4.0	11.5	8.64
	1000	3 or 4/sex/time point	Week 13	1.37	1.10	8.0	4.0	19.5	15.1
Rabbit[a)]	30	4 females	Day 9	–	0.33 ± 0.084	–	1.8 ± 0.75	–	1.27 ± 0.0649
	100	4 females	Day 9	–	0.52 ± 0.14	–	1.5 ± 0.29	–	4.16 ± 1.57
	1000	4 females	Day 9	–	1.93 ± 0.50	–	8.8 ± 5.3	–	39.4 ± 9.20
Dog	5	4/sex	Day 1	0.10 ± 0.0099	0.14 ± 0.044	2.5 ± 0.50	2.5 ± 0.50	0.89 ± 0.092	0.97 ± 0.41
			Week 26	0.084 ± 0.022	0.080 ± 0.0076	2.1 ± 0.72	1.0 ± 0.0	0.91 ± 0.30	0.88 ± 0.11
	25	4/sex	Day 1	0.33 ± 0.040	0.74 ± 0.17	3.0 ± 0.58	2.8 ± 0.75	3.91 ± 0.50	5.78 ± 0.69
			Week 26	0.31 ± 0.048	0.64 ± 0.11	2.0 ± 0.0	1.5 ± 0.29	3.78 ± 0.50	4.45 ± 0.81
	1000	4/sex	Day 1	1.41 ± 0.32	2.08 ± 0.52	15 ± 5.3	20 ± 4.0	23.6 ± 3.45	31.6 ± 4.88

Species	Dose (mg/kg/day)	Number of animals	Sampling time point	C_{max} (μmol/L)		t_{max} (h)		AUC_{0-24} (μmol·h/L)	
				Male	Female	Male	Female	Male	Female
			Week 26	1.11 ± 0.25	1.50 ± 0.28	7.8 ± 5.5	8.5 ± 5.2	15.6 ± 6.24	17.6 ± 2.04

Mean ± SE; －, not determined, suspended in 10% (w/w) polysorbate 80 solution under protection from light; [a)] administered daily from gestation day 7 through day 15

4.7 Distribution (EBR)

4.7.1 Tissue distribution (CTD 4.2.2.3-7)

Tissue distribution of radioactivity was evaluated in albino and pigmented rats (1 male each/time point) following a single 30 mg/kg oral dose of ^{14}C-EBR using quantitative whole-body autoradiography. In albino rats, radioactivity peaked at 2 hours post-dose in most tissues and was below the LLOQ in all tissues by 168 hours post-dose.[13)] In albino rats, EBR-derived radioactivity distributed well to most tissues, particularly concentrating in the adrenal gland, liver, and renal cortex (10.0, 9.74, and 6.45 μg eq./g, respectively). There were no differences in radioactivity in the uveal tract between albino and pigmented rats up to 6 hours post-dose. In albino rats, the concentration of radioactivity in the uveal tract decreased to below the LLOQ by 10 hours post-dose, while it was still quantifiable (1.20 μg eq./g) at 28 days post-dose in pigmented rats, suggesting the melanin affinity of EBR. According to the applicant, the results of a phototoxicity study in pigmented rats [see Section 5.12.2] indicated no safety concerns about binding of EBR to melanin.

4.7.2 Plasma protein binding and distribution in blood cells (CTD 4.2.2.2-4, 4.2.2.3-8, 4.2.2.6-17)

The fraction of EBR (1 or 10 μmol/L) unbound to plasma proteins was 1.2% in rabbit and <0.1% in mouse, rat, dog, monkey, and human. The fraction of EBR (1 and 10 μmol/L) unbound to human serum albumin (40 mg/mL) was both <0.5%.[14)]

Using rat, dog, monkey, and human whole blood, distribution in blood cells of EBR (0.1-10 μmol/L) was determined. The blood/plasma EBR concentration ratios were 0.61 to 0.62, 0.91 to 0.95, 0.55 to 0.58, and 0.61 to 0.64, respectively.

4.7.3 Placental transfer (CTD 4.2.2.3-10, 4.2.2.3-11)

Following repeated-dose administration of EBR to rats on gestation day 6[15)] (n = 4/time point) and rabbits on gestation day 7[16)] (n = 4/time point), the fetal to maternal plasma concentration ratios at 2 and 24 hours after the last dose were 0.00608 and 0.0220, respectively, in rats and 0.00564 and 0.00751, respectively, in rabbits.

[13)] Trace amounts of radioactivity were detected in the Harderian gland, spleen, renal cortex, and liver at 168 hours post-dose.
[14)] The fraction unbound to α1-acid glycoprotein (1 mg/mL) could not be determined due to non-specific binding of EBR to assay plate used.
[15)] EBR 1000 mg/kg QD was administered orally from gestation day 6 through 20, and EBR concentrations in maternal and fetal plasma were measured at 2 and 24 hours post-dose on gestation day 20.
[16)] EBR 1000 mg/kg QD was administered intravenously from gestation day 6 through 20, and EBR concentrations in maternal and fetal plasma were measured at 2 and 24 hours post-dose on gestation day 20.

4.8 Metabolism (EBR)

4.8.1 Proposed metabolic pathways

Based on the results of studies in Sections 4.8.2 and 4.8.3, the proposed metabolic pathways of EBR are shown in Figure 2.

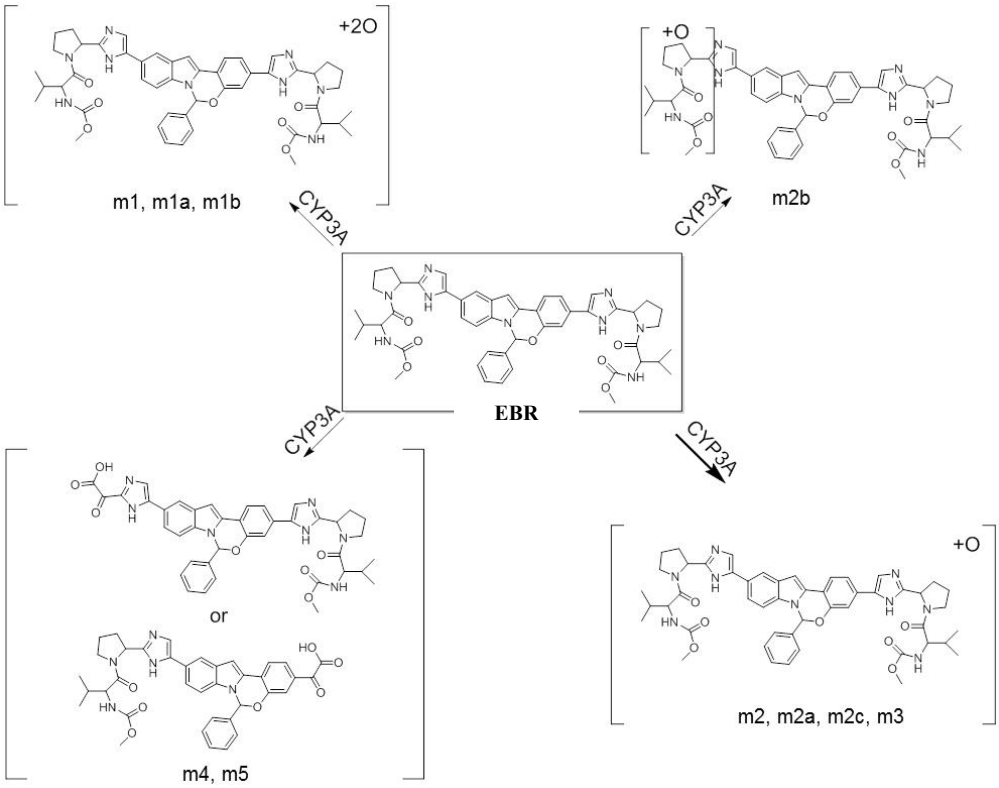


Figure 2. Proposed metabolic pathways of EBR

4.8.2 *In vitro* metabolism (CTD 4.2.2.2-4, 4.2.2.6-17)[17)]

The identification of EBR metabolites were performed using hepatic microsomes from rats, rabbits, dogs and humans and hepatocytes from mice, rats, dogs, and humans. M2/m3 was detected in rat, rabbit, dog, and human liver microsomal or hepatocyte incubations, m2/m3 and m1 in rat, dog, and human hepatocyte incubations, and m1a and m1b in rabbit liver microsomal incubations. M2 alone was detected in mouse hepatocytes.

The metabolism of EBR was investigated using human hepatic microsomes and human CYP expression systems (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). In human liver microsomes, m2/m3 was identified. When the CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A inhibitors[18)] were added, the CYP3A inhibitor inhibited the metabolism of EBR by approximately 64% while the other inhibitors had slight effects. The addition of anti-CYP3A antibody inhibited m2/m3 formation by approximately 91%. M1 and m2/m3 were identified in a CYP3A4 expression system. No metabolites were detected in other CYP expression systems. M2 and m3

[17)] The metabolites listed in this section are as follows: m1 (m1a and m1b), m2/m3, m4, and m5 resulting from oxidation

[18)] The following compounds were used as CYP inhibitors:
CYP1A2: α-naphthoflavone, CYP2B6/2C19: ticlopidine, CYP2C8: montelukast, CYP2C9: sulfaphenazole, CYP2C19: (*S*)-(+)-*N*-3-benzylnirvanol, CYP2D6: quinidine, CYP3A: ketoconazole

formation was biphasic in a CYP3A4 expression system, and when the data were converted into an Eadie-Hofstee plot, the K_{m1} values were 0.7 and 0.8 μmol/L, respectively, the K_{m2} values were 3.7 and 4.6 μmol/L, respectively, the V_{max1} values were 0.4 and 0.6 pmol/min/pmol P450, respectively, and the V_{max2} values were 0.6 and 1.2 pmol/min/pmol P450, respectively.

The above findings indicated that EBR is metabolized primarily by CYP3A.

4.8.3 *In vivo* metabolism (CTD 4.2.2.2-4, 4.2.2.4-6 to 4.2.2.4-9, 4.2.2.5-2 to 4.2.2.5-4)[19)]

Following a single 30 mg/kg oral dose of ^{3}H-EBR in bile duct-cannulated rats (3 or 4 males), no metabolites were detected in urine, the unchanged parent drug, m2/m3, m4, and m5 were detected in bile, and the unchanged parent drug alone was detected in plasma. Following a single 5 mg/kg intravenous dose of ^{14}C-EBR in rats (4 males), the unchanged parent drug and m2/m3 were detected in urine and bile (16.2% and <0.1% of the dose, respectively, were recovered in urine and 20.1% and 15.4% of the dose, respectively, were recovered in bile), and the unchanged parent drug alone was detected in feces.

Following a single 100 mg/kg oral dose of ^{14}C-EBR in rabbits (3 females), the unchanged parent drug was detected in feces and plasma. In addition, trace amounts of m1, m2/m3, and m4 were detected in feces and trace amounts of m2/m3 and m4 were detected in plasma.

The metabolism of EBR was studied in bile duct-cannulated dogs (2 or 3 males) following a single 1 mg/kg intravenous dose of ^{14}C-EBR or a single 2 mg/kg oral dose of ^{14}C-EBR. Following intravenous administration, radioactivity levels in urine were low, and the unchanged parent drug and m2/m3 were detected in feces and bile (31.4% and 2.1% of the dose, respectively, were recovered in feces and 25.7% and 2.2% of the dose, respectively, were recovered in bile). Following oral administration, the unchanged parent drug was the major component in feces and bile and a trace amount of m2/m3 was also detected, and unchanged parent drug alone was detected in plasma.

In a foreign phase I study (MK-8742-014) a single 50 mg oral dose of ^{14}C-EBR was administered. Radioactivity levels in urine were low, the unchanged parent drug and m2/m3 were detected in feces, and the unchanged parent drug only was detected in plasma [see Section 6.2.1.2.2.2].

4.9 Excretion (EBR)

4.9.1 Urinary and fecal excretion and biliary excretion (CTD 4.2.2.2-4, 4.2.2.4-6, 4.2.2.4-8, 4.2.2.4-9, 4.2.2.5-3, 4.2.2.5-4)

Following a single 100 mg/kg oral dose of ^{14}C-EBR in rabbits (3 females), the urinary and fecal excretion of radioactivity over 72 hours post-dose were 1.2% and 69.8% of the dose, respectively. A single 5 mg/kg intravenous dose of ^{14}C-EBR or a single 30 mg/kg oral dose of ^{3}H-EBR was administered to bile duct-cannulated rats (4 males each), and a single 1.0 mg/kg intravenous dose of ^{14}C-EBR or a single

[19)] The metabolites listed in this section are as follows: m1, m2/m3, m4, and m5 resulting from oxidation

2.0 mg/kg oral dose of ^{14}C-EBR was administered to dogs (2 or 3 males). The urinary, fecal, and biliary excretion of radioactivity over 72 hours post-dose were 16.9%, 30.0%, and 41.0% of the intravenous dose, respectively, in rats, 0.8%, 61.0%, and 7.8% of the oral dose, respectively, in rats, 3.3%, 27.9%, and 37.8% of the intravenous dose, respectively, in dogs, and 0.5%, 60.8%, and 8.7% of the oral dose, respectively, in dogs.

4.9.2 Excretion in milk (CTD 4.2.2.3-10)

EBR 1000 mg/kg QD was administered orally to rats (4 females/time point) from gestation day 6 to lactation day 14. Milk concentration of EBR at 2 hours post-dose on lactation day 14 was 5.75 μmol/L, and the milk to maternal plasma radioactivity concentration ratio was 4.15.

4.10 Pharmacokinetic interactions (EBR)

4.10.1 Enzyme inhibition and induction (CTD 4.2.2.6-17, 4.2.2.6-21, 4.2.2.6-24, 4.2.2.6-25)

An inhibitory effect of EBR on the activities of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A), UGT1A1, carboxyesterases 1 and 2, and cathepsin A by in human liver microsomes was assessed. EBR had weak or no inhibitory effects on the above metabolizing enzymes (IC_{50} >100 μmol/L for all CYP isoforms; IC_{50} 71 μmol/L for UGT1A1; IC_{50} >50 μmol/L for carboxyesterases 1 and 2 and cathepsin A), and EBR was also not a time-dependent inhibitor of CYP3A. The applicant explained that given the C_{max} of EBR (0.177 μmol/L) in a Japanese phase II/III study (MK-5172-058) [see Section 6.2.6.2], EBR is unlikely to inhibit the above-mentioned metabolizing enzymes.

The potential for EBR to induce CYP isoforms (CYP1A2, CYP2B6, and CYP3A) was studied using human hepatocytes. Induction of CYP isoforms by EBR was <20% of positive control induction (omeprazole, phenobarbital, and rifampicin).

4.10.2 Characterization of EBR as a potential substrate for drug transporters (CTD 4.2.2.6-17, 4.2.2.6-18)

The hepatic uptake of EBR was studied using human hepatocytes. EBR demonstrated slight temperature-dependent uptake, and its uptake was not inhibited by OATP1B and OCT1 inhibitors, rifamycin SV, rifampicin, and quinidine, but was inhibited by cyclosporine A. The results indicated the possibility that a transporter sensitive to cyclosporine A is involved in EBR uptake.

Using MDCKII cells and MDCKII cells expressing human P-gp or BCRP, the membrane permeability of ^{3}H-EBR 0.5 or 1.0 μmol/L was evaluated. The rate of passive membrane permeability in MDCKII cells was 0.8 to 1.2 × 10^{-6} cm/s, and the efflux ratios in MDCKII cells and MDCKII cells expressing P-gp (EBR, 0.5 and 1.0 μmol/L) and BCRP were 4.7 to 5.1, 19.4 (EBR, 0.5 μmol/L), 21.0 (EBR, 1.0 μmol/L), and 12.6, respectively. It could not be determined whether or not EBR is a substrate for BCRP, due to non-specific binding or endogenous transport. Using MDCKII cells and MDCKII cells expressing human OATP1B1 or 1B3, the membrane permeability of ^{14}C-EBR 0.5 μmol/L was evaluated. The rate of passive membrane permeability in MDCKII cells was 4.7 × 10^{-6} cm/s, and there were no marked

differences in EBR uptake between MDCKII cells and MDCKII cells expressing OATP1B1 or OATP1B3.

The above findings indicated that EBR is a substrate of P-gp but not of OATP1B1 or OATP1B3.

4.10.3 Inhibition of drug transporters (CTD 4.2.2.6-17, 4.2.2.6-18, 4.2.2.6-20, 4.2.2.6-26 to 4.2.2.6-28, 4.2.2.6-30)

An inhibitory effect of EBR on P-gp, BCRP, OATP1B1, OATP1B3, BSEP, MRP2, MRP3, MRP4, OAT1, OAT3, and OCT2 was assessed.[20] The IC_{50} value for P-gp was 0.32 μmol/L[21] or >0.5 μmol/L[22]. The IC_{50} values for BCRP and OATP1B3 were 0.15 and 0.10 μmol/L, respectively, the IC_{50} values for OATP1B1, OAT1, OAT3, and OCT2 were all >0.5 μmol/L, and t for BSEP, MRP2, MRP3, and MRP4 all >0.3 μmol/L. , The clinical dose (50 mg) of EBR was estimated from the results of a Japanese study (MK-5172-058). At the dose, the C_{max} (0.177 μmol/L) [see Section 6.2.6.2] and the fraction unbound to plasma proteins (<0.1%) [see Section 4.7.2] indicated that systemic inhibition of P-gp, BCRP, OAT1, OAT3, and OCT2 does not occur. On the other hand, the theoretical maximum concentration of EBR in the intestine is 227 μmol/L when solubility is not taken into consideration,[15] and this indicated that EBR has the potential to inhibit intestinal P-gp and BCRP. Given the maximum unbound hepatic inlet concentration (approximately 0.04 μmol/L),[17] EBR has the potential to inhibit OATP1B. However, the applicant explained that GZR is a substrate of OATP1B, and EBR had no effects on the PK of concomitant GZR [see Section 6.2.4.1], the inhibition of OATP1B by EBR at the clinical dose (50 mg) is thus not clinically relevant. The applicant further explained that based on relative comparisons with the IC_{50} against OATP1B3 and the above-mentioned inhibition of OATP1B, the inhibitory effect of the clinical dose (50 mg) of EBR on BSEP, MRP2, MRP3, or MRP4 is also not clinically relevant.

4.R Outline of the review conducted by PMDA

PMDA concluded that there are no particular problems with the PK of GZR and EBR based on the non-clinical data submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the results from GZR toxicity studies, namely, repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, and others (mechanistic studies, a phototoxicity study, a 1-month oral GZR+ EBR toxicity study in dogs). While GZR was administered as the free acid or the potassium salt, the doses of GZR are expressed in terms of grazoprevir. Unless otherwise specified, 100% polyethylene glycol 400 was used as the vehicle.

The applicant submitted the results from EBR toxicity studies including repeat-dose toxicity, genotoxicity, reproductive and developmental toxicity, and others (a phototoxicity study, a 1-month oral toxicity study in

[20] Because of low solubility of EBR in buffer, the highest concentration that could be tested was 0.3 to 0.5 μmol/L in transporter inhibition assays.
[21] The IC_{50} value against transport of N-methyl-quinidine in membrane vesicles from *Sf*9 cells expressing human P-gp
[22] The IC_{50} value against transport of ^{3}H-digoxin in LLC-PK cells expressing human P-gp

dogs with a 3-month treatment free period). Unless otherwise specified, 10% (w/w) polysorbate 80 solution was used the vehicle.

5.1 Single-dose toxicity (grazoprevir hydrate [GZR])

No single-dose toxicity studies were conducted.

In a 1-month oral dose range-finding study in rasH2 wild-type mice (CTD 4.2.3.2-1) and a 3-month oral dose range-finding study in CD1 mice (CTD 4.2.3.2-2), up to 500 mg/kg of GZR was administered. No deaths or changes suggestive of acute toxicity occurred after the first dose. Accordingly, the lethal dose was estimated to be >500 mg/kg.

In 1-month oral toxicity studies in rats (CTD 4.2.3.2-4 and 4.2.3.2-6), up to 1000 mg/kg of GZR was administered. No deaths or changes suggestive of acute toxicity occurred after the first dose. Accordingly, the lethal dose was estimated to be >1000 mg/kg.

In a 9-day oral rising-dose tolerability study in dogs (Reference data CTD 4.2.3.2-8) and a 1-month oral toxicity study in dogs (CTD 4.2.3.2-9), up to 600 mg/kg of GZR was administered. Emesis was noted at ≥300 mg/kg. No deaths occurred after the first dose. Accordingly, the lethal dose was estimated to be >600 mg/kg.

5.2 Repeated-dose toxicity (GZR)

Repeated-dose toxicity studies with GZR, namely, oral toxicity studies in mice (1 month and 3 months), rats (1 month and 6 months) and dogs (1 month and 9 months), were conducted. The predominant toxicological changes with GZR were increases in liver enzymes and total bilirubin, inflammation of the gallbladder, villous atrophy in the small intestine, and seminiferous tubule degeneration, etc.

The no-observed-adverse-effect level (NOAEL) was 400 mg/kg in the rat 6-month study and 15 mg/kg in the dog 9-month study. $AUC_{0\text{-}24}$ values at the NOAELs (445 and 367 μmol·h/L, respectively) were approximately 136- and 112-fold the human plasma exposure at the clinical dose ($AUC_{0\text{-}24}$, 3.28 μmol·h/L),[23] respectively.

5.2.1 One-month oral range-finding study in mice (CTD 4.2.3.2-1)

Male and female CB6F1/nonTg rasH2 mice (n = 10/sex/group) received 0 (a spray dried formulation containing 50% (w/w) hydroxypropylmethylcellulose phthalate suspended in vehicle[24]), 20, 100, 200, or 500 mg/kg QD of GZR orally for 1 month. No animals died or were sacrificed moribund. Changes observed were decreases in total white blood cell and lymphocyte counts and increases in serum cholesterol, total bilirubin, and liver weights at ≥100 mg/kg, increases in platelet count, serum ALT, ALP, glucose, and phosphorus, decreases in total protein, albumin, and globulin, and increased hepatocellular size at ≥200 mg/kg, and

[23] GZR plasma exposure at Week 4 in patients with chronic hepatitis C receiving GZR 100 mg and EBR 50 mg QD orally for 12 weeks in a Japanese phase II/III study (MK-5172-058) [see Section 6.2.2.3]

[24] 0.5% (w/v) methylcellulose/0.02% (w/v) sodium lauryl sulfate (with 5 mmol/L hydrochloric acid) solution

decreased body weight gain, increases in red blood cell, total white blood cell, neutrophil, lymphocyte, and eosinophil counts, decreases in hematocrit, mean corpuscular volume, and hemoglobin concentration, increases in serum AST and blood urea nitrogen, increased liver size, degeneration of the renal tubular epithelium, periportal hepatocellular cytoplasmic rarefaction, prominent lobular pattern, and villous atrophy in the small intestine, etc. at 500 mg/kg. Cytoplasmic accumulation of glycogen was identified in periportal and centrilobular hepatocytes by electron microscopy of the liver. The applicant explained that the changes noted at 100 mg/kg were of minimal toxicological significance because of their slight severity, had no impact on the general condition of the animals, and were not associated with histopathological changes. Based on these findings, the NOAEL was determined to be 100 mg/kg.

5.2.2 Three-month oral dose range-finding study in mice (CTD 4.2.3.2-2)

Male and female CD1 mice (n = 10/sex/group) received 0 (a spray dried formulation containing 50% (w/w) hydroxypropylmethylcellulose phthalate suspended in vehicle [24)]), 20, 100, 200, or 500 mg/kg QD of GZR orally for 3 months. GZR-related death occurred in 1 of 20 mice in the 500 mg/kg group. The animal found dead had distended abdomen, but the cause of death was unknown. Other changes observed were increases in serum total bilirubin at 100 mg/kg, increases in serum ALP, ALT, and glucose, increased liver size, increased liver weights, prominent lobular pattern, and increased hepatocellular size accompanied by periportal hepatocellular cytoplasmic rarefaction at ≥200 mg/kg, and decreased body weight gain, decreases in red blood cell count, hemoglobin concentration, hematocrit, and mean corpuscular volume, increases in white blood cell count due to increases in neutrophil and lymphocyte counts, increases in serum cholesterol, focal inflammation of the gallbladder, and degeneration of the renal tubular epithelium, etc. at 500 mg/kg. Cytoplasmic accumulation of glycogen was identified in periportal and centrilobular hepatocytes by electron microscopy of the liver. The applicant explained that the clinical chemistry and histopathological findings noted at ≤200 mg/kg were of minimal toxicological significance because these findings were of slight severity, infrequent, and not associated with necrosis or inflammation in the liver. Accordingly, the NOAEL was determined to be 200 mg/kg.

5.2.3 One-month oral toxicity studies in rats (CTD 4.2.3.2-4, 4.2.3.2-6)

Male and female Wistar rats (n = 10/sex/group) received 0 (vehicle), 25, 50, or 1000 mg/kg QD of GZR orally for 1 month. There were no GZR-related deaths, and no animals were sacrificed moribund. Salivation was noted at ≥25 mg/kg, which was mild and transient. Therefore, the applicant explained that it was considered to be due to preference rather than a centrally-mediated effect of GZR and is of minimal toxicological significance. Based on these findings, the NOAEL was determined to be 1000 mg/kg.

Male and female Wistar rats (n = 10 or 20/sex/group) received 50 or 200 mg/kg QD or 0 (vehicle) or 200 mg/kg BID of GZR orally for 1 month. An interim necropsy was performed on some of the animals in the control, 50 mg/kg QD, and 200 mg/kg BID groups at 2 weeks after the start of dosing. There were no GZR-related deaths, and no animals were sacrificed moribund. Salivation occurred in all GZR groups. Accordingly, the

NOAEL was determined to be 200 mg/kg BID. The highest feasible dose of GZR, i.e. 200 mg/kg BID was expected to provide the maximum achievable systemic exposure.

5.2.4 Six-month oral toxicity study in rats (CTD 4.2.3.2-7)

Male and female Wistar rats (n = 15/sex/group) received 50 or 200 mg/kg QD or 0 (vehicle) or 200 mg/kg BID of GZR orally for 6 months. There were no GZR-related deaths and no animals were sacrificed moribund. Observed changes were salivation in all GZR groups, increases in serum total bilirubin in the 200 mg/kg QD and 200 mg/kg BID groups, decreases in serum sodium, chloride, and potassium in the 200 mg/kg BID group, and focal hemorrhage in the glandular mucosa of the stomach in males in the 200 mg/kg BID group. The applicant explained the toxicological significance and human relevance of the clinical chemistry changes (decreases in sodium, chloride, and potassium) and focal hemorrhage in the glandular mucosa of the stomach as follows:

- The clinical chemistry changes are considered of minimal toxicological significance because these changes were of slight severity and not associated with histopathological changes.
- Focal hemorrhage in the glandular mucosa of the stomach was due to prolonged direct contact of the gastric mucosa to GZR administered BID. The change was observed in males only because of their heavier weight requiring higher doses than females. It was not observed at 200 mg/kg/day, which was approximately 120-fold the clinical dose of GZR (1.67 mg/kg/day based on 60 kg human) and, therefore, is of no human relevance.

Accordingly, the NOAEL was determined to be 200 mg/kg BID (400 mg/kg/day).

5.2.5 One-month oral toxicity study in dogs (CTD 4.2.3.2-9)

Male and female beagle dogs (n = 3/sex/group) received 0 (vehicle), 5, 20, or 600 mg/kg QD of GZR orally for 1 month. No animals died or were sacrificed moribund. Observed changes were increases in serum total bilirubin at ≥20 mg/kg and emesis, decreases in red blood cell count, hemoglobin concentration, and hematocrit and seminiferous tubule degeneration at 600 mg/kg. The seminiferous tubule degeneration was of slight severity and characterized by slight decreases in spermatocytes, spermatids, and spermatozoa, which are more mature than spermatogonia, and no marked changes in Sertoli cells and Leydig cells. Thus, the change is expected to be reversible (*Toxicol Pathol*. 2001; 29: 64-76, *Toxicol Pathol*. 2002; 30: 507-20, etc.). Increase in serum total bilirubin was observed in 1 animal receiving 20 mg/kg. Because the change was mild and not associated with changes in serum AST, ALT, or ALP suggestive of hepatotoxicity or histopathological changes, the applicant considered it minimal toxicological significance. Accordingly, the NOAEL was determined to be 20 mg/kg.

5.2.6 Nine-month oral toxicity study in dogs (CTD 4.2.3.2-10)

Male and female beagle dogs (n = 4 or 7/sex/group) received 0 (vehicle), 5, 15, or 300 mg/kg QD of GZR orally for 38 weeks. At 300 mg/kg, 2 of 8 animals were sacrificed moribund due to poor general condition, and the dose was lowered to 100 mg/kg at Week 12 (hereinafter referred to as "the 300/100 mg/kg group"). Observed changes were increases in serum total bilirubin, decreased testicular weight, seminiferous tubule

degeneration, and microlithiasis in the lumen of the gallbladder and in larger bile ducts at ≥15 mg/kg and unformed/liquid feces, brown or yellow feces, emesis, decreases in body weight gain and food consumption, yellow discoloration of skin, decreases in red blood cell count, hemoglobin concentration, hematocrit, and mean corpuscular volume, increases in reticulocytes, fibrinogen, and platelet count, nucleated erythrocytes, serum ALP elevation, decreases in serum cholesterol, increases in urine bilirubin and liver weights, yellowish discoloration of gingival mucosae, white adipose tissue, and aorta, distended gallbladder with abundant bile content, hemosiderin deposition in hepatic sinusoidal cells and the spleen, increased extramedullary hematopoiesis in the spleen, erythroid hyperplasia of bone marrow, and a decrease in sperm content in the epididymis at 300/100 mg/kg. The applicant explained that the increases in serum total bilirubin, microlithiasis in the lumen of the gallbladder and in larger bile ducts, and testicular changes (decreased testicular weight, seminiferous tubule degeneration) observed at 15 mg/kg were of minimal toxicological significance for the following reasons:

- The increases in serum total bilirubin were of slight severity, did not progress during treatment, and were not associated with serum AST, ALT, and ALP elevations suggestive of hepatobiliary toxicity or histopathological changes.
- The lumen microlithiasis in the gallbladder and larger bile ducts was of slight severity and was not associated with histopathological changes in the gallbladder or liver.
- Only 1 of 4 males had seminiferous tubule degeneration, which was of slight severity, and is expected to be reversible [see Section 5.2.5].

Accordingly, the NOAEL was determined to be 15 mg/kg.

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

A bacterial reverse mutation assay and a chromosomal aberration assay in Chinese hamster ovary cells, and a 1-month oral toxicity study in rats were performed. Micronucleus induction in bone marrow was evaluated in these studies, and GZR was determined to be non-genotoxic.

5.4 Carcinogenicity (GZR)

Carcinogenicity studies were not conducted. Clinical use of GZR is expected to be <6 months and that there were no findings suggestive of carcinogenicity such as proliferative lesions, in repeated-dose toxicity studies, etc.

5.5 Reproductive and developmental toxicity (GZR)

A rat study on fertility and early embryonic development to implantation, embryo-fetal development studies in rats and rabbits, and a rat study on effects on pre- and postnatal development, including maternal function, were conducted. The NOAELs for embryo-fetal developmental toxicity in rats and rabbits were determined to be 400 and 100 mg/kg, respectively. The $AUC_{0\text{-}24}$ values at the NOAELs (217 and 76.1 μmol·h/L, respectively) were approximately 66- and 23-fold the human exposure ($AUC_{0\text{-}24}$, 3.28 μmol·h/L), respectively and the C_{max} values at the NOAELs (48.1 and 67.2 μmol/L, respectively) were approximately 78- and 108-fold

the human exposure (C_{max}, 0.62 μmol/L),[23] respectively. GZR placental transfer and excretion into milk were demonstrated in rats [see Sections 4.2.3 and 4.4.2].

5.5.1 Study of fertility and early embryonic development to implantation

Study of fertility and early embryonic development to implantation in male and female rats (CTD 4.2.3.5.1-1)

Male and female Wistar rats (n = 20/sex/group) received 50 or 200 mg/kg QD or 0 (vehicle) or 200 mg/kg BID of oral GZR. Male animals were treated from 15 days prior to cohabitation, during cohabitation, and through the day prior to scheduled sacrifice (a total of approximately 6 weeks). Female animals were treated from 15 days prior to cohabitation through gestation day 7 or until the day removed from cohabitation. Males in the control, 50 mg/kg QD, and 200 mg/kg QD groups were housed with females within the group they belonged to. Males in the 200 mg/kg BID group were housed with untreated females, and females in 200 mg/kg BID group with untreated males in the same cages. Because there were no effects on clinical observations or fertility and early embryonic development to implantation, the NOAELs for general toxicity and fertility and early embryonic development to implantation were both determined to be 200 mg/kg BID.

5.5.2 Embryo-fetal development studies

5.5.2.1 Oral embryo-fetal developmental toxicity study in rats (CTD 4.2.3.5.2-2)

Pregnant Wistar rats (n = 24 or 28/group) received 0 (vehicle), 50, or 200 mg/kg QD or 0 (vehicle) or 200 mg/kg BID[25] of oral GZR from gestation day 6 through 20. Because there were no effects on maternal general toxicity parameters or embryo-fetal development, the NOAELs for maternal general toxicity and embryo-fetal developmental toxicity were both determined to be 200 mg/kg BID.

5.5.2.2 Preliminary oral embryo-fetal developmental toxicity study in rabbits (CTD 4.2.3.5.2-10)

Pregnant Dutch rabbits (n = 26/group) received 50 or 200 mg/kg QD or 0 (vehicle) or 200 mg/kg BID of oral GZR from gestation day 7 through 20. In maternal animals, vehicle-related toxicities were observed in the control and 200 mg/kg BID groups: 9 of 26 rabbits in the control group and 7 of 26 rabbits in the 200 mg/kg BID group died, sacrificed moribund or aborted, or had unformed stool, decreased food consumption, and body weight loss. In embryos/fetuses, vehicle-related increases in mean post-implantation loss and reductions in the number of live fetuses per litter in the control and 200 mg/kg BID groups were observed.

5.5.2.3 Intravenous embryo-fetal developmental toxicity study in rabbits (CTD 4.2.3.5.2-13)

Pregnant Dutch rabbits (n = 23/group) received 0 (vehicle[26]), 25, 50, or 100 mg/kg QD of intravenous GZR from gestation day 7 through 20. Because there were no effects on maternal general toxicity parameters or embryo-fetal development, the NOAELs for maternal general toxicity and embryo-fetal developmental toxicity were both determined to be 100 mg/kg.

[25] 200 mg/kg BID was expected to provide the maximum achievable systemic exposure [see Section 5.2.3].
[26] 0.15% polyvinylpyrrolidone/0.036% sodium deoxycholate/5% mannitol solution

5.5.3 Rat study on effects on pre- and postnatal development, including maternal function (CTD 4.2.3.5.3-1)

Pregnant Wistar rats (n = 24 or 28/group) received 25 or 100 mg/kg QD or 0 (vehicle) or 200 mg/kg BID of oral GZR from gestation day 6 through lactation day 20. There were no effects on maternal general toxicity parameters or F1 generation parameters (post-implantation survival, external morphology, clinical signs, body weights, sexual maturity, behavioral tests, reproductive performance, and fertility). Based on the findings, the NOAELs for maternal general toxicity and pre- and post-natal developmental toxicity were both determined to be 200 mg/kg BID.

5.6 Other toxicity studies (GZR)

5.6.1 Qualification assessment of impurities

Impurities present at a level greater than the qualification threshold in the GZR drug substance are Impurity A and Impurity B, and based on the following considerations, it was concluded that there are no safety concerns about these impurities.

5.6.1.1 General toxicity of impurities (CTD 4.2.3.2-6)

A 1-month oral toxicity study in rats was conducted with the GZR drug substance containing [redacted]% of Impurity A and [redacted]% of Impurity B [see Section 5.2.3]. When the human equivalent doses[27] of Impurity A and Impurity B determined from the NOAEL for GZR established in this study were compared to the doses of Impurity A and Impurity B at the clinical dose of GZR (100 mg) (both [redacted] mg/m^2), the safety margins were approximately 39- and 15-fold, respectively.

5.6.1.2 Genotoxicity of impurities (CTD 4.2.3.3.2-1)

The applicant explained that the results of *in silico* analyses using DEREK (Deductive Estimation of Risk from Existing Knowledge) and Multi CASE or Leadscope Personal showed no genotoxic potential of Impurity A or Impurity B. Micronucleus induction in bone marrow was evaluated in a 1-month oral toxicity study in rats with the GZR drug substance containing [redacted]% of Impurity A and [redacted]% of Impurity B (CTD 4.2.3.3.2.1). When the human equivalent doses[27] of Impurity A and Impurity B determined from the NOAEL for GZR established in this study were compared to the doses of Impurity A and Impurity B at the clinical dose of GZR (100 mg) (both [redacted] mg/m^2), the safety margins were approximately 97- and 38-fold, respectively.

5.6.2 Three-day oral phototoxicity study in pigmented rats (CTD 4.2.3.7.7-1)

Based on the absorption spectrum of GZR, the wavelength of maximum absorbance is 341 nm and the molar extinction coefficient is >1000 L $mol^{-1}cm^{-1}$. Thus, a phototoxicity study was conducted. Male Long-Evans rats (n= 5/group) received GZR 50 mg/kg QD for 3 days, or 200 mg/kg BID on Days 1 and 2 and a single oral dose of 200 mg/kg on Day 3. At approximately 2 hours after the last dose, eyes and shaved skin were exposed to 0.5 minimal erythema dose of ultraviolet light for 30 minutes. No skin

[27] Guidance for Industry Estimating the maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), July 2005

reactions or histopathological changes in the eyes suggestive of phototoxicity occurred. GZR is, therefore, considered unlikely to have phototoxicity potential.

5.6.3 One-month oral GZR + EBR toxicity study in dogs (CTD 4.2.3.7.7-2)

Male and female beagle dogs (n = 3/sex/group) received 0 + 0 (vehicle[28]), 0 + 25, 5 + 0, or 5 + 25 mg/kg QD of oral GZR + EBR for 1 month.[29] No animals died or were sacrificed moribund. EBR-related phospholipidosis (vacuolated macrophages in the gut-related lymphoid tissues of the small and large intestines and lymph nodes) was observed at 0 + 25 and 5 + 25 mg/kg, which was considered of minimal toxicological significance [see Sections 5.8.6 and 5.8.7]. No toxicologically significant differences were observed between GZR + EBR co-administration and GZR alone. Based on the above, the NOAEL for GZR + EBR was determined to be 5 + 25 mg/kg.

5.7 Single-dose toxicity (Elbasvir: EBR)

No single-dose toxicity studies have been conducted.

In a 1-month oral dose range-finding study in rasH2 wild-type mice (CTD 4.2.3.2-11), up to 1000 mg/kg of EBR was administered. No deaths or changes suggestive of acute toxicity occurred after the first dose. Accordingly, the approximate lethal dose was determined to be >1000 mg/kg.

In a 14-day oral toxicity study in rats (CTD 4.2.3.2-13), up to 1000 mg/kg of oral EBR was administered BID. No deaths or changes suggestive of acute toxicity occurred after the first dose. Accordingly, the approximate lethal dose was determined to be >1000 mg/kg BID.

In a 3-month oral toxicity study in dogs (CTD 4.2.3.2-18) and a 9-month oral toxicity study in dogs (CTD 4.2.3.2-19), up to 1000 mg/kg of EBR was administered. Emesis and white and pale brown discoloration of feces, most likely due to fecal elimination of unabsorbed EBR, were observed at 1000 mg/kg, but no deaths occurred after the first dose. Accordingly, the approximate lethal dose was determined to be >1000 mg/kg.

5.8 Repeated-dose toxicity (EBR)

Repeated-dose toxicity studies with EBR, namely oral toxicity studies in mice (1 month), rats (14 days, 15 days, 3 months, 6 months), and dogs (14 days, 3 months, 9 months), were conducted. The predominant toxicological findings for EBR were vacuolated macrophages in the gut-related lymphoid tissues of the small and large intestines, lymph nodes, solitary lymphoid follicle in the gallbladder, and the spleen, suggestive of phospholipidosis, in dogs.

[28] 10% polysorbate 80 solution was given as EBR vehicle.
[29] GZR or GZR vehicle was followed by EBR or EBR vehicle (polysorbate 80 solution) in all treatment groups.

The NOAELs in the rat 6-month and dog 9-month oral toxicity studies were both determined to be 1000 mg/kg, and the $AUC_{0\text{-}24}$ values at the NOAELs (21.9 and 16.6 μmol·h/L, respectively) were 8.8- and 6.7-fold the human exposure ($AUC_{0\text{-}24}$, 2.48 μmol·h/L),[30] respectively.

5.8.1 One-month oral dose range-finding study in mice (CTD 4.2.3.2-11)

Male and female CB6F1/nonTg rasH2 mice (n = 10/sex/group) received 0 (vehicle), 10, 50, 300, or 1000 mg/kg QD of oral EBR for 1 month. Because there were no EBR-related changes including deaths or animals that were sacrificed moribund, the NOAEL was determined to be 1000 mg/kg.

5.8.2 Fourteen-day oral toxicity study in rats (CTD 4.2.3.2-13)

Male and female Wistar rats (n = 10/sex/group) received 0 (vehicle[31]), 100, or 300 mg/kg QD or 1000 mg/kg BID of oral EBR for 14 days. No animals died or were sacrificed moribund. Decreased body weight gain and increases in neutrophil count at 300 mg/kg and white discoloration of feces, most likely due to fecal elimination of unabsorbed EBR, decreased food consumption, and increases in serum cholesterol were observed at 1000 mg/kg BID. Because the observed changes were of slight severity and not associated with histopathological findings, they all were considered minimal toxicological significance. The NOAEL was thus determined to be 1000 mg/kg BID.

5.8.3 Three-month oral toxicity study in rats (CTD 4.2.3.2-15)

Male and female Wistar rats (n = 10/sex/group) received 0 (vehicle), 50, 300, or 1000 mg/kg QD of oral EBR for 3 months. No animals died or were sacrificed moribund. Salivation was noted at ≥50 mg/kg, which was a mild, transient finding. Thus, it was considered due to preference rather than a centrally-mediated effect of EBR and of minimal toxicological significance. Accordingly, the NOAEL was determined to be 1000 mg/kg.

The AUC and C_{max} at 1000 mg/kg BID in a rat 14-day oral toxicity study were similar to those at 1000 mg/kg in this study.

5.8.4 Six-month oral toxicity study in rats (CTD 4.2.3.2-16)

Male and female Wistar rats (n = 15/sex/group) received 0 (vehicle), 30, 300, or 1000 mg/kg QD of oral EBR for 6 months. There were no EBR-related deaths and no animals were sacrificed moribund. Salivation, increase in urine volume, and decrease in urine specific gravity at ≥30 mg/kg and decrease in food consumption and body weight gain at ≥300 mg/kg were observed. These changes were of slight severity with no impact on the general condition of the animals, and thus considered minimal toxicological significance. Accordingly, the NOAEL was determined to be 1000 mg/kg.

[30] EBR exposure at Week 4 in patients with chronic hepatitis C receiving GZR 100 mg and EBR 50 mg QD orally for 12 weeks in a Japanese study (MK-5172-058) [see Section 6.2.2.3]

[31] 5% (w/w) polysorbate 80 solution was used as vehicle for the EBR 0 (vehicle) and 1000 mg/kg BID groups, and 10% (w/w) polysorbate 80 solution was used as vehicle for other groups.

5.8.5 Fourteen-day oral toxicity study in dogs (CTD 4.2.3.2.17)

Male and female beagle dogs (n = 2/sex/group) received 25 mg/kg QD of oral EBR for 14 days. Because there were no EBR-related changes including deaths or animals that were sacrificed moribund, the NOAEL was determined to be 25 mg/kg.

5.8.6 Three-month oral toxicity study in dogs (CTD 4.2.3.2-18)

Male and female beagle dogs (n = 3/sex/group) received 0 (vehicle), 2, 25, or 1000 mg/kg QD of oral EBR for 3 months. No animals died or were sacrificed moribund. Increased large vacuolated macrophages in the gut-related lymphoid tissues of the small and large intestines and lymph nodes at ≥25 mg/kg and white and pale brown discoloration of feces, most likely due to fecal elimination of unabsorbed EBR, and increased large vacuolated macrophages in the spleen were observed at 1000 mg/kg. Electron microscopy confirmed that these vacuolated macrophages were consistent with lysosomal phospholipid accumulation (phospholipidosis). Because the phospholipidosis was of slight severity and not associated with lymphoid depletion in the lymphoid tissue or inflammation or necrosis, or hematological changes (no decreased white blood cell or lymphocyte counts, no abnormal circulating blood cells), it was considered of minimal toxicological significance. Accordingly, the NOAEL was determined to be 1000 mg/kg.

5.8.7 Nine-month oral toxicity study in dogs (CTD 4.2.3.2-19)

Male and female beagle dogs (n = 4/sex/group) received 0 (vehicle), 5, 25, or 1000 mg/kg QD of oral EBR for 9 months. No animals died or were sacrificed moribund. Vacuolated macrophages in the follicular areas of the lymphoid tissues and the gut-related lymphoid tissue of the small intestine were observed at ≥25 mg/kg. Sporadic emesis, white and pale brown discoloration of feces, most likely due to fecal elimination of unabsorbed EBR, decreases in body weight and food consumption, and vacuolated macrophage in the gut-related lymphoid tissues of the stomach and large intestine and, solitary lymphoid follicle in the gallbladder were observed at 1000 mg/kg. The nature and severity (slight) of the vacuolated macrophages suggesting phospholipidosis were comparable to the change observed in a dog 3-month oral toxicity study [see Section 5.8.6], indicating no progression of this change with prolonged dosing. The vacuolated macrophages was considered minimal toxicological significance because the vacuolar changes were not associated with lymphoid depletion in the lymphoid tissue, or inflammation or necrosis. The changes in clinical observations were considered minimal toxicological significance because they did not significantly affected the physical condition of the animals and were not associated with histopathological changes. Accordingly, the NOAEL was determined to be 1000 mg/kg.

5.9 Genotoxicity (CTD 4.2.3.3.1-3, 4.2.3.3.1-4, 4.2.3.2-13)

A bacterial reverse mutation assay and a chromosomal aberration assay in Chinese hamster ovary cells were performed, and micronucleus induction in bone marrow was evaluated in a 14-day oral toxicity study in rats. EBR was determined to be non-genotoxic.

5.10 Carcinogenicity (EBR)

Carcinogenicity studies were not conducted, given that the human use of EBR is less than 6 months in duration and that there were no findings suggestive of carcinogenicity such as proliferative lesions, in repeated-dose toxicity studies, etc.

5.11 Reproductive and developmental toxicity (EBR)

A rat study on fertility and early embryonic development to implantation, embryo-fetal development studies in rats and rabbits, and a rat study on effects on pre- and postnatal development and maternal function were conducted. The NOAELs for embryo-fetal developmental toxicity in rats and rabbits were both determined to be 1000 mg/kg. The $AUC_{0\text{-}24}$ values at the NOAELs (21.8 and 39.4 μmol·h/L, respectively) were 8.8- and 15.9-fold the human exposure ($AUC_{0\text{-}24}$, 2.48 μmol·h/L), respectively. The C_{max} values at the NOAELs (1.45 and 1.93 μmol/L, respectively) were 7.3- and 9.7-fold the human exposure (C_{max}, 0.20 μmol/L),[30] respectively. EBR placental transfer and excretion into milk were identified in rats [see Sections 4.7.3 and 4.9.2].

5.11.1 Study of fertility and early embryonic development to implantation

Study of fertility and early embryonic development to implantation in male and female rats (CTD 4.2.3.5.1-2)

Male and female Wistar rats (n = 20/sex/group) received 0 (vehicle), 50, 300, or 1000 mg/kg QD of oral EBR from 15 days prior to cohabitation, during cohabitation, and until the day prior to scheduled sacrifice for males (a total of approximately 6 weeks) and from 15 days prior to cohabitation, during cohabitation, and through gestation day 7 for females. Control males were housed with control females, 50 mg/kg males were housed with 50 mg/kg females, 300 mg/kg males were housed with 300 mg/kg females, 1000 mg/kg males were housed with untreated females, and 1000 mg/kg females were housed with untreated males in the same cages. Effects on clinical observation were decreases in body weight gain and food consumption at ≥300 mg/kg. These changes were of slight severity and transient, and thus considered minimal toxicological significance. As an effect on fertility and early embryonic development to implantation, decreased sperm count per gram of cauda epididymis was observed in males at 1000 mg/kg. However, there were no effects on reproductive parameters assessed based on mating performance, fertility, embryonic/fetal survival, testicular weight, and sperm motility. No histopathological testicular changes were seen in a 6-month oral toxicity study in rats and a 9-month oral toxicity study in dogs [see Sections 5.8.4 and 5.8.7]. Thus, the decreased sperm count per gram of cauda epididymis was considered minimal toxicological significance. Accordingly, the NOAELs for general toxicity and fertility and early embryonic development to implantation were both determined to be 1000 mg/kg.

5.11.2 Embryo-fetal development studies

5.11.2.1 Oral embryo-fetal developmental toxicity study in rats (CTD 4.2.3.5.2-15)

Pregnant Wistar rats (n = 24 or 28/group) received 0 (vehicle), 50, 300, or 1000 mg/kg QD of oral EBR from gestation day 6 through 20. An effect on maternal clinical observation was decreased body weight gain observed at 1000 mg/kg. The change was of slight severity thus considered minimal

toxicological significance. There were no effects on embryo-fetal development. Accordingly, the NOAELs for maternal general toxicity and embryo-fetal developmental toxicity were both determined to be 1000 mg/kg.

5.11.2.2 Oral embryo-fetal developmental toxicity study in rabbits (CTD 4.2.3.5.2-17)

Pregnant Dutch rabbits (n = 23/group) received 0 (vehicle), 30, 100, or 1000 mg/kg QD of oral EBR from gestation day 7 through 20. Because there were no effects on maternal general toxicity parameters or embryo-fetal development, the NOAELs for maternal general toxicity and embryo-fetal developmental toxicity were both determined to be 1000 mg/kg.

5.11.3 Rat study on effects on pre- and postnatal development and maternal function (CTD 4.2.3.5.3-2)

Pregnant Wistar rats (n = 20/group) received0 (vehicle), 50, 300, or 1000 mg/kg QD of oral EBR from gestation day 6 through lactation day 20. In maternal clinical observations, decreases in body weight gain and food consumption were observed at 1000 mg/kg. These changes were transient, and thus, were considered minimal toxicological significance. In the F1 generation, there were no effects on post-implantation survival, external morphology, clinical signs, body weights, sexual maturity, behavioral tests, or fertility. Accordingly, the NOAELs for maternal general toxicity and pre- and post-natal developmental toxicity were both determined to be 1000 mg/kg.

5.12 Other toxicity studies (EBR)

5.12.1 Qualification assessment of impurities

Impurities present at a level greater than the qualification threshold in the EBR drug substance are Impurity C, Impurity D, and Impurity E. Based on the following considerations, it was concluded that there are no safety concerns about these impurities.

5.12.1.1 General toxicity of impurities (CTD 4.2.3.2-16)

A 6-month oral toxicity study was conducted in rats with the EBR drug substances containing [redacted]% of Impurity C, [redacted]% of Impurity D, and [redacted]% of Impurity E, or [redacted]% of Impurity C, [redacted]% of Impurity D, and [redacted]% of Impurity E [see Section 5.8.4]. When the human equivalent doses[27)] of Impurities C, D, and E determined from the NOAEL for EBR established in this study were compared to the doses of Impurities C, D, and E at the clinical dose of EBR (50 mg) ([redacted], [redacted], and [redacted] mg/m^2, respectively), the safety margins were 70-, 22-, and ≥186-fold, respectively.

5.12.1.2 Genotoxicity of impurities (CTD 4.2.3.2-13)

The applicant explained that the results of *in silico* analyses using DEREK (Deductive Estimation of Risk from Existing Knowledge) and Multi CASE or Leadscope Personal showed no genotoxic potential of Impurity C, D, or E.

Micronucleus induction in bone marrow was evaluated in a 14-day oral toxicity study in rats. When the human equivalent doses[27)] of Impurities C, D, and E determined from the NOAEL for EBR established in

this study were compared to the doses of Impurities C, D, and E at the clinical dose of EBR (50 mg) ([redacted], [redacted], and [redacted] mg/m^2, respectively), the safety margins were all >100-fold.

5.12.2 Three-day oral phototoxicity study in pigmented rats (CTD 4.2.3.7.7-5)

Based on the absorption spectrum of EBR, the wavelengths of maximum absorbance are 349.7 and 368.0 nm and the molar extinction coefficient is >1000 L mol^{-1}cm^{-1}. Thus, a phototoxicity study was conducted. EBR 100 or 1000 mg/kg QD was administered orally to male Long-Evans rats (n = 5/group) for 3 days. At approximately 4 hours after the last dose in the 100 mg/kg group and at approximately 6 hours after the last dose in the 1000 mg/kg group, eyes and shaved skin were exposed to 0.5 minimal erythema dose of ultraviolet light for 30 minutes. No skin reactions or histopathological changes in the eyes indicative of phototoxicity occurred. Based on the results, EBR is considered unlikely to have phototoxicity potential.

5.12.3 One-month oral toxicity study in dogs with a three-month treatment-free period (CTD 4.2.3.7.7-6)

A study was conducted to evaluate the potential reversibility of phospholipidosis observed in 3-month and 9-month oral toxicity studies in dogs [see Sections 5.8.6 and 5.8.7]. Female beagle dogs (n = 6 or 18/group) received 0 (vehicle) or 1000 mg/kg QD of oral EBR for 1 month, and an approximately 3-month treatment-free period after the end of dosing was scheduled for some of the animals. In this study, electron microscopy of mesenteric lymph nodes was also performed after the end of dosing and after a 3-month treatment-free period. No animals died or were sacrificed moribund. White discoloration of feces, emesis, body weight loss, decreased skin turgor, thin appearance, and vacuolated macrophages in the gut-associated lymphoid tissues of the small and large intestines, the spleen, and lymph nodes indicative of phospholipidosis were observed at 1000 mg/kg. There were no findings suggestive of phospholipidosis at the end of the 3-month treatment-free period, indicating the reversibility of phospholipidosis.

5.R Outline of the review conducted by PMDA

Based on the data submitted and the following considerations, PMDA considers that there are no particular problems with the clinical use of GZR and EBR from a toxicological perspective.

EBR-induced phospholipidosis

Changes indicative of phospholipidosis were observed in macrophages in the spleen and gut-related lymph nodes, etc. in repeated-dose toxicity studies of EBR in dogs [see Sections 5.8.6, 5.8.7, and 5.12.3]. PMDA asked the applicant to explain the toxicological significance of phospholipidosis and the risk of phospholipidosis in clinical use of EBR.

The applicant's explanation:

Drug-induced phospholipidosis occurs after exposure to amphiphilic cationic drugs like EBR, and it is known as an adaptive response to mitigate toxicity to other intracellular structures by lysosomal capture of the drug

(*Biochem Pharmacol*. 1978; 27: 1103-8). The phospholipidosis observed in the repeated-dose toxicity studies of EBR in dogs was also considered of minimal toxicological significance because the change was not associated with tissue injury or dysfunction in the relevant organs, etc [see Sections 5.8.6 and 5.8.7]. Given that no phospholipidosis-related adverse events were reported in EBR clinical studies and that no clear association between the development of phospholipidosis in humans and toxicities in humans has been demonstrated (*Exp Opin Drug Saf*. 2006; 5: 567-83), the phospholipidosis observed in the repeated-dose toxicity studies in dogs should pose no safety concerns for clinical use of EBR.

PMDA's view:
Although the applicant's explanation is in part understandable, human relevance of phospholipidosis cannot be ruled out. The potential risk of EBR-induced phospholipidosis has been suggested in the repeated-dose toxicity studies in dogs. Therefore, the fact that phospholipidosis occurred in the repeated-dose toxicity studies in dogs should be communicated to healthcare professionals via package insert, etc.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

In the clinical development of GZR and EBR, 2 different formulations each (Formulation 1 [tablets containing [redacted]] and Formulation 2 [tablets not containing [redacted]], Formulation 3 [[redacted] capsules] and Formulation 4 [tablets using [redacted]]) were mainly used.[32)] The results of a relative BA study (MK-5172-045) showed that the BA of EBR was largely comparable between Formulations 3 and 4. The effect of gastric pH on the BA of EBR was assessed. The applicant explained that while Formulation 3 using [redacted] is affected by gastric pH, Formulation 4 using [redacted] is unlikely to be affected by gastric pH. In Japan, the final market image formulation of GZR is identical to Formulation 2 except for the deboss, and the final market image formulation of EBR is identical to Formulation 4 except for the deboss and the film coat [redacted]. The bioequivalence between the final market image formulation of EBR and Formulation 4 was demonstrated by dissolution test.[33)]

The results of the main biopharmaceutic studies of Formulations 1 to 4 [absolute BA and food effect studies] are described in this section. Concentrations of GZR and EBR in human plasma and dialysate were determined using HPLC/tandem mass spectrometry [LLOQ, 0.1-1 ng/mL for GZR and 0.20-0.25 ng/mL for EBR].

All doses and plasma concentrations of GZR are expressed in terms of grazoprevir.

[32)] Formulations 1-4 were used in the following main clinical studies:
Formulation 1, Phase I studies (MK-5172-001, MK-5172-004, MK-5172-009, MK-5172-013, MK-5172-014, MK-5172-040, MK-5172-049, and MK-5172-050); Formulation 2, Phase I study (MK-5172-078) and phase II/III study (MK-5172-058); Formulation 3, Phase I studies (MK-7009-050, MK-8742-001, MK-8742-002, MK-8742-004, MK-8742-005, and MK-8742-009); Formulation 4, Phase I studies (MK-5172-050, MK-5172-078, MK-8742-015, and MK-8742-020) and phase II/III study (MK-5172-058).

[33)] Dissolution test was performed according to the Paddle Method using dissolution media maintained at 37°C (pH1.2, [redacted], 6.8, water) (50 and 100 revolutions/minute for dissolution medium of pH of [redacted], 50 revolutions/minute for other dissolution media).

6.1.1 Absolute BA studies

6.1.1.1 Phase I study (Reference data CTD 5.3.1.1-2, Study MK-5172-040 [January 2013 to March 2013])

Non-Japanese healthy subjects (6 subjects included in PK assessment) received single and multiple oral doses of GZR 200 mg or a single oral dose of 25 mg followed 3.25 hours later by a single intravenous dose of ^{14}C-GZR 100 μg. The absolute BA of single and multiple oral doses of GZR was estimated by two analyses.[34)] The results are shown in Table 28.

[34)] A high inter-subject variability was observed in ^{14}C-GZR plasma concentrations at 3.25 hours after the oral dose, i.e. immediately after the intravenous dose (<0.01 to 36 nmol/L). Therefore, alternative values estimated from two analyses were used instead of measured values.

Table 28. Absolute BA of single or multiple oral doses of GZR (%)

Dosing regimen	Dose (mg)	N	Analysis 1 [a)]	Analysis 2 [b)]
Single-dose	25	6	17.0 [13.5, 21.4]	9.58 [7.37, 12.5]
	200		27.3 [21.7, 34.4]	14.9 [11.7, 18.9]
Multiple-dose	200		38.3 [25.6, 57.3]	21.4 [13.4, 34.1]

Geometric mean [90% confidence interval (CI)]

[a)] The C_0 after the intravenous dose was calculated by back-extrapolation from the plasma ^{14}C-GZR concentrations immediately after the intravenous dose at 3.25 hours after the oral dose (at 3.5 and 3.75 hours after the oral dose).

[b)] The plasma ^{14}C-GZR concentration (C_0) after the intravenous dose at 3.25 hours after the oral dose was assumed as 0.0435 μmol Eq (dose/human plasma volume of 3 L).

6.1.1.2 Phase I study (Reference data CTD 5.3.1.1-8, Study MK-8742-020 [February 2015])

Non-Japanese healthy subjects (6 subjects included in PK assessment) received a single dose of EBR 50 mg followed 3.5 hours later by a single intravenous dose of ^{13}C- and ^{15}N-EBR 100 μg, and the absolute BA of a single oral dose of EBR 50 mg was estimated. The absolute BA (geometric mean [90% CI]) was 32.4% [27.0, 38.8]. The geometric mean $V_{d,ss}$ and CL of ^{13}C- and ^{15}N-EBR were 121 L and 5.78 L/h, respectively.

6.1.2 Food effect study (CTD 5.3.1.1-5, Study MK-5172-078 [May 2015 to June 2015])

Japanese healthy subjects (30 subjects included in PK assessment) received single oral doses of GZR (Formulation 2) 100 mg and EBR (Formulation 4) 50 mg under fasting or fed conditions(within 10 minutes following standardized meal [approximately 500 kcal, approximately 10 g fat]), and the effect of food was assessed.[35)] The results are shown in Table 29. The C_{max} and AUC_{inf} geometric mean ratios (fed/fasted) [90% CI] were 1.80 [1.45, 2.24] and 1.48 [1.33, 1.64], respectively, for GZR and 0.99 [0.87, 1.13] and 1.02 [0.91, 1.14], respectively, for EBR. The C_{max} and AUC_{inf} of GZR under fed conditions tended to increase. Food tended to increase the t_{max} of GZR.

Table 29. GZR and EBR PK parameters under fasting or fed conditions

	N	C_{max} (nmol/L)	t_{max} [a)] (h)	AUC_{inf} (nmol·h/L)	$t_{1/2}$ (h)	CL/F (L/h)	V_d/F (L)
GZR							
Fasted	30	53.2 (88.1)	2.5 [1.0 - 6.0]	776 (41.2)	27.0 (43.5)	168 (41.2)	6551 (66.6)
Fed		95.7 (68.3)	4.0 [1.0 - 6.0]	1153 (30.1) [b)]	30.6 (28.8) [b)]	113 (30.1) [b)]	4993 (43.8) [b)]
EBR							
Fasted	30	121 (50.6)	4.0 [2.5 - 4.0]	2288 (45.5)	18.3 (10.2)	24.8 (45.5)	655 (44.7)
Fed		120 (30.7)	4.0 [2.0 - 6.0]	2332 (29.7)	18.2 (9.8)	24.3 (29.7)	637 (28.0)

Geometric mean (CV%), [a)] median [range], [b)] N = 29

6.2 Clinical pharmacology studies

The applicant submitted the results from foreign phase I studies (PK studies in healthy subjects, patients with HCV, subjects with hepatic or renal insufficiency, pharmacokinetic interaction studies, etc.) and the results of physiologically-based pharmacokinetic (PBPK) model analysis and PPK analysis with the application. *In vitro* studies using human biomaterials are described in the non-clinical pharmacokinetics section [see Sections 4.2.2, 4.3.2, 4.5, 4.7.2, 4.8.2, and 4.10].

Unless otherwise specified, PK parameters are expressed as the geometric mean.

[35)] A 2-treatment, 2-period crossover study was conducted. There was a washout period of at least 14 days between the periods.

6.2.1 Studies in healthy subjects

6.2.1.1 Administration of GZR alone

6.2.1.1.1 Phase I study in Japanese subjects (CTD 5.3.3.1-3, Study MK-5172-009 [August 2011 to February 2012])

The PK of GZR were evaluated in Japanese healthy subjects (12 subjects included in PK assessment) following single or multiple oral doses of GZR for 10 days. The results are shown in Table 30. The C_{max} and AUC of GZR following a single dose increased in a greater than dose-proportional manner over the range of 100 to 1200 mg. The 10-day accumulation ratio (AUC_{0-24} on Day 10/AUC_{0-24} on Day 1) was 1.91 at 400 mg and 2.76 at 800 mg.

Table 30. PK parameters in Japanese subjects following single or multiple oral doses of GZR

Dosing regimen	Dose (mg)	N	Time point	C_{max} (nmol/L)	t_{max} [a] (h)	AUC [b] (nmol·h/L)	$t_{1/2}$ (h)
Single-dose	100	6	—	34.3 (44)	3.0 [2.0 - 6.0]	883 (27)	36.5 (30)
	400	6		1830 (78)	5.0 [4.0 - 6.0]	9370 (55)	37.6 (29)
	800	6		10,500 (34)	3.0 [1.0 - 4.0]	45,400 (51)	31.9 (40)
	1200	5		10,900 (39)	4.0 [2.0 - 6.0]	56,700 (63)	20.0 (21)
Multiple-dose	400 QD	6	Day 1	2180 (90)	3.5 [2.0 - 6.0]	9950 (88)	—
			Day 10	4300 (58)	3.0 [2.0 - 6.0]	19,000 (68)	26.4 (15)
	800 QD	6	Day 1	6300 (43)	3.5 [3.0 - 4.0]	28,900 (72)	—
			Day 10	12,600 (22)	4.0 [1.0 - 4.0]	79,600 (27)	20.7 (18)

Geometric mean (CV%), [a] Median [range], [b] AUC_{inf} for single-dose administration, AUC_{0-24} for multiple-dose administration

6.2.1.1.2 Phase I studies in non-Japanese subjects

6.2.1.1.2.1 Phase I study (Reference data CTD 5.3.3.1-1, Study MK-5172-001 [June 2009 to April 2010])

The PK of GZR were evaluated in non-Japanese healthy subjects (48 subjects included in PK assessment) who were enrolled in this study. Following single or multiple oral doses of GZR for 10 days. The results are shown in Table 31. After single- or multiple-dose of oral GZR, the C_{max} and AUC of GZR increased more than dose-proportionally over the dose range tested. The accumulation ratios following multiple doses (AUC_{0-24} on Day 10/AUC_{0-24} on Day 1) were 3.00 at 100 mg, 3.49 at 400 mg, and 1.71 at 1000 mg. A steady-state is estimated to be reached within 2 to 8 days following administration of GZR 100 to 1000 mg.

Table 31. PK parameters in foreign subjects following single or multiple oral doses of GZR

Dosing regimen	Dose (mg)	N	Time point	C_{max} (nmol/L)	t_{max} [a] (h)	AUC [b] (nmol·h/L)	$t_{1/2}$ (h)	CL/F (L/h)	V_d/F (L)
Single-dose	25	6	—	3.09 (41.5)	2.5 [2.0 - 6.0]	—	—	—	—
	50	6		10.9 (58.4)	2.0 [1.0 - 4.0]	275 (37.0)	36.4 (21.6)	237 (37.0)	12,500 (52.2)
	100	6		22.7 (43.8)	3.5 [2.0 - 6.0]	523 (31.9)	28.1 (26.8)	250 (31.9)	10,100 (57.1)
	400	6		432 (103)	4.0 [2.0 - 6.0]	2710 (80.3)	20.8 (19.1)	193 (80.3)	5790 (93.3)
	800	6		3450 (79.4)	4.0 [2.0 - 6.0]	13,600 (53.7)	19.5 (26.7)	76.8 (53.7)	2160 (83.7)
	1200	12		5230 (128)	4.0 [2.0 - 6.0]	27,600 (120)	17.0 (16.4)	56.8 (120)	1390 (130)
	1600	6		12,200 (127)	4.0 [2.0 - 6.0]	68,900 (160)	16.6 (31.9)	30.3 (160)	725 (240)
Multiple-doses	100 QD	6	Day 1	24.4 (38.0)	3.0 [2.0 - 4.0]	238 (42.8)	—	—	—
			Day 10	73.9 (86.4)	4.0 [3.0 - 6.0]	713 (52.1)	—	—	—
	400 QD	6	Day 1	410 (150)	3.5 [3.0 - 6.0]	1860 (68.7)	—	—	—
			Day 10	1830 (41.6)	3.0 [2.0 - 4.0]	6490 (39.1)	—	—	—
	1000 QD	6	Day 1	5790 (73.4)	4.0 [2.0 - 6.0]	19,700 (81.7)	—	—	—
			Day 10	8140 (63.8)	3.0 [2.0 - 4.0]	33,600 (76.5)	—	—	—

Geometric mean (CV%), [a] Median [range], [b] AUC_{inf} for single-dose administration, AUC_{0-24} for multiple-dose administration

6.2.1.1.2.2 Phase I study (Reference data CTD 5.3.3.1-2, Study MK-5172-007 [November 2011 to December 2011])

Following a single oral dose of ^{14}C-GZR 200 mg in non-Japanese healthy subjects (6 subjects included in PK assessment), the mass balance of GZR and its metabolites in plasma and feces were investigated. By

576 hours post-dose, 0.29% and 109.8% of the radioactive dose were excreted in urine and feces, respectively. At 3 and 8 hours post-dose, no metabolites were found in plasma, and only unchanged GZR was detected. The radioactivity in feces at 168 hours post-dose (approximately 102% of the administered dose) was comprised of unchanged GZR (44.8%), a reductive metabolite (M10) (33.9%), and oxidative metabolites (M4a, M4b, M7a, M11a, M11b, and M14) (approximately 21%).

6.2.1.2 Administration of EBR alone

6.2.1.2.1 Phase I study in Japanese subjects (CTD 5.3.3.1-4, Study MK-7009-050 [April 2013 to September 2013])

The PK of EBR were evaluated in Japanese healthy subjects (12 subjects included in PK assessment) following single or multiple oral doses of EBR for 10 days. The results are shown in Table 32. The C_{max} and AUC of EBR following a single dose were largely dose-proportional over the range of 10 to 100 mg, and the accumulation ratio following multiple dosing (C_{24} on Day 10 to C_{24} on Day 1) was 2.56.

Table 32. PK parameters in Japanese subjects following single or multiple oral doses of EBR

Dosing regimen	Dose (mg)	N	Time point	C_{max} (nmol/L)	t_{max} [a)] (h)	AUC [b)] (nmol·h/L)	$t_{1/2}$ (h)
Single-dose	10	6	—	35.9 (31.5)	2.5 [2.0 - 4.0]	595 (26.5)	17.0 (4.7)
	50	5		184 (33.7)	4.0 [2.0 - 4.0]	3092 (40.8)	18.1 (7.9)
	100	5		289 (22.1)	4.0 [4.0 - 4.0]	4996 (33.8)	18.3 (9.8)
Multiple-doses	50 QD	6	Day 10	180 (37.9)	3.5 [2.0 - 4.0]	2166 (35.1)	18.5 (7.0)

Geometric mean (CV%), a) Median [range], b) AUC_{inf} for single-dose administration, AUC_{0-24} for multiple-dose administration

6.2.1.2.2 Phase I studies in non-Japanese subjects

6.2.1.2.2.1 Phase I study (Reference data CTD 5.3.3.1-5, Study MK-8742-001 [September 2011 to February 2012])

The PK of EBR were evaluated in non-Japanese healthy subjects (36 subjects included in PK assessment) enrolled in this study. The PK parameters following single oral doses of EBR 5 to 100 mg or multiple oral doses of EBR 10 to 200 mg QD for 10 days are shown in Table 33. The C_{max} and AUC of EBR following single- and multiple-dose administration were largely dose-proportional over the range of 5 to 100 mg. The accumulation ratios following multiple-dose administration (AUC_{0-24} on Day 10 to AUC_{0-24} on Day 1) were 2.05 at 10 mg, 1.24 at 50 mg, and 1.09 at 200 mg. A steady-state is estimated to be reached within 1 to 2 days following administration of EBR 10 to 200 mg.

Table 33. PK parameters in non-Japanese subjects following single or multiple oral doses of EBR

Dosing regimen	Dose (mg)	N	Time point	C_{max} (nmol/L)	t_{max} [a)] (h)	AUC [b)] (nmol·h/L)	$t_{1/2}$ (h)	CL/F (L/h)	V_d/F (L)
Single-dose	5	6	—	6.34 (57.0)	3.5 [2.0 - 4.0]	123 (50.0)	14.5 (20.4)	46.2 (50.0)	968 (46.5)
	10	6		23.9 (22.3)	4.0 [2.0 - 4.0]	383 (26.5)	15.1 (10.8)	29.6 (26.5)	645 (26.7)
	50	6		104 (42.8)	4.0 [3.0 - 6.0]	1750 (37.0)	15.3 (10.5)	32.4 (37.0)	714 (27.6)
	100	6		175 (69.3)	4.0 [3.0 - 4.0]	3160 (70.0)	18.9 (20.8)	35.9 (70.0)	978 (71.8)
Multiple-doses	10 QD	6	Day 1	14.2 (90.9)	3.0 [2.0 - 8.0]	180 (83.0)	—	—	—
			Day 10	32.4 (47.4)	2.5 [2.0 - 4.0]	369 (47.9)	18.8 (19.7)	—	—
	50 QD	6	Day 1	96.5 (54.1)	3.5 [3.0 - 6.0]	1210 (49.8)	—	—	—
			Day 10	108 (54.6)	4.0 [3.0 - 4.0]	1510 (44.6)	20.7 (17.7)	—	—
	200 QD [c)]	6	Day 1	297 (44.6)	4.0 [3.0 - 4.0]	3240 (51.6)	—	—	—
			Day 10	281 (71.5)	4.0 [2.0 - 4.0]	3540 (73.3)	20.1 (6.7)	—	—

Geometric mean (CV%), [a)] Median [range], [b)] AUC_{inf} for single-dose administration, AUC_{0-24} for multiple-dose administration, [c)] The 100-mg formulation providing lower systemic exposure was used.

6.2.1.2.2.2 Phase I study (Reference data CTD 5.3.3.1-7, Study MK-8742-014 [September 2013 to October 2013])

Following a single oral dose of ^{14}C-EBR 50 mg in non-Japanese healthy subjects (6 subjects included in PK assessment), the mass balance of EBR and its metabolites in plasma and feces were investigated. By 240 hours post-dose, 0.175% and 94.1% of the radioactive dose were excreted in urine and feces, respectively. At 3 and 8 hours post-dose, no metabolites were found in plasma, and only unchanged EBR was detected. The radioactivity in feces at 168 hours post-dose (approximately 94% of the administered dose) was comprised of unchanged EBR (approximately 75%) and oxidative metabolites (m2 and m3) (approximately 19%).

6.2.2 Studies in patients

6.2.2.1 Administration of GZR alone (Reference data CTD 5.3.3.2-1, Study MK-5172-004 [February 2010 to November 2012])

The PK of GZR were evaluated in non-Japanese HCV-infected patients (genotypes 1 and 3) (73 subjects included in PK assessment) following multiple oral doses of GZR 10 to 800 mg QD for 7 days. The results are shown in Table 34.

Table 34. PK parameters in HCV-infected patients following multiple oral doses of GZR

Dose (mg)	N	Time point	C_{max} (nmol/L)	AUC_{0-24} (nmol·h/L)	C_{24} (nmol/L)	Accumulation ratio [a]		
						C_{max}	AUC_{0-24}	C_{24}
10 [b]	5	Day 1	1.36 (129)	15.9 (101)	0.490 (106)	—	—	—
		Day 7	3.77 (196)	62.8 (152)	2.41 (181)	2.77 (40.3)	3.96 (34.3)	4.92 (58.7)
50 [b]	5	Day 1	13.4 (55.0)	92.3 (121)	4.14 (27.5)	—	—	—
		Day 7	46.9 (50.7)	419 (28.8)	12.7 (24.6)	2.98 (54.1)	3.12 (8.6)	3.06 (23.8)
100	10	Day 1	84.2 (39.5)	492 (41.1)	11.3 (55.1)	—	—	—
		Day 7	141 (42.0)	1160 (37.2)	20.1 (54.6)	1.68 (56.2)	2.36 (35.0)	1.78 (29.6)
400	10	Day 1	1680 (80.1)	8040 (63.6)	43.8 (98.4)	—	—	—
		Day 7	3380 (159)	18,200 (126)	70.2 (96.3)	2.02 (168)	2.26 (122)	1.60 (51.3)
800	18	Day 1	5850 (109)	31,700 (114)	96.9 (130)	—	—	—
		Day 7	11,500 (45.5)	74,800 (57.5)	183 (108)	1.88 (76.2)	2.25 (68.5)	1.78 (62.1)

Geometric mean (CV%), [a] PK parameter on Day 7/PK parameter on Day 1, [b] Genotype 1 only

6.2.2.2 Administration of EBR alone (Reference data CTD 5.3.3.2-2, Study MK-8742-002 [February 2012 to May 2013])

The PK of EBR were evaluated in non-Japanese HCV-infected patients (genotypes 1 and 3) (40 subjects included in PK assessment) following multiple oral doses of EBR 5 to 100 mg QD for 5 days. The results are shown in Table 35.

Table 35. PK parameters in HCV-infected patients following multiple oral doses of EBR

Dose (mg)	N	Time point	C_{max} (nmol/L)	AUC_{0-24} (nmol·h/L)	C_{24} (nmol/L)	Accumulation ratio[a]		
						C_{max}	AUC_{0-24}	C_{24}
5	5	Day 1	9.62 (70.6)	101 (54.2)	2.37 (52.8)	—	—	—
		Day 5	12.6 (37.7)	155 (41.6)	3.89 (47.3)	1.31 (37.6)	1.53 (26.0)	1.64 (19.5)
10	15	Day 1	6.08 (112)	77.0 (103)	2.21 (91.0)	—	—	—
		Day 5	10.9 (49.1)	149 (48.3)	4.08 (52.0)	1.79 (71.8)	1.94 (61.8)	1.84 (52.3)
50	15	Day 1	63.5 (85.5)	719 (81.3)	18.1 (74.5)	—	—	—
		Day 5	106 (61.4)	1360 (47.9)	34.3 (38.2)	1.66 (123)	1.89 (98.1)	1.90 (84.3)
100	5	Day 1	133 (26.5)	1410 (20.7)	36.9 (25.0)	—	—	—
		Day 5	170 (43.6)	2080 (39.5)	56.2 (33.5)	1.28 (41.3)	1.47 (35.5)	1.52 (26.4)

Geometric mean (CV%), [a] PK parameter on Day 5/PK parameter on Day 1

6.2.2.3 Co-administration of GZR and EBR (CTD 5.3.5.1-1, Study MK-5172-058 [Ongoing since August 2014])

The PK of GZR and EBR at steady-state were evaluated in chronic hepatitis C patients with (N = 7) or without (N = 29) compensated cirrhosis [For the inclusion criteria, see Section 7.1] among HCV-infected patients enrolled in a Japanese phase II/III study (MK-5172-058) following oral co-administration of GZR 50 or 100 mg and EBR 50 mg QD. Following co-administration of GZR 100 mg and EBR 50 mg to non-cirrhotic patients with chronic hepatitis C, the C_{max}, t_{max}, and AUC_{0-24} of GZR were 620 nmol/mL, 2.0 hours, and 3280 nmol·h/mL, respectively, and those of EBR were 200 nmol/mL, 4.0 hours, and 2480 nmol·h/mL, respectively. In chronic hepatitis C patients with compensated cirrhosis, the C_{max}, t_{max}, and AUC_{0-24} of GZR following the combined treatment were 1180 nmol/mL, 2.0 hours, and 7110 nmol·h/mL, respectively, and those of EBR were 170 nmol/mL, 2.0 hours, and 2360 nmol·h/mL, respectively.

6.2.3 Intrinsic factors

6.2.3.1 Intrinsic factors related to PK of GZR

6.2.3.1.1 Foreign phase I study in subjects with hepatic impairment (Reference data CTD 5.3.3.3-1, Study MK-5172-013 [July 2011 to September 2014], CTD 4.2.2.3-3)

Subjects with hepatic impairment [mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C), 8 subjects each] and 24 subjects with normal hepatic function received multiple oral doses of GZR 50, 100, or 200 mg QD for 10 days, and the PK of GZR were investigated. The results are shown in Table 36. No marked increases in the C_{max} and AUC_{0-24} of GZR were observed in subjects with mild hepatic impairment as compared to subjects with normal hepatic function. The C_{max} and AUC_{0-24} were increased by ≥5-fold in subjects with moderate or severe hepatic impairment as compared to subjects with normal hepatic function. The applicant explained that GZR will be contraindicated in HCV-infected patients with moderate or severe hepatic impairment because of these study data and the lack of data on the efficacy and safety of the clinical dose (100 mg) of GZR in this particular patient population.

Table 36. PK parameters on Day 10 following multiple oral doses of GZR in subjects with hepatic impairment and subjects with normal hepatic function

Dose (mg)	Degree of hepatic impairment	N	C_{max} (nmol/L)	AUC_{0-24} (nmol·h/L)	$t_{1/2}$ (h)	Accumulation ratio [a]	Unbound fraction [b] (%)	Geometric least-squares mean ratio [90% CI] (hepatic impairment/normal hepatic function)	
								C_{max}	AUC_{0-24}
200	Mild	8	1400 (62.4)	6160 (63.0)	54.2 (22.3)	3.65 (32.8)	1.7 ± 0.3	1.37 [0.83, 2.27]	1.66 [1.05, 2.61]
	Normal	8	1020 (51.1)	3770 (39.0)	35.9 (47.2)	2.62 (40.5)	1.2 ± 0.2	—	—
100	Moderate	8	625 (65.7)	4260 (84.2)	39.6 (23.8)	2.62 (36.7)	2.1 ± 1.0	5.98 [2.84, 12.6]	4.82 [2.60, 8.93]
	Normal	8	107 (115)	862 (58.8)	39.8 (17.3)	2.71 (58.7)	1.7 ± 0.2	—	—
50	Severe	8	396 (115)	3000 (98.7)	42.0 (26.6)	2.55 (35.8)	1.9 ± 0.3	13.0 [6.00, 28.2]	11.7 [6.10, 22.4]
	Normal	8	30.4 (64.6)	257 (49.1)	31.0 (42.0)	4.33 (72.3)	1.7 ± 0.3	—	—

Geometric mean (CV%), [a] AUC_{0-24} on Day 10/AUC_{0-24} on Day 1, [b] Mean ± SD

6.2.3.1.2 Foreign phase I study in elderly subjects (Reference data CTD 5.3.3.3-2, Study MK-5172-014 [October 2011])

The PK of GZR were investigated in healthy elderly (65-79 years) subjects (6 men and 6 women) following multiple oral doses of GZR 400 mg QD for 7 days. The C_{max} values of GZR on Day 7 in men and women were 3090 and 5880 nmol/L, respectively, and the AUC_{0-24} values were 14,100 and 24,900 nmol·h/L, respectively. Using the data from the 400 mg group in a non-Japanese phase I study in healthy young (19-45 years) subjects (MK-5172-001) [see Section 6.2.1.1.2.1], the PK parameters at steady-state in elderly men were compared with those in young men. The C_{max} and AUC_{0-24} geometric mean ratios for elderly men vs. young men were 1.68 and 2.18, respectively.

6.2.3.2 Intrinsic factors related to PK of EBR

6.2.3.2.1 Foreign phase I study in subjects with hepatic impairment (Reference data CTD 5.3.3.3-6, Study MK-8742-009 [March 2013 to August 2014], CTD 4.2.2.3.9)

Subjects with hepatic impairment [mild (Child-Pugh A) and moderate (Child-Pugh B), 8 subjects each; severe (Child-Pugh C), 7 subjects] and 8 subjects with normal hepatic function received a single oral dose of EBR 50 mg, and the PK of EBR were investigated. The results are shown in Table 37. The mean unbound fractions of EBR in subjects with normal hepatic function and subjects with mild, moderate, and severe hepatic impairment were all <0.3%.

Table 37. PK parameters following a single oral dose of EBR in subjects with hepatic impairment and subjects with normal hepatic function

Degree of hepatic impairment	N	C_{max} (nmol/L)	AUC_{inf} (nmol·h/L)	$t_{1/2}$ (h)	Geometric least-squares mean ratio [90% CI] (hepatic impairment/normal hepatic function)	
					C_{max}	AUC_{inf}
Normal	8	121 (52.4)	2580 (53.4)	20.7 (12.6)	—	—
Mild	8	70.1 (140)	1560 (90.9)	24.8 (21.7)	0.58 [0.32, 1.05]	0.61 [0.34, 1.08]
Moderate	8	83.0 (44.3)	1860 (60.2) [a]	25.4 (34.2) [a]	0.69 [0.38, 1.24]	0.72 [0.40, 1.31]
Severe	7	70.7 (72.1)	2280 (101)	33.7 (20.8)	0.58 [0.32, 1.08]	0.88 [0.48, 1.61]

Geometric mean (CV%), [a] N = 7

6.2.3.2.2 Foreign phase I study in healthy elderly subjects (Reference data CTD 5.3.3.3-5, Study MK-8742-004 [June 2012 to August 2012])

The PK of EBR were investigated in healthy elderly (65-80 years) subjects (12 men and 12 women) and healthy young (22-45 years) subjects (6 men) following a single oral dose of EBR 100 mg. The C_{max} values of EBR in elderly men, elderly women, and young men were 180, 316, and 226 nmol/L, respectively, and the AUC_{inf} values were 3600, 6000, and 3910 nmol·h/L, respectively.

6.2.3.3 Foreign phase I study of GZR and EBR in subjects with renal impairment (Reference data CTD 5.3.3.3-4, Study MK-5172-050 [September 2013 to December 2013], CTD 4.2.2.3-6, 4.2.2.3-8)

The PK of GZR and EBR were investigated in severe renal impairment subjects with eGFR <30 mL/min not on hemodialysis, patients with end-stage renal disease (ESRD) on hemodialysis, and subjects with normal renal function with eGFR ≥80 mL/min (8 subjects each) following oral co-administration of GZR 100 mg and EBR 50 mg QD for 10 days.[36)] The results are shown in Table 38. The C_{max} and AUC_{0-24} of GZR and EBR tended to be higher in patients with severe renal impairment than in those with normal renal function. No marked differences were observed between ESRD patients on hemodialysis and subjects with normal renal function, and there were also no effects of dialysis. There were no marked differences in the mean unbound fractions of GZR and EBR among subjects with normal renal function, subjects with severe renal impairment, and ESRD patients on hemodialysis; the mean unbound fraction of GZR was 1.6% to 2.2% , and that of EBR was <0.5%.

Table 38. PK parameters following oral co-administration of GZR and EBR in subjects with renal impairment and subjects with normal renal function

Degree of renal impairment	N	C_{max} (nmol/L)	AUC_{0-24} (nmol·h/L)	$t_{1/2}$ (h)	Geometric least-squares mean ratio [90% CI] (renal impairment/normal renal function)	
					C_{max}	AUC_{0-24}
GZR						
Normal	8	156 (63.5)	1140 (42.5)	35.2 (19.6)	—	—
Severe	8	329 (83.9)	2120 (32.0)	36.3 (30.5)	1.66 [0.99, 2.77]	1.65 [1.09, 2.49]
Before hemodialysis	8	112 (57.0)	878 (54.0)	—	0.92 [0.57, 1.48]	0.85 [0.58, 1.25]
After hemodialysis	8	108 (74.1)	855 (56.2)	28.4 (20.9)	0.88 [0.54, 1.42]	0.83 [0.56, 1.22]
EBR						
Normal	8	164 (40.1)	2210 (38.2)	25.0 (19.1)	—	—
Severe	8	303 (25.4)	4560 (21.7)	29.0 (18.3)	1.66 [1.21, 2.28]	1.86 [1.38, 2.51]
Before hemodialysis	8	127 (23.3)	1740 (29.0)	—	0.84 [0.62, 1.13]	0.86 [0.65, 1.14]
After hemodialysis	8	143 (31.9)	1990 (30.1)	23.0 (6.3)	0.94 [0.70, 1.27]	0.99 [0.75, 1.30]

Geometric mean (CV%)

6.2.4 Pharmacokinetic interaction studies

6.2.4.1 Drug interaction between GZR and EBR (Reference data CTD 5.3.3.4-18, Study MK-8742-008 [September 2012 to November 2012])

The PK of GZR and EBR were investigated in non-Japanese healthy subjects (N = 10) following combined oral multiple doses of GZR 200 mg and EBR 20 mg QD. The geometric mean ratios of C_{max}, AUC_{0-24}, and C_{trough} of GZR in GZR + EBR vs. GZR alone [90% CI] were 0.87 [0.50, 1.52], 0.90 [0.63, 1.28], and 0.94 [0.77, 1.15], respectively. The geometric mean ratios of C_{max}, AUC_{0-24}, and C_{trough} of EBR in

[36)] For ESRD patients on hemodialysis, dialysis was withheld during the period from Day 1 through Day 9 and it was performed on Day 10. PK parameters in subjects with severe renal impairment and those with normal renal function were calculated on Day 10. PK parameters in ESRD patients on hemodialysis were calculated on Day 9 (before hemodialysis) and Day 10 (after hemodialysis).

EBR + GZR vs. EBR alone [90% CI] were 0.93 [0.76, 1.13], 1.01 [0.83, 1.24], and 1.02 [0.83, 1.24], respectively.

6.2.4.2 Drug interaction between GZR and co-administered drugs[37)]

Ten studies were conducted to evaluate drug interactions between GZR and concomitant drugs. The geometric mean ratios of PK parameters of GZR or concomitant drugs in combination therapy vs. monotherapy [90% CI] are shown in Tables 39 and 40.

Table 39. Effect of concomitant drugs on PK parameters of GZR

Concomitant drug	Dosage regimen		N	Geometric mean ratio [90% CI]		
	Concomitant drug	GZR		C_{max}	AUC [a)]	C_{24}
Ketoconazole	400 mg QD	100 mg single dose	8	1.13 [0.77, 1.67]	3.02 [2.42, 3.76]	—
Ritonavir	100 mg BID	200 mg single dose	10	1.15 [0.60, 2.18]	2.03 [1.60, 2.56]	1.88 [1.65, 2.14]
Tenofovir Disoproxil Fumarate	300 mg QD	200 mg QD	12	0.78 [0.51, 1.18]	0.86 [0.65, 1.12]	0.89 [0.78, 1.01]
Raltegravir	400 mg BID	200 mg QD	11	0.85 [0.62, 1.16]	0.89 [0.72, 1.09]	0.90 [0.82, 0.99]
Atazanavir/Ritonavir	300/100 mg QD	200 mg QD	12 [b)]	6.24 [4.42, 8.81]	10.6 [7.78, 14.4]	11.6 [7.96, 17.0]
Lopinavir/Ritonavir	400/100 mg BID	200 mg QD	13	7.31 [5.65, 9.45]	12.9 [10.3, 16.1]	21.7 [13.0, 36.3]
Darunavir/Ritonavir	600/100 mg BID	200 mg QD	13 [c)]	5.27 [4.04, 6.86]	7.50 [5.92, 9.51]	8.05 [6.33, 10.2]
Methadone	20-150 mg QD	200 mg QD	12[c)]	0.88 [0.36, 2.14]	1.03 [0.53, 1.97]	0.77 [0.56, 1.04]
Buprenorphine /Naloxone	8-24/2-6 mg QD	200 mg QD	12 [c)]	0.76 [0.40, 1.44]	0.80 [0.53, 1.22]	0.69 [0.54, 0.88]
Rifampicin	600 mg single dose (IV)	200 mg single dose	12	10.9 [8.92, 13.4]	10.2 [8.68, 12.0]	1.77 [1.40, 2.24]
	600 mg single dose (PO)	200 mg QD	12	6.52 [5.16, 8.24]	8.35 [7.38, 9.45]	1.62 [1.32, 1.98]
	600 mg QD (PO)	200 mg QD	12	1.16 [0.82, 1.65]	0.93 [0.75, 1.17]	0.10 [0.07, 0.13]
Efavirenz	600 mg QD	200 mg QD	12 [b)]	0.13 [0.09, 0.19]	0.17 [0.13, 0.24]	0.31 [0.25, 0.38]
Atorvastatin	20 mg single dose	200 mg QD	9	1.26 [0.83, 1.90]	1.26 [0.97, 1.64]	1.11 [1.00, 1.23]
Pitavastatin	1 mg single dose	200 mg QD	9	0.72 [0.57, 0.92]	0.81 [0.70, 0.95]	0.91 [0.82, 1.01]

—, not determined: [a)] AUC_{inf} for single-dose administration; AUC_{0-24} for multiple-dose administration: [b)] with the concomitant drug, N = 11: [c)] without the concomitant drug, N = 6

[37)] Reference data 5.3.3.1-1, Study MK-5172-001 (June 2009 to April 2010); Reference data 5.3.3.4-1, Study MK-5172-006 (May 2011 to August 2011); Reference data 5.3.3.4-2, Study MK-5172-026 (November 2012 to December 2012); Reference data 5.3.3.4-3, Study MK-5172-029 (December 2012 to February 2013); Reference data 5.3.3.4-4, Study MK-5172-030 (October 2012 to December 2012); Reference data 5.3.3.4-5, Study MK-5172-031 (January 2013 to April 2013); Reference data 5.3.3.4-6, Study MK-5172-032 (October 2012 to December 2012); Reference data 5.3.3.4-7, Study MK-5172-046 (March 2013 to May 2013); Reference data 5.3.3.4-9, Study MK-5172-054 (December 2013 to February 2014); Reference data 5.3.3.4-13, Study MK-5172-070 (June 2014 to July 2014)

Table 40. Effect of GZR on PK parameters of concomitant drugs

Concomitant drug	Dosage regimen		N	Geometric mean ratio [90% CI]		
	Concomitant drug	GZR		C_{max}	AUC [a)]	C_{trough}
Tenofovir	Tenofovir Disoproxil Fumarate 300 mg QD	200 mg QD	12	1.14 [1.04, 1.25]	1.18 [1.09, 1.28]	1.24 [1.10, 1.39]
Raltegravir	400 mg BID	200 mg QD	11	1.46 [0.78, 2.73]	1.43 [0.89, 2.30]	1.47 [1.09, 2.00]
Atazanavir	Atazanavir/Ritonavir 300/100 mg QD	200 mg QD	11	1.12 [1.01, 1.24]	1.43 [1.30, 1.57]	1.23 [1.13, 1.34]
Lopinavir	Lopinavir/Ritonavir 400/100 mg BID	200 mg QD	13	0.97 [0.88, 1.08]	1.03 [0.92, 1.16]	0.97 [0.81, 1.15]
Darunavir	Darunavir/Ritonavir 600/100 mg BID	200 mg QD	12 [b)]	1.10 [0.96, 1.25]	1.11 [0.99, 1.24]	1.00 [0.85, 1.18]
R-methadone	Methadone 20-150 mg QD	200 mg QD	12	1.03 [0.96, 1.11]	1.09 [1.02, 1.17]	－
S-methadone				1.15 [1.07, 1.25]	1.23 [1.12, 1.35]	－
Buprenorphine	Buprenorphine/Naloxone 8-24/2-6 mg QD	200 mg QD	12	0.90 [0.76, 1.07][c)]	0.98 [0.81, 1.19][d)]	－
Norbuprenorphine				1.10 [0.97, 1.25][c)]	1.13 [0.97, 1.32][d)]	－
Naloxone				1.00 [0.80, 1.27][c)]	1.10 [0.82, 1.47][d)]	－
Efavirenz	600 mg QD	200 mg QD	11	1.03 [0.99, 1.08]	1.00 [0.96, 1.05]	0.93 [0.88, 0.98]
Midazolam	2 mg single dose	200 mg QD	11 [e)]	1.15 [1.01, 1.31]	1.34 [1.29, 1.39]	－
Atorvastatin	20 mg single dose	200 mg QD	9	5.66 [3.39, 9.45]	3.00 [2.42, 3.72]	－
Pitavastatin	1 mg single dose	200 mg QD	9	1.27 [1.07, 1.52]	1.11 [0.91, 1.34]	－
Ethinyl estradiol	Ethinyl estradiol/Levonorgestrel 0.03/0.15 mg single dose	200 mg QD	20	1.05 [0.98, 1.12]	1.10 [1.05, 1.14]	－
Levonorgestrel				0.93 [0.84, 1.03]	1.23 [1.15, 1.32]	－
Montelukast	10 mg single dose	200 mg QD	23 [f)]	0.92 [0.81, 1.06]	1.11 [1.02, 1.20]	1.39 [1.25, 1.56][g)]
Rosuvastatin	10 mg single dose	200 mg QD	12 [h)]	4.25 [3.25, 5.56]	1.59 [1.33, 1.89][i)]	0.80 [0.70, 0.91]

－, not determined: [a)] AUC_{inf} for single-dose administration; AUC_{0-24} for multiple-dose administration (QD), AUC_{0-12} for multiple-dose administration (BID): [b)] with GZR, N = 11: [c)] C_{max}/dose: [d)] AUC_{0-24}/dose: [e)] with GZR, N = 10: [f)] with GZR, N = 22: [g)] C_{24}: [h)] with GZR, N = 11: [i)] N = 8

6.2.4.3 Drug interaction between EBR and co-administered drugs[38)]

Drug interactions between EBR and concomitant drugs were evaluated in 9 studies. The geometric mean ratios of PK parameters of EBR or concomitant drugs in combination therapy vs. monotherapy [90% CI] are shown in Table 41 andTable 42.

[38)] 5.3.3.1-4, Study MK-7009-050 (April 2013 to September 2013); Reference data 5.3.3.4-17, Study MK-8742-003 (October 2012 to November 2012); Reference data 5.3.3.4-19, Study MK-8742-010 (March 2013 to April 2013); Reference data 5.3.3.4-20, Study MK-8742-011 (May 2014 to August 2014); Reference data 5.3.3.4-21, Study MK-8742-013 (March 2013 to May 2013); Reference data 5.3.3.4-22, Study MK-8742-016 (March 2013 to May 2013); Reference data 5.3.3.4-23, Study MK-8742-017 (March 2013 to May 2013); Reference data 5.3.3.4-24, Study MK-8742-021 (July 2014 to September 2014); Reference data 5.3.3.4-25, Study MK-8742-023 (October 2014 to December 2014)

Table 41. Effect of concomitant drugs on PK parameters of EBR

Concomitant drug	Dosage regimen		N	Geometric mean ratio [90% CI]		
	Concomitant drug	EBR		C_{max}	AUC [a]	C_{24}
Ketoconazole	400 mg QD	50 mg single dose	7 [b]	1.29 [1.00, 1.66]	1.80 [1.41, 2.29]	1.89 [1.37, 2.60]
Methadone	Methadone 20-120 mg QD	50 mg QD	10 [c]	1.93 [1.30, 2.86]	1.71 [1.16, 2.51]	1.86 [1.22, 2.83]
Rifampicin	600 mg single dose (IV)	50 mg single dose	14 [d]	1.41 [1.18, 1.68]	1.22 [1.06, 1.40]	1.31 [1.12, 1.53]
	600 mg single dose (P.O.)	50 mg single dose	14 [d]	1.29 [1.06, 1.58]	1.17 [0.98, 1.39]	1.21 [1.03, 1.43]
Tenofovir Disoproxil Fumarate	300 mg QD	50 mg QD	10	0.88 [0.77, 1.00]	0.93 [0.82, 1.05]	0.92 [0.81, 1.05]
Efavirenz	600 mg QD	50 mg QD	10 [e]	0.55 [0.41, 0.73]	0.46 [0.36, 0.59]	0.41 [0.28, 0.59]
Raltegravir	400 mg single dose	50 mg single dose	10	0.89 [0.61, 1.29]	0.81 [0.57, 1.17]	0.80 [0.55, 1.16]
Atazanavir/Ritonavir	300/100 mg QD	50 mg QD	10 [f]	4.15 [3.46, 4.97]	4.76 [4.07, 5.56]	6.45 [5.51, 7.54]
Lopinavir/Ritonavir	400/100 mg BID	50 mg QD	10 [g]	2.87 [2.29, 3.58]	3.71 [3.05, 4.53]	4.58 [3.72, 5.64]
Darunavir/Ritonavir	600/100 mg BID	50 mg QD	10 [f]	1.67 [1.36, 2.05]	1.66 [1.35, 2.05]	1.82 [1.39, 2.39]
Buprenorphine/Naloxone	8/2 mg single dose	50 mg single dose	15 [d]	1.13 [0.87, 1.46]	1.22 [0.98, 1.52]	1.22 [0.99, 1.51]
Vaniprevir	750 mg BID	50 mg QD	6	1.81 [1.38, 2.37]	1.97 [1.57, 2.46]	2.45 [1.87, 3.20]

－, not determined: [a] AUC_{inf} for single-dose administration; AUC_{0-24} for multiple-dose administration: [b] with the concomitant drug, N = 6: [c] without the concomitant drug, N = 6: [d] with the concomitant drug, N = 13: [e] with the concomitant drug, N = 7: [f] with the concomitant drug, N = 8: [g] with the concomitant drug, N = 9

Table 42. Effect of EBR on PK parameters of concomitant drugs

Concomitant drug	Dosage regimen		N	Geometric mean ratio [90% CI]		
	Concomitant drug	EBR		C_{max}	AUC [a]	C_{trough}
R-methadone	Methadone 20-120 mg QD	50 mg QD	10	1.07 [0.95, 1.20]	1.03 [0.92, 1.15]	1.10 [0.96, 1.26]
S-methadone				1.09 [0.95, 1.25]	1.09 [0.94, 1.26]	1.20 [0.98, 1.47]
Ethinyl estradiol	Ethinyl estradiol/Levonorgestrel 0.03/0.15 mg single dose	50 mg QD	20	1.10 [1.05, 1.16]	1.01 [0.97, 1.05]	－
Levonorgestrel				1.02 [0.95, 1.08]	1.14 [1.04, 1.24]	－
Tenofovir	Tenofovir Disoproxil Fumarate 300 mg QD	50 mg QD	10	1.47 [1.32, 1.63]	1.34 [1.23, 1.47]	1.29 [1.18, 1.41]
Raltegravir	400 mg single dose	50 mg single dose	10	1.09 [0.83, 1.44]	1.02 [0.81, 1.27]	0.99 [0.80, 1.22][b]
Efavirenz	600 mg QD	50 mg QD	7	0.74 [0.67, 0.82]	0.82 [0.78, 0.86]	0.91 [0.87, 0.96]
Atazanavir	Atazanavir/Ritonavir 300/100 mg QD	50 mg QD	8	1.02 [0.96, 1.08]	1.07 [0.98, 1.17]	1.15 [1.02, 1.29]
Lopinavir	Lopinavir/Ritonavir 400/100 mg BID	50 mg QD	9	1.02 [0.92, 1.13]	1.02 [0.93, 1.13]	1.07 [0.97, 1.18]
Darunavir	Darunavir/Ritonavir 600/100 mg BID	50 mg QD	8	0.95 [0.85, 1.05]	0.95 [0.86, 1.06]	0.94 [0.85, 1.05]
Buprenorphine	Buprenorphine/Naloxone 8/2 mg single dose	50 mg single dose	15 [c]	0.94 [0.82, 1.08]	0.98 [0.89, 1.08][d]	0.98 [0.88, 1.09][e]
Norbuprenorphine				1.10 [0.98, 1.23]	0.97 [0.86, 1.09]	0.97 [0.87, 1.09][e]
Naloxone				0.85 [0.66, 1.09]	0.88 [0.78, 1.00]	－
Digoxin	0.25 mg single dose	50 mg QD	18	1.47 [1.25, 1.73]	1.11 [1.02, 1.22]	－
Vaniprevir	750 mg BID	50 mg QD	6	0.84 [0.55, 1.27]	0.74 [0.50, 1.08]	0.63 [0.48, 0.83]

－,not determined: [a] AUC_{inf} for single-dose administration; AUC_{0-24} for multiple-dose administration (QD); AUC_{0-12} for multiple-dose administration (BID): [b] C_{12}: [c] with EBR , N = 13; [d] without EBR, N = 14; with EBR, N = 13: [e] C_{24}

6.2.4.4 Drug interactions between GZR + EBR and concomitant drugs[39)]

Drug interactions between GZR formulation + EBR formulation or GZR-EBR fixed combination formulation and concomitant drugs were evaluated in 9 studies. The geometric mean ratios of PK parameters of GZR and EBR used with concomitant drugs to those used without concomitant drugs [90% CI] are shown in Tables 43 and 44.

[39)] Reference data 5.3.1.1-4, Study MK-5172-072 (June 2014 to September 2014]) Reference data 5.3.3.4-8, Study MK-5172-053 (January 2014 to March 2014); Reference data 5.3.3.4-9, Study MK-5172-054 (December 2013 to February 2014); Reference data 5.3.3.4-10, Study MK-5172-056 (December 2013 to February 2014); Reference data 5.3.3.4-11, Study MK-5172-057 (January 2014 to March 2014); Reference data 5.3.3.4-12, Study MK-5172-063 (May 2014 to July 2014); Reference data 5.3.3.4-14, Study MK-5172-073 (July 2014 to September 2014); Reference data 5.3.3.4-15, Study MK-5172-076 (August 2014 to September 2014); Reference data 5.3.3.4-16, Study MK-5172-081 (September 2015 to November 2015)

Table 43. Effect of concomitant drugs on PK parameters of GZR and EBR

Concomitant drug	Dosage regimen			N	Geometric mean ratio [90% CI]		
	Concomitant drug	Analyte			C_{max}	AUC [a)]	C_{24}
Rilpivirine	25 mg QD	GZR	200 mg QD	19	0.97 [0.83, 1.14]	0.98 [0.89, 1.07]	1.00 [0.93, 1.07]
		EBR	50 mg QD	19	1.07 [0.99, 1.16]	1.07 [1.00, 1.15]	1.04 [0.98, 1.11]
Rosuvastatin	10 mg single dose	GZR	200 mg QD	11	0.97 [0.63, 1.50]	1.01 [0.79, 1.28]	0.95 [0.87, 1.04]
		EBR	50 mg QD	11	1.11 [0.99, 1.26]	1.09 [0.98, 1.21]	0.96 [0.86, 1.08]
Pravastatin	40 mg single dose	GZR	200 mg QD	12	1.42 [1.00, 2.03]	1.24 [1.00, 1.53]	1.07 [0.99, 1.16]
		EBR	50 mg QD	12	0.97 [0.89, 1.05]	0.98 [0.93, 1.02]	0.97 [0.92, 1.02]
Calcium acetate	2668 mg single dose	GZR	100 mg single dose	12 [b)]	0.57 [0.40, 0.83]	0.79 [0.68, 0.91]	0.77 [0.61, 0.99]
		EBR	50 mg single dose	12 [b)]	0.86 [0.71, 1.04]	0.92 [0.75, 1.14]	0.87 [0.70, 1.09]
Sevelamer hydrochloride	2400 mg single dose	GZR	100 mg single dose	12	0.53 [0.37, 0.76]	0.82 [0.68, 0.99][c)]	0.84 [0.71, 0.99]
		EBR	50 mg single dose	12	1.07 [0.88, 1.29]	1.13 [0.94, 1.37][b)]	1.22 [1.02, 1.45]
Dolutegravir	50 mg single dose	GZR	200 mg QD	12	0.64 [0.44, 0.93]	0.81 [0.67, 0.97]	0.86 [0.79, 0.93]
		EBR	50 mg QD	12	0.97 [0.89, 1.05]	0.98 [0.93, 1.04]	0.98 [0.93, 1.03]
Cyclosporine	400 mg single dose	GZR	200 mg QD	14 [d)]	17.0 [12.9, 22.3]	15.2 [12.8, 18.0]	3.39 [2.82, 4.09]
		EBR	50 mg QD	14 [d)]	1.95 [1.84, 2.07]	1.98 [1.84, 2.13]	2.21 [1.98, 2.47]
Tacrolimus	2 mg single dose	GZR	200 mg QD	16	1.07 [0.83, 1.37]	1.12 [0.97, 1.30]	0.94 [0.87, 1.02]
		EBR	50 mg QD	16	0.99 [0.88, 1.10]	0.97 [0.90, 1.06]	0.92 [0.83, 1.02]
Mycophenolate mofetil	1000 mg single dose	GZR	200 mg QD	14	0.58 [0.42, 0.82]	0.74 [0.60, 0.92]	0.97 [0.89, 1.06]
		EBR	50 mg QD	14	1.07 [0.98, 1.16]	1.07 [1.00, 1.14]	1.05 [0.97, 1.14]
Prednisone	40 mg single dose	GZR	200 mg QD	14	1.34 [1.10, 1.62]	1.09 [0.95, 1.25]	0.93 [0.87, 1.00]
		EBR	50 mg QD	14	1.25 [1.16, 1.35]	1.17 [1.11, 1.24]	1.04 [0.97, 1.12]
Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil Fumarate	150/150/200/300 mg QD	GZR	100 mg QD	21	4.59 [3.70, 5.69]	5.36 [4.48, 6.43][e)]	2.78 [2.48, 3.11]
		EBR	50 mg QD	21	1.91 [1.77, 2.05]	2.18 [2.02, 2.35][e)]	2.38 [2.19, 2.60]
Famotidine	20 mg single dose	GZR	100 mg single dose	16 [f)]	0.89 [0.71, 1.11]	1.10 [0.95, 1.28]	1.12 [0.97, 1.30]
		EBR	50 mg single dose	16 [f)]	1.11 [0.98, 1.26]	1.05 [0.92, 1.18]	1.03 [0.91, 1.17]
Pantoprazole	40 mg QD	GZR	100 mg single dose	16 [g)]	1.10 [0.89, 1.37]	1.12 [0.96, 1.30]	1.17 [1.02, 1.34]
		EBR	50 mg single dose	16 [g)]	1.02 [0.92, 1.14]	1.05 [0.93, 1.18]	1.03 [0.92, 1.17]

[a)] AUC_{inf} for single-dose administration; AUC_{0-24} for multiple-dose administration: [b)] with the concomitant drug, N = 11: [c)] with the concomitant drug, N = 10: [d)] with the concomitant drug, N = 13: [e)] with the concomitant drug, N = 20: [f)] with the concomitant drug, N = 14: [g)] with the concomitant drug, N = 12

Table 44. Effect of GZR and EBR on PK parameters of concomitant drugs

Concomitant drug	Dosage regimen			N	Geometric mean ratio [90% CI]		
	Concomitant drug	GZR	EBR		C_{max}	AUC [a]	C_{trough}
Rilpivirine	25 mg QD	200 mg QD	50 mg QD	19	1.07 [0.97, 1.17]	1.13 [1.07, 1.20]	1.16 [1.09, 1.23]
Rosuvastatin	10 mg single dose	200 mg QD	50 mg QD	12 [b]	5.49 [4.29, 7.04]	2.26 [1.89, 2.69][c]	0.98 [084, 1.13]
Pravastatin	40 mg single dose	200 mg QD	50 mg QD	12	1.28 [1.05, 1.55]	1.33 [1.09, 1.64][d]	—
Dolutegravir	50 mg single dose	200 mg QD	50 mg QD	12	1.22 [1.05, 1.40]	1.16 [1.00, 1.34]	1.14 [0.95, 1.36]
Sofosbuvir	Sofosbuvir 400 mg single dose	200 mg QD	50 mg QD	16	2.43 [2.12, 2.79][e]	2.27 [1.72, 2.99]	—
GS-331007		200 mg QD	50 mg QD	16	0.87 [0.78, 0.96]	1.13 [1.05, 1.21]	1.53 [1.43, 1.63]
Cyclosporine	400 mg single dose	200 mg QD	50 mg QD	14[f]	0.90 [0.85, 0.97]	0.96 [0.90, 1.02]	1.00 [0.92, 1.08][g]
Tacrolimus	2 mg single dose	200 mg QD	50 mg QD	16	0.60 [0.52, 0.69]	1.43 [1.24, 1.64]	1.70 [1.49, 1.94][g]
Mycophenolate mofetil	1000 mg single dose	200 mg QD	50 mg QD	14	0.85 [0.67, 1.07]	0.95 [0.87, 1.03]	—
Prednisone	Prednisone 40 mg single dose	200 mg QD	50 mg QD	14	1.05 [1.00, 1.10]	1.08 [1.00, 1.17]	—
Prednisolone		200 mg QD	50 mg QD	14	1.04 [0.99, 1.09]	1.08 [1.01, 1.16]	—
Atorvastatin	10 mg single dose	200 mg QD	50 mg QD	16	4.34 [3.10, 6.07]	1.94 [1.63, 2.33][h]	0.21 [0.17, 0.26]
Tenofovir	Tenofovir Disoproxil Fumarate 300 mg QD	100 mg QD	50 mg QD	13	1.14 [0.95, 1.36]	1.27 [1.20, 1.35][i]	1.23 [1.09, 1.40]
Elvitegravir	Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Disoproxil Fumarate 150/150/200/300 mg QD	100 mg QD	50 mg QD	22[j]	1.02 [0.93, 1.11]	1.10 [1.00, 1.21]	1.31 [1.11, 1.55]
Cobicistat				22[j]	1.39 [1.29, 1.50]	1.49 [1.42, 1.57]	—
Emtricitabine				22[j]	0.96 [0.90, 1.02]	1.07 [1.03, 1.10]	1.19 [1.13, 1.25]
Tenofovir				22[j]	1.25 [1.14, 1.37]	1.18 [1.13, 1.24]	1.20 [1.15, 1.26]

[a] AUC_{inf} for single-dose administration; AUC_{0-24} for multiple-dose administration: [b] with GZR + EBR, N = 11: [c] N = 8:
[d] pravastatin alone, N = 10: [e] sofosbuvir alone, N = 12; with GZR + EBR, N = 14: [f] with GZR + EBR, N = 13: [g] C_{12}: [h] with GZR + EBR, N = 15: [i] with GZR + EBR, N = 12: [j] with GZR + EBR, N = 21

6.2.5 QT/QTc studies

6.2.5.1 GZR QT/QTc study (CTD 5.3.4.1-1, Study MK-5172-049 [December 2013 to February 2014])

A 3-treatment, 3-period crossover study was conducted in non-Japanese healthy subjects (41 in the GZR group, 40 in the placebo group, 40 in the moxifloxacin group) to assess the effects of single oral doses of placebo, GZR 1600 mg, and moxifloxacin 400 mg as a positive control on the QT/QTc interval.[40] The maximum mean difference between moxifloxacin and placebo [90% CI] in change from baseline in QT interval corrected for heart rate using Fridericia's formula (QTcF) was 14.5 [12.5, 16.6] milliseconds at 3 hours post-dose. The maximum mean difference in QTcF change from baseline between GZR and placebo [90% CI] was -0.48 [-2.54, 1.58] milliseconds at 8 hours post-dose. The applicant explained that the upper limit of the 90% confidence interval was <10 milliseconds, indicating no prolongation of QTc interval at doses up to 1600 mg. The C_{max} and AUC_{0-24} after administration of GZR 1600 mg were 14,100 nmol/L and 77,000 nmol·h/L, respectively.

6.2.5.2 EBR QT/QTc study (CTD 5.3.4.1-2, Study MK-8742-015 [October 2013 to February 2014])

A 3-treatment, 3-period crossover study was conducted in non-Japanese healthy subjects (39 in the EBR group, 38 in the moxifloxacin group, 39 in the placebo group) among subjects enrolled in this study to assess the effects of single oral doses of placebo, EBR 700 mg, and moxifloxacin 400 mg as a positive control on the QT/QTc interval.[41] The maximum mean difference between moxifloxacin and placebo [90% CI] in QTcF change from baseline was 8.60 [6.67, 10.5] milliseconds at 3 hours post-dose. The maximum mean difference between EBR and placebo [90% CI] in QTcF change from baseline was 0.86 [-1.06,

[40] There was a washout period of ≥10 days between the periods.
[41] There was a washout period of ≥7 days between the periods.

2.78] milliseconds at 1.5 hours post-dose. The applicant explained that the upper limit of the 90% confidence interval was below 10 milliseconds, indicating no prolongation of QTc interval at doses up to 700 mg. The C_{max} and AUC_{0-24} after administration of EBR 700 mg were 567 nmol/L and 6200 nmol·h/L, respectively.

6.2.6 PPK analyses and exposure-response analyses

6.2.6.1 GZR PPK analyses (Reference data CTD 5.3.3.5-1)

PPK analyses (NONMEM version 7.3) were performed using GZR PK data (2848 subjects, 25,075 sampling points) from healthy subjects or HCV-infected patients in 2 Japanese clinical studies (MK-5172-009 and MK-5172-058) and 19 foreign clinical studies.[42)] The final model was a 2-compartment model with first order elimination, oral absorption described by 2 parallel first order pathways.[43)] The following covariates were selected: age, sex, race (Black, non-Japanese Asian, Japanese, and others), body weight, HCV genotype (genotype 1b, 3, 4, and 6), and compensated cirrhosis on CL/F; sex, race (Black, Asian, and others), body weight, HCV genotype (genotype 6), prior treatment with DAA, compensated cirrhosis, HIV co-infection, and food on apparent central volume of distribution (V_2/F); HCV-infected patients, age, race (Asian), ethnicity (Hispanic), body weight, prior treatment with DAA, concomitant EBR, and dialysis on the rate constant for distribution from the central to peripheral compartment (k_{23}); food on the first order absorption rate constant (k_a); and dose (≤100 mg or >100 mg) on the first order absorption rate constant for the secondary pathway (k_a2).[44)] Japanese and non-Japanese Asian were tested as potential covariates on CL/F and V_2/F separately, and Japanese was selected as a covariate on CL/F. However, the difference in the estimated CL between Japanese and non-Japanese Asians was approximately 11%, indicating that the impact of Japanese on CL/F was similar to that of non-Japanese Asians. Therefore, Asians including Japanese was selected as a covariate on CL/F in the model. The steady-state PK parameters in chronic hepatitis C patients with or without compensated cirrhosis following oral administration of GZR 100 mg QD, predicted by simulations using the final model, are shown in Table 45. The geometric mean C_{max} and AUC in subjects of a Japanese phase II/III study in HCV-infected patients (MK-5172-058), estimated from the PPK model, were 617 nmol/L and 4438 nmol·h/L, respectively.

Table 45. GZR PK parameters at steady-state (predicted by simulations using the final model)

	C_{max} (nmol/L)		AUC_{0-24} (nmol·h/L)		C_{trough} (nmol/L)	
	Compensated cirrhotic chronic	Non-cirrhotic chronic hepatitis	Compensated cirrhotic chronic	Non-cirrhotic chronic hepatitis	Compensated cirrhotic chronic	Non-cirrhotic chronic hepatitis

[42)] Phase I studies (MK-5172-001, MK-5172-004, MK-8742-008, MK-5172-014, MK-5172-040, MK-5172-042, and MK-5172-069) and phase II and III studies (MK-5172-003, MK-5172-035, MK-5172-038, MK-5172-039, MK-5172-047, MK-5172-048, MK-5172-052, MK-5172-059, MK-5172-060, MK-5172-061, MK-5172-068, and MK-5172-074)

[43)] A pathway responsible for the majority of absorption (approximately 64%) that has a food-dependent absorption rate that, for HCV-infected patients, is faster compared to the second pathway, and a secondary pathway with an absorption rate that is slower than the majority pathway, especially for lower doses (≤100 mg).

[44)] In the preceding PPK analyses (CTD 5.3.3.5.3) using GZR PK data (2602 subjects, 23,271 sampling points) from healthy subjects or HCV-infected patients in 21 clinical studies (phase I studies [MK-5172-001, MK-5172-004, MK-5172-009, MK-5172-014, MK-5172-040, MK-5172-042, MK-5172-069, and MK-8742-008], phase II studies [MK-5172-003, MK-5172-035, MK-5172-038, MK-5172-039, MK-5172-047, MK-5172-048, MK-5172-058, MK-5172-059, and MK-5172-074], and phase III studies [MK-5172-052, MK-5172-060, MK-5172-061, and MK-5172-068]), the following factors were tested as potential covariates in the present analyses (For race, additional Japanese and non-Japanese Asian were tested). CL/F: dose, age, sex, race (Black, Asian, and others), ethnicity (Hispanic), body weight, HCV genotype (genotype 6), cirrhosis (decompensated cirrhosis and compensated cirrhosis), and concomitant PegIFN, V_2/F: food, dose, age, sex, race (Black, Asian, and others), body weight, HCV genotype (genotype 6), prior treatment with DAA, cirrhosis (decompensated cirrhosis and compensated cirrhosis), HIV co-infection, and concomitant PegIFN, k_{23}: HCV-infected patients, dose, age, race (Asian), ethnicity (Hispanic), body weight, prior treatment with DAA, concomitant EBR, concomitant RBV, and concomitant PegIFN, the rate constant for distribution from the peripheral to central compartment (k_{32}): dose, k_a: HCV-infected patients, and food effect in healthy subjects and HCV-infected subjects, k_a2: dose

	hepatitis C	C	hepatitis C	C	hepatitis C	C
Japanese	939 [860, 1053]	632 [590, 705]	7004 [6342, 7721]	4537 [4192, 4919]	66.6 [59.3, 74.3]	40.3 [36.3, 44.3]
Non-Japanese	359 [342, 398]	222 [212, 241]	3113 [2914, 3353]	1927 [1804, 2059]	40.5 [36.9, 43.4]	24.6 [22.3, 26.1]

Geometric mean [90% CI]

6.2.6.2 EBR PPK analyses (Reference data CTD 5.3.3.5-2)

PPK analyses (NONMEM version 7.2.0) were performed using EBR PK data (2429 subjects, 19,164 sampling points) from healthy subjects or HCV-infected patients in 2 Japanese clinical studies (MK-5172-058 and MK-7009-050) and 14 foreign clinical studies.[45)] The final model was a 2-compartment model with lagged first order absorption. The following covariates were selected: age, eGFR, sex, race (Black, Asian), and concomitant use of RBV, moderate CYP3A inhibitors, or methadone on CL/F; body weight, sex, and HCV-infected patients on V_2/F; age on k_a; and formulation (100 mg potency capsule) on oral BA (F1).[46)] Japanese and non-Japanese Asian were tested as potential covariates on CL/F and V_2/F separately, and Japanese was selected as a covariate on CL/F. However, there were no marked differences in its impact when Asian race was included as a covariate as compared to when Japanese or other Asians was included as a covariate.[47)] Therefore, Asians including Japanese was selected as a covariate on CL/F in the model. The steady-state PK parameters in chronic hepatitis C patients with or without compensated cirrhosis following oral administration of EBR 50 mg QD, predicted by simulations using the final model, are shown in Table 46. The geometric mean C_{max} and AUC for subjects in a Japanese phase II/III study in HCV-infected patients (MK-5172-058), estimated from the PPK model, were 177 nmol/L and 2775 nmol·h/L, respectively.

Table 46. EBR PK parameters at steady-state (predicted by simulations using the final model)

	C_{max} (nmol/L)		$AUC_{0\text{-}24}$ (nmol·h/L)		C_{trough} (nmol/L)	
	Compensated cirrhotic chronic hepatitis C	Non-cirrhotic chronic hepatitis C	Compensated cirrhotic chronic hepatitis C	Non-cirrhotic chronic hepatitis C	Compensated cirrhotic chronic hepatitis C	Non-cirrhotic chronic hepatitis C
Japanese	164 [160, 174]	168 [165, 179]	2619 [2565, 2793]	2687 [2630, 2850]	68.5 [66.0, 73.0]	70.0 [67.6, 74.3]
Non-Japanese	139 [136, 145]	138 [135, 143]	2244 [2169, 2315]	2206 [2141, 2275]	57.5 [54.8, 59.0]	55.9 [53.3, 57.3]

Geometric mean [90% CI]

6.2.6.3 Exposure-response analyses (Reference data CTD 5.3.5.3-1 to 5.3.5.3-4)

The relationship between $AUC_{0\text{-}24}$ and the sustained viral response 12 (SVR12) rate of GZR and EBR in Japanese HCV-infected patients treated with the Japanese recommended clinical doses of GZR and EBR (GZR 100 mg + EBR 50 mg QD for 12 weeks) was assessed by quartile analysis. There was no apparent correlation between $AUC_{0\text{-}24}$[48)] and the SVR12 rate of the 2 drugs.

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45) Phase I studies (MK-8742-001, MK-8742-002, MK-8742-003, MK-8742-004, and MK-8742-008) and phase II and III studies (MK-5172-035, MK-5172-047, MK-5172-048, MK-5172-052, MK-5172-059, MK-5172-060, MK-5172-061, MK-5172-068, and MK-5172-074)

46) In the preceding PPK analyses (CTD 5.3.3.5.4) using EBR PK data (2167 subjects, 17,042 sampling points) from healthy subjects or HCV-infected patients in 16 clinical studies (phase I studies [MK-7009-050, MK-8742-001, MK-8742-002, MK-8742-003, MK-8742-004, and MK-8742-008] and phase II and III studies [MK-5172-035, MK-5172-047, MK-5172-048, MK-5172-052, MK-5172-058, MK-5172-059, MK-5172-060, MK-5172-061, MK-5172-068, and MK-5172-074]), the following factors were tested as potential covariates in the present analyses (For race, additional Japanese and non-Japanese Asian were tested). CL/F; age, eGFR, sex, race (Black, Asian), ethnicity (Hispanic), prior treatment with PegIFN and RBV, concomitant RBV, concomitant use of moderate CYP3A inhibitors, and concomitant methadone, V_2/F: body weight, sex, and HCV-infected patients, k_a: age, oral BA (F1): formulation (100 mg potency capsule)

47) The values of the objective function calculated for the covariates of Asian; and Japanese or non-Japanese Asian were -14172.5 and -14174.1, respectively.

48) $AUC_{0\text{-}24}$ estimated from the PPK analysis [see Sections 6.2.6.1 and 6.2.6.2]

Since late increases in ALT/AST elevation[49)] were observed in a foreign phase II study in which GZR 100 to 800 mg was co-administered with PegIFN and RBV (MK-5172-003), a logistic regression model was developed using the data from HCV-infected patients in a Japanese phase II/III study (MK-5172-058) and foreign phase II and III studies[50)] to characterize the relationship between the C_{max}, AUC_{0-24}, and C_2 of GZR and late ALT/AST elevations. The C_{max}, AUC_{0-24}, and C_2 of GZR were correlated with the increased incidence of late ALT/AST elevation.

In the Japanese phase II/III study (MK-5172-058), in which GZR 100 mg and EBR 50 mg QD were co-administered, subjects were divided into 4 subgroups by quartile of AUC_{0-24} of GZR and EBR to investigate the relationship between AUC_{0-24} and the safety of GZR and EBR. There were no clear differences in the incidence of adverse events, serious adverse events, deaths, or adverse events leading to discontinuation among these subgroups.

6.2.7 PBPK model analyses (Reference data CTD 5.3.3.3-7, Reference data CTD 5.3.3.3-8)

A GZR PBPK analysis (software, SimCYP version 14) was performed to investigate effects of intrinsic factors on GZR PK and identify factors contributing to PK differences among various populations. Using the data from foreign phase I studies (MK-5172-001 and MK-5172-040) [see Sections 6.2.1.1.2.1 and 6.1.1.1] and non-clinical studies [see Sections 4.2.2, 4.3.2, and 4.5] etc., the GZR model was developed.[51)]

An EBR PBPK model analysis (software, SimCYP version 13) was performed to investigate effects of intrinsic factors on EBR PK and identify factors contributing to PK differences among various populations. Using the data from a foreign phase I study (MK-8742-001) [see Section 6.2.1.2.2.1] and non-clinical studies [see Sections 4.7.2, 4.8.2, and 4.10] etc., the EBR model was developed.[52)]

[49)] An ALT or AST elevation >5-fold the upper limit of normal (ULN) occurring after ≥4 weeks of blinded treatment in subjects who achieved an ALT/AST ≤ the ULN after 2 to 4 weeks of blinded treatment

[50)] Studies MK-5172-003, MK-5172-035, MK-5172-038, MK-5172-039, MK-5172-047 (Parts A and B), MK-5172-048, MK-5172-052, MK-5172-059 (Part A), MK-5172-060, MK-5172-061, MK-5172-068, and MK-5172-074

[51)] A first order absorption model and a full PBPK distribution model that incorporated saturable liver uptake via OATP1B were selected, and a model with biliary excretion and CYP3A-mediated metabolism as the primary elimination pathways was developed. The validity of the model was assessed by comparing the actual C_{max} and AUC values of GZR in clinical interaction studies with ketoconazole, rifampicin, or efavirenz (Studies MK-5172-001 and MK-5172-031) [see Section 6.2.4.2] with the model-predicted values.

[52)] A first order absorption model and a minimal PBPK distribution model with a single adjusting compartment (SAC) were selected, and a model with biliary excretion and CYP3A-mediated metabolism as the primary elimination pathways was developed. The validity of the model was assessed by comparing the actual C_{max} and AUC values of EBR in clinical interaction studies with ketoconazole or efavirenz (Studies MK-8742-003 and MK-8742-016) [see Section 6.2.4.3] with the model-predicted values.

In order to estimate differences in GZR PK among subpopulations (race, age, sex,[53] and HCV-infection[54]) and differences in EBR PK among subpopulations (race, age, and sex[53]), the PK of GZR and EBR PK were simulated using the models. The applicant discusses the effects of intrinsic factors on PK as follows:

(GZR + EBR)

- The simulation suggested higher GZR + EBR exposure in Japanese than in Caucasians. It was considered attributable to lower live weights (Compilation of Anatomical, Physiological and Metabolic Characteristics for a Reference Asian Man. IAEA, 1998), lower of CYP expression (*Xenobiotica*. 2006; 36: 499-513), and lower activity and expression of a transporter (*Clin Pharmacol Ther.* 2013; 94: 37-51), etc. Higher GZR + EBR exposure was suggested in women than in men. It was considered attributable to lower hepatic blood flow (*J Pharmacokinet Pharmacodyn*. 2007; 34: 401-31) and lower liver weights (*Ann ICRP*. 2002; 32: 5-265), etc.

(GZR)

- Higher GZR exposure was suggested in elderly patients than in young patients, which was considered attributable to reduced hepatic blood flow and smaller liver size (*Pharmacol Rev*. 2004 ;56: 163-84) and reduced CYP3A expression (*J Pharmacol Exp Ther*. 2004; 308: 874-9), etc.
- Higher GZR exposure was suggested in HCV-infected patients than in healthy subjects, which was considered attributable to reduced hepatic blood flow (*Clin Pharmacokinet*. 2010; 49: 189-206), decreased functional liver weight (*Nucl Med Commun*. 1991; 12: 507-17), and decreased expression of CYP3A and OATP1B (*Drug Metab Dispos*. 2008; 36 : 1786-93), etc.

(EBR)

- Unlike in a clinical study (MK-8742-004) [see Section 6.2.3.2.2], the simulation suggested higher EBR exposure in elderly patients than in young patients.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in PK of GZR and EBR between Japan and overseas

The applicant's explanation about differences in PK of GZR and EBR between Japanese and non-Japanese subjects:

Using the data from a Japanese phase I study (MK-5172-009) [see Section 6.2.1.1.1] and a foreign phase I study (MK-5172-001) [see Section 6.2.1.1.2.1] in healthy adult subjects, the steady-state GZR PK following multiple-doses of GZR 400 mg QD were compared. In Japanese healthy adult subjects, C_{max} and $AUC_{0\text{-}24}$ were 2.3- and 2.9-fold higher, respectively, than in non-Japanese healthy adult subjects. In the GZR PPK analyses [see Section 6.2.6.1], race was selected as a covariate on CL/F, V_2/F, and the rate constant for distribution from the central to peripheral compartment (k_{23}). AUC in Japanese HCV-infected patients was estimated to be 1.9-fold higher than in Caucasian HCV-infected patients. AUC values in Japanese and non-Japanese non-cirrhotic HCV-infected patients were simulated by incorporating the distributions of the covariates other than race used in a Japanese phase II/III study (MK-5172-058) into the PPK model. The AUC of Japanese non-cirrhotic HCV-infected patients was estimated to be approximately 2-fold higher

[53] The default values in the SimCYP database were used.

[54] It was assumed that HCV infection resulted in 19% decrease in functional liver weight (*Nucl Med Commun.* 1991; 12: 507-17) and approximately 20% decrease in CYP3A expression and 17% decrease in OATP1B expression (*Drug Metab Dispos*. 2008; 36: 1786-93).

than in non-Japanese non-cirrhotic HCV-infected patients.

Using the data from a Japanese phase I study (MK-7009-050) [see Section 6.2.1.2.1] and a foreign phase I study (MK-8742-001) [see Section 6.2.1.2.2.1] in healthy adult subjects, the steady-state EBR PK following multiple doses of EBR 50 mg QD were compared. In Japanese healthy adult subjects, the C_{max} and AUC_{0-24} were 1.7- and 1.4-fold higher, respectively, than in foreign healthy adult subjects. In the EBR PPK analyses [see Section 6.2.6.2], race was selected as a covariate on CL/F. The AUC in Japanese HCV-infected patients was estimated to be 1.1-fold higher than in Caucasian HCV-infected patients. AUC in non-Japanese non-cirrhotic HCV-infected patients was simulated by incorporating the distributions of the covariates other than race used in a Japanese phase II/III study (MK-5172-058) into the PPK model. The AUC in Japanese non-cirrhotic HCV-infected patients was estimated to be 1.1-fold higher than in non-Japanese non-cirrhotic HCV-infected patients.

The factors contributing to differences in PK of GZR and EBR between Japan and overseas are discussed in the PBPK model analyses [see Section 6.2.7].

PMDA confirmed that GZR exposure is higher in Japanese patients and that there are no major differences in EBR exposure between Japanese and non-Japanese patients.

6.R.2 PK in Japanese HCV-infected patients with renal impairment

The applicant's explanation about PK of GZR and EBR in Japanese HCV-infected patients with renal impairment:

In a clinical study in foreign subjects with renal impairment (MK-5172-050), the C_{max} and AUC_{0-24} of GZR and EBR were higher in subjects with severe renal impairment than in those with normal renal function. On the other hand, no differences were observed between ESRD subjects on hemodialysis and subjects with normal renal function, and no effects of dialysis were shown [see Section 6.2.3.3].

In the GZR PPK analyses [see Section 6.2.6.1], eGFR or dialysis was not selected as a covariate for any of the PK parameters. The C_{max} and AUC of GZR in Japanese HCV-infected patients with severe renal impairment were estimated to be 630 nmol/L and 4540 nmol·h/mL, respectively, which were expected to be similar to those in Japanese HCV-infected patients without severe renal impairment.

In the EBR PPK analyses [see Section 6.2.6.2], dialysis was not selected as a covariate for any of the PK parameters and eGFR was selected as a covariate on CL/F. The C_{max} and AUC_{0-24} of EBR at steady-state in Japanese HCV-infected patients with severe renal impairment were estimated to be 230 nmol/L and 3580 nmol·h/mL, respectively, which were 1.33-fold higher than those values (170 nmol/L and 2690 nmol·h/mL, respectively) in Japanese HCV-infected patients without severe renal impairment. However, the increased exposure of EBR is not considered clinically relevant.

The estimated C_{max} and AUC of GZR and EBR in Japanese HCV-infected patients with severe renal impairment were within the range of the steady-state C_{max} and AUC_{0-24} estimates in a Japanese phase II/III study in HCV-infected patients with creatinine clearance ≥50 mL/min (GZR, 150-3630 nmol/L and 1030-

31,600 nmol·h/L, respectively; EBR, 58-420 nmol/L and 770-6970 nmol·h/L, respectively). Based on this and the earlier explanation, changes in GZR and EBR exposures in patients with renal impairment are not clinically relevant also in the Japanese population. No dose adjustment is, therefore, required for Japanese patients with renal impairment.

PMDA considers that the applicant's explanation is acceptable. The efficacy and safety of GZR and EBR in HCV-infected patients with renal impairment are reviewed in Section 7.R.3.

6.R.3 Selection of dosing regimen for Japanese phase II/III study (MK-5172-058)

The applicant's explanation about the dosing rationale for GZR and EBR in Part 1 of a Japanese phase II/III study (MK-5172-058):

For Part 1 of the Japanese phase II/III study (MK-5172-058), the dosing regimens of GZR 50 and 100 mg QD were selected based on the following points.

- In 2 foreign phase II studies in which GZR was co-administered with PegIFN and RBV in HCV-infected patients, a dose-response relationship for the SVR12 rate was observed with GZR 25 to 100 mg QD (MK-5172-038),[55)] and no dose-response relationship in the SVR12 rate was observed across the doses ranging from 100 to 800 mg QD (MK-5172-003). Thus, GZR 50 or 100 mg QD was expected to demonstrate its efficacy.
- Because late ALT/AST elevation[49)] was observed in subjects who received ≥200 mg of GZR in the above-mentioned foreign phase II study (MK-5172-003), GZR 100 mg QD was selected for further evaluation.
- Based on comparison of PK between a Japanese phase I study (MK-5172-009) and a foreign phase I study (MK-5172-001), C_{max} and AUC_{0-24} of GZR were estimated to be 2.3- and 2.9-fold higher in Japanese healthy adult subjects than in non-Japanese healthy adult subjects [see Section 6.R.1], and 50 mg QD was selected for further evaluation as a dose that would provide similar plasma exposure as the 100 mg QD dose in non-Japanese patients.

In Part 1, unblinding occurred when all patients had completed Follow-up Week 4, and safety, tolerability, and efficacy were evaluated. The evaluation revealed no particular safety or tolerability concerns with GZR 50 or 100 mg and no major differences between the GZR 50 and 100 mg groups. There were no differences in the SVR4 rate between the 50 and 100 mg groups, and the proportion of subjects who achieved unquantifiable HCV RNA at Week 2 was approximately 70% in the 100 mg group and approximately 60% in the 50 mg group. Generally, antiviral therapy is performed with the maximum tolerated dose to block the emergence of drug-resistant virus. Therefore, GZR 100 mg QD was selected for Part 2.

[55)] Because GZR 30 mg reduced HCV RNA in a foreign phase I study (MK-5172-004), 25 mg was determined as the lowest dose for a foreign phase II study (MK-5172-038). Since ALT elevation was observed in subjects who received GZR 400 or 800 mg in a foreign phase II study in which GZR was co-administered with PegIFN and RBV (MK-5172-003), 100 mg was determined as the highest dose for the foreign phase II study (MK-5172-038) to provide a safety margin. Doses (10-800 mg) for the foreign phase I study (MK-5172-004) were determined as follows: Based on the preliminary analyses of GZR exposure and HCV RNA reduction, the AUC_{0-24} and C_{trough} that provide a 3 log_{10} IU/mL decline in HCV RNA are 3.2 nmol·h/mL and 28 nmol/L, respectively. Because GZR 400 mg was expected to achieve these levels, the doses from 400 to 800 mg were selected. After that, the dose of 400 mg was found to exceed these levels, and lower doses of 10 to 200 mg were then added.

For Part 1 of the Japanese phase II/III study (MK-5172-058), EBR 50 mg QD was selected based on the following findings. Because Part 1 of the study demonstrated the efficacy of EBR 50 mg QD in combination with GZR, EBR 50 mg QD was selected for Part 2.

- The SVR12 rates with EBR 20 and 50 mg QD were both >95% in Part 1 of a foreign phase II study in HCV-infected patients (MK-5172-035).[56] Meanwhile, based on an *in vitro* study on antiviral activity of EBR [see Section 3.4.2.3.2] and the C_{trough} value at EBR 10 mg (4.08 nmol/L), EBR 50 mg, which provides a C_{trough} value of 34.3 nmol/L, can suppress the emergence of new variants by its activity against many resistant viruses as compared to EBR 20 mg.
- Based on comparison of PK between a Japanese phase I study (MK-7009-050) and a foreign phase I study (MK-8742-001), the C_{max} and AUC_{0-24} of EBR were estimated to be approximately 1.7- and 1.4-fold higher in Japanese healthy adult subjects than in non-Japanese healthy adult subjects [see Section 6.R.1]. The following 2 points indicated that there are no particular safety concerns about EBR 50 mg QD in Japanese HCV-infected patients.
  - Although the steady-state AUC_{0-24} values in foreign phase I studies (the 200 mg group in Study MK-8742-001 and the EBR + atazanavir/ritonavir group in Study MK-8742-017) were 1.6- and 3.1-fold higher, respectively, than the steady-state AUC_{0-24} (2166 nmol·h/L) after multiple-dose administration of EBR 50 mg QD in Japanese healthy subjects in the Japanese phase I study (MK-7009-050), they did not affect safety.
  - Foreign phase I studies (MK-8742-001 and MK-8742-002) indicated no major differences in PK between HCV-infected patients and healthy subjects.

PMDA's view on the dosing regimen for the Japanese phase II/III study (MK-5172-058):
Given that a dose-response relationship for the SVR12 rate was observed at GZR doses of 25 to 100 mg QD and that the efficacy and safety of GZR 100 mg QD were demonstrated in Part 1 of the Japanese phase II/III study (MK-5172-058) [see Section 7.1], the rationale for selecting GZR 100 mg QD for Part 2 is acceptable.

Although there are no clear data from an *in vitro* study on antiviral activity, etc. showing that EBR 50 mg QD may suppress the emergence of new NS5A resistance-associated variants, EBR 50 mg QD is reasonably expected to show activity against more resistant viruses than 20 mg QD does, and the efficacy and safety of EBR 50 mg QD were demonstrated in Part 1 of the Japanese phase II/III study (MK-5172-058) [see Section 7.1]. Therefore, the rationale for selecting EBR 50 mg QD for Part 2 is acceptable.

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

The applicant submitted the results from of 13 studies (1 Japanese and 12 foreign studies) with the application, including efficacy and safety evaluation data from 2 studies and reference data from 11 studies.

[56] EBR 10 and 50 mg both reduced HCV RNA in a short-term regimen in a foreign phase I study (MK-8742-002). Because it was suggested that EBR 50 mg may suppress HCV RNA more sustainably than EBR 10 mg, EBR 20 and 50 mg were selected for Study MK-5172-035. The rationale for dose selection (5-100 mg) for the foreign phase I study (MK-8742-002) was as follows: According to a result from a non-clinical study on the anti-HCV activity of EBR, etc., sufficient activity is maintained at the C_{trough} of 3 nmol/L, and the required dose of EBR was estimated to be 6 mg. However, because of the low BA of EBR indicated in non-clinical studies, and a higher dose was considered necessary against mutant viruses, and the 10 mg dose was chosen. Other doses were selected to determine the dose-response relationship.

An overview of the main clinical studies is presented in Table 47.

Table 47. Overview of main clinical studies

	Phase	Study Number	Study population	Primary objectives	N	Dosing regimen
Evaluation data						
Japan	II/III	MK-5172-058	HCV genotype 1 chronic hepatitis C patients with or without compensated cirrhosis (treatment-naive or treatment-experienced)	PK Efficacy Safety	399	Part 1, GZR 50 mg + EBR 50 mg or GZR 100 mg + EBR 50 mg QD for 12 weeks Part 2, GZR 100 mg + EBR 50 mg or placebo QD for 12 weeks
Foreign	II/III	MK-5172-052	HCV genotype 1 with severe renal impairment chronic hepatitis C patients with or without compensated cirrhosis (treatment-naive or treatment-experienced)	PK Efficacy Safety	237	Blinded Part, GZR 100 mg + EBR 50 mg or placebo QD for 12 weeks Open-label (intensive PK) Part, GZR 100 mg + EBR 50 mg QD for 2 weeks
Reference data						
Foreign	III	MK-5172-060	HCV genotype 1, 4, 6 chronic hepatitis C patients with or without compensated cirrhosis (treatment-naive)	PK Efficacy Safety	421	GZR + EBR fixed-dose combination tablet (100 + 50 mg) or placebo QD for 12 weeks
	III	MK-5172-068	HCV genotype 1, 4, 6 chronic hepatitis C patients with or without compensated cirrhosis (treatment-experienced)	PK Efficacy Safety	420	GZR + EBR fixed-dose combination tablet (100 + 50 mg) with or without RBV QD for 12 or 16 weeks

7.1 Japanese phase II/III study (CTD 5.3.5.1-1, Study MK-5172-058 [Ongoing since August 2014]) (December 2015 Data Cutoff)

A Japanese phase II/III study (MK-5172-058) consisted of Part 1 (to study the efficacy and safety of GZR 50 or 100 mg plus EBR 50 mg administered for 12 weeks) and Part 2 (to study the efficacy and safety of GZR at the dose selected based on Part 1 data plus EBR 50 mg administered for 12 weeks).

(Part 1)

A randomized, double-blind, parallel-group study was conducted in non-cirrhotic patients with chronic hepatitis C (genotype 1) (target sample size, 60 subjects) at 19 sites in Japan.

GZR 50 or 100 mg + EBR 50 mg QD were administered orally for 12 weeks (Figure 3).

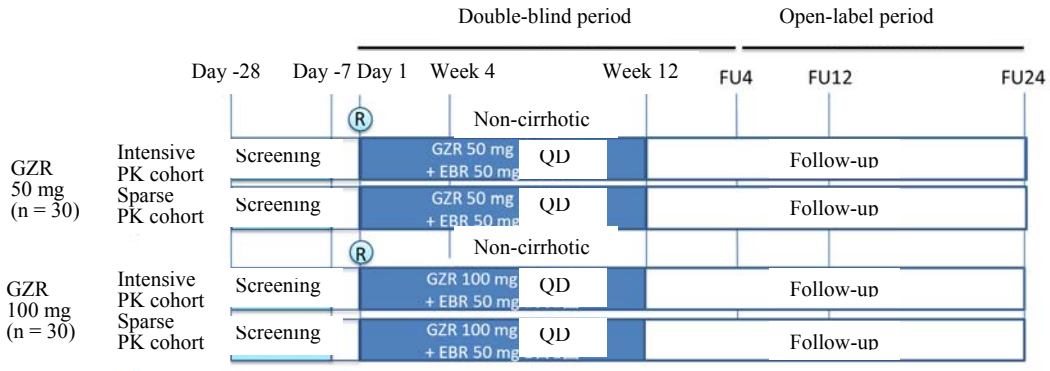

Figure 3. Study design (Part 1)

Of 63 randomized subjects, 62 subjects who received ≥1 dose of study drug (31 each in the GZR 50 mg + EBR 50 mg group and the GZR 100 mg + EBR 50 mg group) were included in the full analysis set (FAS) and in the safety and efficacy analysis populations.

The SVR12 rates[57] [95% CI] in the GZR 50mg + EBR 50 mg and GZR 100 mg + EBR 50 mg groups were 100% [88.8, 100] (31 of 31 subjects) and 96.8% [83.3, 99.9] (30 of 31 subjects), respectively.

The safety analysis revealed that the incidences of adverse events (including abnormal laboratory changes) during treatment and the first 4 follow-up weeks were 67.7% (21 of 31 subjects) in the GZR 50 mg + EBR 50 mg group and 74.2% (23 of 31 subjects) in the GZR 100 mg + EBR 50 mg group. The incidences of adverse drug reactions (including abnormal laboratory changes)[58] were 32.3% (10 of 31 subjects) in the GZR 50 mg + EBR 50 mg group and 29.0% (9 of 31 subjects) in the GZR100 mg + EBR 50 mg group. Adverse events or adverse drug reactions with an incidence of ≥5% in either group are in Table 48.

Table 48. Adverse events or adverse drug reactions with an incidence of ≥5% in either group (Part 1, Safety analysis population)

Event term	Adverse events		Adverse drug reactions	
	GZR50 mg + EBR 50 mg	GZR 100 mg + EBR 50 mg	GZR 50 mg + EBR 50 mg	GZR 100 mg + EBR 50 mg
N	31	31	31	31
All events	21 (67.7)	23 (74.2)	10 (32.3)	9 (29.0)
Nasopharyngitis	7 (22.6)	10 (32.3)	0	1 (3.2)
Headache	4 (12.9)	3 (9.7)	4 (12.9)	3 (9.7)
Pyrexia	3 (9.7)	1 (3.2)	1 (3.2)	0
Dry eye	2 (6.5)	0	0	0
Abdominal pain upper	2 (6.5)	1 (3.2)	1 (3.2)	0
Diarrhoea	2 (6.5)	1 (3.2)	0	1 (3.2)
Accidental overdose	1 (3.2)	2 (6.5)	0	0

N (%)

No deaths or adverse events leading to discontinuation were reported. Serious adverse events occurred in 1 subject (acute coronary syndrome) in the GZR 50 mg + EBR 50 mg group and 1 subject (haematochezia and large intestine polyp [the subject had ≥ 1 event]) in the GZR 100 mg + EBR 50 mg group. Their causal relationship to study drug was ruled out and their outcomes were "resolved."

(Part 2)

A placebo-controlled, randomized, double-blind, parallel-group study (non-cirrhotic patients only) and an open-label, uncontrolled study (compensated cirrhotic patients only)[59] were conducted in chronic hepatitis C patients with or without compensated cirrhosis[60] (genotype 1)[61] (target sample size, 270 subjects) at 50 sites in Japan.

[57] Proportion of subjects with undetectable HCV RNA at 12 weeks after the end of study treatment. Since a concordance between SVR12 rate and SVR rate at 24 weeks post-treatment follow-up (SVR24 rate) has been reported (*Hepatology*. 2010; 51: 1122-6), SVR12 rate was chosen as the primary endpoint.

[58] An event assessed by the investigator (sub-investigator) as causally "related" to study drug

[59] Non-cirrhotic patients were stratified by age and prior treatment response.

[60] Cirrhotic patients who met any of the following criteria were enrolled [(1) and (2) prevailed over (3)]. However, patients with decompensated cirrhosis manifested by the signs and symptoms or history of ascites, gastric or esophageal variceal bleeding, hepatic encephalopathy, etc. were excluded. Cirrhotic patients with Child-Pugh B or C, or a Child-Pugh-Turcotte score >6 were excluded.

(a) Liver biopsy prior to the start of study treatment showing cirrhosis (F4).

(b) The result of calculation of the following "discriminant function for differentiating cirrhosis from chronic hepatitis" >0 at screening.
Discriminant function, 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

(c) Fibroscan result >12.5 kPa within 12 months prior to the start of study treatment

[61] Subjects with creatinine clearance <50 mL/min were excluded.

GZR 100 mg + EBR 50 mg[62] or placebo QD for non-cirrhotic patients and GZR 100 mg + EBR 50 mg QD for compensated cirrhotic patients were administered orally for 12 weeks (Figure 4). Subjects who completed 12 weeks of placebo treatment received oral GZR 100 mg + EBR 50 mg QD for 12 weeks after 4 weeks of follow-up.

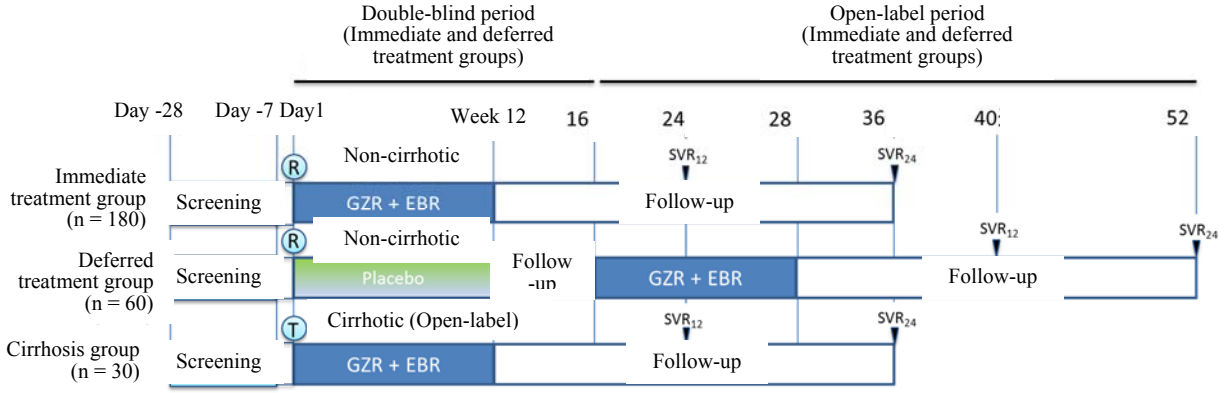

Figure 4. Study design (Part 2)

A total of 301 non-cirrhotic patients with chronic hepatitis C who were randomized and received ≥1 dose of study drug (198 treatment-naïve patients[63] [149 in the GZR 100 mg + EBR 50 mg group, 49 in the placebo group], 103 IFN-experienced patients[64] [78 in the GZR 100 mg + EBR 50 mg group, 25 in the placebo group]) were included in the FAS and in the safety and efficacy analysis populations. A total of 35 compensated cirrhotic patients with chronic hepatitis C who received open-label study treatment (20 treatment-naïve patients, 15 IFN-experienced patients) were included in the FAS and in the safety and efficacy analysis populations.

The primary endpoint of the SVR12 rate [95% CI] in treatment-naïve non-cirrhotic patients with chronic hepatitis C in the GZR 100 mg + EBR 50 mg group was 96.6% [92.3, 98.9] (144 of 149 subjects). The lower bound of the 95% confidence interval exceeded the pre-specified reference SVR12 rate (75%[65]), demonstrating the efficacy of GZR 100 mg + EBR 50 mg. The SVR12 rate [95% CI] in IFN-experienced non-cirrhotic patients with chronic hepatitis C in the group was 96.2% [89.2, 99.2] (75 of 78 subjects). The SVR12 rates [95% CI] with GZR 100 mg + EBR 50 mg in treatment-naïve and IFN-experienced compensated cirrhotic patients with chronic hepatitis C were 100% [83.2, 100] (20 of 20 subjects) and 93.3% [68.1, 99.8] (14 of 15 subjects), respectively. The SVR12 rates in treatment-naïve and IFN-experienced non-cirrhotic patients with chronic hepatitis C who received open-label GZR 100 mg + EBR 50 mg after placebo treatment were 93.9% (46 of 49 subjects) and 100% (24 of 24 subjects), respectively.

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[62] In Part 1, unblinding occurred after all patients completed Follow-up Week 4 and safety, tolerability, and efficacy were evaluated, and the 100 mg dose of GZR was chosen for Part 2.

[63] Patients naïve to IFN-based therapy or DAA therapy, regardless of IFN eligibility.

[64] IFN-experienced patients who met any of the following criteria.

- Intolerance, patients who were intolerant to IFN and discontinued IFN.
- Relapse, patients who had detectable HCV RNA during the follow-up period after becoming undetectable at the end of treatment with IFN (relapse) or patients who had detectable HCV RNA during treatment after being undetectable while on treatment (breakthrough).
- Non-response, patients without undetectable HCV RNA on treatment with IFN, including patients who had ≥2 $\log_{10}$ IU/mL decrease in HCV RNA by Week 12 of blinded period (partial response) and patients who had <2 $\log_{10}$ IU/mL decrease in HCV RNA by Week 12 of blinded period (null response).

[65] Based on the SVR24 rate of 73% with a triple regimen of PegIFN/RBV and NS3/4A protease inhibitor, i.e. the standard of care treatment at the time of planning this study, in a Japanese clinical study (*J Hepatol*. 2012; 56: 78-84).

The safety analysis revealed that the incidences of adverse events (including abnormal laboratory changes) in non-cirrhotic patients with chronic hepatitis C during treatment and the first 4 follow-up weeks were 64.8% (147 of 227 subjects) in the GZR 100 mg + EBR 50 mg group and 67.6% (50 of 74 subjects) in the placebo group. Adverse events occurred in 80.0% (28 of 35) of compensated cirrhotic patients with chronic hepatitis C. The incidences of adverse drug reactions (including abnormal laboratory changes) were 25.6% (58 of 227 subjects) in the GZR 100 mg + EBR 50 mg group and 18.9% (14 of 74 subjects) in the placebo group of non-cirrhotic patients with chronic hepatitis C and 37.1% (13 of 35 subjects) in compensated cirrhotic patients with chronic hepatitis C. Adverse events or adverse drug reactions with an incidence of ≥5% in any group are shown in Table 49.

Table 49. Adverse events or adverse drug reactions with an incidence of ≥5% in any group (Part 2, Safety analysis population)

Event term	Adverse events			Adverse drug reactions		
	Non-cirrhotics		Cirrhotics	Non-cirrhotics		Cirrhotics
	GZR 100 mg + EBR 50 mg	Placebo	GZR 100 mg + EBR 50 mg	GZR 100 mg + EBR 50 mg	Placebo	GZR 100 mg + EBR 50 mg
N	227	74	35	227	74	35
All events	147 (64.8)	50 (67.6)	28 (80.0)	58 (25.6)	14 (18.9)	13 (37.1)
Nasopharyngitis	34 (15.0)	12 (16.2)	5 (14.3)	2 (0.9)	1 (1.4)	0
ALT increased	13 (5.7)	1 (1.4)	5 (14.3)	12 (5.3)	1 (1.4)	5 (14.3)
AST increased	11 (4.8)	2 (2.7)	5 (14.3)	9 (4.0)	2 (2.7)	5 (14.3)
Diarrhoea	11 (4.8)	2 (2.7)	3 (8.6)	2 (0.9)	1 (1.4)	3 (8.6)
Headache	10 (4.4)	1 (1.4)	2 (5.7)	3 (1.3)	0	1 (2.9)
Rash	9 (4.0)	1 (1.4)	3 (8.6)	5 (2.2)	0	0
Constipation	8 (3.5)	3 (4.1)	3 (8.6)	2 (0.9)	1 (1.4)	2 (5.7)
Malaise	7 (3.1)	3 (4.1)	2 (5.7)	4 (1.8)	3 (4.1)	2 (5.7)
Blood creatine phosphokinase increased	6 (2.6)	4 (5.4)	1 (2.9)	1 (0.4)	1 (1.4)	0
Anaemia	1 (0.4)	0	2 (5.7)	1 (0.4)	0	1 (2.9)

N (%)

In the GZR 100 mg + EBR 50 mg group, 1 non-cirrhotic patient with chronic hepatitis C died during the follow-up period.[66] A causal relationship to the study drug was ruled out for the death.

Serious adverse events occurred in 11 non-cirrhotic patients with chronic hepatitis C receiving GZR 100 mg + EBR 50 mg (cataract in 2 subjects; cardiac sarcoidosis, haemorrhagic erosive gastritis, inguinal hernia, large intestine polyp, ALT increased, AST increased, arthritis, benign anorectal neoplasm, renal cell carcinoma, cerebral infarction, and sciatica in 1 subject each [some subjects had ≥1 event]) and 1 non-cirrhotic patient receiving placebo (hepatocellular carcinoma in 1 subject). Those events reported by 2 non-cirrhotic patients receiving GZR 100 mg + EBR 50 mg (cerebral infarction, ALT increased, and AST increased in 1 subject each [1 subject had ≥1 event]) were assessed as causally related to the study drug. Sciatica and cerebral infarction remained unresolved, and all other events resolved.

Adverse events leading to discontinuation occurred in 3 non-cirrhotic patients receiving GZR 100 mg + EBR 50 mg (cardiac sarcoidosis, cerebral infarction, ALT increased, and AST increased in 1 subject each [1 subject had ≥1 event]) and 1 non-cirrhotic patient receiving placebo (hepatocellular carcinoma). Those events reported by 2 non-cirrhotic patients receiving GZR 100 mg + EBR 50 mg (cerebral infarction,

[66] A 77-year-old woman. The patient did not visit at follow-up week 12 and it was found that she had died 77 days after the end of treatment. The cause of death was unknown, and there were no adverse events or laboratory or ECG abnormalities during treatment and the first 4 follow-up weeks.

ALT increased, and AST increased in 1 subject each [1 subject had ≥1 event]) were assessed as causally related to the study drug. Cerebral infarction remained unresolved, and all other events resolved.

The incidences of adverse events (including abnormal laboratory changes) and adverse drug reactions (including abnormal laboratory changes) in subjects who received open-label GZR 100 mg + EBR 50 mg were 65.8% (48 of 73) and 26.0% (19 of 73), respectively. Adverse events or adverse drug reactions reported by ≥5% of subjects are shown in Table 50.

Table 50. Adverse events or adverse drug reactions reported by ≥5% of subjects who received open-label GZR + EBR combination regimen

Event term	Adverse events	Adverse drug reactions
N	73	73
All events	48 (65.8)	19 (26.0)
Nasopharyngitis	13 (17.8)	0
Constipation	4 (5.5)	0
Diarrhoea	4 (5.5)	3 (4.1)
Malaise	4 (5.5)	4 (5.5)

N (%)

No deaths or adverse events leading to discontinuation were reported. A serious adverse event occurred in 1 subject (colitis ischaemic). A causal relationship with the study drug was ruled out for the event, and its outcome was "resolved."

7.2 Foreign phase II/III study (CTD 5.3.5.1-3, Study MK-5172-052 [Ongoing since March 2014]) (March 2015 Data Cutoff)

An open-label, uncontrolled study (intensive PK cohort) and a placebo-controlled, randomized, double-blind, parallel-group study were conducted at 79 sites overseas including the US, Canada, and Israel to investigate the efficacy and safety of the GZR + EBR combination regimen in non-Japanese non-cirrhotic or compensated cirrhotic [67)] patients with chronic hepatitis C and severe renal impairment[68)] (genotype 1) (target sample size, 220 subjects).

Subjects in the intensive PK cohort and subjects in the GZR 100 mg + EBR 50 mg group received oral GZR 100 mg + EBR 50 mg QD for 12 weeks, and subjects in the placebo group received placebo QD orally for 12 weeks (Figure 5). Subjects in the placebo group who had completed 12 weeks of placebo treatment received oral GZR 100 mg + EBR 50 mg QD for 12 weeks after 4 weeks of follow-up.

67) Cirrhotic patients were enrolled if any of the following was met. However, patients with decompensated cirrhosis manifested by the presence or history of ascites, gastric or esophageal variceal bleeding, hepatic encephalopathy, or other signs or symptoms of advanced liver disease were excluded.
(a) Liver biopsy prior to the start of study treatment showing cirrhosis (F4)
(b) Fibroscan result >12.5 kPa within 12 months prior to the start of study treatment
(c) FibroTest score of >0.75 and AST to platelet ratio index (APRI) of >2 at screening

68) CKD stage 4 (eGFR, ≥15 mL/min/1.73 m^2 and <30 mL/min/1.73 m^2) or stage 5 (eGFR <15 mL/min/1.73 m^2) non-dialysis patients or CKD stage 4 or 5 patients on dialysis for ≥3 months (including patients listed for kidney transplant and patients not on immunosuppressant therapy after unsuccessful kidney transplant).

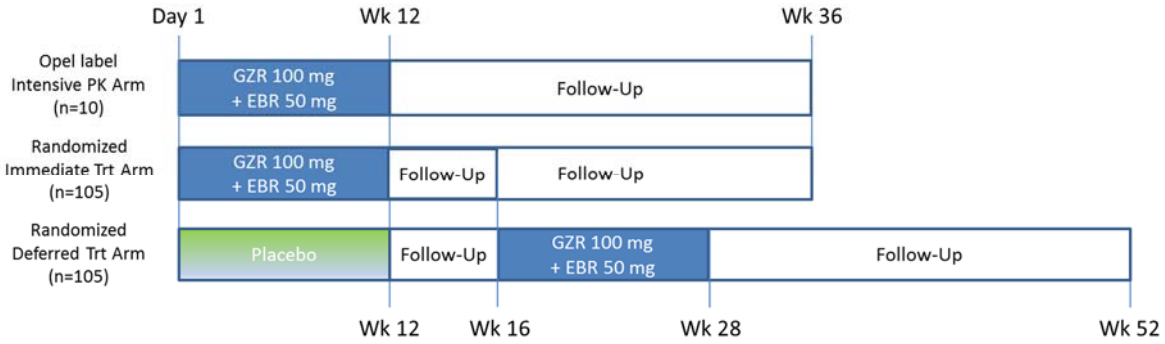

Figure 5. Study design

The FAS and the safety analysis population included 11 subjects who received the study drug in the intensive PK cohort (10 treatment-naïve subjects, 1 IFN-experienced subject) and 224 subjects who received ≥1 dose of study drug out of 226 patients randomized to the GZR 100 mg + EBR 50 mg or placebo group (179 treatment-naïve[63)] subjects [91 in the GZR 100 mg + EBR 50 mg group and 88 in the placebo group], 45 IFN-experienced[69)] subjects [20 in the GZR 100 mg + EBR 50 mg group and 25 in the placebo group]). Other than the placebo group patients and 6 patients with missing HCV RNA data,[70)] 116 patients were included in the Modified full analysis set (mFAS) for efficacy analyses.

The primary endpoint of the SVR12 rate[71)] [95% CI] with GZR 100 mg + EBR 50 mg in treatment-naïve or IFN-experienced chronic hepatitis C patients with or without compensated cirrhosis (11 in the intensive PK cohort plus 105 in the GZR 100 mg + EBR 50 mg group) was 99.1% [95.3, 100] (115 of 116 subjects).

The incidences of adverse events (including abnormal laboratory changes) during treatment and the first 14 follow-up days were 81.8% (9 of 11 subjects) in the intensive PK cohort, 75.7% (84 of 111 subjects) in the GZR 100 mg + EBR 50 mg group, and 84.1% (95 of 113 subjects) in the placebo group. The incidences of adverse drug reactions were 36.4% (4 of 11 subjects) in the intensive PK cohort, 34.2% (38 of 111 subjects) in the GZR 100 mg + EBR 50 mg group, and 34.5% (39 of 113 subjects) in the placebo group. Adverse events or adverse drug reactions with an incidence of ≥10% in any group are shown in Table 51.

[69)] IFN-experienced patients who met any of the following criteria.
- Intolerance: Patients who were intolerant to IFN and discontinued IFN.
- Relapse: Patients who had quantifiable HCV RNA during the follow-up period after becoming undetectable at the end of treatment with IFN.
- Partial response: Patients who had HCV RNA ≥LLOQ at the end of treatment with IFN after having >2 $\log_{10}$ IU/mL decrease in HCV RNA at Week 12.
- Null response: Patients who had <2 $\log_{10}$ IU/mL decrease in HCV RNA following 12 weeks of treatment with IFN or <1 $\log_{10}$ IU/mL decrease in HCV RNA at Week 4.

[70)] Patients with missing HCV RNA data due to the following were excluded.
- Death for reasons unrelated to study drug or reasons other than liver disease
- Discontinuation for reasons other than response to HCV treatment, progression of liver disease, or study drug.

[71)] Proportion of subjects with HCV RNA <LLOQ at 12 weeks after the end of study treatment

Table 51. Adverse events or adverse drug reactions with an incidence of ≥10% in any group

Event term	Adverse events			Adverse drug reactions		
	Intensive PK	GZR 100 mg + EBR 50 mg	Placebo	Intensive PK	GZR 100 mg + EBR 50 mg	Placebo
N	11	111	113	11	111	113
All events	9 (81.8)	84 (75.7)	95 (84.1)	4 (36.4)	38 (34.2)	39 (34.5)
Headache	4 (36.4)	19 (17.1)	19 (16.8)	1 (9.1)	13 (11.7)	6 (5.3)
Insomnia	3 (27.3)	7 (6.3)	12 (10.6)	1 (9.1)	4 (3.6)	6 (5.3)
Fatigue	2 (18.2)	11 (9.9)	17 (15.0)	0	6 (5.4)	9 (8.0)
Dizziness	2 (18.2)	6 (5.4)	18 (15.9)	1 (9.1)	3 (2.7)	4 (3.5)
Diarrhoea	1 (9.1)	6 (5.4)	15 (13.3)	0	2 (1.8)	6 (5.3)
Nausea	1 (9.1)	17 (15.3)	18 (15.9)	0	14 (12.6)	9 (8.0)

N (%)

There were 1 death (cardiac arrest) in the GZR 100 mg + EBR 50 mg group and 4 deaths (death, haemorrhagic shock, aortic aneurysm, and pneumonia, 1 case each) in the placebo group, and a causal relationship to the study drug was ruled out for all cases.

During treatment and the first 14 follow-up days, serious adverse events occurred in 16 subjects in the GZR 100 mg + EBR 50 mg group (pneumonia and hypertension [2 subjects each]; cardiac arrest, myocardial infarction, diarrhoea, pancreatitis, abscess limb, appendicitis, Citrobacter sepsis, Enterobacter sepsis, osteomyelitis, dialysis related complication, procedural pain, dehydration, fluid overload, intervertebral disc protrusion, prostate cancer, presyncope, acute respiratory failure, pleural effusion, extremity necrosis, and hypertensive crisis [1 subject each, some subjects had ≥1 event]) and 19 subjects in the placebo group (upper gastrointestinal haemorrhage and aortic aneurysm [2 subjects each]; acute myocardial infarction, angina unstable, atrial fibrillation, cardiomyopathy, myocardial infarction, gastritis, localised intraabdominal fluid collection, death, haematoma infection, infected fistula, pneumonia, arteriovenous fistula aneurysm, postoperative fever, blood ALP increased, lipase increased, fluid overload, hyperglycaemia, hyperkalaemia, myositis, depressed level of consciousness, dizziness, headache, cardiac failure chronic, pleural effusion, hypertension, orthostatic hypotension, and peripheral venous disease, [1 subject each, some subjects had ≥1 event]). Of these, 1 event occurred in 1 subject in the placebo group (lipase increased) was assessed as causally related to the study drug. Except for 1 death (cardiac arrest [1 subject]) and of abscess limb (1 subject) in the GZR 100 mg + EBR 50 mg group and 4 deaths (death, haemorrhagic shock, aortic aneurysm, and pneumonia, [1 subject each]), blood ALP increased, and headache (1 subject each) in the placebo group, all other events resolved or were resolving.[72)]

Adverse events leading to discontinuation occurred in 5 subjects in the placebo group (ALT increased, AST increased, acute myocardial infarction, abdominal pain, atrial fibrillation, myocardial infarction, and lipase increased, [1 subject each, some subjects had ≥1 event]). All events except for acute myocardial infarction, atrial fibrillation, and myocardial infarction were assessed as causally related to study drug. All events were resolved or resolving.

[72)] Congestive heart failure (a serious adverse drug reaction) occurred in the GZR 100 mg + EBR 50 mg group after >14 follow-up days, but resolved approximately 4.5 months after its onset.

7.R Outline of the review by PMDA

7.R.1 Efficacy

Based on the following considerations, PMDA concluded that the GZR + EBR combination regimen is expected to have efficacy in Japanese chronic hepatitis C patients with or without compensated cirrhosis (genotype 1).

However, because of limited clinical study data on the association between the presence or absence of resistance-associated variants and the efficacy of the combination regimen, post-marketing data including the published literature on the above-mentioned association, the emergence of resistance-associated variants in patients who did not achieve SVR with the combination regimen, etc. should be collected and obtained findings should be promptly communicated to healthcare professionals.

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

7.R.1.1 Efficacy

The applicant's explanation about the efficacy of the GZR + EBR combination regimen in Japanese chronic hepatitis C patients with or without compensated cirrhosis (genotype 1):

In Part 2 of a Japanese phase II/III study (MK-5172-058), the primary endpoint of the SVR12 rate in treatment-naïve non-cirrhotic patients with chronic hepatitis C in the GZR + EBR group [95% CI] was 96.6% [92.3, 98.9] (144 of 149), and the lower bound of the 95% confidence interval exceeded the pre-specified reference SVR12 rate (75%) [see Section 7.1]. The results of subgroup analyses of subjects in the GZR + EBR group are shown in Table 52. The efficacy of GZR + EBR was demonstrated. In Part 2, the SVR24 rates in treatment-naïve and IFN-experienced non-cirrhotic patients with chronic hepatitis C receiving GZR + EBR were 96.6% (144 of 149) and 96.2% (75 of 78), respectively, which were similar to the SVR12 rates. The SVR24 rates with GZR + EBR in treatment-naïve and IFN-experienced compensated cirrhotic patients with chronic hepatitis C were 100% (20 of 20) and 86.7% (13 of 15), respectively, which were similar to the SVR12 rates.

Based on the above, the GZR + EBR combination regimen is expected to have efficacy in Japanese chronic hepatitis C patients with or without compensated cirrhosis (genotype 1).

Table 52. SVR12 rate in Part 2 of Japanese phase II/III study (MK-5172-058) (FAS, subgroup analyses)

Patient characteristics		GZR + EBR	
		Treatment-naïve (N = 169)	Treatment-experienced (N = 93)
Overall		164/169 (97.0)	89/93 (95.7)
Genotype	1a	2/2 (100)	3/3 (100)
	1b	162/167 (97.0)	86/90 (95.6)
Degree of liver fibrosis	Non-cirrhotic chronic hepatitis C	144/149 (96.6)	75/78 (96.2)
	Compensated cirrhotic chronic hepatitis C	20/20 (100)	14/15 (93.3)
Age	<65 years	97/98 (99.0)	41/41 (100)
	≥65 years	67/71 (94.4)	48/52 (92.3)
IFN eligibility	Eligible	141/145 (97.2)	—
	Ineligible	23/24 (95.8)	—
Response to prior treatment	Non-response	—	31/33 (93.9)
	Relapse	—	46/46 (100)
	IFN-intolerant	—	12/14 (85.7)
HCV RNA	<100,000 IU/mL	4/4 (100)	—
	≥100,000 IU/mL	160/165 (97.0)	89/93 (95.7)
IL28B polymorphism rs12979860	CC	110/114 (96.5)	38/39 (97.4)
	Non CC	54/55 (98.2)	51/54 (94.4)

n/N (%); —, not applicable

PMDA's view:

In Part 2 of the Japanese phase II/III study (MK-5172-058), the lower bound of the 95% confidence interval for the SVR12 rate was higher than the pre-specified reference SVR12 rate in treatment-naïve non-cirrhotic patients with chronic hepatitis C receiving GZR + EBR. In addition, the SVR12 rates in IFN-experienced non-cirrhotic patients and treatment-naïve and IFN-experienced compensated cirrhotic patients were 96.2% (75 of 78), 100% (20 of 20), and 93.3% (14 of 15), respectively. Accordingly, the GZR + EBR combination regimen is expected to have efficacy in Japanese treatment-naïve or IFN-experienced chronic hepatitis C patients with or without compensated cirrhosis (genotype 1).

7.R.1.2 Viral resistance mutations

The applicant's explanation about the emergence of virus resistant to the GZR + EBR combination regimen and the effects of resistant virus on the efficacy of the combination regimen:

Table 53 shows the SVR12 rates in subjects with or without baseline NS3[73)] or NS5A[74)] resistance-associated polymorphisms in the resistance analysis population[75)] of a Japanese phase II/III study (MK-5172-058). The SVR12 rates were almost comparable between subjects with and without baseline polymorphisms at NS3 or NS5A resistance-associated amino acid positions.

[73)] Samples were analyzed for resistance-associated substitutions conferring a reduced susceptibility observed in GZR *in vitro* studies [see Section 3.1.3] and with the administration of other NS3/4A protease inhibitors (Sovriad Capsules 100 mg package insert, 7th edition, Vanihep Capsules 150 mg package insert, 5th edition, etc.), namely, V36A/G/L/M/I, T54A/C/G/S, V55A/I, Y56H, Q80K/R, V107I, 122A/G/R, I132V, R155X, A156S/T/V/F/G, V158I, D168X, I/V170A/F/T/V, and M175L (X denotes any amino acid substitution at the relevant position).

[74)] Samples were analyzed for resistance-associated substitutions conferring a reduced susceptibility observed in EBR *in vitro* studies [see Section 3.4.2] and with the administration of other NS5A inhibitors (Daklinza Tablets 60 mg package insert, 10th edition, Harvoni Combination Tablets package insert, second edition, etc.), namely, M28T/V/A/G, Q30E/H/R/G/K/L/D, L31M/V/F, H58D, and Y93C/H/N/S (genotype 1a patients), and L28T/V/A, R30E/H/G/K/L/D, L31M/V/F, P58D, and Y93C/H/N/S (genotype 1b patients).

[75)] The resistance analysis population include patients in both groups in Part 1 and patients treated with the GZR + EBR combination regimen and compensated cirrhotic patients in Part 2 who achieved SVR12 or met the criteria for virologic failure. The resistance analysis population does not include any patient who discontinued treatment for reasons other than virologic failure. Viral genetic analyses were performed using population sequencing, and resistant virus representing ≥25% of the viral population was identified.

Table 53. SVR12 rates in subjects with or without baseline NS3 or NS5A resistance-associated polymorphisms in Japanese phase II/III study (MK-5172-058)

	Polymorphism	Non-cirrhotic chronic hepatitis C						Compensated cirrhotic chronic hepatitis C	
		Part 1				Part 2		Part 2	
		GZR 50 mg + EBR 50 mg		GZR 100 mg + EBR 50 mg		GZR 100 mg + EBR 50 mg		GZR 100 mg + EBR 50 mg	
		With polymorphism	Without polymorphism	With polymorphism	Without polymorphism	With polymorphism	Without polymorphism	With polymorphism	Without polymorphism
NS3									
Genotype 1a	Q80K	—	—	—	—	100 (2/2)	100 (2/2)	—	100 (1/1)
Genotype 1b	V36L	—	100 (31/31)	—	96.8 (30/31)	100 (1/1)	97.7 (214/219)	—	97.1 (33/34)
	T54S	100 (2/2)	100 (29/29)	100 (2/2)	96.6 (28/29)	100 (8/8)	97.6 (207/212)	100 (1/1)	97.0 (32/33)
	V55A	—	100 (31/31)	—	96.8 (30/31)	100 (1/1)	97.7 (214/219)	—	97.1 (33/34)
	Q80K	—	100 (31/31)	—	96.8 (30/31)	100 (2/2)	97.7 (213/218)	—	97.1 (33/34)
	V107I	100 (1/1)	100 (30/30)	100 (1/1)	96.7 (29/30)	—	97.7 (215/220)	—	97.1 (33/34)
	S122A/G/T	100 (7/7)	100 (24/24)	100 (7/7)	95.8 (23/24)	100 (49/49)	97.1 (166/171)	100 (9/9)	96.0 (24/25)
	V158I	—	100 (31/31)	—	96.8 (30/31)	100 (1/1)	97.7 (214/219)	—	97.1 (33/34)
	D168E	—	100 (31/31)	—	96.8 (30/31)	100 (5/5)	97.7 (210/215)	—	97.1 (33/34)
	V170I/M/T	100 (1/1)	100 (30/30)	—	96.8 (30/31)	100 (8/8)	97.6 (207/212)	100 (2/2)	96.9 (31/32)
	M175L	—	100 (31/31)	—	96.8 (30/31)	100 (3/3)	97.7 (212/217)	—	97.1 (33/34)
NS5A									
Genotype 1a	M28V	—	—	—	—	100 (1/1)	100 (3/3)	—	100 (1/1)
	Y93C	—	—	—	—	100 (1/1)	100 (3/3)	—	100 (1/1)
Genotype 1b	R30H/Q	—	100 (31/31)	—	96.8 (30/31)	100 (2/2)	97.7 (213/218)	—	97.1 (33/34)
	L31I/M/V	100 (2/2)	100 (29/29)	100 (1/1)	96.7 (29/30)	85.7 (6/7)	98.1 (209/213)	100 (3/3)	96.8 (30/31)
	Y93H/C	100 (2/2)	100 (29/29)	80.0 (4/5)	100 (26/26)	93.1 (27/29)	98.4 (188/191)	100 (7/7)	96.3 (26/27)

% (n/N); —, not applicable

In the Japanese phase II/III study (MK-5172-058), while an NS3 resistance-associated substitution was not detected after the end of treatment in any of 7 virologic failure subjects (all relapsers), NS5A resistance-associated substitutions were detected after the end of treatment in all 7 subjects (Table 54). Especially, NS5A Y93H was detected in all 7 subjects, and L31M in 4 of them. Treatment-emergent resistance-associated substitutions were detected after the end of treatment in 6 of the 7 patients, and Y93H in all 6 patients. In 3 patients with baseline Y93H and 1 patient with baseline L31M, these substitutions were detected also after the end of treatment. These results indicate a possibility that these substitutions may be associated with virologic failure with GZR + EBR.

Table 54. NS3 and NS5A resistance substitutions in virologic failure subjects

Patients	NS3			NS5A		
	Baseline resistance-associated polymorphism	Time virologic failure was observed		Baseline resistance-associated polymorphism	Time virologic failure was observed	
		Resistance substitution	Fold-shift[a)]		Resistance substitution	Fold-shift[a)]
Non-cirrhotic chronic hepatitis C	None	None	—	Y93Y/H	L31M, Y93H	7.0, 16.7
	None	None	—	None	Y93H	16.7
	None	None	—	L31M	L31M, Y93H	7.0, 16.7
	None	None	—	Y93H	Y93H	16.7
	None	None	—	Y93H	L31M, Y93H	7.0, 16.7
	None	None	—	None	L31M, Y93H	7.0, 16.7
Compensated cirrhotic chronic hepatitis C	None	None	—	None	Y93H	16.7

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

PMDA's view:

There were no apparent differences in the SVR12 rate with GZR + EBR between subjects with and without baseline NS3 or NS5A resistance-associated polymorphisms. In subjects who experienced virologic failure with GZR + EBR, an NS3 resistance substitution was not detected and treatment-emergent NS5A substitutions at positions L31 and Y93 were detected, and these substitutions were found to be associated with virologic failure. In light of limited clinical study data on the association between resistance-associated variants and the efficacy of GZR + EBR, post-marketing data including published literature should be collected regarding resistance-associated polymorphisms before the start of treatment with GZR + EBR and resistance-associated variants in patients who did not achieve SVR with GZR + EBR, etc. Obtained findings should be communicated promptly to healthcare professionals.

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

7.R.2 Safety

As a result of the following review, PMDA concluded that the GZR + EBR combination regimen in Japanese chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) has acceptable safety.

However, because of limited clinical experience with GZR + EBR in Japanese elderly patients, post-marketing data should be collected from this patient population. Since elevated ALT and AST were observed in Japanese and foreign clinical studies, relevant post-marketing data should be collected to investigate the occurrence of these events as well.

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

7.R.2.1 Summary of safety of the GZR + EBR combination regimen

The applicant's explanation about the safety of GZR + EBR in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1):

The summary of safety in a Japanese phase II/III study (MK-5172-058) is shown in Table 55.

Table 55. Summary of safety in Part 2 of Japanese phase II/III study (MK-5172-058) (FAS, during treatment and the first 4 follow-up weeks)

	Non-cirrhotic chronic hepatitis C		Compensated cirrhotic chronic hepatitis C
	GZR 100 mg + EBR 50 mg	Placebo	GZR 100 mg + EBR 50 mg
N	227	74	35
All adverse events	147 (64.8)	50 (67.6)	28 (80.0)
Severe adverse events[a)]	5 (2.2)	1 (1.4)	1 (2.9)
Serious adverse events	11 (4.8)	1 (1.4)	0
Deaths	0 [b)]	0	0
Adverse events leading to discontinuation	3 (1.3)	1 (1.4)	0

N (%)

[a)] Adverse events were assessed on the following 3-point scale: mild (signs or symptoms that are well-tolerated), moderate (discomfort causing some interference with usual activities), and severe (incapacitating with inability to do work or usual activities).

[b)] 1 death occurred during the follow-up period [see Section 7.1 for details].

Serious adverse events assessed as causally related to the study drug occurred in 2 non-cirrhotic patients with chronic hepatitis C receiving GZR + EBR (cerebral infarction, ALT increased, and AST increased, 1 subject each [1 subject had ≥1 event]). Cerebral infarction was unresolved while all the other events resolved. Besides serious adverse events, vertigo (1 subject) was rated as severe. A causal relationship to the study drug was ruled out for the event, and it resolved. The incidence of adverse events leading to discontinuation was similar between the GZR + EBR and placebo groups. Those events reported by 2 subjects in the GZR + EBR group (cerebral infarction, ALT increased, and AST increased, 1 subject each [1 subject had ≥1 event]) were assessed as causally related to the study drug. Cerebral infarction was unresolved while all other events resolved. The adverse event reported at a ≥3% higher incidence in the GZR + EBR group than in the placebo group among non-cirrhotic patients with chronic hepatitis C was ALT increased (5.7% [13 of 227] in the GZR + EBR group, 1.4% [1 of 74] in the placebo group).

PMDA's view:

In light of GZR + EBR-associated serious adverse events, etc. observed in the Japanese phase II/III study (MK-5172-058), the safety of GZR + EBR is acceptable as long as they are used under the supervision of a physician with knowledge and experience in viral liver disease. Hepatic dysfunction including ALT and AST elevations and safety in elderly patients are detailed in the following section. Safety in chronic hepatitis C patients with compensated cirrhosis is described in Section 7.R.4.2.

7.R.2.2 Hepatic dysfunction

The applicant's explanation about the occurrence of hepatic function-related adverse events with GZR + EBR and the need for relevant precautionary advice:

ALT/AST elevations in Part 2 (chronic hepatitis C patients with or without compensated cirrhosis) of a Japanese phase II/III study (MK-5172-058) and the foreign pooled analysis[76)] are summarized in Table 56. Other hepatic function-related events reported were blood lactate dehydrogenase increased, prothrombin time prolonged (2 subjects each), blood alkaline phosphatase increased, and blood bilirubin increased (1 subject each) in the GZR + EBR group and blood alkaline phosphatase increased (1 subject) in the placebo group in Part 2 of the Japanese phase II/III study (MK-5172-058), and blood alkaline phosphatase increased and prothrombin time prolonged (1 subject each) in the GZR + EBR group in

[76)] Pooled data from a Japanese phase II/III study (MK-5172-058, Part 1), foreign phase II studies (MK-5172-035, MK-5172-047, MK-5172-048, MI-5172-059), and foreign phase III studies (MK-5172-060, MK-5172-061, MK-5172-068).

the foreign pooled analysis. No severe or serious adverse events, deaths, or adverse events leading to discontinuation were reported.

Table 56. Summary of ALT/AST elevations observed in Japanese and foreign clinical studies

	Japanese phase II/III study (MK-5172-058)				Foreign pooled analysis	
	GZR 100 mg + EBR 50 mg		Placebo		GZR 100 mg + EBR 50 mg	
	ALT increased	AST increased	ALT increased	AST increased	ALT increased	AST increased
N	262	262	74	74	1033	1033
All adverse events	18 (6.9)	16 (6.1)	1 (1.4)	2 (2.7)	15 (1.5)	9 (0.9)
Severe adverse events[a)]	1 (0.4)	1 (0.4)	0	0	6 (0.6)	3 (0.3)
Serious adverse events	1 (0.4)	1 (0.4)	0	0	0	0
Deaths	0	0	0	0	0	0
Adverse events leading to discontinuation	1 (0.4)	1 (0.4)	0	0	3 (0.3)	3 (0.3)

N (%)

[a)] Adverse events were assessed on the following 3-point scale: mild (signs or symptoms that are well-tolerated), moderate (discomfort causing some interference with usual activities), and severe (incapacitating with inability to do work or usual activities).

In the early development stage, GZR (100 mg, 200 mg, 400 mg, or 800 mg) was co-administered with PegIFN and RBV QD for 12 weeks in a foreign phase II study (MK-5172-003). ALT/AST elevations exceeding the ULN were observed in patients receiving GZR 200, 400, or 800 mg in whom baseline ALT was within the normal range or was higher but later returned to normal with decreased HCV RNA. These elevations had the following characteristics:

- ALT/AST elevated at treatment week 8 and resolved during ongoing treatment or after discontinuation in most patients.
- Abnormal changes in other liver function tests (total bilirubin, direct bilirubin, indirect bilirubin, INR, albumin) were rare.

The above study results identified a potential safety signal for GZR-associated ALT/AST elevations. The occurrence of ALT/AST elevation was investigated in detail in the subsequent studies.

Table 57 shows the incidence of ALT/AST elevations by time from the start of treatment in the GZR + EBR group (chronic hepatitis C patients with or without compensated cirrhosis) in the Japanese phase II/III study (MK-5172-058) and the foreign pooled analysis.[76)] The incidence of ALT/AST elevations tended to be higher in the Japanese phase II/III study (MK-5172-058) than in the foreign pooled analysis, which was considered attributable to higher GZR exposure in Japanese patients than in foreign patients.

Table 57. Summary of hepatic function-related adverse events
[Japanese phase II/III study (MK-5172-058) (Part 2, blinded period [up to follow-up week 4]), foreign pooled analysis]

	Time from the start of treatment							
	<4 weeks		≥4 weeks and <8 weeks		≥8 weeks and <12 weeks		≥12 weeks	
	Japanese phase II/III study [a)]	Foreign pooled analysis [b)]	Japanese phase II/III study [a)]	Foreign pooled analysis [b)]	Japanese phase II/III study [a)]	Foreign pooled analysis [b)]	Japanese phase II/III study [a)]	Foreign pooled analysis [b)]
N	262	1033	262	1030	260	1027	259	990
ALT increased	0	2 (0.2)	2 (0.8)	3 (0.3)	7 (2.7)	7 (0.7)	9 (3.5)	3 (0.3)
AST increased	0	0	3 (1.1)	3 (0.3)	6 (2.3)	5 (0.5)	7 (2.7)	1 (0.1)

N (%)

[a)] Part 2, blinded period and the first 4 follow-up weeks, [b)] blinded period and the first 14 follow-up days

In Part 2 of the Japanese phase II/III study (MK-5172-058), grade ≥3 (>5-fold the ULN) ALT/AST elevation occurred in the GZR + EBR group (chronic hepatitis C patients with or without compensated cirrhosis) only and time to the first onset of ALT/AST elevation was 8 to <12 weeks in all patients except for 1 patient (7-8 weeks [50 days] from the start of treatment). Grade ≥3 ALT/AST elevations

were all transient and reversible and were not associated with clear changes in other hepatic laboratory tests (total bilirubin, INR, eosinophil count). These events resolved during continued treatment in 5 of 6 subjects or following treatment discontinuation in 1 subject. Only 1 subject experienced ALT/AST elevation that was severe and serious and led to discontinuation after 7 to 8 weeks of treatment (Day 50).

To date, ALT/AST elevation has been identified as a safety signal associated with GZR in its clinical development [see Section 6.2.6.3], and Grade ≥3 ALT/AST elevations tended to occur at treatment week 8 or later. Grade ≥3 ALT/AST elevations are expected to resolve during continued treatment or after treatment discontinuation, and are reversible and rarely accompanied by other hepatic laboratory abnormalities or clinical symptoms. Liver functions, therefore, do not need to be tested frequently, but a testing at treatment week 8 will be of great relevance in terms of risk monitoring and decision making on treatment discontinuation as needed. The package insert should advise the conduct of liver function testing at baseline, treatment week 8, and as required and the consideration of the discontinuation of treatment with GZR + EBR as necessary for careful risk monitoring.

PMDA's view:
Although patients in the Japanese phase II/III study (MK-5172-058) experienced ALT/AST elevations while on treatment with GZR + EBR, grade ≥3 adverse events were all transient, reversible, and resolved, and were not associated with clear changes in other hepatic laboratory tests (total bilirubin, INR, eosinophil count). Meanwhile, though grade ≥3 ALT/AST elevations occurred at treatment week 8 or later, ALT/AST elevations of any severity occurred before treatment week 8 as well. Therefore, healthcare professionals should be warned of the occurrence of hepatic dysfunction and advised on regular liver function testing and appropriate actions taken, e.g. discontinuation of the combination regimen according to the patient's condition (not limited to treatment week 8). Post-marketing data on the occurrence of hepatic dysfunction including ALT/AST elevations should also be collected.

7.R.2.3 Safety in the elderly

The applicant's explanation about safety in the elderly:
Safety in non-elderly (<65 years) and elderly (≥65 years) chronic hepatitis C patients with or without compensated cirrhosis in Part 2 of a Japanese phase II/III study (MK-5172-058) is summarized in Table 58.

Table 58. Safety in patients <65 years of age and patients ≥65 years of age (Part 2)

	GZR 100 mg + EBR 50 mg		Placebo	
	<65 years	≥65 years	<65 years	≥65 years
N	139	123	40	34
All adverse events	92 (66.2)	83 (67.5)	30 (75.0)	20 (58.8)
Severe adverse events[a)]	3 (2.2)	3 (2.4)	0	1 (2.9)
Serious adverse events	3 (2.2)	8 (6.5)	0	1 (2.9)
Deaths	0	0	0	0
Adverse events leading to discontinuation	1 (0.7)	2 (1.6)	0	1 (2.9)

N (%)
[a)] Adverse events were assessed on the following 3-point scale: mild (signs or symptoms that are well-tolerated), moderate (discomfort causing some interference with usual activities), and severe (incapacitating with inability to do work or usual activities).

The incidence of adverse events with GZR + EBR was similar between non-elderly and elderly patients. On the other hand, the incidence of adverse events with placebo was higher in non-elderly patients than in elderly patients. The incidence of serious adverse events with GZR + EBR was slightly higher in elderly patients than in non-elderly patients. However, cataract was the only serious adverse event reported by ≥2 patients and there was no particular trend. Accordingly, there were no clear differences by age group in the safety profile of GZR + EBR.

PMDA's view:

There were no clear differences between elderly and non-elderly patients in the safety profile of GZR + EBR. However, because of their reduced physiological function, etc., the possibility to have adverse events cannot be denied, and thus post-marketing safety data should be further collected from elderly patients.

7.R.3 Use in non-cirrhotic and compensated cirrhotic chronic hepatitis C patients with severe renal impairment

7.R.3.1 Efficacy

The applicant's explanation about the efficacy of the GZR + EBR combination regimen in non-cirrhotic and compensated cirrhotic chronic hepatitis C patients with severe renal impairment:

Table 59 summarizes efficacy by baseline eGFR and hemodialysis status in a foreign phase II/III study in non-cirrhotic and compensated cirrhotic chronic hepatitis C patients with severe renal impairment (genotype 1) (MK-5172-052). With its similarity between subgroups according to baseline eGFR or hemodialysis status, the efficacy of GZR + EBR in non-cirrhotic and compensated cirrhotic chronic hepatitis C patients with severe renal impairment was demonstrated.

Table 59. SVR12 rate with GZR + EBR in each subgroup (mFAS, Study MK-5172-052)

		N	SVR12 rate [95% CI]
Overall		116	99.1% [95.3, 100] (115/116)
Baseline eGFR	15-30 mL/min/1.73 m^2	22	100% [84.6, 100] (22/22)
	<15 mL/min/1.73 m^2	94	98.9% [94.2, 100.0] (93/94)
Hemodialysis at baseline	Yes	87	98.9% [93.8,100.0] (86/87)
	No	29	100% [88.1,100] (29/29)

PMDA's view:

Based on the results from the foreign phase II/III study (MK-5172-052), GZR + EBR is expected to have efficacy in non-cirrhotic and compensated cirrhotic chronic hepatitis C patients with severe renal impairment (genotype 1). However, because of no clinical experience with the combination regimen in Japanese non-cirrhotic and compensated cirrhotic chronic hepatitis C patients with severe renal impairment, post-marketing data on the efficacy of the combination regimen should be collected from these patients, and available findings should be promptly communicated to healthcare professionals.

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

7.R.3.2 Safety

The applicant's explanation about the safety of GZR + EBR in non-cirrhotic and compensated cirrhotic chronic hepatitis C patients with severe renal impairment:

In a foreign phase II/III study in non-cirrhotic and compensated cirrhotic chronic hepatitis C patients with severe renal impairment (MK-5172-052), the incidences of adverse events were 75.7% (84 of 111 subjects) in the GZR + EBR group and 84.1% (95 of 113 subjects) in the placebo group, adverse drug reactions [34.2% (38 of 111 subjects) and 34.5% (39 of 113 subjects), respectively], and serious adverse events [14.4% (16 of 111 subjects) and 16.8% (19 of 113 subjects), respectively], showing similarity between GZR + EBR and placebo.

There were 1 death (cardiac arrest) in the GZR 100 mg + EBR 50 mg group and 4 deaths (death, haemorrhagic shock, aortic aneurysm, and pneumonia; 1 subject each) in the placebo group. The death of a patient receiving GZR 100 mg + EBR 50 mg was considered due to latent cardiovascular disease, and its causal relationship to study drug was ruled out. No serious adverse events or adverse events leading to discontinuation with suspected causality to study drug were observed with GZR + EBR.

eGFR over time in non-dialysis subjects in the intensive PK cohort or the GZR 100 mg + EBR 50 mg group of the foreign phase II/III study (MK-5172-052) is presented in Table 60. There were no effects of GZR + EBR on renal functions.

Table 60. eGFR over time in non-dialysis subjects in the intensive PK cohort or the GZR 100 mg + EBR 50 mg group (Foreign phase II/III study [MK-5172-052] [blinded period and the first 4 follow-up weeks])

	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	4 weeks post-treatment
N	27	27	28	29	30	29	30	30	29
eGFR (mL/min/1.73 m^2)	18.9 ± 7.9	18.9 ± 8.0	19.6 ± 7.9	18.3 ± 7.3	18.2 ± 8.0	19.1 ± 8.4	18.2 ± 7.9	18.2 ± 8.0	18.6 ± 7.4
Change from baseline (mL/min/1.73 m^2)	—	0 ± 1.9	- 0.0 ± 3.4	- 0.9 ± 2.6	- 0.9 ± 5.4	- 0.0 ± 4.9	- 0.9 ± 4.8	- 1.0 ± 4.6	- 0.9 ± 4.8

Mean ± SD

Table 61 shows grading of increased serum creatinine before and after treatment with GZR + EBR in the intensive PK cohort and the GZR 100 mg + EBR 50 mg group (dialysis or non-dialysis subjects) of the foreign phase II/III study (MK-5172-052). There were no clear effects of GZR + EBR on grades of increased serum creatinine.

Table 61. Grading of increased serum creatinine before and after treatment with GZR + EBR in the intensive PK cohort and the GZR 100 mg + EBR 50 mg group (Foreign phase II/III study [MK-5172-052] [blinded period and the first 14 follow-up days])

Grade at baseline [a]		Grade at the time of maximum serum creatinine (blinded period and the first 14 follow-up days)				
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Grade 0	1	1 (0.8)	0	0	0	0
Grade 1	1	0	0	1 (0.8)	0	0
Grade 2	4	0	0	2 (1.6)	2 (1.6)	0
Grade 3	25	0	0	0	21 (17.2)	4 (3.3)
Grade 4	91	0	0	0	0	91 (74.6)
Total	122	1 (0.8)	0	3 (2.5)	23 (18.9)	95 (77.9)

N (%)

[a] Grade 0, <1.1-fold the ULN; Grade 1, 1.1-1.3-fold the ULN; Grade 2, 1.4-1.8-fold the ULN; Grade 3, 1.9-3.4-fold the ULN; Grade 4, ≥3.5-fold the ULN

Based on the above, GZR 100 mg and EBR 50 mg QD administered for 12 weeks are well-tolerated in HCV-infected patients with renal impairment.

PMDA's view:
The safety of the combination regimen in non-cirrhotic and compensated cirrhotic chronic hepatitis C patients with severe renal impairment is acceptable. However, considering no clinical experience with GZR + EBR in Japanese non-cirrhotic and compensated cirrhotic chronic hepatitis C patients with severe renal impairment, post-marketing data on its safety in these patients, and available findings should be promptly communicated to healthcare professionals.

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

7.R.4 Indication

Based on the discussions in the following subsections and the results of a Japanese phase II/III study (MK-5172-058), the GZR + EBR combination regimen is expected to have efficacy in genotype 1 chronic hepatitis C patients with or without compensated cirrhosis with no particular safety concerns [see Sections 7.R.1 and 7.R.2]. Thus, PMDA concluded that the proposed indication of the GZR+ EBR combination regimen of "suppression of viremia in serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis" is acceptable.

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

7.R.4.1 Genotype

The applicant's explanation about the efficacy of the GZR + EBR combination regimen by subtype of genotype 1 HCV:
In Part 2 of a Japanese phase II/III study (MK-5172-058), the SVR12 rates with GZR + EBR in treatment-naïve or treatment-experienced non-cirrhotic patients with chronic hepatitis C were 100% (4 of 4) in genotype 1a patients and 96.4% (215 of 223) in genotype 1b patients. Although the data from genotype 1a patients in the Japanese phase II/III study (MK-5172-058) are limited, a pooled analysis of the SVR12 rate with GZR + EBR without RBV in foreign clinical studies showed that the SVR12 rates were 92.9% (379 of 408) in non-cirrhotic chronic hepatitis C (genotype 1a) patients and 93.7% (104 of 111) in chronic hepatitis C (genotype 1a) patients with compensated cirrhosis. Thus, there should be no major differences in the efficacy of the GZR + EBR combination regimen between genotype 1 subtypes.

PMDA accepts the applicant's explanation and agrees that the GZR+ EBR combination regimen is expected to have efficacy in genotype 1a and 1b patients.

7.R.4.2 Use in chronic hepatitis C patients with compensated cirrhosis

The applicant's explanation about the efficacy and safety of the GZR + EBR combination regimen in chronic hepatitis C patients with compensated cirrhosis:
In a Japanese phase II/III study (MK-5172-058), the SVR12 rates with GZR + EBR in treatment-naïve and IFN-experienced chronic hepatitis C patients with compensated cirrhosis were 100% (20 of 20) and 93.3%

(14 of 15), respectively. Table 62 summarizes the safety of GZR + EBR in chronic hepatitis C patients with or without compensated cirrhosis.

Table 62. Safety summary in Part 2 of Japanese phase II/III study (MK-5172-058)
(Safety analysis population, blinded period and the first 4 follow-up weeks)

	Non-cirrhotic chronic hepatitis C	Compensated cirrhotic chronic hepatitis C
	GZR 100 mg + EBR 50 mg	GZR 100 mg + EBR 50 mg
N	227	35
All adverse events	147 (64.8)	28 (80.0)
Severe adverse events	5 (2.2)	1 (2.9)
Serious adverse events	11 (4.8)	0
Deaths	0	0
Adverse events leading to discontinuation	3 (1.3)	0

N (%)

There were no deaths, serious adverse events, or adverse events leading to discontinuation in chronic hepatitis C patients with compensated cirrhosis. The presence of cirrhosis did not affect the safety profile.

PMDA's view:

Based on the results of the Japanese phase II/III study (MK-5172-058), the GZR + EBR combination regimen is expected to have efficacy in treatment-naïve and IFN-experienced chronic hepatitis C patients with compensated cirrhosis is expected. Because of no clear differences in the safety profile of GZR + EBR between non-cirrhotic and compensated cirrhotic patients, GZR + EBR provides acceptable safety in chronic hepatitis C patients with compensated cirrhosis as long as appropriate measures, e.g. monitoring and management of hepatic dysfunction and other adverse events, and treatment suspension or discontinuation, are taken under the supervision of a physician with adequate knowledge and experience in the treatment of viral liver disease. The applicant's explanation (GZR will be contraindicated in non-cirrhotic and compensated cirrhotic chronic hepatitis C patients with moderate or severe hepatic impairment) [see Section 6.2.3.1.1] is acceptable.

However, because of limited clinical experience with the combination regimen in Japanese chronic hepatitis C patients with compensated cirrhosis, safety and efficacy data in chronic hepatitis C patients with compensated cirrhosis should be collected via post-marketing surveillance, and any new findings should be communicated to healthcare professionals in an appropriate manner.

7.R.4.3 Use in NS3/4A protease inhibitor- or NS5A inhibitor-experienced patients

The applicant's explanation about the efficacy of the GZR + EBR combination regimen in genotype 1 chronic hepatitis C patients with or without compensated cirrhosis who did not achieve SVR with prior treatment with an NS3/4A protease inhibitor or an NS5A inhibitor.

7.R.4.3.1 Use in NS3/4A protease inhibitor-experienced patients

Data of NS3/4A protease inhibitor-experienced patients are available from a foreign clinical study in patients who have a history of treatment with PegIFN/RBV + an NS3/4A protease inhibitor. In a foreign phase II study conducted in patients who have a history of treatment with PegIFN/RBV + an NS3/4A protease inhibitor received the combination regimen of GZR + EBR + RBV (MK-5172-048, CTD 5.3.5.2-6). The SVR12 rates in patients with and without baseline NS3 resistance-associated substitutions[73)]

were 91.1% (31 of 34) and 100% (44 of 44), respectively. Of the 3 patients who failed to achieve SVR12, 2 had baseline NS5A resistance-associated polymorphisms.

In Part 1 and Part 2 of a Japanese phase II/III study (MK-5172-058), the SVR12 rates with GZR + EBR in patients with and without baseline NS3 resistance-associated polymorphisms were 100% (92 of 92) and 96.5% (191 of 198), respectively. The presence of baseline NS3 resistance-associated polymorphisms did not affect the efficacy of GZR + EBR.

Because there is no clinical experience with GZR + EBR in NS3/4A protease inhibitor- or NS5A inhibitor-experienced patients, the efficacy of the regimen is unknown with no sufficient evidence on its clinical effects. Thus, it is difficult to recommend the use of GZR + EBR in this patient group. However, the combination regimen may be considered as a therapeutic option based on its safety and less restrictions on concomitant drugs to be used, provided that the presence of resistance-associated variants in NS3/4A inhibitor-experienced patients is taken into account based on the data on *in vitro* antiviral activity.

7.R.4.3.2 Use in NS5A inhibitor-experienced patients

Since there is no clinical experience with GZR + EBR in NS5A inhibitor-experienced patients, its efficacy in these patients is unknown and there is no sufficient evidence on its clinical effects. Thus, it is difficult to recommend the use of the combination regimen. However, GZR + EBR may be considered as a therapeutic option from the standpoint of its safety and less restrictions on concomitant drugs to be used, provided that the presence of resistance-associated variants in NS5A inhibitor-experienced patients is taken into account based on the data on *in vitro* antiviral activity.

PMDA's view:

There are no data adequate enough to recommend the use of GZR + EBR in patients who have failed prior combination therapy with an NS3/4A protease inhibitor or an NS5A inhibitor due to no clinical experience with the combination regimen in this patient population in Japanese or foreign clinical studies.

However, the following findings support the use of GZR + EBR in patients who have a treatment history with other NS3/4A protease inhibitors or NS5A inhibitors, provided that patients are carefully checked for resistance-associated variants in advance.

- The resistance profiles to various NS3/4A protease inhibitors and NS5A inhibitors are not necessarily the same. In non-clinical studies, GZR and EBR showed anti-HCV activity against some of NS3 and NS5A substitutions conferring resistance to other drugs [see Sections 3.1.3.3 and 3.4.2.3].
- The Japanese phase II/III study (MK-5172-058) demonstrated the efficacy of GZR+ EBR in patients with baseline NS3 or NS5A resistance-associated polymorphisms.

Eligibility of NS3/4A protease inhibitor- or NS5A inhibitor-experienced patients for the GZR + EBR combination regimen must be decided carefully by physicians with knowledge and experience in the treatment of viral liver disease, based on their condition including the presence or absence of resistance-

associated variants. Data to date on variants associated with resistance to GZR + EBR should be provided to healthcare professionals. Then, if NS3/4A protease inhibitor- and/or NS5A inhibitor-experienced patients are treated with the combination regimen in a post-marketing surveillance study, data on resistance-associated variants and the efficacy and safety of GZR + EBR, etc. should be collected, and the obtained findings should be communicated to healthcare professionals appropriately.

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

7.R.5 Dosage and administration

Based on the discussion in the paragraph below, PMDA concluded that the following proposed dosage and administration for GZR and EBR is acceptable.

Dosage and administration for GZR

The usual adult dosage is 100 mg of Grazoprevir Hydrate, administered orally once daily in combination with Elbasvir for 12 weeks.

Dosage and administration for EBR

The usual adult dosage is 50 mg of Elbasvir, administered orally once daily in combination with Grazoprevir Hydrate for 12 weeks.

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

GZR and EBR dosage and administration and duration of treatment

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

GZR inhibits the function of NS3/4A protease and EBR inhibits the function of NS5A. When combined, GZR and EBR exhibited higher anti-HCV activity than alone [see Section 3.1.4], showing their non-overlapping resistance profiles [see Sections 3.1.3.3 and 3.4.2.3] in the non-clinical pharmacology studies. Since clinical studies demonstrated the efficacy and favorable safety profile of the combined GZR and EBR, the use of the GZR + EBR combination regimen in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) is of significance.

The dosing regimen of GZR in Part 2 of a Japanese phase II/III study (MK-5172-058) was planned to be determined based on the interim data from Part 1. The Part 1 interim data were collected until unblinding after all patients had completed Follow-up Week 4, and safety, tolerability, and efficacy were evaluated. No particular safety or tolerability concerns with GZR 50 or 100 mg or no major differences between the GZR 50 and 100 mg groups were observed. There were no differences in the SVR4 rate between the 50 and 100 mg groups. The proportions of subjects who achieved unquantifiable HCV RNA at Week 2 were approximately 70% in the 100 mg group and approximately 60% in the 50 mg group. Generally, for the purpose to block the emergence of drug-resistant virus, antiviral therapy uses the maximum tolerated dose. Accordingly, GZR 100 mg QD was selected for Part 2. Further, based on the results from foreign clinical studies and Part

1 of the Japanese phase II/III study (MK-5172-058), EBR 50 mg QD was selected to be combined with GZR in Part 2 of the Japanese phase II/III study (MK-5172-058) [see Section 6.R.3].

The treatment duration of 12 weeks was selected for the following reasons: According to the preliminary data from Part B of a foreign phase II study (MK-5172-035) (8, 12, or 18 weeks of treatment with the GZR + EBR dual regimen or GZR + EBR + RBV triple regimen), which were available at the time of planning the Japanese phase II/III study (MK-5172-058), the SVR8 rate in non-cirrhotic patients with chronic hepatitis C treated with GZR + EBR QD for 12 weeks was 100% for genotype 1b and >90% for genotype 1a. On the other hand, the SVR8 rate in non-cirrhotic patients with genotype 1a chronic hepatitis C treated for 8 weeks was approximately 80%, and the SVR8 rate was similar between the 12-week and 18-week treatment regimens, etc.

Since Part 2 of the Japanese phase II/III study (MK-5172-058) demonstrated the efficacy and favorable tolerability profile of the GZR + EBR combination regimen in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1), the proposed dosing regimen is to take GZR 100 mg in combination with EBR 50 mg QD for 12 weeks.

Based on the discussions in Sections 7.R.1 and 7.R.2, PMDA concluded that the applicant's explanation about dosage and administration of GZR and EBR for chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) is acceptable.

7.R.6 Clinical positioning

The applicant's explanation about the clinical positioning of the GZR + EBR combination regimen in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1):

In Japan, the following approved therapeutic agents are available for chronic hepatitis C patients with or without compensated cirrhosis (genotype 1): IFN preparations, RBV, NS3/4A protease inhibitors (telaprevir, simeprevir sodium, asunaprevir, vaniprevir), an NS5A inhibitor (daclatasvir hydrochloride), and an NS5B polymerase inhibitor (sofosbuvir); and the combination product of sofosbuvir and ledipasvir acetonate (an NS5A inhibitor) and the combination product of paritaprevir hydrate (an NS3/4A protease inhibitor), ombitasvir hydrate (an NS5A inhibitor), and ritonavir (a CYP3A inhibitor). Remaining issues of the IFN-free regimens like GZR + EBR are treatment failure due to drug resistance mutations and adverse drug reactions such as hepatic dysfunction (Sunvepra Capsules 100 mg package insert, 10th edition, Daklinza Tablets 60 mg package insert, 10th edition). Non-cirrhotic or cirrhotic chronic hepatitis C patients are aging in Japan as compared to the US and Europe (*Journal of Japanese Society of Gastroenterology*. 2008; 105: 191-8), and given that elderly patients often have reduced physiological function and complications, a more effective and safer treatment is in demand. The Japanese clinical practice guidelines (Guidelines for the Management of Hepatitis C Virus Infection, 5th edition. Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology ed.; 2016) recommend the combination product of sofosbuvir + ledipasvir as the first-line treatment for genotype 1 patients, but the product is contraindicated in patients with severe renal impairment (Harvoni Combination Tablets package insert, second edition). According to 2 recent reports on the daclatasvir +

asunaprevir combination regimen in Japanese patients on hemodialysis (*J Gastroenterol*. 2016; 51: 733-40, *J Gastroenterol.* 2016; 51: 741-7), the SVR12 rate was 95.5% (20 of 21 patients) in 1 report and 100% (28 of 28 patients) in another, and no safety issues were identified. Based on these findings, daclatasvir + asunaprevir is recommended as the first-line drug for genotype 1 patients on hemodialysis. However, the regimen is known to reduce SVR12 rate in patients with an NS5A amino acid polymorphism at position Y93 (Sunvepra Capsules 100 mg package insert, 10th edition, Daklinza Tablets 60 mg package insert, 10th edition) and to require longer term of treatment (24 weeks). Caution should be used with treatment with ombitasvir + paritaprevir + ritonavir fixed-dose combination tablets because patients with moderate or severe renal impairment were excluded from a Japanese phase III study. Further, the package insert of the tablet product contraindicates or gives precautionary advice on concomitant use of calcium blockers, which are commonly used in dialysis patients.

In a Japanese phase II/III study in chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) (MK-5172-058), GZR 100 mg + EBR 50 mg QD for 12 weeks achieved high SVR12 rates, regardless of the presence or absence of baseline HCV NS3 or NS5A resistance-associated polymorphisms [see Section 7.R.1]. Its safety profile was favorable with low incidence of adverse events leading to discontinuation [see Section 7.R.2]. Foreign clinical studies demonstrated high efficacy and favorable tolerability of GZR + EBR in chronic hepatitis C patients with severe renal impairment [see Section 7.R.3] and in those co-infected with HIV/HCV.[77)] The US clinical practice guidelines (HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C)[78)] recommends GZR + EBR as a therapeutic option for chronic hepatitis C patients with severe renal impairment including dialysis patients.

Based on the above, the GZR + EBR combination regimen has a potential to be a new therapeutic option for chronic hepatitis C patients with or without compensated cirrhosis (genotype 1), regardless of whether these patients have renal impairment.

PMDA's view:

The Japanese or foreign clinical studies did not use active control groups, precluding rigorous comparisons with existing therapies. Nevertheless, as concluded in Sections 7.R.1 and 7.R.2, the GZR + EBR combination regimen has potential to be a new therapeutic option for chronic hepatitis C patients with or without compensated cirrhosis (genotype 1) including those with severe renal impairment, as long as appropriate measures, e.g. monitoring and management of hepatic dysfunction and other adverse events, and treatment suspension or discontinuation, are taken under the supervision of a physician with adequate knowledge and experience in the treatment of viral liver disease.

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

[77)] A foreign phase III study in which treatment-naïve, non-cirrhotic and compensated cirrhotic patients with chronic hepatitis C (genotype 1, 4, and 6) and HIV co-infection received GZR + EBR fixed-dose combination tablets (100 + 50 mg) QD for 12 weeks (MK-5172-061). In this study, the SVR12 rate was 95.0% (207 of 218) (94.4% [136 of 144] in genotype 1a patients and 95.5% [(42 of 44] in genotype 1b patients).

[78)] http://www.hcvguidelines.org/printpdf/159 [June 2016]

7.R.7 Post-marketing investigations

The applicant's plan of a post-marketing surveillance study of GZR and EBR.

Drug use-results survey

- Objective, to collect safety and efficacy data in routine clinical settings.
- Planned sample size, 1000 patients
  A target sample size of 1000 should be sufficient to assess unknown adverse drug reactions with a certain accuracy. Of all chronic hepatitis C patients enrolled in the survey, approximately 200 patients are expected to have compensated cirrhosis.
- Observation period, 36 weeks (12-week treatment period and 24-week follow-up period)
- Survey period, 3 years (enrollment, 2 years)

PMDA's view on specific post-marketing data to be collected:

- Safety and efficacy in elderly patients, patients with compensated cirrhosis, and patients with severe renal impairment (including those requiring dialysis)
- Occurrence of hepatic dysfunction
- Association between efficacy and resistance-associated variants present before the start of treatment or those resulting from treatment failure
- Resistance-associated variants and efficacy, etc. in NS3/4A protease inhibitor- or NS5A inhibitor-experienced patients receiving GZR + EBR

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

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

The inspections and assessment are ongoing. The results of inspections and PMDA's conclusion are reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that the grazoprevir hydrate + elbasvir combination regimen has efficacy in the treatment of chronic hepatitis C with or without compensated cirrhosis (genotype 1), and that the regimen has acceptable safety in view of its benefits.

PMDA has concluded that the grazoprevir hydrate + elbasvir combination regimen may be approved if the regimen are not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 26, 2016

Products Submitted for Approval

Brand Name	(a) Grazyna Tablets 50 mg
	(b) Erelsa Tablets 50 mg
Non-proprietary Name	(a) Grazoprevir Hydrate
	(b) Elbasvir
Applicant	MSD K.K.
Date of Application	March 11, 2016

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during Expert Discussion were nominated based on their declarations etc. concerning the products 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.2 Safety," "7.R.3 Use in non-cirrhotic and compensated cirrhotic chronic hepatitis C patients with severe renal impairment," "7.R.5 Dosage and administration," and "7.R.7 Post-marketing investigations") were supported by the expert advisors at the Expert Discussion.

PMDA conducted an additional review of the following points and took necessary actions.

1.1 Efficacy

PMDA's conclusion on efficacy (Section "7.R.1 Efficacy") was supported at the Expert Discussion. The expert advisors made the following comments.

- In some patients who failed treatment with daclatasvir+ asunaprevir, an NS5A R30H/Q polymorphism was not detected at baseline. However, multiple mutations, i.e. R30H/Q plus Y93H, L31M/V, or Q54H were identified after treatment, which revealed high resistance of NS5A to daclatasvir + asunaprevir. In light of this, the efficacy data of the Grazoprevir Hydrate/Elbasvir (GZR + EBR) combination regimen in patients with baseline multiple mutations should be checked.
- According to a pooled analysis of the SVR12 rate with GZR + EBR without RBV in foreign clinical studies, the SVR12 rate with GZR + EBR in genotype 1a chronic hepatitis C patients with or without compensated cirrhosis having baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, or 93 was 70.0% (39 of 56), which was lower than the SVR12 rate in patients without baseline NS5A resistance-associated polymorphisms (98.0%, [441 of 450]). In Japan, 1% to

3% of genotype 1 chronic hepatitis C patients are reported to have genotype 1a infection (*J Med Virol*. 2012; 84: 438-44). The number of genotype 1a patients is small in Japan as compared to the US, etc. and these patients with baseline NS5A resistance-associated polymorphisms should be even fewer. Though the SVR12 rate with GZR + EBR in genotype 1a chronic hepatitis C patients with or without compensated cirrhosis in a Japanese phase II/III study was 100%, it was achieved only in 5 patient with genotype 1a. Thus, in terms of genotype 1a chronic hepatitis C patients with or without baseline NS5A resistance-associated polymorphisms, foreign study data should be provided to healthcare professionals.

Taking account of the comments from the Expert Discussion, PMDA asked the applicant to explain the efficacy of GZR + EBR in patients with baseline multiple mutations, and confirmed the study results below. Further, the SVR12 rate with GZR + EBR was lower in genotype 1a chronic hepatitis C patients with baseline NS5A resistance-associated polymorphisms than in those without baseline NS5A resistance-associated polymorphisms in foreign studies. PMDA instructed the applicant to communicate this finding to healthcare professionals appropriately, and the applicant agreed.

- In Parts 1 and 2 of the Japanese phase II/III study (MK-5172-058), 293 chronic hepatitis C patients with or without compensated cirrhosis received GZR + EBR. Of these, 29 patients (including 5 patients with compensated cirrhosis) had baseline multiple mutations. All of the 29 patients had genotype 1b infection, and the SVR12 rate was 100% (29 of 29). Meanwhile, the SVR12 rate in 164 patients without resistance-associated variants (including 18 patients with compensated cirrhosis) was 98.2% (161 of 164 patients).
- In the foreign pooled analysis, both NS3/4A and NS5A sequencing data were available at baseline in 797 genotype 1 chronic hepatitis C patients with or without compensated cirrhosis who received GZR + EBR. Of these, 83 patients (including 22 patients with compensated cirrhosis) had baseline multiple mutations. The 83 patients comprised 66 genotype 1a and 17 genotype 1b patients. The SVR12 rate was 84.8% (56 of 66) in the genotype 1a patients and 88.2% (15 of 17) in the genotype 1b patients. Meanwhile, in the foreign pooled analysis, the SVR12 rate in 428 patients without resistance-associated variants (including 90 patients with compensated cirrhosis) was 98.1% (420 of 428 patients).

1.2 Indication

PMDA's conclusion on the indication (Section "7.R.4 Indication") was supported at the Expert Discussion. The expert advisors made the following comment.

- In light of the resistance profiles of GZR and EBR, the efficacy of the GZR + EBR combination regimen may be reduced in NS3/4A protease inhibitor- or NS5A inhibitor-experienced patients. Thus, the GZR/EBR combination regimen cannot be recommended for this patient population.

PMDA's view:

There is no experience with GZR + EBR in patients who failed prior combination therapy with an NS3/4A protease inhibitor or an NS5A inhibitor in Japanese or foreign clinical studies. The use of the combination regimen thus cannot be highly recommended for these patients. However, because of limited therapeutic options for these patients, there is a possibility that GZR + EBR is used at the discretion of a physician in clinical settings. When these patients are treated with GZR + EBR, data on resistance-associated variants and efficacy, etc. should be collected.

1.3 Draft risk management plan

PMDA's conclusion described in Section "7.R.7 Post-marketing investigations" of the Review Report (1) was supported at the Expert Discussion. Based on the comments from the expert advisors, PMDA considers that the following additional points should be investigated via post-marketing surveillance.

- Safety and efficacy in elderly patients, patients with compensated cirrhosis, and patients with severe renal impairment (including those requiring dialysis)
- Occurrence of hepatic dysfunction
- Association between resistance-associated variants prior to the initiation of therapy and at the time of failure and efficacy
- Resistance-associated variants and efficacy, etc. in NS3/4A protease inhibitor- or NS5A inhibitor-experienced patients receiving GZR + EBR

PMDA instructed the applicant to investigate the above points via post-marketing surveillance and the applicant agreed.

Taking account of the above discussion, PMDA concluded that the safety and efficacy specifications listed in Table 63 should be included in the current draft risk management plan for Grazyna Tablets 50 mg and Erelsa Tablets 50 mg and that additional pharmacovigilance activities and risk minimization activities listed in Table 64 should be carried out, and accepted an outline of the draft drug use-results survey plan as shown in Table 65.

Table 63. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
・Hepatic dysfunction ・Reactivation of hepatitis B virus	None	None
Efficacy specification		
・Drug resistance ・Efficacy in routine clinical settings		

Table 64. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

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

Table 65. Outline of the drug use-results survey (draft)

Objective	To collect safety and efficacy data in routine clinical settings.
Survey method	Central registry system
Population	Serogroup 1 (genotype 1) chronic hepatitis C patients with or without compensated cirrhosis
Observation period	3 years (up to 24 weeks post-therapy)
Planned sample size	1000 patients (including 300 patients with compensated cirrhosis)
Main survey items	Hepatic dysfunction, safety and efficacy in elderly patients, patients with compensated cirrhosis, and patients with severe renal impairment (including patients requiring dialysis), the occurrence of resistance-associated variants, etc.

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 Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its regulatory review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the products may be approved for the indication and dosage and administration shown below with the following condition. Grazyna Tablets 50 mg and Erelsa Tablets 50 mg are drugs with a new active ingredient. For both products, the re-examination period is 8 years, neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug, and the product is not classified as a biological product or a specified biological product.

Indication

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

Dosage and Administration

Grazyna Tablets 50 mg

The usual adult dosage is 100 mg of Grazoprevir, administered orally once daily in combination with Elbasvir for 12 weeks.

Erelsa Tablets 50 mg

The usual adult dosage is 50 mg of Elbasvir, administered orally once daily in combination with Grazoprevir Hydrate for 12 weeks.

Condition of approval

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