Report on the Deliberation Results

September 12, 2017

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

Brand Name	Maviret Combination Tablets
Non-proprietary Name	Glecaprevir Hydrate/Pibrentasvir (JAN*)
Applicant	AbbVie GK
Date of Application	February 14, 2017

Results of Deliberation

In its meeting held on September 8, 2017, the Second Committee on New Drugs concluded that the product may be approved for the dosage and administration modified as shown below and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Condition of Approval

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

Before the committee meeting	After the committee meeting
Dosage and Administration • Serogroup 1 (genotype 1) or serogroup 2 (genotype 2) chronic hepatitis C virus infection The usual adult dosage is 3 tablets (300 mg of glecaprevir and 120 mg of pibrentasvir) orally administered once daily after a meal. The duration of treatment is 8 weeks. It may be extended to 12 weeks depending on the history of previous treatment for chronic hepatitis C. • Serogroup 1 (genotype 1) or serogroup 2 (genotype 2) compensated cirrhosis type C • Non-serogroup 1 (-genotype 1) or non-serogroup 2 (-genotype 2) chronic hepatitis C or compensated cirrhosis type C The usual adult dosage is 3 tablets (300 mg of glecaprevir and 120 mg of pibrentasvir) orally administered once daily after a meal. The duration of treatment is 12 weeks.	**Dosage and Administration** ○ Serogroup 1 (genotype 1) or serogroup 2 (genotype 2) chronic hepatitis C virus infection The usual adult dosage is 3 tablets (300 mg of glecaprevir and 120 mg of pibrentasvir) orally administered once daily after a meal. The duration of treatment is 8 weeks. It may be extended to 12 weeks depending on the history of previous treatment for chronic hepatitis C. ○ Serogroup 1 (genotype 1) or serogroup 2 (genotype 2) compensated cirrhosis type C ○ Non-serogroup 1 (-genotype 1) or non-serogroup 2 (-genotype 2) chronic hepatitis C or compensated cirrhosis type C The usual adult dosage is 3 tablets (300 mg of glecaprevir and 120 mg of pibrentasvir) orally administered once daily after a meal. The duration of treatment is 12 weeks.

(Underline denotes modification.)

**Japanese Accepted Name (modified INN)*

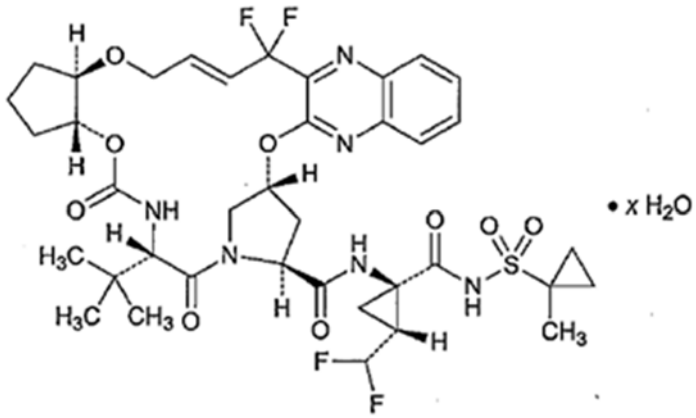
Review Report

August 21, 2017

Pharmaceuticals and Medical Devices Agency

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

Brand Name	Maviret Combination Tablets
Non-proprietary Name	Glecaprevir Hydrate/Pibrentasvir
Applicant	AbbVie GK
Date of Application	February 14, 2017
Dosage Form/Strength	Tablets each containing Glecaprevir Hydrate (100 mg as Glecaprevir) and 40 mg of Pibrentasvir
Application Classification	Prescription drug, (1) Drug with a new active ingredient, (2) New combination drug
Chemical Structure	Glecaprevir Hydrate

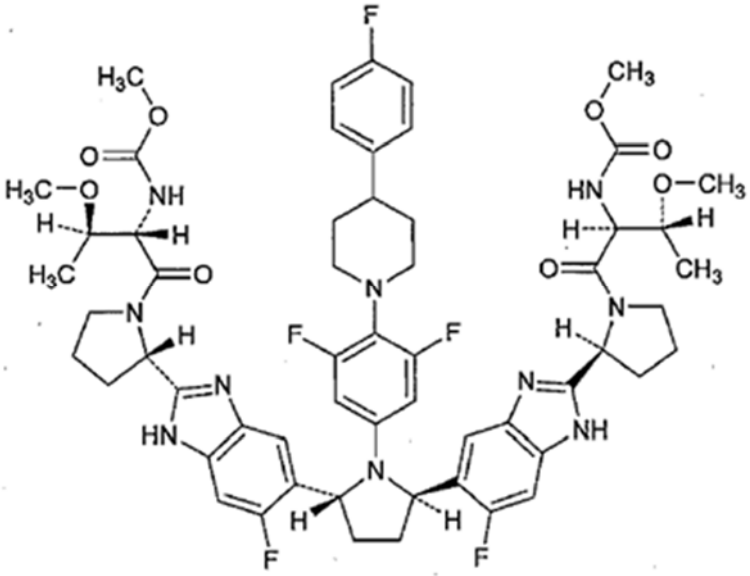


Molecular formula: $C_{38}H_{46}F_4N_6O_9S \cdot xH_2O$

Molecular weight: 838.87 (as anhydride)

Chemical name: (3a*R*,7*S*,10*S*,12*R*,21*E*,24a*R*)-7-(1,1-Dimethylethyl)-*N*-{(1*R*,2*R*)-2-(difluoromethyl)-1-[(1-methylcyclopropane-1-sulfonyl)carbamoyl]cyclopropyl}-20,20-difluoro-5,8-dioxo-2,3,3a,5,6,7,8,11,12,20,23,24a -dodecahydro-1*H*,10*H*-9,12-methanocyclopenta[18,19] [1,10,17,3,6] trioxadiazacyclononadecino[11,12-*b*]quinoxaline-10-carboxamide hydrate

Pibrentasvir



Molecular formula: $C_{57}H_{65}F_5N_{10}O_8$

Molecular weight: 1113.18

Chemical name: Dimethyl *N*,*N*'-([(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl} pyrrolidine-2,5-diyl]bis{(6-fluoro-1*H*-benzimidazole-5,2-diyl) [(2*S*)-pyrrolidine-2,1-diyl] [(2*S*,3*R*)-3-methoxy-1-oxobutane- 1,2-diyl]}) dicarbamate

Items Warranting Special Mention

Priority Review (PSEHB/PED Notification No. 0302-7 dated March 2, 2017, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with chronic hepatitis C or compensated cirrhosis type C, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indication

Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C

Dosage and Administration

- Serogroup 1 (genotype 1) or serogroup 2 (genotype 2) chronic hepatitis C virus infection
  The usual adult dosage is 3 tablets (300 mg of glecaprevir and 120 mg of pibrentasvir) orally administered once daily after a meal. The duration of treatment is 8 weeks. It may be extended to 12 weeks depending on the history of previous treatment for chronic hepatitis C.
- Serogroup 1 (genotype 1) or serogroup 2 (genotype 2) compensated cirrhosis type C
- Non-serogroup 1 (-genotype 1) or non-serogroup 2 (-genotype 2) chronic hepatitis C or compensated cirrhosis type C
  The usual adult dosage is 3 tablets (300 mg of glecaprevir and 120 mg of pibrentasvir) orally administered once daily after a meal. The duration of treatment is 12 weeks.

Condition of Approval

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

Attachment

Review Report (1)

July 4, 2017

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 (PMDA).

Product Submitted for Approval

Brand Name	Maviret Combination Tablets
Non-proprietary Name	Glecaprevir Hydrate/Pibrentasvir
Applicant	AbbVie GK
Date of Application	February 14, 2017
Dosage Form/Strength	Tablets each containing Glecaprevir Hydrate (100 mg as Glecaprevir) and 40 mg of Pibrentasvir
Proposed Indication	Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C

Proposed Dosage and Administration

The usual adult dosage is 3 tablets (300 mg of glecaprevir and 120 mg of pibrentasvir) orally administered once daily after a meal. The treatment duration is as follows:

- Patients with serogroup 1 or 2 (genotype 1 or 2) chronic hepatitis C who have not received direct-acting antiviral therapy: 8 weeks
- Patients other than the above: 12 weeks

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List of Abbreviations

ALT	Alanine aminotransferase
Ames test	Test for reverse mutation in bacteria
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
AUC_{0-t}	Area under plasma concentration-time curve up to t hours
AUC_{inf}	Area under plasma concentration-time curve up to infinity
BCRP	Breast cancer resistance protein
BID	bis in die
BMI	Body mass index
BSEP	Bile salt export pump
C_{24}	Plasma concentration at 24 hours postdose
CL	Clearance
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
C_{trough}	Trough plasma concentration
CV%	Coefficient of variation %
DAA	Direct acting antivirals
EC_{50}	50% effective concentration
Efflux ratio	Basal-to-apical versus apical-to-basal ratio
eGFR	Estimated glomerular filtration rate
FMO	Flavin-containing monooxygenase
GLE	Glecaprevir hydrate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV-1	Human immunodeficiency virus type 1
IC_{50}	50% inhibitory concentration
ICH M7 Guideline	Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (PSEHB/ELD Notification No. 1110-3 dated November 10, 2015)
ICH Q1E Guideline	Evaluation for Stability Data (PFSB/ELD Notification No.0603004 dated June 3, 2003)
IFN	Interferon
ITT	Intention-to-Treat
JSH Guidelines for the Management of Hepatitis C Virus Infection Version 5.4	Guidelines for the Management of Hepatitis C Virus Infection (Version 5.4), by the Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology; 2017
MATE	Multidrug and toxin extrusion
Maviret	Maviret Combination Tablets
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OBV/PTV/r	Ombitasvir/paritaprevir/ritonavir
OCT	Organic cation transporter
PegIFN	Peginterferon
P-gp	P-glycoprotein
PIB	Pibrentasvir
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
QD	quaque die
QTc	Corrected QT interval
RBV	Ribavirin
SOF	Sofosbuvir

SVR12	Sustained viral response 12
$t_{1/2}$	Elimination half-life
t_{max}	Time to reach maximum plasma concentration
UGT	Uridine diphosphate glucuronosyltransferase

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

Maviret Combination Tablets is a combination product containing glecaprevir hydrate (hereinafter referred to as "glecaprevir [GLE]"), a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir (PIB), a HCV NS5A inhibitor, as active ingredients, and currently being developed by AbbVie Inc. as a therapeutic drug product for HCV infection.

The number of patients with HCV infection is estimated to be approximately 170 million in the world, and 1.5 to 2 million in Japan (JSH Guidelines for the Management of Hepatitis C Virus Infection Version 5.4). HCV is classified into genotypes 1 to 6. Approximately 70% of Japanese patients with HCV have genotype 1 virus, approximately 30% genotype 2 virus, and approximately 2% genotype 3, 4, 5, or 6 virus (*Epidemiol Infect.* 2014;142:2624-8, *Hepatol Res.* 2003;25:409-14 and others). Table 1 shows interferon (IFN) -free direct acting antiviral (DAA) therapy regimens that have been approved for the treatment of chronic hepatitis C or compensated cirrhosis type C in Japan.

Table 1. IFN –free DAA therapy regimens for patients with chronic hepatitis C or compensated cirrhosis type C

Genotype	Therapeutic regimen
Genotype 1	• Concomitant use of daclatasvir hydrochloride with asunaprevir • Ledipasvir acetonate/sofosbuvir (SOF) combination drug • Ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) • Concomitant use of elbasvir with grazoprevir • Daclatasvir hydrochloride/asunaprevir/beclabuvir hydrochloride combination drug
Genotype 2	• Concomitant use of SOF with ribavirin (RBV) • Concomitant use of OBV/PTV/r with RBV[a)]
Genotype 3, 4, 5, 6	• Concomitant use of SOF with RBV

a) Indicated for chronic hepatitis C only

The applicant has submitted a marketing application for Maviret based on results from Japanese and foreign clinical studies in patients with genotype 1 to 6 chronic hepatitis C or compensated cirrhosis type C.

As of June 2017, Maviret has not been approved in foreign countries, but the review is underway in Europe and the US.

In this report, NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors are collectively described as DAA.

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

2.1 Drug substance (GLE)

2.1.1 Characterization

The drug substance occurs as a white crystalline powder. The determined general properties include solubility, membrane permeability, melting point (thermolysis), acid dissociation constant, distribution coefficient, optical isomer, crystalline polymorphism, and hygroscopicity. Of the drug substance, 4 crystalline forms have been observed. By the commercial manufacturing process, however, only Form I crystals of the nonstoichiometric polyhydrate are produced, and the crystalline form has been demonstrated to be stable at room temperature.

The chemical structure of the drug substance has been elucidated by mass spectrometry, infrared spectrophotometry (IR), and nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR). In addition, the drug substance has 7 stereogenic centers.

2.1.2 Manufacturing process

The drug substance is synthesized from the starting materials of [redacted], and [redacted].

Based on the following investigation, control strategy of the quality has been constructed:

- Identification of [redacted] as critical quality attributes
- Identification of critical step parameters and critical step control based on quality risk assessment, experimental design, and systemic understanding of manufacturing process

As critical steps, [redacted] have been identified. As critical intermediates, [redacted] have been identified, and the corresponding control parameters and control values have been specified.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (liquid chromatography [LC] and IR), particle size distribution, purity (related substances [LC] and residual solvents [gas chromatography (GC)]), water content, residue on ignition, microbial limit, and assay (LC).

2.1.4 Stability of drug substance

The major stability studies conducted on the drug substance are as shown in Table 2. Photostability data showed that the drug substance is unstable to light.

Table 2. Stability studies for drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term testing	Pilot 3 batches	30ºC	75%RH	Polyethylene bag (double-layered)	18 months
Accelerated testing	Pilot 3 batches	40ºC	75%RH	Polyethylene bag (double-layered)	6 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance when stored in double polyethylene bags, and the bags are then stored in a light-resistant, high-density polyethylene

[redacted]

drum at room temperature in accordance with ICH Q1E Guideline. The long-term testing will be continued up to [redacted] months.

2.2 Drug substance (PIB)

2.2.1 Characterization

The drug substance occurs as a white to pale yellow crystalline powder. The determined general properties include solubility, membrane permeability, melting point, acid dissociation constant, distribution coefficient, optical isomer, crystalline polymorphism, and hygroscopicity. Of the drug substance, 5 crystalline forms have been observed. By the commercial manufacturing process, however, only Form III crystals of the anhydrous desolvate are produced, and the concerned crystalline form has been demonstrated to be stable at room temperature.

The chemical structure of the drug substance has been elucidated by mass spectrometry, IR, and nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR). In addition, the drug substance has 8 stereogenic centers.

2.2.2 Manufacturing process

The drug substance is synthesized from the starting materials of [redacted].

Based on the following investigation, control strategy of the quality has been constructed:

- Identification of [redacted] as critical quality attributes
- Identification of critical step parameters based on quality risk assessment, experimental design, and systemic understanding of manufacturing process

As critical steps, [redacted] have been identified. As critical intermediates, [redacted] have been identified, and the corresponding control parameters and control values have been specified.

2.2.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (LC and IR), particle size distribution, purity (related substances [LC], elemental impurities [inductively coupled plasma emission spectrometry], and residual solvents [GC]), water content, residue on ignition, microbial limit, and assay (LC).

2.2.4 Stability of drug substance

The major stability studies conducted on the drug substance are as shown in Table 3. Photostability data showed that the drug substance is unstable to light.

Table 3. Stability studies for drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term testing	Pilot 3 batches	30ºC	75%RH	Polyethylene bag (double-layered)	18 months
Accelerated testing	Pilot 3 batches	40ºC	75%RH	Polyethylene bag (double-layered)	6 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance when stored in double polyethylene bags, and the bags are then stored in a light-resistant, high-density polyethylene drum at room temperature, in accordance with the ICH Q1E Guideline. The long-term testing will be continued up to [redacted] months.

2.3 Drug product

2.3.1 Description and composition of drug product and formulation development

The drug product is film-coated tablets, each containing the drug substances, GLE at 100 mg (as glecaprevir) and PIB at 40 mg. The drug product also contains copolyvidone, d-α-tocopherol polyethylene glycol succinate, propylene glycol fatty acid ester, light anhydrous silicic acid, croscarmellose sodium, sodium stearyl fumarate, and [redacted] as excipients.

2.3.2 Manufacturing process

The manufacturing process of the drug product consists of [redacted] ([redacted] and [redacted]), [redacted], blending, compression, film-coating, filling, packaging, labeling, storage, and testing steps. Of these steps, [redacted] ([redacted] and [redacted]) have been identified as critical steps, and the corresponding process control parameters and process control values have been specified.

Based on the following investigation, control strategy of the quality has been constructed:

- Identification of [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] as critical quality attributes
- Identification of critical step parameters based on quality risk assessment and experimental design

2.3.3 Control of drug product

The proposed specifications for the drug product include content, description, identification (ultraviolet spectrophotometry [UV] and LC), purity (degradation products [LC]), water content, uniformity of dosage units (content uniformity [LC]), dissolution (LC), microbial limit, and assay (LC).

2.3.4 Stability of drug product

The stability studies conducted on the drug product are as shown in Table 4. Photostability data showed that the drug product is photostable.

Table 4. Stability of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term testing	Pilot 3 batches	30°C	75%RH	PTP package	18 months
Accelerated testing	Pilot 3 batches	40°C	75%RH		6 months

Based on the above, a shelf-life of 30 months has been proposed for the drug product when stored in a PTP (polyvinyl chloride/polyethylene/polychlorotrifluoroethylene) at room temperature in accordance with the ICH Q1E Guideline. The long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

As a result of review of the submitted data and the following considerations on a novel excipient, PMDA has concluded that the quality of the drug substance and drug product is appropriately controlled.

2.R.1 Novel excipients

The content of copolyvidone in the drug product exceeds the amounts that have been previously used in oral pharmaceutical products.

2.R.1.1 Specifications and stability

Because copolyvidone in use conforms to the requirements in the Japanese Pharmaceutical Excipients, PMDA has concluded that the specifications and stability are acceptable.

2.R.1.2 Safety

Based on the submitted data, PMDA has concluded that the safety of copolyvidone does not have any particular problems at the clinical dose of the drug product.

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

The pharmacological effects of GLE and PIB were evaluated for primary pharmacodynamics, secondary pharmacodynamics, and safety pharmacology. For GLE, pharmacodynamic drug interaction studies were also conducted. In non-clinical pharmacology studies, anhydride of GLE was used, and the concentration is indicated on the basis of glecaprevir.

3.1 Primary pharmacodynamics (GLE)

3.1.1 Inhibitory effect against NS3/4A protease (CTD 4.2.1.1-1, 4.2.1.1-2)

The inhibitory effect of GLE against NS3/4A protease derived from each HCV genotype was investigated, and the results are as shown in Table 5. In addition, the effect against various human proteases (chymase, elastase, cathepsin B, chymotrypsin, kallikrein, and urokinase) was investigated, but the 50% inhibitory concentration (IC_{50}) of GLE against any of them exceeded 200 μmol/L.

Table 5. Inhibitory effect of GLE against NS3/4A protease derived from each HCV genotype

Genotype	IC_{50} (nmol/L)
1a	4.6
1b	8.9
2a	3.5
2b	3.8
3a	7.9
4a	6.1
5a	8.1
6a	11.3

Mean

3.1.2 *In vitro* antiviral activity (CTD 4.2.1.1-1 to 4.2.1.1-3)

The antiviral activity of GLE in HCV replicon cells of each genotype was investigated by HCV replicon assay (detection system, luciferase reporter gene assay), and the results are as shown in Table 6. The applicant explained that preparation of HCV replicon cells of genotype 5 derived from a laboratory isolate by integrating the corresponding amino acid sequence was not possible.

Table 6. Antiviral activity of GLE against each genotype

Genotype (virus strain)	EC_{50} (nmol/L)
1a (H77)	0.85
1a (H77) (with 40% human plasma)	5.3
1a (clinical isolate)[a)]	0.05-0.12[g)]
1b (Con1)	0.94
1b (Con1) (with 40% human plasma)	10
1b (clinical isolate)[b)]	0.20-0.68[h)]
2a (JFH1)	2.2
2a (clinical isolate)[c)]	0.66-1.9[i)]
2b[d)]	4.6
2b (clinical isolate)[c)]	1.4-3.2[i)]
3a[e)]	1.9
3a (clinical isolate)[b)]	0.71, 3.8[j)]
4a[e)]	2.8
4a (clinical isolate)[b)]	0.31-0.55[k)]
4b (clinical isolate)[b)]	0.13-0.25[l)]
5a (clinical isolate)[f)]	0.12[m)]
6a[e)]	0.86

Mean

a) Genotype 1a (H77) replicon cells in which amino acid sequence in the NS3 region derived from a patient with genotype 1a is integrated; b) Genotype 1b (Con1) replicon cells in which amino acid sequence in the NS3 region derived from a patient with the relevant genotype is integrated; c) Genotype 2a (JFH1) replicon cells in which amino acid sequence in the NS3 region derived from a patient with the relevant genotype is integrated; d) Genotype 2a (JFH1) replicon cells in which amino acid sequence in the NS3 region derived from a laboratory isolate of genotype 2b is integrated; e) Genotype 1b (Con1) replicon cells in which amino acid sequence in the NS3 region derived from a laboratory isolate of the relevant genotype is integrated; f) Genotype 5a (SA13) replicon cells in which amino acid sequence in the NS3 region derived from a patient with genotype 5a is integrated; g) Range obtained from 11 isolates; h) Range obtained from 9 isolates; i) Range obtained from 4 isolates; j) Range obtained from 2 isolates; k) Range obtained from 6 isolates; l) Range obtained from 3 isolates; m) Value from 1 isolate

In addition, cytotoxicity of GLE against various cell lines was investigated. The 50% cytotoxic concentrations of GLE against HepG2 cells, MT 4 cells, and Huh-7 cells with genotype 1a (H77) replicon were 62, 59, and 72 μmol/L, respectively.

3.1.3 Resistance profile

3.1.3.1 Resistance selection study (CTD 4.2.1.1-2, 4.2.1.1-3)

After culture of HCV replicon cells with GLE for approximately 3 weeks, amino acid mutations were found in the NS3 region, as shown in Table 7.

Table 7. Amino acid mutations in the NS3 region in HCV replicon cells

Genotype (virus strain)	GLE concentration (multiple of EC_{50})[c)]	Amino acid mutation (number of colonies formed[d)])
1a (H77)	10	Q41R (13/28), I170V (10/28)
	100	A156T (8/17), A156V (3/17), Q89R + A156T (4/17)
	500	-[e)]
1b (Con1)	10	A156T (3/25), A156V (7/25), P89L + A156V (6/25)
	100	A156V (5/25), P89L + A156V (5/25), A156V + D168V (5/25)
	500	A156V (5/24), P89L + A156V (6/24), A156V + D168V (8/24)
2a (JFH1)	10	A156T (13/24), A156V (9/24), G15D + A156T (2/24)
	100	A156T (5/23), A156V (16/23), G15D + A156V (2/23)
	500	-
2b[a)]	10	A156T (21/23), A156V (2/23)
	100	A156T (16/20), A156V (4/20)
	500	A156M (1/21), A156V (20/21)
3a[b)]	10	P89L (2/10), P89S (2/10)
	100	Y56H + Q168R (2/3), A156G (1/3)
	500	-[e)]
4a[b)]	10	A156T (23/26), A156V (9/36)
	100	A156T (6/9), A156V (1/9)
	500	A156T (5/14), A156V (4/14)
6a[b)]	10	D168H (13/25), D168V (7/25)
	100	-[e)]
	500	-[e)]

-, Not investigated or not detected

a) Genotype 2a (JFH1) replicon cells in which amino acid sequence in the NS3 region derived from genotype 2b is integrated; b) Genotype 1b (Con1) replicon cells in which amino acid sequence in the NS3 region derived from the relevant genotype is integrated; c) For 50% effective concentration (EC_{50}) of GLE, see Section "3.1.2 *In vitro* antiviral activity"; d) Number of colonies with the concerned substitution/number of viable colonies; e) No cell growth observed, not investigated.

3.1.3.2 Antiviral activity of GLE against mutants (CTD 4.2.1.1-2, 4.2.1.1-4)

The antiviral activity of GLE was investigated in HCV replicon cells in which amino acid mutations in the NS3 region detected in the *in vitro* resistance selection study [see Section "3.1.3.1 Resistance selection study"] and in clinical studies[2)] of GLE/PIB as well as amino acid mutations in the NS3 region[3)] reported with the other NS3/4A protease inhibitors were introduced. The results are as shown in Table 8.

Table 8. Antiviral activity of GLE against wild-type and mutant HCV replicon cells

Genotype (virus strain)	Amino acid mutation in the NS3 region	EC_{50} (nmol/L)	EC_{90} (nmol/L)	Change in susceptibility[a)]
1a (H77)	Wild-type	0.21	0.77	-
	V36A	0.18	1.1	0.8
	V36L	0.16	1.2	0.8
	V36M	0.28	1.1	1.4
	Q41R	0.33	1.7	1.6
	F43L	0.05	0.27	0.3
	T54S	0.20	0.79	1.0
	V55I	0.05	0.29	0.2
	Y56H	0.21	1.9	1.0
	Q80K	0.19	0.65	0.9
	Q89R	0.34	1.5	1.6
	R155K	0.11	0.48	0.5
	R155M	0.18	0.86	0.9
	R155S	0.34	2.4	1.6
	R155T	0.39	2.0	1.9
	R155V	0.21	1.8	1.0

2) Japanese phase III study (Study M15-594), foreign phase II studies (Studies M14-868 and M15-410), and foreign phase III studies (Studies M13-590, M13-594, and M14-172)

3) Subjected to resistance mutations in the NS3 region reported in the package inserts and literature of boceprevir, telaprevir, paritaprevir, grazoprevir, vaniprevir, faldaprevir, asunaprevir, and simeprevir

Genotype (virus strain)	Amino acid mutation in the NS3 region	EC_{50} (nmol/L)	EC_{90} (nmol/L)	Change in susceptibility[a)]
	A156G	0.13	1.1	0.6
	A156T	286	1527	1361
	A156V[b)]	-	-	-
	D168A	0.84	7.5	4.0
	D168E	0.27	1.7	1.3
	D168F	11.5	18.9	55
	D168H	0.91	7.0	4.3
	D168N	0.08	0.60	0.4
	D168V	0.93	8.8	4.4
	D168Y	8.6	24.8	41
	I170V	0.21	1.1	1.0
	V36M + R155K	0.14	0.60	0.7
	Y56H + D168A	8.2	33.3	39
	Y56H + D168V	8.9	46.8	42
	Y56H + D168Y	9.4	34.8	45
	Q89R + A156T	753	>10,000	3585
	R155T + D168N	5.9	28.5	28
	V36M + Y56H + D168A	33.9	116	162
	V36M + Y56H + D168E	26.7	101	127
	Y56H + A156G + D168A[b)]	-	-	-
	R155K + A156V + D168A[b)]	-	-	-
1b (Con1)	Wild-type	0.47	1.9	-
	T54A	0.45	1.9	1.0
	T54S[b)]	-	-	-
	V55A	0.21	2.2	0.4
	Y56H[b)]	-	-	-
	P89L	1.1	3.7	2.4
	R155K	0.27	1.5	0.6
	R155Q[b)]	-	-	-
	A156S	0.20	2.0	0.4
	A156T	301	1545	640
	A156V	839	3440	1786
	D168A	0.69	1.8	1.5
	D168E	0.40	1.8	0.9
	D168F	2.5	10.3	5.3
	D168H	0.68	3.1	1.4
	D168K	5.3	20.6	11
	D168V	1.5	5.9	3.2
	D168Y	0.99	4.5	2.1
	Y56H + D168A	8.0	32.0	17
	Y56H + D168E[b)]	-	-	-
	Y56H + D168V	7.2	32.9	15
	Y56H + D168Y	35.6	73.1	76
	P89L + A156V	1994	5894	4243
	A156V + D168V	2465	6167	5244
2a (JFH1)	Wild-type	2.5	6.2	-
	G15D	1.1	4.0	0.5
	V55A	2.3	5.6	0.9
	Y56H	1.4	3.8	0.6
	A156T	541	957	216
	A156V	2857	4203	1143
	D168A	4.8	9.3	1.9
	D168E	8.1	16.1	3.3
	D168V	4.9	13.2	2.0
	D168Y	6.0	17.7	2.4
	G15D + A156T	871	1647	348
	G15D + A156V	3470	5646	1388
	Y56H + D168A	2.3	7.8	0.9
	Y56H + D168E	4.6	14.3	1.8
	Y56H + D168V	7.5	28.7	3.0

Genotype (virus strain)	Amino acid mutation in the NS3 region	EC_{50} (nmol/L)	EC_{90} (nmol/L)	Change in susceptibility[a)]
2b[c)]	Wild-type	3.1	8.9	-
	A156M	3370	4347	1087
	A156T	460	788	148
	A156V	4510	4298	1455
	D168A	3.9	10.9	1.3
	D168E	6.6	13.4	2.1
	D168V	9.1	23.6	2.9
	D168Y	6.6	16.7	2.1
3a[d)]	Wild-type	0.55	7.2	-
	Y56H[b)]	-	-	-
	Q80R	11.5	296	21
	R155K	0.28	2.7	0.5
	A156G	909	3245	1654
	S166A[b)]	-	-	-
	S166T	2.6	75.5	4.7
	Q168H	0.40	9.0	0.7
	Q168K[b)]	-	-	-
	Q168L	6.9	211	13
	Q168R	30.0	305	54
	Y56H + Q168R	763	4259	1387
	Q80R + S166T	29.8	904	54
4a[d)]	Wild-type	0.67	2.8	-
	R155C	1.7	9.2	2.6
	A156T	962	1511	1436
	A156V	2081	6561	3106
	D168H	14.6	29.5	22
	D168V	6.5	24.5	9.7
4d[d)]	Wild-type	0.15	0.88	-
	Y56H	0.69	5.8	4.6
	D168V	0.28	1.6	1.9
	Y56H + D168V	8.7	26.3	58
6a[d)]	Wild-type	0.15	1.0	-
	D168A	12.2	32.0	81
	D168G	28.6	59.2	191
	D168H	22.0	77.7	146
	D168V	5.8	24.3	38
	D168Y	16.3	34.2	109

Mean

-, Not investigated or not detected

a) EC_{50} for mutant replicon/EC_{50} for wild-type replicon; b) No cell growth observed, not investigated; c) Genotype 2a (JFH1) replicon cells in which amino acid sequence in the NS3 region derived from genotype 2b is integrated; d) Genotype 1b (Con1) replicon cells in which amino acid sequence in the NS3 region derived from the relevant genotype is integrated

3.1.3.3 Cross resistance

3.1.3.3.1 Antiviral activity of GLE against HCV replicon cells with resistance mutations in the NS5A or NS5B region (CTD 4.2.1.1-2, 4.2.1.1-4)

Antiviral activity of GLE was investigated in HCV replicon cells with major resistance mutations[4)] in the NS5A or NS5B region. The results are as shown in Table 9.

[4)] Subjected to resistance mutations in the NS5A or NS5B region reported from *in vitro* resistance selection studies and clinical studies as well as in literature of daclatasvir, ombitasvir, ledipasvir, elbasvir , sofosbuvir, beclabuvir, and PIB.

Table 9. Antiviral activity of GLE against replicon cells with major resistance mutations in the NS5A or NS5B region

Genotype (virus type)	Region	Amino acid mutation	EC_{50} (nmol/L)	Change in susceptibility[a)]
1a (H77)	NS5A	Wild-type	0.46	-
		M28T	0.44	1.0
		M28V	0.50	1.1
		Q30D	0.31	0.7
		Q30R	0.59	1.3
		Y93C	0.57	1.2
		Y93H	0.52	1.1
		Y93N	0.60	1.3
	NS5B	Wild-type	0.14	-
		C316Y	0.15	1.1
		M414T	0.35	2.5
		Y448C	0.22	1.6
		Y448H	0.27	2.0
		S556G	0.20	1.4
		S559G	0.31	2.2
		S282T	0.05	0.2[b)]
1b (Con1)	NS5A	Wild-type	0.33	-
		L28T	0.15	0.4
		Y93H	0.45	1.4
	NS5B	Wild-type	0.26	-
		C316Y	0.22	0.9
		Y448H	0.21	0.8
		S556G	0.30	1.2
		S282T	0.20	0.4[c)]

a) EC_{50} for mutant replicon/EC_{50} for wild-type replicon; b) Ratio to EC_{50} (0.21 nmol/L) for wild-type replicon; c) Ratio to EC_{50} (0.47 nmol/L) for wild-type replicon

3.1.3.3.2 Antiviral activity of GLE and the other NS3/4A protease inhibitors against HCV replicon cells with resistance mutations in the NS3 region (CTD 4.2.1.1-4)

Antiviral activity of GLE and the other NS3/4A protease inhibitors was investigated in HCV replicon cells with amino acid mutations[2),3)] in the NS3 region. The results are as shown in Table 10.

Table 10. Antiviral activity of GLE and the other NS3/4A protease inhibitors against HCV replicon cells with each resistance mutation in the NS3 region

Genotype (virus type)	Amino acid mutation	Change in susceptibility[a)]		
		GLE	Grazoprevir	Paritaprevir
1a (H77)	V36L	0.8	1.6	2
	V36M	1.4	1.9	2
	F43L	0.3	1.4	20
	T54S	1.0	-	0.4
	V55I	0.2	0.7	1
	Y56H	1.0	16	3
	Q80K	0.9	1.8	3
	R155K	0.5	4.2	37
	R155M	0.9	5.1	1
	A156T	1361	-	17
	D168A	4.0	154	50
	D168E	1.3	33	14
	D168V	4.4	211	96
	D168Y	41	379	219
	V36M + R155K	0.7	5.6	79
	F43L + R155K	0.8	8.1	99
	F43L + D168V	13	143	176
	Y56H + D168A	39	2065	352
	Y56H + D168V	42	1126	561
	Y56H + D168Y	45	1232	451

Genotype (virus type)	Amino acid mutation	Change in susceptibility[a)]		
		GLE	Grazoprevir	Paritaprevir
1b (Con1)	T54A	1.0	-	0.8
	V55A	0.4	-	0.6
	R155K	0.6	-	40
	A156T	640	-	7
	D168A	1.5	-	27
	D168E	0.9	4.1	4
	D168V	3.2	-	159
	D168Y	2.1	-	337
	Y56H + D168A	17	-	700
	Y56H + D168V	15	-	2472
	Y56H + D168Y	76	-	4118
2a (JFH1)	Y56H	0.6	5.6	3.8
	D168A	1.9	13	18
	D168E	3.3	5.9	5.3
	D168V	2.0	-	13
	D168Y	2.4	-	13
2b[b)]	D168A	1.3	57	11
	D168E	2.1	5.7	2.2
	D168V	2.9	14	9.4
	D168Y	2.1	11	7.0
3a[c)]	Q80R	21	0.9	7
	R155K	0.5	0.1	5
	A156G	1654	-	57
	Q168H	0.7	0.3	6
	Q168L	13	0.1	4
	Q168R	54	-	29
4a[c)]	R155C	2.6	-	59
	A156T	1436	-	40
	A156V	3106	-	155
	D168H	22	-	252
	D168V	9.7	-	323
4d[c)]	Y56H	4.6	-	8
	D168V	1.9	-	313
	Y56H + D168V	58	-	12,533

-, Not calculated because EC_{50} was not determined.
a) EC_{50} for mutant replicon/EC_{50} for wild-type replicon; b) Genotype 2a (JFH1) replicon cells in which amino acid sequence in the NS3 region derived from genotype 2b is integrated; c) Genotype 1b (Con1) replicon cells in which amino acid sequence in the NS3 region derived from the relevant genotype is integrated

3.1.4 Antiviral activity against HIV-1 and HBV (CTD 4.2.1.1-2)

Antiviral activity of GLE against human immunodeficiency virus type 1 (HIV-1) (IIIB)-infected CEM-SS cells and hepatitis B virus (HBV)-infected HepG2 2.2.15 cells was investigated, and the 50% effective concentration (EC_{50}) of GLE was >22,000 nmol/L and >32,000 nmol/L, respectively.

3.2 Secondary pharmacodynamics (GLE) (CTD 4.2.1.2-1, 4.2.1.2-2)

The inhibitory effect of GLE against ligand binding to 79 G-protein-coupled receptors, ion channels, and transporters was investigated *in vitro*. GLE (10 μmol/L) inhibited ligand binding to chloride channel by 55%, and IC_{50} was 11 μmol/L, which was 7.9 fold the human clinical exposure (maximum plasma concentration [C_{max}]).[5)] GLE did not inhibit any other ligand binding investigated by ≥50%.

3.3 Safety pharmacology (GLE) (CTD 4.2.1.3-2, 4.2.1.3-4, 4.2.1.3-6, 4.2.1.3-7, 4.2.3.2-GLE-5, 4.2.3.2-GLE-8; Reference data CTD 4.2.1.3-1, 4.2.1.3-3, 4.2.1.3-5)

Effects of GLE on central nervous, cardiovascular, and respiratory systems were investigated (Table 11).

[5)] From the PPK analysis, C_{max} of GLE in Japanese patients with chronic hepatitis C who received GLE 300 mg and PIB 120 mg was estimated to be 1170 ng/mL [see Section "6.2.2.1 PPK analysis"].

Table 11. Summary of safety pharmacology studies

Organ investigated	Test system	Endpoint and evaluation method	Dose or concentration	Route of administration	Special findings
Central nervous system	Male rats (n = 4/group)[a)]	Irwin method	3, 10, 30, 100 mg/kg	Oral	None
	Male rats (n = 10/group)[a)]	Locomotor activity	3, 10, 30, 100 mg/kg	Oral	None
	Male rats (n = 10/group)[a)]	Seizure induction	3, 10, 30, 100 mg/kg	Oral	None
	Male rats (n = 20/group)[a)]	Ethanol-induced sleep	3, 10, 30, 100 mg/kg	Oral	None
	Female rats (n = 8/group)	FOB	5, 20, 60 mg/kg	Oral	None
Cardiovascular system	Human embryonic kidney cells (n = 4)[a)]	hERG current	24.7 µg/mL	*In vitro*	Tail current inhibited by 28.8%
	Human embryonic kidney cells (n = 3/concentration)	hERG current	8.4, 25, 84 µg/mL	*In vitro*	8.4 µg/mL: Inhibited by 1.3% 25 µg/mL: Inhibited by 17.4% 84 µg/mL: Inhibited by 47.9% IC_{50}: 85.6 µg/mL
	Anesthetized male beagle dogs (n = 6)[a)]	Electrocardiogram parameters	1.7, 5.5, 16.6 mg/kg/ 30 min	Ascending dose continuous intravenous infusion	None
	Unanesthetized male beagle dogs (n = 6/group)	Heart rate, PR interval, QRS interval, QTc interval, and mean arterial pressure	10, 30, 100 mg/kg	Oral	None
Respiratory system	Male rats (n = 8/group)	Whole-body plethysmograph	5, 20, 60 mg/kg	Oral	At 60 mg/kg, the respiratory rate increased, the tidal volume reduced, but the total ventilation volume unchanged.

a) Non-GLP study

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

No effects on the central nervous system were observed in the FOB study in rats at 60 mg/kg, and C_{max} (56.2 µg/mL) at this dose was 48 fold[5)] the human clinical exposure (C_{max}). In the cardiovascular system, hERG current was inhibited by GLE in a concentration-dependent manner *in vitro*, but IC_{50} (85.6 µg/mL) was 73.2 fold the human clinical exposure (C_{max}). In addition, no effects on this system were observed in dogs at 100 mg/kg, and C_{max} (85.8 µg/mL) at this dose was approximately 73.3 fold[5)] the human clinical exposure (C_{max}).

In the respiratory system, the respiratory rate and tidal volume were slightly changed at 60 mg/kg (C_{max} 56.7 µg/mL, 48.5 fold[5)] the human clinical exposure [C_{max}]), the maximum dose in studies in rats, but the total ventilation volume (minute ventilation) remained unchanged.

Based on the above, GLE is considered unlikely to affect the central nervous, cardiovascular, or respiratory system during its clinical use.

3.4 Pharmacodynamic drug interactions (GLE) (CTD 4.2.1.4-1)

Effects of GLE (9.6 nmol/L, 10 fold EC_{50}) on anti-HIV activity of an HIV protease inhibitor (lopinavir and darunavir) were investigated using HIV-1 pNL4-3-infected MT4 cells. GLE did not affect EC_{50} of any of the anti-HIV drugs.

In addition, effects of HIV protease inhibitors (lopinavir and darunavir at 100 nmol/L for each, concentrations approximately 5 and 10 fold their EC_{50} values, respectively) on anti-HCV activity of GLE were investigated using genotype 1b (Con1) replicon cells (detection system, luciferase reporter gene assay). Neither anti-HIV drug affected EC_{50} of GLE.

3.5 Primary pharmacodynamics (PIB)

3.5.1 *In vitro* antiviral activity (CTD 4.2.1.1-6, 4.2.1.1-7)

The antiviral activity of PIB in HCV replicon cells of each genotype was investigated by HCV replicon assay (detection system, luciferase reporter gene assay), and the results are as shown in Table 12.

Table 12. Antiviral activity of PIB against each genotype

Genotype (virus strain)	EC_{50} (pmol/L)
1a (H77)	1.8
1a (H77) (with 40% human plasma)	64
1a (clinical isolate)[a)]	0.55-1.7[c)]
1b (Con1)	4.3
1b (Con1) (with 40% human plasma)	200
1b (clinical isolate)[a)]	1.4-3.5[d)]
2a (JFH1)	5.0
2a[b)]	2.3
2a (clinical isolate) [a)]	0.52-1.9[e)]
2b[b)]	1.9
2b (clinical isolate) [a)]	1.1-1.9[c)]
3a[b)]	2.1
3a (clinical isolate)[a)]	0.47-1.7[f)]
4a[b)]	1.9
4a (clinical isolate)[a)]	0.27-1.3[d)]
4b (clinical isolate)[a)]	0.45-1.8[g)]
4d (clinical isolate)[a)]	0.98-1.8[h)]
5a[b)]	1.4
5a (clinical isolate)[a)]	1.1[i)]
6a[b)]	2.8
6a (clinical isolate)[a)]	0.63-1.0[g)]
6e (clinical isolate)[a)]	0.83[i)]
6p (clinical isolate)[a)]	0.50[i)]

Mean

a) Genotype 1b (Con1) replicon cells in which amino acid sequence in the NS5 region derived from the relevant genotype is integrated; b) Genotype 1b (Con1) replicon cells in which amino acid sequence in the NS5 region derived from a laboratory isolate of the relevant genotype is integrated; c) Range obtained from 11 isolates; d) Range obtained from 8 isolates; e) Range obtained from 6 isolates; f) Range obtained from 14 isolates; g) Range obtained from 3 isolates; h) Range obtained from 7 isolates; i) Value obtained from 1 isolate

In addition, cytotoxicity of PIB against various cell lines was investigated. The 50% cytotoxic concentrations of PIB against HepG2 cells, MT 4 cells, and Huh-7 with genotype 1a (H77) replicon cells were >10 μmol/L, >10 μmol/L, and >32 μmol/L, respectively.

3.5.2 Resistance profile

3.5.2.1 Resistance selection study (CTD 4.2.1.1-6, 4.2.1.1-7)

After culture of HCV replicon cells with PIB for approximately 3 weeks, amino acid mutations were found in the NS5A region, as shown in Table 13.

Table 13. Amino acid mutations in the NS5A region in HCV replicon cells

Genotype (virus strain)	PIB concentration (multiple of EC_{50})[b)]	Amino acid mutation (number of colonies formed[c)])
1a (H77)	10	Y93H (18/20), Y93N (1/20),
	100	Q30D (1/4), Y93D (1/4), Q30 deletion (1/4), H58D + Y93H (1/4)
	1000	-[d)]
1b (Con1)	10	-[d)]
	100	-
	1000	-
2a[a)]	10	F28S + M31I (2/3), P29S + K30G (1/3)
	100	-[d)]
	1000	-
2b[a)]	10	-[d)]
	100	-[d)]
	1000	-
3a[a)]	10	Y93H (3/3)
	100	-[d)]
	1000	-
4a[a)]	10	-[d)]
	100	-[d)]
	1000	-
5a[a)]	10	-[d)]
	100	-[d)]
	1000	-
6a[a)]	10	-[d)]
	100	-[d)]
	1000	-

-,Not investigated or not detected
a) Genotype 1b (Con1) replicon cells in which amino acid sequence in the NS5A region derived from the relevant genotype is integrated; b) For EC_{50} of PIB, see Section "3.5.1 *In vitro* antiviral activity"; c) Number of colonies with the concerned substitution/number of viable colonies; d) No cell growth observed, not investigated.

3.5.2.2 Antiviral activity of PIB against mutants (CTD 4.2.1.1-4, 4.2.1.1-7)

The antiviral activity of PIB was investigated in HCV replicon cells in which detected in the *in vitro* resistance selection study [see Section "3.5.2.1 Resistance selection study"] and in clinical studies[2)] of GLE/PIB as well as amino acid mutations in the NS5A region reported with the other NS5A inhibitors[6)] were introduced. The results are as shown in Table 14.

[6)] Subjected to amino acid mutation s in the NS5A region reported in the package inserts and literature of ombitasvir, ledipasvir, daclatasvir, velpatasvir, and elbasvir.

Table 14. Antiviral activity of PIB against wild-type and mutant HCV replicon cells

Genotype (virus strain)	Amino acid mutation in the NS5A region	EC_{50} (pmol/L)	EC_{90} (pmol/L)	Change in susceptibility[a)]
1a (H77)	Wild-type	0.72	1.8	-
	K24R	0.25	0.72	0.3
	M28A	1.4	4.7	2.0
	M28G	176	704	244
	M28T	1.5	4.1	2.0
	M28V	1.3	3.7	1.8
	Q30D	67.7	244	94
	Q30E	1.7	5.1	2.4
	Q30G	0.93	3.5	1.3
	Q30H	0.74	2.4	1.0
	Q30K	0.69	2.9	1.0
	Q30L	0.21	0.67	0.3
	Q30R	1.2	3.9	1.7
	L31M	0.76	1.6	1.1
	L31V	0.96	2.4	1.3
	P32L	1.2	5.1	1.7
	H58C	0.68	2.5	0.9
	H58D	0.80	3.9	1.1
	H58P	0.46	1.5	0.6
	E62A	3.7	12.2	5.2
	A92T	0.28	1.6	0.4
	Y93C	1.2	3.5	1.7
	Y93H	4.8	22.9	6.7
	Y93N	5.1	19.6	7.0
	Y93S	1.2	8.6	1.6
	K24R + M28V	0.42	1.4	0.6
	K24R + M28T	0.41	1.5	0.6
	K24R + Q30R	0.29	1.3	0.4
	M28G + Q30R	15,713	113,030	21,824
	M28V + Q30H	0.33	1.2	0.5
	M28V + Q30R	0.82	5.9	1.1
	M28T + Q30R	1.2	5.2	1.6
	M28T + Y93C	2.2	9.0	3.1
	Q30H + Y93H	12.3	59.8	17
	Q30K + H58D	170	1249	235
	Q30K + Y93H	1286	7584	1786
	Q30L + Y93H	0.42	1.8	0.6
	Q30R + L31M	2.1	7.7	3.0
	Q30R + H58D	91.0	604	126
	Q30R + Y93C	2.8	11.1	3.8
	Q30R + Y93H	187	661	260
	Q30R + Y93N	94.6	647	131
	L31M + H58D	16.6	109	23
	L31M + Y93C	4.4	19.0	6.1
	L31M + Y93H	54.3	295	75
	L31M + Y93N	140	748	195
	L31V + Y93H	67.8	328	94
	P32L + Y93C	124	755	172
	H58D + Y93C	168	2392	233
	H58D + Y93H	1612	7764	2238
	H58D + Y93N	1418	7773	1969
	H58D + Y93S	1058	8701	1469
	M28G + Q30R + H58C	679	7268	942
	M28T + Q30R + L31M	3.3	14.2	4.6
	Q30H + H58D + Y93H	6737	30,913	9357
	Q30K + H58D + E62A	99.5	543	138
	Q30R + L31M + H58D	1227	7298	1704
	Q30R + L31M + Y93C	30.0	136	42

Genotype (virus strain)	Amino acid mutation in the NS5A region	EC_{50} (pmol/L)	EC_{90} (pmol/L)	Change in susceptibility[a)]
1b (Con1)	Wild-type	1.9	3.8	-
	L28M	1.8	3.5	1.0
	R30Q	0.88	2.2	0.5
	L31F	2.3	4.5	1.2
	L31M	2.9	5.8	1.5
	L31V	1.5	2.8	0.8
	P32 deletion	1968	7459	1036
	Q54Y	2.3	7.1	1.2
	P58S	2.4	4.7	1.2
	A92E	0.92	2.7	0.5
	Y93H	1.1	3.9	0.6
	Y93N	1.2	3.7	0.6
	Y93S	0.74	3.0	0.4
	R30Q + Y93H	2.3	4.8	1.2
	L31F + P32 deletion	38,877	83,827	20,461
	L31F + Y93H	2.8	8.4	1.5
	L31M + Y93H	1.3	4.3	0.7
	L31V + Y93H	1.7	4.5	0.9
	Q54Y + Y93H	2.0	7.0	1.0
	P58S + Y93H	1.5	5.7	0.8
	L28M + R30Q + Y93H	1.0	3.2	0.5
	L31F + Q54H + A92E	3.2	8.2	1.7
	Q54H + A92V + Y93H	1.8	5.2	1.0
2a[b)]	Wild-type	0.99	4.4	-
	T24A	1.3	4.5	1.3
	T24S	1.0	4.8	1.1
	F28C	1.3	4.5	1.3
	F28S	1.2	7.4	1.2
	K30M	1.2	4.6	1.2
	M31V[c)]	-	-	-
	M31I	1.2	5.6	1.2
	C92S	1.6	10	1.6
	Y93H[c)]	-	-	-
	T24A + M31L	0.80	5.8	0.8
	T24A + C92S	1.7	5.1	1.7
	T24S + F28C	1.4	6.0	1.4
	F28S + M31I	14,303	39,977	14,448
	P29S + K30G	2.3	12.9	2.3
2b[b)]	Wild-type	1.2	4.8	-
	L28F	0.94	4.7	0.8
	L31I	1.8	4.9	1.5
	L31M	1.5	5.7	1.2
	L31V	0.64	2.8	0.5
	C92S	1.1	4.4	0.9
	C92Y	0.69	4.6	0.6
	Y93H[c)]	-	-	-
	L28F + L31I	1.3	6.1	1.1
	L28F + L31M	1.4	8.4	1.2
	L31M + C92Y	0.80	4.6	0.7
	L31V + C92S	0.59	2.9	0.5
	L28F + L31M + C92S	2.0	14.3	1.6

Genotype (virus strain)	Amino acid mutation in the NS5A region	EC_{50} (pmol/L)	EC_{90} (pmol/L)	Change in susceptibility[a)]
3a[b)]	Wild-type	0.65	1.7	-
	S24F[c)]	-	-	-
	M28G[c)]	-	-	-
	M28K[c)]	-	-	-
	M28T	1.1	2.1	1.7
	A30K	0.71	2.8	1.1
	L31F[c)]	-	-	-
	L31I[c)]	-	-	-
	Y93H	1.5	9.5	2.3
	S24F + M28K	173	865	267
	S24F + A30K	2.1	4.4	3.3
	A30K + L31I	2.4	11.6	3.6
	A30K + Y93H	45.1	180	69
	L31I + Y93H	9.6	58.3	15
	S24F + M28K + A30K	8932	38,547	13,742
	A30K + L31I + Y93H	2770	9134	4262
4a[b)]	Wild-type	0.78	2.0	-
	L28I	0.80	2.3	1.0
	L28M	0.63	1.8	0.8
	L28V	0.85	2.7	1.1
	L30H	1.1	2.6	1.3
	P58L	0.75	2.5	1.0
	Y93H[c)]	-	-	-
	L28I + P58L	1.3	3.5	1.7
4d[b)]	Wild-type	1.5	4.1	-
	L28S[c)]	-	-	-
	L28V	1.7	8.2	1.1
	M31I	2.1	4.3	1.4
	M31L	1.4	4.6	1.0
	T58A	1.8	6.3	1.2
	T58P	1.7	6.7	1.1
	T58S	1.5	4.1	1.0
	Y93H[c)]	-	-	-
	L28V + T58S	1.7	6.9	1.1
	K24Q + T58P + Y93H	1.5	6.3	1.0
5a[b)]	Wild-type	0.93	4.3	-
	L28I	0.98	6.2	1.1
	L31F	1.9	10.5	2.1
	L31V	0.75	3.3	0.8
6a[b)]	Wild-type	1.0	3.3	-
	L31V	1.0	3.1	1.0
	T58A	1.4	4.5	1.4
	T58N	1.8	9.6	1.8

Mean
-, Not investigated or not detected
a) EC_{50} for mutant replicon/EC_{50} for wild-type replicon; b) Genotype 1b (Con1) replicon cells in which amino acid sequence in the NS5 region derived from the relevant genotype is integrated; c) No cell growth observed, not investigated.

3.5.2.3 Cross resistance

3.5.2.3.1 Antiviral activity of PIB against HCV with resistance mutations in the NS3 or NS5B region (CTD 4.2.1.1-4, 4.2.1.1-6)

Antiviral activity of PIB was investigated in HCV replicon cells with major resistance mutations[7)] in the NS3 or NS5B region. The results are as shown in Table 15.

[7)] Subjected to amino acid mutations in the NS3 or NS5B region reported from *in vitro* resistance studies and clinical studies as well as in the literature of grazoprevir, paritaprevir, sofosbuvir, beclabuvir, and GLE

Table 15. Antiviral activity of PIB against replicon cells with major resistance mutations in the NS3 or NS5B region

Genotype (virus type)	Region	Amino acid mutation	EC_{50} (pmol/L)	Change in susceptibility[a)]
1a (H77)	NS3	Wild-type	0.94	-
		R155K	0.72	0.8
		D168A	0.77	0.8
		D168V	0.79	0.8
	NS5B	Wild-type	1.3	-
		C316Y	1.3	1.0
		M141T	1.6	1.2
		Y448C	1.0	0.8
		Y448H	1.0	0.8
		S556G	1.6	1.2
		S559G	0.60	0.46
		S282T	0.99	1.4[b)]
1b (Con1)	NS3	Wild-type	2.7	-
		R155K	1.4	0.5
		A156T	1.4	0.5
		D168V	2.5	0.9
	NS5B	Wild-type	1.8	-
		C316Y	1.8	1.0
		Y448H	1.9	1.1
		S556G	1.9	1.1
		S282T	2.0	1.1[c)]

Mean
a) EC_{50} for mutant replicon/EC_{50} for wild-type replicon; b) Ratio to EC_{50} (0.72 pmol/L) for wild-type replicon; c) Ratio to EC_{50} (1.9 pmol/L) for wild-type replicon

3.5.2.3.2 Antiviral activity of PIB and the other NS5A inhibitors against HCV with resistance mutations in the NS5A region (CTD 4.2.1.1-4)

Antiviral activity of PIB and the other NS5A inhibitors was investigated in HCV replicon cells with major resistance mutations[2),6)] in the NS5A region. The results are as shown in Table 16.

Table 16. Antiviral activity of PIB and the other NS5A inhibitors against cells with HCV replicon with each resistance mutation in the NS5A region

Genotype (virus type)	Amino acid mutation	Change in susceptibility[a)]		
		PIB	Daclatasvir	Ombitasvir
1a (H77)	M28T	2	437	8965
	M28V	1.8	1.0	58
	Q30E	2.4	-	1326
	Q30H	1.0	154	3
	Q30R	1.7	178	800
	L31M	1.1	140	2
	L31V	1.3	614	155
	H58D	1.1	124	243
	Y93C	1.7	383	1675
	Y93H	6.7	2324	41,383
	Y93N	7.0	8641	66,740
	Q30R + L31M	3	16,785	504
	Q30R + H58D	126	64,004	320,751
	Q30R + Y93H	260	-	351,081
	L31M + Y93C	6.1	-	1973
1b (Con1)	L28M	1.0	1.2	2.0
	L31F	1.2	1.4	10
	L31M	1.5	1.4	0.9
	L31V	0.8	2.5	8
	Y93H	0.6	7.3	77
	L31V + Y93H	0.9	1225	12,328
2a[b)]	T24A	1.3	-	38
	T24S	1.1	-	67
	F28C	1.3	-	501
	F28S	1.2	-	11,618
2b[b)]	L28F	0.8	-	47
	L31I	1.5	-	28
	L31M	1.2	-	1.5
	L31V	0.5	-	511
3a[b)]	M28T	1.7	-	659
	A30K	1.1	44	-
	Y93H	2.3	2154	6728
4a[b)]	L28V	1.1	-	21
5a[b)]	L28I	1.1	-	79
	L31F	2.1	-	289
	L31V	0.8	-	243
6a[b)]	L31V	1.0	-	68
	T58A	1.4	-	18
	T58N	1.8	-	101

-, Not calculated because EC_{50} was not determined.
a) EC_{50} for mutant replicon/EC_{50} for wild-type replicon; b) Genotype 1b (Con1) replicon cells in which amino acid sequence in the NS5 region derived from the relevant genotype is integrated

3.5.3 Antiviral activity against HIV-1 and HBV (CTD 4.2.1.1-6)

Antiviral activity of PIB against HIV-1 (IIIB)-infected CEM-SS cells and HBV-infected HepG2 2.2.15 cells was investigated, and EC_{50} of PIB was >900 nmol/L and >32,000 nmol/L, respectively.

3.6 Secondary pharmacodynamics (PIB) (CTD 4.2.1.2-3)

Inhibitory effect of PIB against ligand binding to 79 G-protein-coupled receptors, ion channels, and transporters was investigated *in vitro*. PIB (10 μmol/L) (67.5 fold the human clinical exposure [C_{max}]) did not inhibit ligand binding to any of the above by >50%.

3.7 Safety pharmacology (PIB) (CTD 4.2.1.3-9, 4.2.1.3-11, 4.2.1.3-13, 4.2.1.3-14, 4.2.3.2-PIB-4, 4.2.3.4.2.3.2-PIB-9; Reference data CTD 4.2.1.3-8, 4.2.1.3-10, 4.2.1.3-12)

Effects of PIB on central nervous, cardiovascular, and respiratory systems were investigated (Table 17).

Table 17. Summary of safety pharmacology studies

Organ investigated	Test system	Endpoint and evaluation method	Dose or concentration	Route of administration	Special findings
Central nervous system	Male mice (n = 10/group)[a)]	Locomotor activity	0.6, 2, 6, 20, 60 mg/kg	Oral	None
	Female mice (n = 8/group)	FOB	3, 10, 100 mg/kg	Oral	None
Cardiovascular system	Human embryonic kidney cells (n = 5)[a)]	hERG current	0.51 μg/mL	*In vitro*	Inhibited by 8.4% 3.1 fold the human C_{max}
	Human embryonic kidney cells (n = 3)	hERG current	1.11 μg/mL	*In vitro*	None
	Anesthetized male beagle dogs (n = 6)[a)]	Electrocardiogram parameters	56, 187, 562 mg/kg/30 min	Ascending dose continuous intravenous infusion	None
	Unanesthetized male beagle dogs (n = 6/group)	Heart rate, PR interval, QRS interval, QTc interval, and mean arterial pressure	3, 10, 100 mg/kg	Oral	None
Respiratory system	Male mice (n = 8/group)	Whole-body plethysmograph	3, 10, 100 mg/kg	Oral	None

a) Non-GLP study

No effects of PIB were observed on the central nervous, cardiovascular, or respiratory system. The applicant therefore explained that PIB is unlikely to affect the central nervous, cardiovascular, or respiratory system during its clinical use.

3.8 Effects of concomitant use of GLE and PIB (CTD 4.2.1.1-5)

Using genotype 1b (Con1) replicon cells, effects[8)] of concomitant use of GLE (6 doses in the concentration range, 0.234-7.5 nmol/L) and PIB (6 doses in the concentration range, 0.0008-0.025 nmol/L) were investigated. Combinations at low doses showed additive or synergistic effects, and those at high doses showed additive effects.

Genotype 1a (H77) or genotype 1b (Con1) replicon cells were cultured with GLE or PIB alone or with GLE and PIB in combination, and an effect of the combination was investigated using the number of viable colonies as an indicator. The results are as shown in Table 18.

Table 18. Viable colonies of replicon cells in concomitant use of GLE and PIB

	Concentration (multiple of EC_{50})[a)]	Percentage of viable colonies[b)] (%)	
		Genotype 1a (H77)	Genotype 1b (Con1)
GLE	10	0.0432	0.0467
	100	0.0029	0.0298
PIB	10	0.0065	0[c)]
	100	0.0002	0[c)]
GLE and PIB	10 and 10	0[c)]	0[c)]

a) For EC_{50} of the drugs, see Section "3.1.2 *In vitro* antiviral activity" and Section "3.5.1 *In vitro* antiviral activity"; b) Number of viable colonies/number of cells seeded × 100; c) No viable colonies detected.

8) According to the method of Prichard and Shipman (*Antiviral Res.* 1990;14:181-206), 95% CI of the mean of differences between measured values and theoretical values on inhibitory rate at each concentration in the concomitant use was calculated. When the lower limit of the 95% CI is >0, the effect is considered "synergistic"; when the upper limit of the 95% CI is <0, the effect is considered "antagonistic"; and when either of the above is not applicable, the effect is considered "additive". The theoretical value was calculated according to the following formula: Z = X + Y (1 – X)
Z, Inhibitory rate (%) when Test articles X and Y are used concomitantly; X, Inhibitory rate (%) when Test article X is used alone; Y, Inhibitory rate (%) when Test article Y is used alone.

3.R Outline of the review conducted by PMDA

3.R.1 Antiviral activity of GLE and PIB

PMDA's view:

The submitted data have demonstrated the antiviral activity of GLE against HCV genotypes 1 to 4 and 6 and that of PIB against HCV genotypes 1 to 6. The *in vitro* antiviral activity of GLE against HCV genotype 5 was investigated only in 1 cell line of genotype 5a replicon cells in which amino acid sequence in the NS3 region derived from a patient with genotype 5a was integrated, and EC_{50} of GLE in this investigation was 0.12 nmol/L. Therefore, none of the results available deny the antiviral activity of GLE against HCV genotype 5. In addition, results from concomitant use of GLE with PIB in HCV genotype 1a and genotype 1b replicon cells have demonstrated pharmacodynamic effects of concomitant use of GLE with PIB. Furthermore, the efficacy of GLE/PIB in patients with chronic hepatitis C or compensated cirrhosis type C is described in Section "7.R.3. Efficacy."

3.R.2 Resistance to GLE and PIB

The applicant's explanation about resistance profiles of HCV genotypes 1 to 6 to GLE and PIB:

Single amino acid mutations that reduced the antiviral activity of GLE to ≤1/5 of the original *in vitro* included substitutions at the amino acid position 156 in the genotypes 1a, 1b, 2a, 2b, 3a, and 4a; at the position 80 in genotype 3a; and at the position 168 in the genotypes 1a, 1b, 3a, 4a, and 6a [see Section "3.1.3.2 Antiviral activity of GLE against mutants"]. Drug resistance development in genotype 5 has not been investigated due to a failure of preparation of genotype 5 replicon cells.

Single amino acid mutations that reduced the antiviral activity of PIB to ≤1/5 of the original *in vitro* included substitutions at the amino acid positions 28, 30, 62, and 93 in the genotypes 1a and deletion at the position 32 in the genotype 1b [see Section "3.5.2.2 Antiviral activity of PIB against mutants"].

Of mutations observed in patients who received GLE/PIB but experienced a virologic failure in Japanese and foreign clinical studies, mutations in the NS3 region that reduced the activity to ≤1/5 of the original *in vitro* included single substitution at the position 156 and multiple substitutions involving the positions 36, 56, or 168 in the genotype 1a; single substitution at the position 156 in the genotype 1b; and single substitution at the position 156 or 168 and double substitutions at the positions 56 and 168 or 80 and 166 in the genotype 3a. Corresponding mutations in the NS5A region included single substitution at the position 28 or 93 and multiple substitutions involving the position 28, 30, 31, 58, or 93 in the genotype 1a; deletion at the position 32 and multiple substitutions involving deletion at the positions 28 and 32 in the genotype 1b; and multiple substitutions involving the positions 30 and 93 in the genotype 3a.

PMDA's view:

In clinical use, attention should be paid to resistance mutations [see Sections "3.1.3 Resistance profile" and "3.5.2 Resistance profile"] that were observed in patients with a virologic failure in Japanese and foreign clinical studies and led to reduction of the activity *in vitro*. Resistance to GLE was associated with substitutions at the positions 156 and 168 in the NS3 region, and resistance to PIB was associated with substitutions at the positions 28, 30, and 93 and deletion at the position 32 in the NS5A region. These mutations were found in patients with a virologic failure and also reduced the antiviral activity *in vitro*.

In addition, resistance to GLE was increased with double substitutions at the positions 156 and 168 in the NS3 region, and resistance to PIB was increased with double substitutions at the positions 30 and 93 or substitution at the position 31 and deletion at the position 32 in the NS5A region *in vitro*, when compared with the resistance resulting from single substitution or deletion alone of the above combinations [see Sections "3.1.3.2 Antiviral activity of GLE against mutants" and "3.5.2.2 Antiviral activity of PIB against mutants"]. Because information from the clinical studies is limited, and presence or absence of resistance mutations is considered critical, determining the efficacy of GLE/PIB, the applicant is required to continue collecting information on resistance to GLE and PIB even after the market launch and, when a new finding become available, to provide the information to healthcare professionals immediately. Relationships between resistance mutations and efficacy of GLE/PIB in clinical studies are described in Sections "7.R.3.2 Resistance mutations in virus."

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

GLE or ^{14}C-GLE and PIB, ^{3}H-, or ^{14}C-PIB were administered to mice, rats, dogs, monkeys, and rabbits to evaluate the pharmacokinetics (PK). In addition, biological samples taken from humans or animals were used to evaluate GLE and PIB in relation to plasma protein binding, drug-metabolizing enzymes, and transporters.

Concentrations of GLE and PIB in biological samples were measured by high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS).[9)] Radioactivity concentrations of GLE, PIB, and their metabolites in biological samples were measured by a liquid scintillation counting method, and radioactivity concentrations in the tissues were measured by quantitative whole-body autoradiography.[10)] In non-clinical pharmacokinetic studies, anhydride of GLE was used, and the dose and concentration are indicated on the basis of glecaprevir. Unless otherwise specified, PK parameters are expressed as the mean.

4.1 Absorption (GLE)

4.1.1 Single-dose studies (CTD 4.2.2.2-2, 4.2.2.2-12, 4.2.2.2-14, 4.2.2.2-15)

Table 19 shows PK parameters of GLE in plasma following a single intravenous administration or a single oral administration in mice (n = 3 males/time point), rats (n = 3-5 males each), dogs (n = 3/sex), and monkeys (n = 3 females each).

Following a single intravenous administration of GLE at 5 or 3 mg/kg in mice or dogs, the ratio of hepatic area under concentration-time curve (AUC) to plasma AUC was 168 in mice and 13.9 in dogs. Following a single intravenous administration of GLE at 1 mg/kg in rats, the ratio of hepatic concentrations to plasma concentrations at 24 hours was 288.

In dogs, plasma GLE concentrations following administration under fed conditions were lower than those following administration under fasted conditions. The applicant explained that this was attributable to reduced solubility of GLE in response to a change in gastric pH caused by food.

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9) Lower limit of quantitation of GLE, approximately 1 or 39.2 ng/mL in mouse samples, approximately 1 or 65.1 ng/mL in rat samples, approximately 1 or 18.6 ng/mL in dog samples; lower limit of PIB, approximately 10 or 36.7 ng/mL in mouse samples, approximately 10 or 4.95 ng/mL in rat samples, approximately 10 or 36.6 ng/mL in dog samples, approximately 10 or 36.1 ng/mL in rabbit samples.

10) Lower limit of quantitation 56.6 ng eq./g for radioactivity derived from GLE, 48.5 ng eq./g for radioactivity derived from PIB

Table 19. PK parameters following a single intravenous or oral administration of GLE

Animal species	Route of administration	Dose (mg/kg)	Number of animals	Feeding status	C_{max} (μg/mL)	t_{max} (h)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ [a] (h)	V_{ss} (L/kg)	CL (L/h/kg)	F (%)
Mouse	Intravenous	5	3 males/ time point	Fed	-	-	3.09	2.7	3.3	1.6	-
	Oral	5	3 males/ time point	Fed	0.92	1.0	3.81	4.3	-	-	123
Rat	Intravenous	5	5 males	Fasted	-	-	24.1 ± 3.36	3.1	0.40 ± 0.12	0.21 ± 0.03	-
	Oral	5	3 males	Fasted	6.25 ± 1.24	0.5 [b]	22.4 ± 2.0	2.0	-	-	92.9 ± 8.4
Dog	Intravenous	1	3 female(s) and male(s) in total	Fasted	-	-	0.52 ± 0.15	0.58	1.5 ± 1.4	2.0 ± 0.61	-
		3	3 female(s) and male(s) in total	Fasted	-	-	3.4 ± 1.5	3.7	0.64 ± 0.31	0.99 ± 0.37	-
	Oral	3	3 female(s) and male(s) in total	Fasted	0.79 ± 0.19	0.8 ± 0.3	1.49 ± 0.47	1.7	-	-	43.9 ± 13.9
		10	3 female(s) and male(s) in total	Fasted	12.9 ± 7.5	1.3 ± 0.3	26.9 ± 19.4	0.9	-	-	-
		10	3 female(s) and male(s) in total	After fed	6.5 ± 7.3	1.3 ± 0.8	12.4 ± 13.0	1.3	-	-	-
Monkey	Intravenous	5	3 females	Fasted	-	-	3.18 ± 0.91	1.7	1.2 ± 0.7	1.7 ± 0.5	-
	Oral	5	3 females	Fasted	0.26 ± 0.13	2.8 ± 1.3	0.83 ± 0.35	2.0	-	-	26.0 ± 11.0

Mean ± standard deviation (SD)
-, Not investigated or not applicable; V_{ss}, Distribution volume at steady state; F, Bioavailability
a) Harmonic mean, b) Same value for all

4.1.2 Repeated-dose studies (CTD 4.2.3.2-GLE-3, 4.2.3.2-GLE-6, 4.2.3.2-GLE-9)

Table 20 shows PK parameters of GLE following repeated oral administration of GLE quaque die (QD) or bis in die (BID) in mice, rats, and dogs. No consistent differences in C_{max} or AUC_{0-24} between males and females were observed in any animal species. In the dose range investigated, C_{max} and AUC_{0-24} of GLE increased almost dose-proportionally in mice and dogs, and more than dose-proportionally in rats. The repeated administration resulted in an increasing trend in C_{max} and AUC_{0-24} of GLE in rats and dogs.

Table 20. PK parameters following repeated oral administration of GLE

Animal species	Dose (mg/kg)	Date of measurement (Day)	Number of animals	C_{max} [a] (μg/mL)		t_{max} [a] (h)		AUC_{0-24} (μg·h/mL)	
				Male	Female	Male	Female	Male	Female
Mouse	40 QD	28	3/sex/time point	8.79	18.8	1.0	1.0	41.6	36.9
	125 QD	28	3/sex/time point	80.8	119	1.0	1.0	376	422
	300 QD	28	3/sex/time point	164	205	3.0	1.0	706	767
Rat	5 BID	1	5/sex/time point	1.32	3.77	0.5	0.5	25.3	29.4
		181	5/sex/time point	4.40	5.07	0.5	0.5	33.5	42.3
	20 BID	1	5/sex/time point	11.3	17.4	0.5	0.5	190	250
		181	5/sex/time point	21.7	31.5	1.5	0.5	241	308
	60 BID	1	5/sex/time point	88.5	71.8	1.5	6	1030	934
		181	5/sex/time point	98.5	101	1.5	1.5	626	843
Dog	10 BID	1	4/sex	5.95 ± 2.63	5.62 ± 3.90	1.5 [b]	1.5 [b]	23.2 ± 9.89	18.5 ± 11.7
		273	4/sex	15.5 ± 9.35	9.92 ± 6.52	1.5 [b]	1.5 [b]	60.2 ± 34.1	40.8 ± 29.0
	25 BID	1	4/sex	16.1 ± 10.9	19.8 ± 14.6	1.5 [b]	2.1 ± 1.3	112 ± 52.8	114 ± 89.7
		273	4/sex	54.7 ± 12.1	60.7 ± 20.3	1.5 [b]	2.1 ± 1.3	252 ± 71.4	221 ± 12.9
	100 BID	1	6/sex	68.1 ± 61.2	30.1 ± 35.5	2.6 ± 1.6	2.3 ± 1.3	1750 ± 1160	873 ± 596
		273	6/sex	110 ± 45.4	124 ± 35.0	2.8 ± 1.4	2.8 ± 1.4	1500 ± 839	1380 ± 761

Mean ± SD
a) C_{max} or time to reach maximum plasma concentration (t_{max}) following the first dose on the day of measurement in rats and dogs, b) Same value for all

4.1.3 Membrane permeability *in vitro* (CTD 4.2.2.2-1)

Membrane permeability of GLE was investigated using Madin-Darby canine kidney (MDCK) cells expressing P-glycoprotein (P-gp). In the presence of cyclosporine, a P-gp inhibitor, apparent

permeability coefficient of GLE at 1 μmol/L in the apical to basolateral surface ($P_{app\ A \rightarrow B}$) was 1.4×10^{-6} cm/s, while $P_{app\ A \rightarrow B}$ of quinidine, positive control, at 1 μmol/L was 24.4×10^{-6} cm/s.

4.2 Distribution (GLE)

4.2.1 Tissue distribution (CTD 4.2.2.3-4)

Following a single oral administration of ^{14}C-GLE at 5 mg/kg in pigmented rats (n = 1 male/time point), tissue distribution of radioactivity as well as concentrations in bile and urine were investigated by whole-body autoradiography. The radioactivity concentration reached the maximum up to 2 hours post-dose in most of the tissues, and the highest concentration was found in the liver at 0.5 to 96 hours post-dose. The concentration decreased to below the lower limit of quantitation in most of the tissues up to 24 hours post-dose, and no radioactivity was detected in any tissue at 168 hours post-dose. No clear differences were observed in radioactivity concentration between pigmented and non-pigmented skin sites at 0.5 to 8 hours post-dose, and no accumulation of the radioactivity was observed in the uvea, suggesting that GLE has low affinity to melanin-containing tissues.

4.2.2 Plasma protein binding and distribution into blood cells (CTD 4.2.2.3-1)

The plasma protein binding rates of GLE (0.1-30 μmol/L) in plasma samples from mice, rats, dogs, monkeys, and humans were almost consistent irrespective of animal species or GLE concentration, and these rates were 97.4%, 99.7%, 98.2%, 95.1%, and 97.5%, respectively, at the GLE concentration of 1 μmol/L.

In addition, the distribution of GLE (1 μmol/L) into blood cells from mice, rats, dogs, monkeys, and humans was investigated, and the ratios of GLE concentration in blood to that in plasma were 0.64, 0.60, 0.55, 0.75, and 0.57, respectively.

4.2.3 Transfer into placenta (CTD 4.2.2.3-5)

Following a single oral administration of ^{14}C-GLE at 5 mg/kg in rats on Gestation Day 18 (n = 1/time point), transfer of GLE through the placenta and into fetuses was investigated. The radioactivity was distributed into the fetal tissues, and the radioactivity concentrations in the liver and blood were higher than those in the other tissues. In maternal animals, the radioactivity was detected in the placenta, uterus, and amniotic fluid at 72 hours post-dose.

The applicant explained that the above results suggest that GLE crossed the placenta and is distributed into the fetuses.

4.3 Metabolism (GLE)[11)]

4.3.1 Possible metabolic pathways

Investigation results in Sections “4.3.2 *In vitro* metabolism” and “4.3.3 *In vivo* metabolism” showed the possible metabolic pathway of GLE as shown in Figure 1.

[11)] Metabolites described in this section are as follows:
M1, M2, M4, and M5, hydroxide; M6, acylsulfonamide hydrolysate; M7, M13, and M14, defluoride/oxide; M8, 1-methylcyclopropane-1-sulfonamide; M15a, glutathione conjugate; M15b and M15c, degradation products of M15a; M15d, cysteine conjugate; M16a, oxide/glutathione conjugate; M16b and M19, degradation products of M16a; M17, oxide/cysteine conjugate; M18, defluoride/cysteine conjugate; M20 (a/b), oxide of M15d; M21 (a/b), cysteine conjugate of M7; M22, degradation product of M4/M5; M24, degradation product of M2

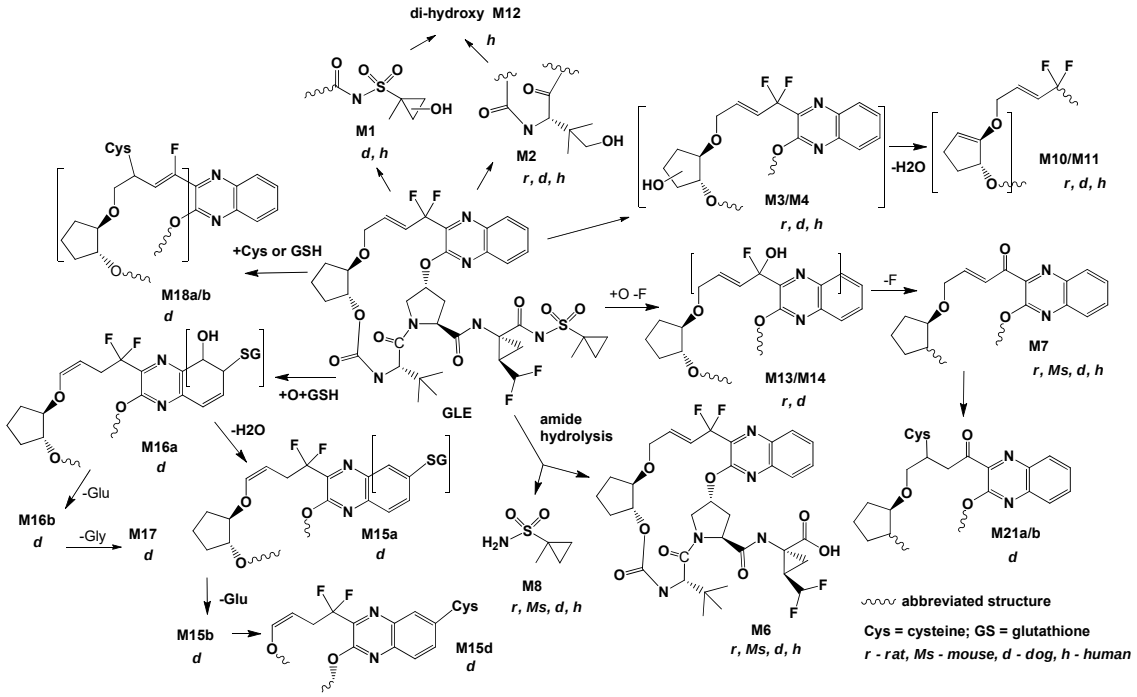

Figure 1. Possible metabolic pathway of GLE (source, CTD 2.6.4 Figure 2.6.4-6)

4.3.2 *In vitro* metabolism (CTD 4.2.2.4-1, 4.2.2.4-2)

Liver microsomes and hepatocytes from mice, rats, dogs, monkeys, and humans were incubated with ^{14}C-GLE (1 or 10 μmol/L) to investigate metabolites of GLE. Irrespective of animal species or specimen type, unchanged GLE was mainly detected (70.2%-75.7% in dog liver microsomes, ≥90% in the other specimens [≥99% in either human specimen type]). Metabolites found included M4 and M5 in human liver microsomes, and M7 in human hepatocytes.

To investigate enzymes involved in metabolism of GLE in humans, recombinant human cytochrome P-450 (CYP) isoform (CYP1A2, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, and CYP3A5) expression systems and recombinant human flavin-containing monooxygenase (FMO) isoform (FMO1 and FMO3) expression systems were incubated with ^{14}C-GLE. As a result, GLE was metabolized in the CYP2D6, CYP2C9, CYP2C8, CYP3A4, and CYP3A5 expression systems. From the specific clearance (CL), contribution rates of CYP2C8, CYP2C9, CYP2D6, and CYP3A to metabolism of GLE were calculated to be 0.7%, 3.7%, 3.8%, and 91.9%, respectively.

The above results suggest that GLE is metabolized mainly by CYP3A in humans, but contribution of the liver metabolism to elimination of GLE is considered small [see Section "6.2.1.3 Mass balance"]. The applicant therefore explained that, in clinical use of GLE, pharmacokinetic interactions with drugs that inhibit or induce CYP3A are unlikely to occur.

4.3.3 *In vivo* metabolism (CTD 4.2.2.4-3, 4.2.2.4-4, 4.2.2.4-7, 4.2.2.4-8)

Following repeated oral administration of GLE at 75 mg/kg BID in mice (n = 5/sex) for 7 days, unchanged GLE was mainly found in plasma at 99.5%, and its metabolites, M6 and M7, were found at 0.1% and 0.3%, respectively.

Following a single intravenous administration of ^{14}C-GLE at 1 mg/kg or a single oral administration at 5 or 60 mg/kg in bile-duct-cannulated rats or non-cannulated rats (n = 3 males each), metabolites of GLE in plasma, bile, urine, and feces were investigated. The results are as shown below.

- Following the intravenous administration in bile-duct-cannulated rats, unchanged GLE (92.0% of the radioactivity in plasma) and M8 (8.0%) were found in plasma up to 48 hours-post-dose, while only unchanged GLE was found in bile up to 72 hours post-dose (99.7% of the administered radioactivity).

- Following the oral administration in bile-duct-cannulated rats, unchanged GLE (45.8% of the radioactivity in plasma) and M8 (54.2%) were mainly found in plasma up to 48 hours post-dose, and M6 and M7 were additionally detected. Up to 72 hours following the oral administration, unchanged GLE (60.3% of the administered radioactivity) and its metabolites, M2, M3, M4, M5, and M8 (<1% for each), were mainly found in bile. In urine, unchanged GLE and M8 were found in small amounts (0.1% and 1.1%, respectively).

- In non-cannulated rats, the radioactivity was hardly detected in urine at 48 hours post-dose (0.1% of the administered radioactivity), while in feces, unchanged GLE (78.0%) and its metabolites, M2, M4, M5, M6, and M24 (4.4%, 1.9%, 1.8%, 11.1%, and 1.5%, respectively) were mainly found. For others, M7 was detected.

Following a single oral administration of ^{14}C-GLE at 30 mg/kg or repeated oral administration of GLE at 100 mg/kg BID for 39 weeks in dogs (n = 3 males and 6/sex), metabolites of GLE in plasma, urine, and feces were investigated. The results are as shown below.

- In plasma up to 72 hours following the single oral administration of ^{14}C-GLE, unchanged GLE (78% of the radioactivity in plasma) was mainly found, and for others, M1, M2, M4/M5, M6, M7, M10, M11, M13, M14, M15a/b/c/d, M16a/b, M17, M18, M19, M20a/b, and M21 (a/b) were found. In addition, in urine up to 72 hours post-dose, unchanged GLE (1.4% of the administered radioactivity) and its metabolite, M5 (1.1%), were found. In feces, unchanged GLE (33.7%) and its metabolites, M4, M5, M6, M7, M15d, and M22 (5.1%, 22.6%, 5.5%, 1.2%, 2.4%, and 6.6%, respectively), were mainly found.

- Following the repeated oral administration of GLE, unchanged GLE was mainly found in plasma at 93.0%, and its major metabolites, M10 and M11, were found at 1.9% and 1.6%, respectively.

4.4 Excretion (GLE)

4.4.1 Excretion into bile, urine, and feces (CTD 4.2.2.2-3, 4.2.2.4-4, 4.2.2.3-5)

The applicant explained that the following results suggest that GLE is excreted through bile into feces:

- Up to 48 hours following a single oral administration of ^{14}C-GLE at 60 mg/kg in rats (n = 3 males), 0.1% and 98.6% of the administered radioactivity were excreted into urine and feces, respectively.

- Up to 72 hours following a single intravenous administration of ^{14}C-GLE at 1 mg/kg or a single oral administration at 5 mg/kg in bile-duct-cannulated rats (n = 3 males each), 99.7%, 0.3%, and 1% of the intravenously administered radioactivity and 62.5%, 1.9%, and 23.3% of the orally administered radioactivity were excreted into bile, urine, and feces, respectively.
- Up to 72 hours following a single oral administration of ^{14}C-GLE at 30 mg/kg in dogs (n = 3 males), 5.3% and 76.4% of the administered radioactivity were excreted into urine and feces, respectively.

4.4.2 Excretion into milk (CTD 4.2.2.4-16)

Following a single oral administration of ^{14}C-GLE at 5 mg/kg in lactating rats (Lactation Days 8-12) (n = 3/time point), the radioactivity concentration in milk reached the maximum (24.3 ng eq./g) at 1 hour, and then decreased with the elimination half-life ($t_{1/2}$) of 7.6 hours. The radioactivity was detected in milk up to 4 hours post-dose, and the ratio of the radioactivity concentration in milk to that in plasma was 0.08. In addition, the radioactivity excreted into milk was detected as unchanged GLE (96.5% of the radioactivity in milk).

4.5 Pharmacokinetic drug interactions (GLE)

4.5.1 Enzyme inhibition and induction (CTD 4.2.2.6-1, 4.2.2.6-3, 4.2.2.6-4)

An inhibitory effect of GLE (200 μmol/L) against metabolism of substrates[12)] of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) was investigated using human liver microsomes. GLE inhibited metabolism of substrates of CYP2C8 and CYP2C9 with IC_{50} of 31.7 and 175 μmol/L, respectively. GLE, on the other hand, did not clearly inhibit metabolism of substrates of CYP1A2, CYP2B6, CYP2C19, CYP2D6, and CYP3A. No time-dependent inhibitory effect was observed against any of the CYP isoforms investigated.

An inhibitory effect of GLE (500 μmol/L) was investigated using recombinant human CYP3A4. GLE inhibited metabolism of a substrate (midazolam) of CYP3A4 with IC_{50} of 28.3 μmol/L.

The applicant explained that, in clinical use of GLE, pharmacokinetic interactions mediated by the inhibition against CYP2C8 and CYP 2C9 are unlikely to occur, based on the above results and in consideration of the clinical exposure to GLE (C_{max} [estimated values], 1170 ng/mL for patients with chronic hepatitis C and 2810 ng/mL for patients with compensated cirrhosis type C; [see Section "6.2.2.1 PPK analysis"]).

An inhibitory effect of GLE (50 μmol/L) against metabolism of substrates of uridine diphosphate glucuronosyltransferase (UGT) isoforms (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7)[13)] was investigated. As a result, GLE inhibited metabolism of substrates of UGT1A1 and UGT1A4 with IC_{50} of 17.2 and 14.6 μmol/L, respectively. GLE, on the other hand, did not inhibit metabolism of substrates of UGT1A6, UGT1A9, and UGT2B7.

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12) CYP1A2, phenacetin; CYP2B6, bupropion; CYP2C8, paclitaxel; CYP2C9, diclofenac; CYP2C19, *S*-mephenytoin; CYP2D6, dextromethorphan; CYP3A, midazolam and testosterone

13) UGT1A1, β-estradiol; UGT1A4, trifluoperazine; UGT1A6, 5-hydroxytryptophol; UGT1A9, propofol; and UGT2B7, zidovudine

An induction effect of GLE (0.1-50 μmol/L) on CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) was investigated in human hepatocytes using mRNA as an indicator, and none of the CYP isoforms were induced.

4.5.2 Property as a substrate of drug transporters (CTD 4.2.2.6-5)

The applicant explained that the following investigation results suggest that GLE is a substrate of organic anion transporting polypeptide (OATP) 1B1, OATP1B3, P-gp, and breast cancer resistance protein (BCRP):

- Using human embryonic kidney cell line (HEK293 cell line) expressing OATP1B1, OATP1B3, or Organic cation transporter (OCT) 1, transport of GLE (0.03-1 μmol/L for OATP1B, 1-10 μmol/L for OCT1) mediated by each transporter was investigated. The intracellular uptake of GLE was higher in OATP1B1- and OATP1B3-expressing cells than in original cells, while no clear difference was observed between OCT1-expressing cells and original cells.
- Using MDCKII cell line expressing P-gp or BCRP, transport of GLE (1 μmol/L) mediated by each transporter was investigated. The basal-to-apical versus apical-to-basal ratio (efflux ratio) for GLE was 7.8 in P-gp-expressing cells and 9.3 in BCRP-expressing cells. These ratios decreased to 3.8 to 4.7 and 2.7 to 6.2, respectively, in the presence of chemical compounds that inhibit P-gp and BCRP.[14)]

4.5.3 Inhibitory effect against drug transporters (CTD 4.2.2.6-5)

Using HEK293 cell line expressing OATP1B1, OATP1B3, OCT1, OCT2, organic anion transporter (OAT)3, multidrug and toxin extrusion (MATE) 1, or MATE2K, an inhibitory effect of GLE[15)] against transport of substrates[16)] of each transporter was investigated. GLE inhibited transport of substrates of OATP1B1 and OATP1B3 with IC_{50} of 0.017 and 0.064 μmol/L, respectively. In the GLE concentration range investigated, GLE did not clearly inhibit transport of substrates of the other transporters.

Using membrane vesicles prepared from cells[17)] expressing P-gp, BCRP, or bile salt export pump (BSEP), an inhibitory effect of GLE[18)] against transport of substrates[19)] of each transporter was investigated. GLE inhibited transport of substrates of P-gp, BCRP, and BSEP with IC_{50} of 0.33, 2.3, and 0.95 μmol/L, respectively.

4.6 Absorption (PIB)

4.6.1 Single-dose studies (CTD 4.2.2.2-10, 4.2.2.2-16, 4.2.2.2-17, 4.2.2.2-18, 4.2.2.2-19, 4.2.2.2-20)

Table 21 shows PK parameters of PIB following a single intravenous administration or a single oral administration in mice (n = 3 males/time point), rats (n = 3 males each), dogs (n = 3/sex), rabbits (n = 2 females each), and monkeys (n = 3 females each). In dogs, plasma PIB concentrations following

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14) P-gp, LY335979 and cyclosporine A; BCRP, cyclosporine A and Ko143
15) OATP1B1 and OATP1B3, 0.001 to 1 μmol/L; OCT1, MATE1, and MATE2K, 3 and 30 μmol/L; OCT2, OAT1, and OAT3, 10 and 100 μmol/L
16) OATP1B1 and OATP1B3, eestradiol-17β-D-glucuronide; OAT1, *p*-aminohippuric acid; OAT3, estrone-3-sulfate; OCT1, OCT2, MATE1, and MATE2K, 1-methyl-4-phenylpyridinium (^{3}H-labeled for all)
17) P-gp, human chronic myelogenous leukemic K562 cell line; BCRP, human breast cancer MCF-7 cell line; BSEP, insect ovary Sf-9 cell line
18) P-gp, 0.0012 to 20 μmol/L; BCRP, 0.012 to 200 μmol/L; BSEP, 0.0085 to 1000 μmol/L
19) P-gp, ^{3}H-*N*-methylquinidine, BCRP, Lucifer Yellow; BSEP, ^{3}H-taurocholic acid

administration under fasted conditions were comparable to those following administration under fed conditions.

Table 21. PK parameters following a single intravenous or oral administration of PIB

Animal species	Route of administration	Dose (mg/kg)	Number of animals	Feeding status	C_{max} (μg/mL)	t_{max} (h)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ [a] (h)	V_{ss} (L/kg)	CL (L/h/kg)	F (%)
Mouse	Intravenous	3	3 males/ time point	Fed	-	-	468.8	24	0.22	0.0064	-
	Oral	3	3 males/ time point	Fed	1.59	9.0	41.2	12.9	-	-	8.8
Rat	Intravenous	3	3 males	Fasted	-	-	41.0 ± 7.26	6.2	0.49 ± 0.08	0.075 ± 0.012	-
	Oral	3	3 males	Fasted	0.28 ± 0.045	5.3 ± 1.2	4.07 ± 0.59	7.0	-	-	9.9 ± 1.4
Rabbit	Intravenous	1	2 females	Fasted	-	-	2.05 ± 0.21	8.4	3.7 ± 1.4	0.49 ± 0.05	-
Dog	Intravenous	1	3 female(s) and male(s) in total	Fasted	-	-	10.6 ± 2.0	7.1	0.85 ± 0.34	0.097 ± 0.021	-
	Oral	2.5	3 female(s) and male(s) in total	Fasted	0.63 ± 0.155	3.7 ± 0.6	7.86 ± 2.11	8.3	-	-	29.8 ± 8.0
		10	3 female(s) and male(s) in total	Fasted	1.32 ± 0.12	1.8 ± 0.3	11.1 ± 0.96 [b]	-	-	-	-
		10	3 female(s) and male(s) in total	After fed	1.10 ± 0.69	2.5 ± 1.3	10.7 ± 7.64 [b]	-	-	-	-
Monkey	Intravenous	1	3 females	Fasted	-	-	6.85 ± 1.45	8.3	0.79 ± 0.23	0.15 ± 0.03	-
	Oral	2.5	3 females	Fasted	0.291 ± 0.091	4.0 [C]	2.42 ± 0.70	5.7	-	-	14.1 ± 4.1

Mean ± SD
-, Not investigated or not applicable; V_{ss}, Distribution volume at steady state; F, Bioavailability
a) Harmonic mean, b) AUC_{0-24}, c) Same value for all

4.6.2 Repeated-dose studies (CTD 4.2.3.2-PIB-5, 4.2.3.2-PIB-7, 4.2.3.2-PIB-10)

Table 22 shows PK parameters of PIB following repeated oral QD administration in mice, rats, and dogs. No consistent differences in C_{max} or AUC_{0-24} between males and females were observed in mice or dogs, but in rats, AUC_{0-24} of PIB was higher in males than in females. In the dose range investigated, C_{max} and AUC_{0-24} of PIB increased less than dose-proportionally in any animal species. The repeated administration did not result in any change in C_{max} or AUC_{0-24} of PIB in mice or rats, but in dogs, it resulted in an increasing trend in AUC_{0-24} of PIB.

Table 22. PK parameters following repeated oral administration of PIB

Animal species	Dose (mg/kg)	Date of measurement (Day)	Number of animals	C_{max} (μg/mL)		t_{max} (h)		AUC_{0-24} (μg·h/mL)	
				Male	Female	Male	Female	Male	Female
Mouse	3	1	3/sex/time point	0.581	0.543	6.0	3.0	10.8	10.7
		182	3/sex/time point	0.908	0.642	12.0	3.0	18.4	13.6
	10	1	3/sex/time point	2.22	1.84	6.0	6.0	32.9	32.0
		182	3/sex/time point	2.39	2.82	9.0	9.0	44.1	53.9
	100	1	3/sex/time point	5.58	6.50	9.0	6.0	91.8	96.3
		182	3/sex/time point	5.72	6.87	3.0	9.0	104	141
Rat	3	1	3-4/sex/time point	0.132	0.0845	3.0	3.0	1.26	0.790
		85	2-4/sex/time point	0.149	0.131	3.0	3.0	2.12	1.23
	10	1	3-4/sex/time point	0.296	0.285	3.0	3.0	3.07	2.24
		85	3-4/sex/time point	0.613	0.298	6.0	3.0	7.89	2.85
	30	1	3-4/sex/time point	0.988	0.725	3.0	1.0	7.70	6.13
		85	3-4/sex/time point	0.832	0.601	3.0	1.0	10.2	5.61
Dog	3	1	4/sex	0.265 ± 0.114	0.224 ± 0.125	3.0[a)]	4.5 ± 1.7	1.64 ± 0.671	1.45 ± 0.775
		98	4/sex	0.292 ± 0.150	0.461±0.0952	3.0 [a)]	3.0 [a)]	2.74 ± 1.56	4.58 ± 1.27
		280	4/sex	0.349 ± 0.0740	0.529 ± 0.206	5.3 ± 2.9	3.8 ± 1.5	4.26 ± 0.800	5.14 ± 2.27
	10	1	4/sex	0.466 ± 0.341	1.34 ± 0.785	3.8 ± 1.5	4.5 ± 1.7	2.80 ± 2.15	9.11 ± 6.02
		98	4/sex	0.850 ± 0.448	1.42 ± 0.600	3.8 ± 1.5	5.3 ± 1.5	10.0 ± 5.96	16.9 ± 7.61
		280	4/sex	0.702 ± 0.370	1.49 ± 0.550	5.3 ± 4.5	5.3 ± 1.5	8.35 ± 3.46	19.1 ± 8.48
	100	1	6/sex	1.08 ± 0.476	1.76 ± 0.345	3.5 ± 1.2	3.0[a)]	7.56 ± 3.70	11.9 ± 2.12
		98	6/sex	2.14 ± 0.289	2.27 ± 0.297	3.5 ± 1.2	4.0 ± 1.5	27.5 ± 6.21	27.5 ± 5.08
		280	6/sex	1.83 ± 0.331	2.01 ± 0.584	4.0 ± 1.5	4.0 ± 1.5	25.5 ± 9.46	24.9 ± 7.13

Mean ± SD
a) Same value for all

4.6.3 Membrane permeability *in vitro* (CTD 4.2.2.2-7)

Membrane permeability of PIB was investigated using P-gp-expressing MDCK cells. In the presence of cyclosporine, a P-gp inhibitor, $P_{app\ A \rightarrow B}$ of PIB at 1 μmol/L was 1×10^{-6} cm/s, while $P_{app\ A \rightarrow B}$ of quinidine, positive control, at 1 μmol/L was 20.7×10^{-6} cm/s.

4.7 Distribution (PIB)

4.7.1 Tissue distribution (CTD 4.2.2.3-8)

Following a single oral administration of ^{14}C-PIB at 5 mg/kg in pigmented rats (n = 1 male/time point), tissue distribution of radioactivity as well as concentrations in bile and urine were investigated by whole-body autoradiography. The radioactivity concentration reached the maximum at 4 hours post-dose in most of the tissues, and the highest concentration was found in bile at 1 to 8 hours post-dose. The concentration decreased to below the lower limit of quantitation (48.5 ng.eq./g) in all of the tissues except for the large intestine up to 48 hours post-dose, in which the concentration decreased to below the lower limit of quantitation up to 96 hours post-dose. In the uvea and skin, the radioactivity was detected only at 2 and 8 hours post-dose, respectively, and no clear differences were observed in radioactivity concentration between pigmented and non-pigmented skin sites, suggesting that PIB has low affinity to melanin-containing tissues.

4.7.2 Plasma protein binding and distribution into blood cells (CTD 4.2.2.3-7)

The plasma protein binding rates of PIB (1-30 μmol/L) in plasma samples from mice, rats, dogs, monkeys, and humans were almost consistent irrespective of animal species or PIB concentration, and the mean rates for all the concentrations investigated were ≥99.9%.

In addition, the distribution of PIB (1 μmol/L) into blood cells from mice, rats, dogs, monkeys, and humans was investigated, and the ratios of PIB concentration in blood to that in plasma were 0.59, 0.57, 0.66, 0.60, and 0.62, respectively.

4.7.3 Transfer into placenta (CTD 4.2.2.3-5)

Following a single oral administration of ^{14}C-PIB at 5 mg/kg in rats on Gestation Day 18 (n = 1/time point), transfer of PIB through the placenta and into fetuses was investigated. In fetuses, the radioactivity was detected in blood (19.8 ng eq./g) at 2 hours post-dose and in the liver at 4 to 12 hours post-dose (5.46-6.96 ng eq./g). No radioactivity was detected in the other fetal tissues.

In maternal animals, the radioactivity was detected in the placenta, uterus, and amniotic fluid at 72 hours post-dose.

The applicant explained that the above results suggest that PIB crossed the placenta and is distributed into the fetuses.

4.8 Metabolism (PIB)[20)]

4.8.1 Possible metabolic pathways

Investigation results in Sections “4.8.2 *In vitro* metabolism” and “4.8.3 *In vivo* metabolism” showed the possible metabolic pathway of PIB as shown in Figure 2.

[20)] Metabolites described in this section are as follows:
m1 and m3, hydroxide; m2, monoxide; m4, *O*-desmethyl form; m8, monoxide; m9, amide hydrolysate; m10, monoxide, m11, monoxide

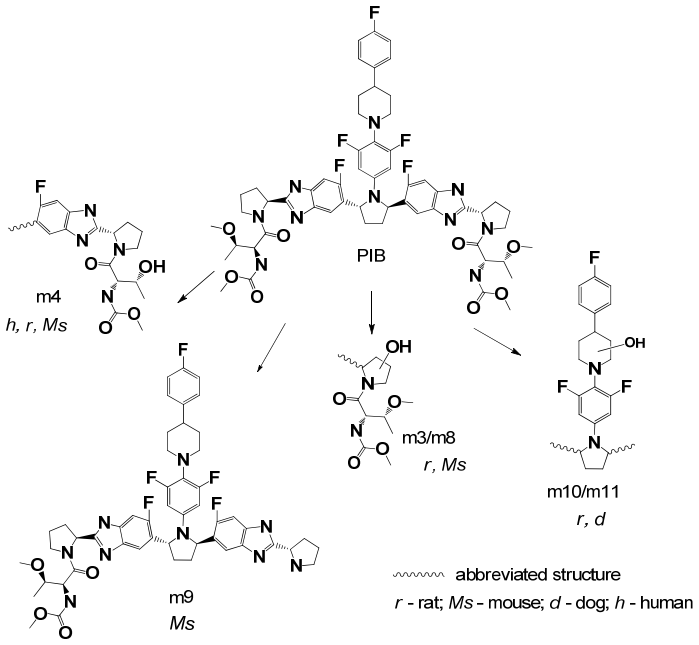

Figure 2. Possible metabolic pathway of PIB (source, CTD 2.6.4 Figure 2.6.4-8)

4.8.2 *In vitro* metabolism (CTD 4.2.2.4-10, 4.2.2.4-11)

Liver microsomes from mice, rats, dogs, monkeys, and humans were incubated with ^{14}C-PIB (2 μmol/L) to investigate metabolites of PIB. In any animal species, unchanged PIB (≥94% of the administered radioactivity) was mainly detected. In the investigation using human liver microsomes, as metabolites of PIB, m1 to m4 were found.

To investigate enzymes involved in metabolism of PIB in humans, CYP isoform (CYP1A2, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, and CYP3A5) expression systems and recombinant human FMO isoform (FMO1 and FMO3) expression systems were incubated with ^{14}C-PIB. As a result, PIB was slightly metabolized in the CYP3A4 expression system (95.5% remained as unchanged PIB).

4.8.3 *In vivo* metabolism (CTD 4.2.2.2-9, 4.2.2.4-12, 4.2.2.4-14, 4.2.2.4-17, 4.2.2.4-18)

Following repeated oral administration of PIB at 100 mg/kg QD in mice (n = 5/sex) for 8 days, unchanged PIB was mainly found in plasma at 96.5%, and its metabolites, m4, m8, and m9, were found at 0.7%, 0.5%, and 0.4%, respectively.

Following a single intravenous or oral administration of ^{3}H-PIB at 1 or 10 mg/kg or ^{14}C-PIB at 5 mg/kg in bile-duct-cannulated rats or non-cannulated rats (n = 3 males each), metabolites of PIB in plasma, bile, urine, and feces were investigated. The results are as shown below.

- Up to 72 hours following the intravenous or oral administration in bile-duct-cannulated rats, unchanged PIB (95.3% and 92.4%, respectively, of the radioactivity in plasma, 84.0% and 2.1%, respectively, of the administered radioactivity in bile) was mainly found in plasma and bile, and m3 and m4 were detected as its metabolites in bile.

- Up to 72 hours following the oral administration in non-cannulated rats, no radioactivity was detected in urine, and unchanged PIB (97.4% of the administered radioactivity) was found in feces.

Following a single oral administration of ^{14}C-PIB at 10 mg/kg or repeated oral administration of PIB at 100 mg/kg QD for 280 day in dogs (n = 3 males and 3/sex), metabolites of GLE in plasma, urine, and feces were investigated. The results are as shown below.

- Up to 72 hours following the single oral administration of ^{14}C-PIB, only unchanged PIB was mainly found in plasma. In addition, in urine and feces up to 72 hours post-dose, unchanged PIB (0.08% and 85%, respectively, of the administered radioactivity) was mainly found, and no metabolites were detected.

- Following the repeated oral administration of PIB, unchanged PIB was mainly found in plasma at 91.5%, and its major metabolites, m10 and m11, were found at 7.7% and 0.8%, respectively.

4.9 Excretion (PIB)

4.9.1 Excretion into bile, urine, and feces (CTD 4.2.2.2-9, 4.2.2.4-12, 4.2.2.4-14, 4.2.2.4-17)

The applicant explained that the following results suggest that PIB is excreted through bile into feces:

- Up to 48 hours following a single oral administration of ^{14}C-PIB at 50 mg/kg in mice (n = 9 males), 0% and 95.2% of the administered radioactivity were excreted into urine and feces, respectively.
- Up to 72 hours following a single oral administration of ^{14}C-PIB at 5 mg/kg in rats (n = 3 males), 0% and 107% of the administered radioactivity were excreted into urine and feces, respectively.
- Up to 72 hours following a single intravenous administration of ^{3}H-PIB at 1 mg/kg or a single oral administration at 10 mg/kg in bile-duct-cannulated rats (n = 3 males each), 84.1%, 0.9%, and 2.6% of the intravenously administered radioactivity and 2.8%, 0.4%, and 91.5% of the orally administered radioactivity were excreted into bile, urine, and feces, respectively.
- Up to 72 hours following a single oral administration of ^{14}C-PIB at 10 mg/kg in dogs (n = 3 males), 0.1% and 85.0% of the administered radioactivity were excreted into urine and feces, respectively.

4.9.2 Excretion into milk (CTD 4.2.2.3-5)

Following a single oral administration of ^{14}C-PIB at 5 mg/kg in lactating rats (Lactation Days 8-12) (n = 3 females/time point), the radioactivity concentration in milk reached the maximum (72.2 ng eq./g) at 4 hours, and then decreased with the $t_{1/2}$ of 7.3 hours. The radioactivity was detected in milk up to 12 hours post-dose, and the ratio of the radioactivity concentration in milk to that in plasma was 1.5. In addition, the radioactivity excreted into milk was detected as unchanged PIB.

4.10 Pharmacokinetic drug interactions (PIB)

4.10.1 Enzyme inhibition and induction (CTD 4.2.2.6-6, 4.2.2.6-7, 4.2.2.6-8)

An inhibitory effect of PIB (30 μmol/L) against metabolism of substrates[21] of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) was investigated using human liver microsomes. PIB did not clearly inhibit metabolism of substrates of any CYP isoform.

An inhibitory effect of PIB (50 μmol/L) against metabolism of substrates of UGT isoforms (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7)[22] was investigated. As a result, PIB inhibited metabolism of substrates of UGT1A1 and UGT1A4 with IC_{50} of 2.54 and 0.027 μmol/L, respectively, but did not inhibit metabolism of substrates of UGT1A6, UGT1A9, or UGT2B7.

An induction effect of PIB (0.1-3 μmol/L) on CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) was investigated in human hepatocytes using mRNA as an indicator, none of the CYP isoforms were induced.

4.10.2 Property as a substrate of drug transporters (CTD 4.2.2.6-8, 4.2.2.6-9)

Using HEK293 cell line expressing OATP1B1, OATP1B3, or OCT1, transport of PIB (0.012-0.092 μmol/L for OATP1B, 0.02-0.114 μmol/L for OCT1) mediated by each transporter was investigated. No clear difference was observed in intracellular uptake of PIB between any transporter-expressing cells and original cells.

- Using P-gp- or BCRP-expressing MDCKII cell line, transport of PIB (100 nmol/L) mediated by each transporter was investigated. Intracellular accumulation of PIB in the P-gp-expressing cells increased in the presence of LY335979 or cyclosporine A that inhibits the P-gp function. In the BCRP-expressing cells, on the other hand, intracellular accumulation of PIB did not change irrespective of presence or absence of Ko143 that inhibits the BCRP function.

4.10.3 Inhibitory effect against drug transporters (CTD 4.2.2.6-9)

Using HEK293 cell line expressing OATP1B1, OATP1B3, OCT1, OCT2, OAT3, MATE1, or MATE2K, an inhibitory effect of PIB[23] against transport of substrates[24] of each transporter was investigated. PIB inhibited transport of a substrate of OATP1B1 with IC_{50} of 1.3 μmol/L. In the PIB concentration range investigated, PIB did not clearly inhibit transport of substrates of the other transporters.

Using membrane vesicles prepared from cells[25] expressing P-gp, BCRP, or BSEP, an inhibitory effect of PIB[26] against transport of substrates[27] of each transporter was investigated. PIB inhibited transport of substrates of P-gp, BCRP, and BSEP with IC_{50} of 0.036, 14, and 39 μmol/L, respectively.

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[21] CYP1A2, phenacetin; CYP2B6, bupropion; CYP2C8, paclitaxel; CYP2C9, diclofenac; CYP2C19, *S*-mephenytoin; CYP2D6, dextromethorphan; CYP3A, midazolam and testosterone
[22] UGT1A1, β-estradiol; UGT1A4, trifluoperazine; UGT1A6, 5-hydroxytryptophol; UGT1A9, propofol; UGT2B7, zidovudine
[23] OATP1B1, 0.03 to 300 μmol/L; OATP1B3, OCT1, OCT2, OAT3, MATE1, and MATE2K, 3 and 30 μmol/L
[24] OATP1B1 and OATP1B3, pitavastatin; OAT1 and OAT3, methotrexate; OCT1, OCT2, MATE1, and MATE2K, metformin (^{3}H-labeled for all)
[25] P-gp, human chronic myelogenous leukemic K562 cell line; BCRP, human breast cancer MCF-7 cell line; BSEP, insect ovary Sf-9 cell line
[26] P-gp, 0.0018 to 1500 μmol/L; BCRP, 0.0054 to 1500 μmol/L; BSEP, 0.019 to 5000 μmol/L
[27] P-gp, ^{3}H-N-methylquinidine, BCRP, Lucifer Yellow; BSEP, ^{3}H-taurocholic acid

4.R Outline of the review conducted by PMDA

PMDA has concluded that the submitted non-clinical PK data on GLE and PIB have no particular problems.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the results from toxicity studies of GLE and PIB, including repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, and other toxicity studies (phototoxicity, study on impurity, concomitant use toxicity studies). In toxicity studies, anhydride of GLE was used, and the dose and concentration are indicated on the basis of glecaprevir. Unless otherwise specified, PEG-400/Teen 20/Poloxamer 124 (mass ratio, 7:2:1) was used as vehicle in toxicity studies of GLE, and Phosal 53 MCT/PEG-400/Poloxamer 124/CremophorRH40 (mass ratio, 2:1:1:1) was used as vehicle in toxicity studies of PIB.

5.1 Single-dose toxicity (GLE)

No single-dose toxicity studies were conducted, but the approximate lethal dose following a single oral administration of GLE was determined to be 300 mg/kg in mice, 2000 mg/kg in rats, and >200 mg/kg in dogs, because no deaths occurred on Day 1 of administration in any of the repeated-dose studies (CTD 4.2.3.2-GLE-3 and CTD 4.2.3.2-GLE-8) and rat micronucleus study (CTD 4.2.3.3.2-GLE-1), except for abnormal stool in rats and dogs. In addition, plasma GLE concentrations leveled off at doses ≥120 mg/kg/day in rats.

5.2 Repeated-dose toxicity (GLE)

Repeated oral dose toxicity studies were conducted in mice (4 weeks), rats (13 and 26 weeks), and dogs (13 and 39 weeks). The maximum dose in each study was selected as a dose that was feasible for administration and led to the maximum exposure. In mice and rats, no toxicological target organs were identified. In dogs, mucosal edema in the gallbladder, increased serum alkaline phosphatase (ALP), and increased serum alanine aminotransferase (ALT) were observed, but the applicant explained that they were toxicologically insignificant changes, because their severity was slight, and they were reversible without any histopathological changes in the liver. The plasma exposures ($AUC_{0\text{-}24}$) to GLE at the no-observed-adverse-effect level (NOAEL) (120 mg/kg/day and 200 mg/kg/day) in 26-week and 39-week oral dose toxicity studies in rats and dogs were 735 and 1440 μg·h/mL, respectively, which were 24 and 47 fold, respectively, the plasma exposure (AUC, 30.4 μg·h/mL)[4)] in humans at the clinical dose.

5.2.1 Four-week repeated oral dose toxicity study in mice (CTD 4.2.3.2-GLE-3)

Mice (n = 10/sex/group) orally received GLE at 0 (vehicle), 40, 125, or 300 mg/kg/day for 4 weeks. Findings included increased serum total bilirubin in the ≥40 mg/kg/day groups, increases in serum cholesterol and ALP in the ≥125 mg/kg/day groups, and increased liver weight in the 300 mg/kg/day group. The applicant explained that these findings were toxicologically insignificant, because the extent of the increase was slight for any finding, and no histopathological findings were additionally observed. Based on the above, the NOAEL was determined to be 300 mg/kg/day.

5.2.2 Thirteen-week oral dose toxicity study in rats (CTD 4.2.3.2-GLE-5)

Rats (n = 15/sex/group) orally received GLE at 0 (vehicle), 5, 20, and 60 mg/kg BID for 13 weeks. No abnormalities were observed on any test parameters, and the NOAEL was determined to be 120 mg/kg/day.

5.2.3 Twenty-six-week oral dose toxicity study in rats (CTD 4.2.3.2-GLE-6)

Rats (n = 20/sex/group) orally received GLE at 0 (vehicle), 5, 20, and 60 mg/kg BID for 26 weeks (including evaluation for reversibility with a 4-week recovery period). In the ≥40 mg/kg/day groups, decreases in serum potassium and phosphorus were observed, and similar findings were also observed even after the end of the recovery period. The applicant explained that these findings were toxicologically insignificant changes, because the extent of the decrease was slight for either finding. Based on the above, the NOAEL was determined to be 120 mg/kg/day.

5.2.4 Thirteen-week oral dose toxicity study in dogs (CTD 4.2.3.2-GLE-8)

Dogs (n = 4/sex/group) orally received GLE at 0 (vehicle), 10, 30, and 100 mg/kg BID for 13 weeks (including evaluation for reversibility with a 4-week recovery period). Findings included mucosal edema in the gallbladder in the ≥20 mg/kg/day groups, abnormal stool (mucous stool, watery stool, green stool) in the ≥60 mg/kg/day groups, and increased serum ALP in the 200 mg/kg/day group. The applicant explained that these findings were toxicologically insignificant changes, for the following reasons: (1) Abnormal stool was observed sporadically and did not affect the body weight; (2) the increase in serum ALP was slight in extent and not limited to animals with mucosal edema in the gallbladder, resulting in a failure to demonstrate clear correlation of the increase in question to the histopathological finding; and (3) mucosal edema in the gallbladder was slight in severity without inflammatory reactions. In addition, abnormal stool and mucosal edema in the gallbladder were reversible. Based on the above, the NOAEL was determined to be 200 mg/kg/day.

5.2.5 Thirty-nine-week oral dose toxicity study in dogs (CTD 4.2.3.2-GLE-9)

Dogs (n = 4/sex/group) orally received GLE at 0 (vehicle), 10, 25, and 100 mg/kg BID for 39 weeks (including evaluation for reversibility with an 8-week recovery period). Findings included increased serum ALT in the ≥50 mg/kg/day groups and increased serum γ-glutamyltransferase in the 200 mg/kg group. The applicant explained that they were toxicologically insignificant changes, because these changes were small in extent; no related histopathological changes were observed; and they were reversible. Based on the above, the NOAEL was determined to be 200 mg/kg/day.

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

In vitro genotoxicity studies of GLE conducted were test for reverse mutation in bacteria (Ames test) and chromosome aberration assay using human lymphocytes, and micronucleus assay using rat bone marrow cells was conducted as an *in vivo* study. All the assays produced negative results, and thus GLE was determined to exhibit no genotoxicity.

5.4 Carcinogenicity (GLE)

No carcinogenicity studies were conducted, because the treatment duration of GLE in clinical settings is planned to be shorter than 6 months; and neither genotoxicity nor repeated-dose toxicity studies presented any finding suggestive of carcinogenicity.

5.5 Reproductive and developmental toxicity (GLE)

Reproductive and developmental toxicity studies of GLE conducted include fertility and early embryonic development to implantation in rats, embryo-fetal development toxicity studies in rats and rabbits, and a study of effects on pre- and postnatal development, including maternal function in rats. No abnormalities were observed in rats, while total embryonic resorption and increased post-implantation loss were observed in rabbits. $AUC_{0\text{-}24}$ and C_{max}, plasma exposure parameters, at the NOAEL for embryo-fetal development (rats, 120 mg/kg/day; rabbits, 60 mg/kg/day) were 559 μg·h/mL and 66.8 μg/mL in rats and 0.4 μg·h/mL and 0.0986 μg/mL in rabbits, respectively. The plasma exposure parameter values in rats were 18 and 24 fold, respectively, the corresponding parameter values in humans at the clinical dose (AUC, 30.4 μg·h/mL; C_{max}, 2.81 μg/mL),[5)] while the values in rabbits were less than the corresponding values in humans at the clinical dose.

The applicant explained that GLE may be used in pregnant women or women who may possibly be pregnant if the expected therapeutic benefit outweighs the possible risk associated with treatment, taking into account that (1) the effects on the embryo-fetal development (total embryonic resorption, etc.) in rabbits were considered as the secondary changes in response to the maternal toxicity (decreases in body weight and food consumption) (*Fundam Appl Toxicol.* 1993;21:517-22, *Birth Defects Res B Dev Reprod Toxicol.* 2005;74:424-30, and others); (2) no effects on the embryo-fetal development were observed in rats even at the plasma exposure substantially above that in humans at the clinical dose; and (3) the embryo-fetal development toxicity study of PIB did not show any findings suggestive of embryo-fetal toxicity [see Sections "5.11 Reproductive and developmental toxicity (PIB)"].

5.5.1 Fertility and early embryonic development to implantation in rats (CTD 4.2.3.5.1-GLE-1)

Rats (n = 25/sex/group) orally received GLE at 0 (vehicle), 5, 20, and 60 mg/kg BID. Males received GLE from 14 days prior to mating until the day of necropsy including the mating period, and females received GLE from 14 days prior to mating to Gestation Day 7 including the mating period. In either females or males, no effects on the clinical signs, reproductive function, or early embryonic development were observed. Based on the above, the NOAEL was determined to be 120 mg/kg/day for the clinical signs, reproductive function, and early embryonic development in parent male and female animals.

5.5.2 Embryo-fetal development study in rats (CTD 4.2.3.5.2-GLE-2)

Pregnant rats (n = 25/group) orally received GLE at 0 (vehicle), 5, 20, and 60 mg/kg BID from Gestation Day 6 to Gestation Day 18. No abnormalities were observed in maternal animals or embryo-fetuses. Based on the above, the NOAEL was determined to be 120 mg/kg/day in maternal animals and for embryo-fetal development.

5.5.3 Embryo-fetal development study in rabbits (preparatory study) (4.2.3.5.2-GLE-3)

Pregnant rabbits (n = 10/group) orally received GLE at 0 (vehicle), 50, and 300 mg/kg QD from Gestation Day 7 to Gestation Day 19. In the 300 mg/kg/day group, some maternal animals were found dead or moribund. In addition, because serious maternal toxicity findings such as weight loss and remarkably decreased food consumption were observed, all the surviving maternal animals were sacrificed on Gestation Day 17. The applicant explained that weight loss and decreased food consumption were observed even in the vehicle group and 50 mg/kg/day group, and the above effects are possibly attributable to vehicle. No abnormalities were observed in embryos or fetuses from 5 maternal animals in the 50 mg/kg/day group.[28)]

5.5.4 Embryo-fetal development study in rabbits (preparatory study 2) (4.2.3.5.2-GLE-4)

Pregnant rabbits (n = 10/group) orally received GLE at 0 (vehicle[29)]), 30, 100, and 300 mg/kg QD from Gestation Day 7 to Gestation Day 19. Findings in maternal animals included premature birth, decreased body weight gain or weight loss, decreased food consumption, abnormal stool (mucous stool, watery stool, green stool, etc.), decreased urinary volume, discoloration of urine (red urine, orange urine), soiled fur in the anogenital region, and emaciation in the ≥100 mg/kg/day groups. Findings in embryos and fetuses included decreased fetal weight in the ≥100 mg/kg/day groups, and increases in total embryonic resorption and the number of resorptions, increased post-implantation loss in the 300 mg/kg/day group. No abnormalities were observed in fetal appearance and viscera at the examination. The applicant explained that the changes observed in the embryos and fetuses were attributable to maternal toxicity. Based on the above, the NOAEL was determined to be 30 mg/kg/day in maternal animals and for embryo-fetal development.

5.5.5 Embryo-fetal development study in rabbits (CTD 4.2.3.5.2-GLE-5)

Pregnant rabbits (n = 20/group) orally received GLE at 0 (vehicle[29)]), 20 and 60 mg/kg/day QD from Gestation Day 7 to Gestation Day 19. No abnormalities were observed in maternal animals or embryo-fetal development. Based on the above, the NOAEL was determined to be 60 mg/kg/day in maternal animals and for embryo-fetal development.

5.5.6 Study of effects on pre- and postnatal development, including maternal function in rats (CTD 4.2.3.5.3-GLE-1)

Pregnant rats (n = 22/group) orally received GLE at 0 (vehicle), 5, 20, and 60 mg/kg BID from Gestation Day 6 to Lactation Day 20 (up to Gestation Day 24 in the case of non-delivery). No abnormalities were observed in maternal animals or offspring. Based on the above, the NOAEL was determined to be 120 mg/kg/day in maternal animals and offspring.

[28)] The numbers of evaluated embryos and fetuses in the 50 mg/kg/day group were determined to be insufficient. In the 300 mg/kg/day group, the effects on fetuses were not evaluated, because maternal animals died or were sacrificed until Gestation Day 17.

[29)] As vehicle, ethanol/PEG-400/Phosal 53 MCT (mass ratio, 1:3:6) was used.

5.6 Other toxicity studies (GLE)

5.6.1 Phototoxicity study (CTD 4.2.3.7.7-GLE-1 and 4.2.3.7.7-GLE-2)

5.6.1.1 *In vitro* phototoxicity study

GLE or the positive control (promethazine) were added to 3T3 fibroblast (Balb/c 3T3) culture up to 100 mg/L to evaluate the phototoxicity. As a result, both GLE and promethazine were considered phototoxic.

5.6.1.2 *In vivo* phototoxicity studies

Rats (n = 5 females/group) orally received GLE at 0 (vehicle), 5, 20, and 300 mg/kg BID for 3 days or orally received a single dose of the positive control (8-methoxsalen) at 50 mg/kg. At 1 hour after administration of the study drug, rats were exposed to UVA and UVB rays for 1 hour to investigate the phototoxicity. In the GLE group, no findings such as skin reactions and ocular changes suggestive of phototoxicity were observed. Based on results from this study and information on distribution of GLE in skin and eyes [see Section "4.2.1 Tissue distribution"], the applicant explained that GLE is unlikely to exhibit phototoxicity *in vivo*.

5.6.2 Studies on impurities (CTD 4.2.3.7.6-GLE-1 to 4.2.3.7.6-GLE-17)

Mutagenesis of impurities contained in GLE was evaluated by the *in silico* prediction model for the structure activity relationship, etc.[30)] in accordance with the Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (PSEHB/ELD Notification No. 1110-3 dated November 10, 2015) (ICH M7 Guideline). Ames test was performed on impurities with structural alerts (standard method[31)] or 6-well plate method[32)]). Impurities A, B, C, D and E showed the positive results. The applicant explained that the impurities tested positive are to be controlled at the acceptable levels by the manufacturing process control.

5.7 Single-dose toxicity (PIB)

No single oral dose toxicity studies of PIB were conducted, but the approximate lethal dose of oral administration of PIB was determined to be 2000 mg/kg in mice, 30 mg/kg in rats, and >100 mg/kg in dogs, because no abnormalities in clinical signs or deaths occurred on Day 1 of administration in any of the repeated-dose toxicity studies (CTD 4.2.3.2-PIB-7 and CTD 4.2.3.2-PIB-8) and mouse micronucleus study (CTD 4.2.3.3.2-PIB-1). In addition, plasma PIB concentrations leveled off at doses ≥100 mg/kg/day in mice.

5.7.1 Single intravenous dose study in rabbits (Reference data, CTD 4.2.3.1-PIB-1)

Rabbits (n = 2 females/group) intravenously received PIB at 5 and 50 mg/kg as a single dose.[33)] Death occurred 6 minutes post-dose in the 50 mg/kg group. The dose of 5 mg/kg was well tolerated. The approximate lethal dose of intravenous administration of PIB was determined to be 50 mg/kg in rabbits. In a study in which rabbits (n = 2 females) intravenously received PIB at 10 mg/kg over 15 minutes [see Section "4.6.1 Single-dose studies"], the dose was well tolerated, and the estimated C_{max} was 38 μg/mL, of which concentration was almost equivalent to the solubility of PIB. The applicant explained that a

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30) Impurity F was determined to be negative for mutagenesis based on the literature information (*Environ Mutagen.* 1986;8:1-199).
31) Test methods described in the Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (PFSB/ELD Notification No. 0920-2 dated September 20, 2012)
32) *Environ Mol Mutagen.* 2000;35:72-7, *Environ Mol Mutagen.* 2016;57:483-96, and others
33) As vehicle, PEG-300/D5W/Tween 80 (mass ratio, 89.5:10:0.5) was used.

dose of 50 mg/kg led to the plasma concentration above the solubility of 40 μg/mL, resulting in precipitation of the study drug, which then possibly caused the death.

5.8 Repeated-dose toxicity (PIB)

Repeated oral dose toxicity studies were conducted in mice (4, 13, and 26 weeks), rats (13 weeks), and dogs (13 and 39 weeks). The maximum dose in each study was a dose that was feasible for administration and led to the maximum exposure. In any animal species, no toxicological target organs were identified. The plasma exposures (AUC_{0-24}) to PIB at the NOAEL (100 mg/kg/day for either animal species) in 26-week and 39-week oral dose toxicity studies in mice and dogs were 123 and 25 μg·h/mL, which were 40 and 8 fold, respectively, the plasma exposure (AUC, 3.10 μg·h/mL)[5)] in humans at the clinical dose.

5.8.1 Four-week repeated oral dose toxicity study in mice (CTD 4.2.3.2-PIB-3)

Wild-type CByB6F1 Tg(HRAS)2Jic mice (n = 10/sex/group) orally received PIB at 0 (vehicle), 3, 10, and 100 mg/kg QD for 4 weeks. No abnormalities were observed on any test parameters, and the NOAEL was determined to be 100 mg/kg/day.

5.8.2 Thirteen-week oral dose toxicity study in mice (CTD 4.2.3.2-PIB-4)

CD-1 mice (n = 10/sex/group) orally received PIB at 0 (vehicle), 3, 10, and 100 mg/kg QD for 13 weeks (including evaluation for reversibility with 4-week recovery period). Although decreased spleen weight was observed in the ≥3 mg/kg/day groups, the applicant explained that this change was toxicologically insignificant, because an extent of the decrease did not correlate to the dose, and no histopathological findings were obtained. Based on the above, the NOAEL was determined to be 100 mg/kg/day.

5.8.3 Twenty-six-week oral dose toxicity study in mice (CTD 4.2.3.2-PIB-5)

CD-1 mice (n = 20/sex/group) orally received PIB at 0 (vehicle), 3, 10, and 100 mg/kg QD for 26 weeks (including evaluation for reversibility with 8-week recovery period). No abnormalities were observed on any test parameters, and the NOAEL was determined to be 100 mg/kg/day.

5.8.4 Thirteen-week oral dose toxicity study in rats (CTD 4.2.3.2-PIB-7)

Rats (n = 10/sex/group) orally received PIB at 0 (vehicle), 3, 10, and 30 mg/kg QD for 13 weeks. Although increased thyroid weight was observed in the ≥10 mg/kg/day groups, the applicant explained that this change was toxicologically insignificant, because no related histopathological changes were obtained. Based on the above, the NOAEL was determined to be 30 mg/kg/day.

5.8.5 Thirteen-week oral dose toxicity study in dogs (CTD 4.2.3.2-PIB-9)

Dogs (n = 4/sex/group) orally received PIB at 0 (vehicle), 3, 10, and 100 mg/kg QD for 13 weeks (including evaluation for reversibility with 4-week recovery period). No abnormalities were observed on any test parameters, and the NOAEL was determined to be 100 mg/kg/day.

5.8.6 Thirty-nine-week oral dose toxicity study in dogs (CTD 4.2.3.2-PIB-10)

Dogs (n = 4/sex/group) orally received PIB at 0 (vehicle), 3, 10, and 100 mg/kg QD for 39 weeks (including evaluation for reversibility with 8-week recovery period). In the 100 mg/kg/day group,

decreased reticulocyte count was observed from Day 92 onward. The applicant explained that this change was toxicologically insignificant, because the extent of the change was small, and the other erythroid parameter values remained unchanged. This change was reversible after the 8-week recovery period. Based on the above, the NOAEL was determined to be 100 mg/kg/day.

5.9 Genotoxicity (PIB) (CTD 4.2.3.1-PIB-1, 4.2.3.1-PIB-2, 4.2.3.2-PIB-1)

In vitro genotoxicity studies of PIB conducted were Ames test and chromosome aberration assay using human lymphocytes, and micronucleus assay using mouse bone marrow cells was conducted as an *in vivo* study. All the assays produced negative results, and thus PIB was determined to exhibit no genotoxicity.

5.10 Carcinogenicity (PIB)

No carcinogenicity studies were conducted, because the treatment duration of PIB in clinical settings is planned to be shorter than 6 months; and neither genotoxicity nor repeated-dose toxicity studies presented any finding suggestive of carcinogenicity.

5.11 Reproductive and developmental toxicity (PIB)

Reproductive and developmental toxicity studies of PIB conducted include fertility and early embryonic development to implantation in mice, embryo-fetal development toxicity studies in mice and rabbits, and a study of effects on pre- and postnatal development, including maternal function in mice. No abnormalities were observed in mice. In rabbits, deaths and abortion occurred in all the dose groups including the vehicle group. The applicant explained that these events were caused by toxicity attributable to vehicle. $AUC_{0\text{-}24}$ and C_{max}, plasma exposure parameters, at the NOAEL for embryo-fetal development (100 mg/kg/day for either animal species) were 73.1 μg·h/mL and 3.48 μg/mL, respectively, in mice and 2.11 μg·h/mL and 0.259 μg/mL, respectively, in rabbits. The plasma exposure parameter values in mice were 26 and 18 fold, respectively, the corresponding parameter values in humans at the clinical dose (2.83 μg·h/mL and 0.193 μg/mL)[5)], while the values in rabbits were similar to the corresponding values in humans at the clinical dose.

5.11.1 Fertility and early embryonic development to implantation in mice (CTD 4.2.3.5.1-PIB-1)

Mice (n = 25/sex/group) orally received PIB at 0 (vehicle), 3, 10, and 100 mg/kg QD. Males received PIB from 14 days prior to mating until the day of necropsy including the mating period, and females received PIB from 14 days prior to mating to Gestation Day 6 including the mating period. In either females or males, no effects on the clinical sign, reproductive function, or early embryonic development were observed. Based on the above, the NOAEL was determined to be 100 mg/kg/day for the clinical sign, reproductive function, and early embryonic development in parent male and female animals.

5.11.2 Embryo-fetal development study in mice (CTD 4.2.3.5.2-PIB-2)

Pregnant mice (n = 25/group) orally received PIB at 0 (vehicle), 3, 10, and 100 mg/kg QD from Gestation Day 6 to Gestation Day 15. No abnormalities were observed in maternal animals or embryo-fetuses. Based on the above, the NOAEL was determined to be 100 mg/kg/day in maternal animals and for embryo-fetal development.

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

Pregnant rabbits (n = 25/group) orally received PIB at 0 (vehicle), 10, and 100 mg/kg QD from Gestation Day 7 to Gestation Day 19. Some of the maternal animals in all the dose groups including the vehicle group were found dead or sacrificed moribund (3 animals in the control group, 3 animals in the 10 mg/kg group, 1 animal in the 100 mg/kg group) and had abortion (2 animals in the control group, 1 animal in the 10 mg/kg group, 2 animals in the 100 mg/kg group). In these animals, decreased body weight gain or weight loss, decreased food consumption, emaciation, and dehydration occurred. Even in surviving animals including animals in the control group, decreased body weight gain or weight loss, decreased food consumption, watery stool, and worsened fur were observed. No abnormalities were observed in embryo-fetuses. The applicant explained that the toxicological findings in maternal animals including deaths and abortion were caused by vehicle, and no abnormalities related to PIB were observed. Based on the above, the NOAEL of PIB was determined to be 100 mg/kg/day in maternal animals and for embryo-fetal development.

5.11.4 Study of effects on pre- and postnatal development, including maternal function in mice (CTD 4.2.3.5.3-PIB-1)

Pregnant mice (n = 25/group) orally received PIB at 0 (vehicle), 3, 10, and 100 mg/kg QD from Gestation Day 6 to Lactation Day 20. No abnormalities were observed in maternal animals or offspring. Based on the above, the NOAEL was determined to be 100 mg/kg/day in maternal animals and offspring.

5.12 Other toxicity studies (PIB)

5.12.1 Phototoxicity study (CTD 4.2.3.7.7-PIB-1)

PIB or the positive control (promethazine) were added to 3T3 fibroblast (Balb/c 3T3) culture up to 3 mg/L and 100 mg/L, respectively, to evaluate the phototoxicity. Irrespective of photoirradiation, no cytotoxicity was observed in the cells with PIB, and thus PIB was determined to have no phototoxicity.

5.12.2 Studies on impurities (CTD 4.2.3.7.6-PIB-2 to 4.2.3.7.6-PIB-13, 4.2.3.7.6-PIB-15 to 4.2.3.7.6-PIB-17)

Seven impurities[34)] each of which the amount exceeded the qualification threshold specified in the "Revised Guideline for Impurities in New Drug Substances" (PFSB/ELD Notification No. 1216001, dated December 16, 2002) were determined to raise no concerns about the general toxicity, based on comparison of the administered amount of the impurities through the study drug in the repeated-dose toxicity studies of PIB with the potential maximum intake of the impurities at the clinical dose. Genotoxicity of the impurities, each of which the maximum intake is <1 mg/day, was evaluated by the *in silico* prediction model for the structure activity relationship. These impurities were determined to raise no concerns about genotoxicity. In addition, mutagenesis of impurities contained in PIB was evaluated by the *in silico* prediction model for the structure activity relationship in accordance with the ICH M7 Guideline. Ames test was performed on impurities with structural alerts (standard method[31)] or 6-well plate method[32)]). Impurities G, H, I, and J showed positive results. The applicant explained that

[34)] K, L, M, N, O, P, and Q

the impurities tested positive are to be controlled at the acceptable levels by the manufacturing process control.

5.12.3 Four-week oral dose toxicity study in mice (CTD 4.2.3.7.6-PIB-1)

Mice (n = 10/sex/group) orally received PIB at 0 (vehicle) and 100 mg/kg (with or without the additional impurities[35]) for 4 weeks. In any dose group, no abnormalities were observed on any test parameters.

5.13 Toxicity study of concomitant use of GLE and PIB (Reference data, CTD 4.2.3.7.7-GLE-4)

Rats (n = 10/sex/group) orally received GLE/PIB at 0/0 (vehicle[36]) and 12.5/20 mg/kg QD for 4 weeks. No abnormalities were observed on any test parameters, and the concomitant use did not suggest safety concerns.

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following investigation, PMDA has concluded that clinical use of GLE and PIB has no particular problems from a toxicological viewpoint.

Extend of fulfillment of impurity evaluation

Mutagenesis of the impurities in the manufacturing process in which structural alerts were identified by the *in silico* prediction model for the structure activity relationship was evaluated using the 6-well plate method. PMDA asked the applicant to explain whether the above evaluation method was appropriate.

The applicant's explanation:

Because, of impurities in the manufacturing process, amounts necessary for a standard Ames test are hardly available, a test for reverse mutation using the 6-well plate method was selected to reduce the necessary amount of the impurities to be evaluated. In the 6-well plate method in which treatment surface is small, the amount of a test article is reduced to approximately 20% of that of the standard method, but test conditions such as bacterial strains and presence or absence of metabolism activation are equivalent to conditions in the conventional standard method. The 6-well plate method has been improved since the report in 2000 (*Environ Mol Mutagen.* 2000;35:72-7, *Environ Mol Mutagen.* 2016;57:483-96, etc.). To verify the reliability of the concerned test method, the applicant compared the standard method with the 6-well plate method in details using their test data and literature data. The comparison revealed that of 222 chemical compounds, 221 were given consistent results by these methods (99.5%) (AbbVie. R&D/15/0441). The remaining 1 chemical compound was tested positive by the 6-well plate method, but negative by the standard method. The inconsistent results in question, however, were considered potentially attributable to use of different testing facilities[37] and difference in impurity profile between the batches. As described in the ICH M7 Guideline, mutagenesis evaluation "using a miniaturized assay format with proven high concordance to the ICH-compliant assay" is accepted. Therefore, the use of the 6-well plate method is appropriate for mutagenesis evaluation of process-related impurities.

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35) R was added at 0.17%.
36) 0.5% hydroxypropylmethylcellulose solution
37) Reproducibility of Ames test by the standard method among different facilities was reported to be approximately 85% (*J Med Chem.* 2005;48:312-20).

PMDA has concluded that the applicant's explanation is acceptable.

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

For clinical development of GLE and PIB, tablets containing GLE at 2.5 to 200 mg and tablets containing PIB at 1.5 to 100 mg were used in major Japanese and foreign phase I and phase II studies. For clinical development of the GLE/PIB, film-coated tablets containing GLE at 100 mg and PIB at 40 mg were mainly used. The film-coated tablets used in Japanese phase III studies (Studies M15-594 and M15-828) were determined as the commercial formulation (Maviret).

Amounts of GLE and PIB in human plasma and urine were determined by LC/MS/MS (lower limits of quantitation for both ingredients, 1.0 ng/mL).

Unless otherwise specified, PK parameters are expressed as the geometric mean, and the dose and concentration of GLE are indicated on the basis of glecaprevir.

6.1.1 Food effect (Reference data CTD 5.3.1.1-5, Study M[redacted]-714 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The food effect on PK of Maviret (commercial formulation) was investigated in a four-treatment four-period crossover study[38)] in non-Japanese healthy subjects (23 subjects included in PK analysis) in which subjects orally received 3 tablets of Maviret (commercial formulation) (GLE/PIB 300/120 mg) as a single dose under fasted conditions, or under fed conditions with medium-fat diet (with approximately 500-750 kcal, containing fat at approximately 30%) or with high-fat diet (with approximately 750-1000 kcal, containing fat at approximately 50%). The results are as shown in Table 23. The exposure to GLE and PIB administered under fed conditions with the medium-fat or high-fat diet was greater than that of GLE and PIB administered under fasted conditions. The applicant explained the above result for the following reasons: The dietary intake enhanced secretion of digestive juice such as bile acid, which increased solubility of GLE and PIB, leading to their increased absorption in the digestive tract.

[38)] Relative bioavailability of 3 dosage units of Maviret (film-coated tablets containing GLE at 100 mg and PIB at 40 mg) to 3 dosage units each of GLE 100 mg tablets and PIB 40 mg tablets was also investigated.

Table 23. Food effect on PK of GLE/PIB

Study population	Diet condition	Number of subjects	C_{max} (ng/mL)	t_{max} [a)] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ [b)] (h)	Relative bioavailability to administration under fasted conditions [90% confidence interval (CI)]	
							C_{max}	AUC_{inf}
GLE	Fasted	23	294 (78)	3.0 [1.5, 5.0]	1150 (69)	6.0 (23.7)	-	-
	Fed with medium-fat diet	23	937 (84)	4.0 [3.0, 5.0]	3040 (60)	6.0 (16.1)	3.16 [2.58, 3.87]	2.63 [2.18, 3.17]
	Fed with high-fat diet	23	633 (54)	5.0 [4.0, 6.0]	2110 (54)	6.3 (17.9)	2.14 [1.75, 2.62]	1.83 [1.52, 2.21]
PIB	Fasted	23	116 (60)	4.0 [2.0, 5.0]	960 (64)	13.3 (8.9)	-	-
	Fed with medium-fat diet	23	221 (44)	5.0 [3.0, 5.0]	1346 (49)	13.0 (9.6)	1.90 [1.49, 2.41]	1.40 [1.11, 1.78]
	Fed with high-fat diet	23	237 (45)	5.0 [4.0, 6.0]	1460 (50)	13.5 (8.8)	2.05 [1.60, 2.62]	1.5 3[1.20, 1.95]

Geometric mean (coefficient of variation [CV]%)
a) Median [minimum, maximum], b) Harmonic mean (apparent CV%)

6.2 Clinical Pharmacology

In this application, the applicant submitted clinical pharmacology data from phase I clinical studies in healthy subjects and population pharmacokinetics (PPK) analysis results on data from Japanese phase III clinical studies in patients with Chronic hepatitis C or compensated cirrhosis type C. Data from *in vitro* studies using human biological samples are described in the sections for non-clinical pharmacokinetics [see Sections "4.2.2 Plasma protein binding and distribution into blood cells," "4.3.2 *In vitro* metabolism," "4.5 Pharmacokinetic drug interactions," "4.7.2 Plasma protein binding and distribution into blood cells," "4.8.2 *In vitro* metabolism," and "4.10 Pharmacokinetic drug interactions"].

6.2.1 Investigations in healthy subjects

6.2.1.1 Phase I study (CTD 5.3.3.3-1, Study M[redacted]-432 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Japanese, Caucasian, and Chinese healthy subjects living in the US (45 for each of Japanese, Caucasian, and Chinese subjects included in PK analysis) orally received GLE alone (100, 200 or 300 mg) or PIB alone (80 or 120 mg) QD under fed conditions from Day 1 to Day 7, and then GLE + PIB (GLE/PIB 100/120 mg, 200/80 mg, 200/120 mg, or 300/120 mg) QD under fed conditions from Day 8 to Day 14, for investigation of PK of GLE and PIB. Table 24 shows PK parameter values of GLE and PIB on Day 7 (after administration of GLE or PIB alone) and Day 14 (after concomitant use of GLE with PIB). In the dose range investigated, C_{max} and $AUC_{0\text{-}24}$ of GLE increased more than dose-proportionally. In addition, concomitant PIB did not affect the exposure to GLE, but concomitant GLE increased the exposure to PIB.

Table 24. PK parameter values following repeated oral administration of GLE and/or PIB in healthy subjects (Day 7 or 14)

Study population	Dose (mg) GLE	Dose (mg) PIB	Race	Number of subjects	C_{max} (ng/mL)	t_{max} [a)] (h)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ [b)] (h)
GLE	100	0	Japanese	9	63.4 (33)	2.0 [1.0, 4.0]	218 (34)	-
			Caucasian	9	61.1 (38)	3.0 [1.0, 4.0]	203 (32)	-
			Chinese	9	52.6 (34)	3.0 [2.0, 4.0]	176 (38)	-
	200	0	Japanese	9	318 (51)	3.0 [2.0, 3.0]	993 (37)	-
			Caucasian	9	292 (114)	2.0 [2.0, 4.0]	1143 (105)	-
			Chinese	9	369 (70)	3.0 [2.0, 4.0]	1217 (68)	-
	300	0	Japanese	9	1160 (91)	3.0 [2.0, 4.0]	3229 (81)	-
			Caucasian	9	583 (78)	3.0 [2.0, 4.0]	2191 (61)	-
			Chinese	9	1193 (51)	4.0 [3.0, 5.0]	3767 (47)	-
	100	120	Japanese	9	84.9 (60)	3.0 [1.0, 5.0]	350 (42)	7.3 (14)
			Caucasian	9	71.2 (41)	2.0 [1.0, 3.0]	297 (39)	6.8 (30)
			Chinese	9	63.2 (41)	3.0 [1.0, 5.0]	288 (35)	6.8 (18)
	200	80	Japanese	9	297 (67)	4.0 [2.0, 5.0]	1039 (45)	7.0 (22)
			Caucasian	9	311 (60)	3.0 [2.0, 5.0]	1220 (65)	9.7 (36)
			Chinese	8	267 (72)	4.0 [2.0, 4.0]	1021 (56)	6.5 (17)
	200	120	Japanese	8	346 (55)	3.5 [2.0, 5.0]	1173 (57)	5.9 (35)
			Caucasian	9	393 (227)	3.0 [2.0, 5.0]	1499 (213)	8.6 (35)
			Chinese	9	374 (81)	4.0 [3.0, 5.0]	1292 (75)	6.4 (11)
	300	120	Japanese	18	1390 (81)	4.0 [2.0, 5.0]	3932 (63)	6.5 (18)
			Caucasian	18	1271 (190)	3.0 [2.0, 5.0]	4500 (270)	8.7 (37)
			Chinese	18	1154 (58)	4.0 [3.0, 5.0]	3635 (60)	5.9 (26)
PIB	0	80	Japanese	9	37.2 (57)	5.0 [3.0, 5.0]	241 (42)	-
			Caucasian	9	43.9 (34)	4.0 [2.0, 5.0]	316 (35)	-
			Chinese	8	46.2 (58)	4.5 [2.0, 5.0]	303 (48)	-
	0	120	Japanese	9	84.1 (38)	4.0 [2.0, 5.0]	539 (50)	-
			Caucasian	9	109 (55)	4.0 [2.0, 5.0]	803 (62)	-
			Chinese	9	84.4 (47)	5.0 [3.0, 5.0]	463 (44)	-
	200	80	Japanese	9	128 (32)	5.0 [3.0, 6.0]	740 (37)	27.0 (23)
			Caucasian	9	110 (34)	4.0 [3.0, 6.0]	825 (34)	27.3 (18)
			Chinese	8	150 (30)	5.0 [4.0, 5.0]	940 (26)	25.4 (7)
	100	120	Japanese	9	187 (56)	5.0 [3.0, 5.0]	1308 (59)	23.8 (24)
			Caucasian	9	123 (44)	4.0 [2.0, 5.0]	865 (45)	28.6 (23)
			Chinese	9	115 (27)	5.0 [3.0, 6.0]	755 (30)	26.2 (11)
	200	120	Japanese	8	201 (39)	5.0 [3.0, 5.0]	1238 (35)	19.3 (101)
			Caucasian	9	209 (41)	5.0 [3.0, 5.0]	1534 (69)	26.2 (26)
			Chinese	9	187 (48)	5.0 [3.0, 5.0]	1236 (59)	24.9 (14)
	300	120	Japanese	18	281 (30)	5.0 [3.0, 6.0]	1872 (37)	24.6 (22)
			Caucasian	18	244 (52)	5.0 [3.0, 5.0]	1896 (80)	28.1 (27)
			Chinese	18	230 (34)	5.0 [5.0, 5.0]	1445 (40)	24.4 (30)

Geometric mean (CV%)
-, Not investigated
a) Median [minimum, maximum], b) Harmonic mean (apparent CV%)

6.2.1.2 Phase I study (CTD 5.3.3.3-2, Study M[redacted]-066 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Japanese, Caucasian, and Chinese healthy subjects living in the US (12 Japanese subjects, 12 Caucasian subjects, and 11 Chinese subjects included in PK analysis) orally received GLE alone at 700 mg or PIB alone at 160 mg QD under fed conditions from Day 1 to Day 7, and then GLE at 700 mg and PIB at 160 mg concomitantly QD under fed conditions from Day 8 to Day 14, for investigation of PK of GLE and PIB following multiple administration. The results are as shown in Table 25.

Table 25. PK parameter values following multiple oral administration of GLE and PIB in healthy subjects

Study population	Dose (mg)		Race	Number of subjects	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$[b] (h)
	GLE	PIB						
GLE	700	0	Japanese	6	13,700 (64)	4.5 [3.0, 5.0]	46,500 (80)	3.8 (5)
			Caucasian	6	10,600 (70)	3.0 [2.0, 4.0]	43,900 (96)	3.5 (4)
			Chinese	6	10,400 (53)	4.0 [4.0, 5.0]	36,900 (61)	3.6 (4)
	700	160	Japanese	12	16,700 (48)	4.0 [3.0, 6.0]	67,500 (68)	7.3 (10)
			Caucasian	12	15,300 (59)	4.0 [2.0, 4.0]	66,000 (85)	8.9 (14)
			Chinese	11	13,900 (51)	4.0 [3.0, 5.0]	49,400 (63)	8.6 (13)
PIB	0	160	Japanese	6	63.5 (51)	5.0 [3.0, 5.0]	382 (62)	12.5 (17)
			Caucasian	6	61.1 (69)	4.5 [2.0, 5.0]	424 (65)	12.6 (16)
			Chinese	5	96.6 (32)	5.0 [3.0, 5.0]	587 (39)	12.7 (16)
	700	160	Japanese	12	326 (34)	5.0 [4.0, 8.0]	3070 (50)	20.2 (30)
			Caucasian	12	289 (37)	5.0 [4.0, 6.0]	2910 (47)	21.9 (33)
			Chinese	11	288 (29)	5.0 [5.0, 5.0]	2570 (42)	25.4 (15)

Geometric mean (CV%)
a) Median [minimum, maximum], b) Harmonic mean (apparent CV%)

6.2.1.3 Mass balance (Reference data CTD 5.3.3.1-1, sub-study 2 for Study M[redacted]-890 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Non-Japanese healthy subjects (6 subjects each included in PK analysis) orally received ^{14}C-GLE at 400 mg and ^{14}C-PIB at 120 mg under fed conditions for investigation of mass balance. For GLE, 92.8% of the administered radioactivity was recovered until 168 hours post-dose (92.1% in feces, 0.67% in urine). In the feces, unchanged GLE (22.6% of the administered radioactivity) and 7 metabolites (M6, M23, M22, M24, M5, M2, and M4) were detected (41.7%, 12.3%, 8.3%, 2.0%, 1.8%, 1.5%, and 0.3%, respectively, of the administered radioactivity). In plasma, only unchanged GLE was detected. For PIB, 96.6% of the administered radioactivity was recovered in feces until 144 hours post-dose, while no radioactivity was detected in urine. In plasma and feces, only unchanged PIB was detected.

6.2.2 Investigations in patients

6.2.2.1 PPK analysis (Reference data CTD 5.3.3.5-6)

Using PK data obtained from 2 Japanese phase III studies in patients with chronic hepatitis C or compensated cirrhosis type C (Studies M15-594 and M15-828) (1840 GLE measurement points and 1850 PIB measurement points in 332 patients), PPK analysis (NONMEM version 7.3) was performed. The final model was described as a 1-compartment model with first-order absorption and first-order elimination for GLE and as a 2-compartment model with first-order absorption and first-order elimination for PIB. As statistically significant covariates, age on apparent clearance (CL/F) of GLE, presence or absence of hepatic cirrhosis on the bioavailability, and body weight and age on CL/F of PIB

were selected.[39] Based on the above, PPK model revealed that AUC_{0-24} of GLE and PIB in patients aged >75 years were estimated to be approximately 54% and 28%, respectively, higher than those in patients ≤75 years, and AUC_{0-24} of PIB in patients weighing ≥85 kg was estimated to be approximately 34% lower than that in patients with weighing ≤55 kg. The applicant, however, explained that these estimated changes were clinically insignificant.

Table 26 shows PK parameter values at steady state estimated using the final model in patients with chronic hepatitis C or compensated cirrhosis type C who orally received 3 GLE/PIB tablets (300/120 mg) QD under fed conditions.

Table 26. PK parameter values of GLE and PIB at steady state (estimated by simulation using the final model)

Study population	C_{max} (ng/mL)		AUC_{0-24} (ng·h/mL)		C_{trough} (ng/mL)	
	Chronic hepatitis C	Compensated cirrhosis type C	Chronic hepatitis C	Compensated cirrhosis type C	Chronic hepatitis C	Compensated cirrhosis type C
GLE	1170 (124)	2810 (60)	11,600 (154)	30,400 (73)	33.7 (361)	118 (173)
PIB	165 (40)	193 (34)	2560 (48)	3100 (40)	41.3 (75)	55.0 (62)

Geometric mean (CV%)

6.2.3 Investigations of intrinsic factors

6.2.3.1 Foreign study in subjects with hepatic impairment (Reference data CTD 5.3.3.3-3, Study M[redacted]-604 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Combination of GLE at 300 mg and PIB at 120 mg was orally administered at a single dose to subjects with hepatic impairment (7 subjects with mild impairment classified as Child-Pugh Class A, 6 subjects with moderate impairment classified as Class B, and 7 subjects with severe impairment classified as Class C) and 7 subjects with normal hepatic function. The resultant PK parameter values are as shown in Table 27.

Based on the above results, the applicant explained that Maviret should be contraindicated in patients with severe hepatic impairment, because C_{max} and area under plasma concentration-time curve up to infinity (AUC_{inf}) of GLE in subjects with severe hepatic impairment were 4.78 and 11.1 fold, respectively, higher than those in subjects with normal hepatic function.

[39] Potential covariates analyzed included body weight, body mass index (BMI), body surface area, age, sex, genotype, presence or absence of hepatic cirrhosis, renal function, presence or absence of dialysis, presence or absence of history of prior treatment, and concomitant drug on CL/F; and body weight, BMI, body surface area, age, and sex on V_c/F; and presence or absence of hepatic cirrhosis and concomitant drug on bioavailability.

Table 27. PK parameter values by hepatic function following single concomitant dose of GLE at 300 mg and PIB at 120 mg

Study population	Severity of hepatic impairment	Number of subjects	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$[b] (h)	Geometric least squares mean ratio[c] [90% CI]	
							C_{max}	AUC_{inf}
GLE	Normal	6	1050 (118)	3.0 [1.0, 4.0]	3900 (116)	7.1 (27)	-	-
	Mild	6	923 (70)	3.5 [2.0, 6.0]	4470 (104)	6.7 (49)	1.01 [0.38, 2.70]	1.33 [0.49, 3.58]
	Moderate	6	1390 (94)	4.0 [2.0, 4.0]	7380 (110)	7.3 (40)	1.38 [0.53, 3.59]	2.00 [0.76, 5.25]
	Severe	6	7540 (12)	3.0 [2.0, 9.0]	61,600 (42)	8.6 (39)	4.78 [1.75, 13.1]	11.1 [4.0, 30.8]
PIB	Normal	6	205 (41)	4.0 [3.0, 6.0]	1740 (44)	35.0 (33)	-	-
	Mild	6	163 (49)	5.0 [3.0, 6.0]	1320 (53)	37.2 (18)	0.84 [0.58, 1.21]	0.80 [0.48, 1.34]
	Moderate	6	193 (51)	5.0 [3.0, 6.0]	1630 (64)	48.3 (33)	1.26 [0.85, 1.86]	1.26 [0.73, 2.16]
	Severe	6	131 (40)	6.0 [3.0, 9.0]	4050 (79)	84.8 (45)	0.59 [0.41, 0.85]	2.14 [1.28, 3.58]

Geometric mean (CV%)
-, Not applicable
a) Median [minimum, maximum], b) Harmonic mean (apparent CV%), c) Hepatic impairment/normal hepatic function

6.2.3.2 Foreign study in subjects with renal impairment (Reference data CTD 5.3.3.3-4, Study M[redacted]-600 [[redacted] 20[redacted] to [redacted] 20[redacted])

Combination of GLE at 300 mg and PIB at 120 mg was orally administered at a single dose to subjects with renal impairment (8 subjects with mild impairment presenting estimated glomerular filtration rate [eGFR] of 60 to 89 mL/min/1.73 m^2, 8 subjects with moderate impairment presenting eGFR of 30 to 59 mL/min/1.73 m^2, and 8 subjects with severe impairment presenting eGFR of 15 to 29 mL/min/1.73 m^2), 6 subjects who had a renal disease with eGFR of <15 mL/min/1.73 m^2 but did not undergo blood dialysis, and 8 subjects with normal renal function presenting eGFR ≥90 mL/min/1.73 m^2. The resultant PK parameter values are as shown in Table 28.

In addition, combination of GLE at 300 mg and PIB at 120 mg was orally administered at a single dose to 8 subjects with renal impairment presenting eGFR <15 mL/min/1.73 m^2 who were undergoing blood dialysis for ≥1 month, and then subjects underwent or did not undergo dialysis. The resultant PK was compared between subjects who underwent dialysis after the above single dose and subjects who did not.[40] In subjects who underwent dialysis and subjects who did not, C_{max} of GLE was 671 ng/mL and 723 ng/mL, respectively, and AUC_{inf} was 3010 ng·h/mL and 2840 ng·h/mL, respectively. C_{max} of PIB was 128 ng/mL and 156 ng/mL, respectively, and AUC_{inf} was 1020 ng·h/mL and 1120 ng·h/mL, respectively.

The applicant explained that C_{max} and AUC_{inf} of GLE and PIB in subjects with renal impairment were not remarkably different from those in subjects with normal renal function, irrespective of the severity of the impairment, and the dialysis did not affect these PK parameters.

[40] Subjects with renal impairment who were undergoing blood dialysis received GLE at 300 mg and PIB at 120 mg in combination as a single dose, and at 3 hours post-dose the blood dialysis was started followed by collection of blood samples (in the case where dialysis was implemented). After a washout period for at least 7 days, they received GLE at 300 mg and PIB at 120 mg in combination as a single dose again followed by collection of blood samples (in the case where dialysis was not implemented).

Table 28. PK parameter values by renal function following single concomitant dose of GLE at 300 mg and PIB at 120 mg

Study population	Severity of renal impairment	Number of subjects	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$[b] (h)	Geometric least squares mean ratio[c] [90% CI]	
							C_{max}	AUC_{inf}
GLE	Normal	8	652 (54)	3.5 [2.0, 4.0]	2650 (42)	6.8 (10)	-	-
	Mild	8	683 (73)	4.0 [2.0, 9.0]	2950 (48)	7.3 (46)	1.02 [0.89, 1.17]	1.13 [1.01, 1.26]
	Moderate	8	1150 (63)	4.0 [3.0, 6.0]	5340 (41)	6.5 (28)	1.05 [0.77, 1.42]	1.30 [1.02, 1.66]
	Severe	8	542 (56)	5.0 [3.0, 9.0]	3400 (48)	8.4 (37)	1.07 [0.70, 1.64]	1.45 [1.03, 2.04]
	Renal disease without dialysis	6	488 (94)	5.0 [2.0, 6.0]	3140 (101)	8.2 (25)	1.08 [0.65, 1.80]	1.56 [1.03, 2.35]
PIB	Normal	8	181 (46)	6.0 [3.0, 6.0]	1490 (50)	36.8 (30)	-	-
	Mild	8	216 (37)	6.0 [3.0, 6.0]	1750 (33)	34.0 (59)	1.06 [0.98, 1.15]	1.11 [1.02, 1.20]
	Moderate	8	279 (31)	6.0 [3.0, 6.0]	2300 (31)	45.7 (24)	1.14 [0.95, 1.37]	1.25 [1.05, 1.50]
	Severe	8	236 (52)	6.0 [4.0, 6.0]	2230 (42)	41.4 (27)	1.20 [0.93, 1.55]	1.37 [1.07, 1.77]
	Renal disease without dialysis	6	170 (42)	5.0 [4.0, 6.0]	1730 (52)	42.6 (44)	1.25 [0.92, 1.70]	1.46 [1.08, 1.97]

Geometric mean (CV%)
-, Not applicable
a) Median [minimum, maximum], b) Harmonic mean (apparent CV%), c) Ratio of C_{max} or AUC_{inf} of GLE and PIB estimated by the regression model in subjects with renal impairment to that in subjects with normal renal function

6.2.4 Investigations of drug interactions[41)]

A study to investigate drug interactions of GLE and PIB with concomitant drugs was conducted. Table 29 and Table 30 show the geometric least squares mean ratio of PK parameter value of GLE, PIB, or concomitant drug in subjects receiving GLE or PIB concomitantly with the other drug to that in subjects receiving GLE or PIB alone [90% confidence interval (CI)]. Based on these results, the applicant explained that cautions have to be provided for concomitant use of P-gp inducers and inhibitors, OATP1B inhibitors, and substrates of OATP1B, P-gp, and BCRP.

41) Reference data 5.3.3.4-2, Study M[redacted]-605 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-4, Study M[redacted]-582 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-5, Study M[redacted]-585 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-6, Study M[redacted]-724 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-7, Study M[redacted]-723 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-8, Study M[redacted]-578 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-9, Study M[redacted]-599 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-10, Study M[redacted]-598 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-11, Study M[redacted]-579 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-12, Study M[redacted]-721 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-13, Study M[redacted]-715 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-14, Study M[redacted]-602 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-15, Study M[redacted]-584 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-16, Study M[redacted]-592 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-17, Study M[redacted]-593 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-18, Study M[redacted]-577 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-19, Study M[redacted]-587 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-20, Study M[redacted]-603 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-21, Study M[redacted]-597 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-22, Study M[redacted]-584 ([redacted] 20[redacted] to [redacted] 20[redacted]); Reference data 5.3.3.4-23, Study M[redacted]-532 ([redacted] 20[redacted] to [redacted] 20[redacted])

Table 29. Effects of concomitant drugs on PK parameter values of GLE and PIB

Concomitant drug	Dosage regimen			Number of subjects	Geometric least squares mean ratio [90% CI]		
	Concomitant drug	Study population			C_{max}	AUC[a)]	C_{trough} or C_{24}
Cyclosporine	100 mg Single dose	GLE	300 mg QD	12	1.30 [0.95, 1.78]	1.37 [1.13, 1. 66]	1.34 [1.12, 1.60]
		PIB	120 mg QD	12	1.11 [0.92, 1.33]	1.22 [1.10, 1.36]	1.26 [1.15, 1.37]
	400 mg Single dose	GLE	300 mg, single dose	11	4.51 [3.36, 6.05]	5.08 [4.11, 6.29]	-
		PIB	120 mg, single dose	11	1.22 [1.08, 1.38]	1.93 [1.78, 2.09]	-
Digoxin	0.5 mg Single dose	GLE	400 mg QD	12	1.10 [0.80, 1.50]	1.05 [0.83, 1.31]	0.94 [0.88, 1.01]
		PIB	120 mg QD	12	1.16 [1.07, 1.27]	1.08 [1.02, 1.14]	1.01 [0.96, 1.06]
Dabigatran etexilate	150 mg Single dose	GLE	300 mg QD	11	0.82 [0.69, 0.97]	0.80 [0.69, 0.93]	1.04 [0.88, 1.23]
		PIB	120 mg QD	11	0.86 [0.78, 0.96]	0.91 [0.83, 0.99]	0.95 [0.85, 1.06]
Lamotrigine	50 mg Single dose	GLE	300 mg QD	12	0.75 [0.61, 0.94]	0.80 [0.69, 0.92]	0.78 [0.70, 0.87]
		PIB	120 mg QD	12	0.91 [0.83, 0.99]	0.98 [0.92, 1.03]	0.93 [0.89, 0.96]
Carbamazepine	200 mg BID	GLE	300 mg, single dose	10	0.33 [0.27, 0.41]	0.34 [0.28, 0.40]	-
		PIB	120 mg, single dose	10	0.50 [0.42, 0.59]	0.49 [0.43, 0.55]	-
Rifampicin	600 mg Single dose	GLE	300 mg, single dose	12	6.52 [5.06, 8.41]	8.55 [7.01, 10.4]	-
		PIB	120 mg, single dose	12	0.91 [0.76, 1.10]	1.04 [0.89, 1.22]	-
	600 mg QD	GLE	300 mg, single dose	12	1.40 [0.95, 2.06]	1.05 [0.75, 1.46]	-
		PIB	120 mg, single dose	12	0.21 [0.16, 0.27]	0.17 [0.14, 0.21]	-
	600 mg QD[b)]	GLE	300 mg, single dose	12	0.14 [0.11, 0.19]	0.12 [0.09, 0.15]	-
		PIB	120 mg, single dose	12	0.17 [0.14, 0.20]	0.13 [0.11, 0.15]	-
Felodipine	2.5 mg Single dose	GLE	300 mg QD	11	0.86 [0.72, 1.03]	0.90 [0.81, 1.01]	1.19 [1.05, 1.35]
		PIB	120 mg QD	11	0.97 [0.86, 1.10]	1.02 [0.94, 1.11]	1.13 [1.05, 1.21]
Amlodipine	5 mg Single dose	GLE	300 mg QD	12	0.75 [0.65, 0.87]	0.82 [0.75, 0.89]	1.13 [1.02, 1.24]
		PIB	120 mg QD	12	0.99 [0.93, 1.05]	1.02 [0.97, 1.08]	1.04 [1.00, 1.08]
Losartan	50 mg Single dose	GLE	300 mg QD	12	0.93 [0.78, 1.11]	1.00 [0.90, 1.11]	0.83 [0.69, 1.02]
		PIB	120 mg QD	12	1.15 [1.03, 1.29]	1.02 [0.95, 1.10]	0.99 [0.93, 1.05]
Valsartan	80 mg Single dose	GLE	300 mg QD	12	0.85 [0.78, 0.94]	0.86 [0.79, 0.93]	0.77 [0.69, 0.87]
		PIB	120 mg QD	12	0.97 [0.87, 1.08]	0.92 [0.85, 1.00]	0.88 [0.80, 0.96]
Ethinyl estradiol/norgestimate	35/250 µg QD	GLE	300 mg QD	9	1.00 [0.85, 1.19]	0.95 [0.78, 1.15]	0.81 [0.59, 1.13]
		PIB	120 mg QD	9	1.00 [0.92, 1.10]	0.92 [0.82, 1.02]	0.82 [0.67, 1.01]
Norethisterone	0.35 mg QD	GLE	300 mg QD	12	1.31 [1.09, 1.57]	1.20 [1.06, 1.35]	0.83 [0.63, 1.10]
		PIB	120 mg QD	12	1.00 [0.92, 1.09]	0.95 [0.88, 1.02]	0.84 [0.76, 0.94]
Ethinyl estradiol/levonorgestrel	20/100 µg QD	GLE	300 mg QD	12	0.87 [0.77, 0.98]	0.84 [0.77, 0.92]	0.88 [0.74, 1.04]
		PIB	120 mg QD	12	0.85 [0.78, 0.93]	0.83 [0.77, 0.90]	0.80 [0.73, 0.88]
Pravastatin	10 mg QD	GLE	400 mg QD	12	1.59 [1.25, 2.03]	1.44 [1.25, 1.67]	-
		PIB	120 mg QD	12	1.24 [1.13, 1.37]	1.23 [1.13, 1.35]	-
Rosuvastatin	5 mg QD	GLE	400 mg QD	11	1.25 [0.93, 1.67]	1.21 [0.98, 1.49]	-
		PIB	120 mg QD	11	1.23 [1.11, 1.37]	1.20 [1.12, 1.29]	-
Atorvastatin	10 mg QD	GLE	400 mg QD	11	0.90 [0.70, 1.15]	0.97 [0.83, 1.14]	-
		PIB	120 mg QD	11	1.05 [0.91, 1.21]	1.09 [0.96, 1.23]	-
Simvastatin	5 mg QD	GLE	300 mg QD	12	0.80 [0.65, 0.99]	0.91 [0.78, 1.06]	-
		PIB	120 mg QD	12	0.96 [0.79, 1.17]	1.10 [0.93, 1.30]	-
lovastatin	10 mg QD	GLE	300 mg QD	12	1.34 [0.97, 1.85]	1.09 [0.91, 1.31]	-
		PIB	120 mg QD	12	0.99 [0.87, 1.13]	0.98 [0.91, 1.05]	-
Omeprazole	20 mg QD	GLE	300 mg, single dose	12	0.78 [0.60, 1.00]	0.71 [0.58, 0.86]	-
		PIB	120 mg, single dose	12	1.00 [0.83, 1.22]	0.97 [0.80, 1.18]	-
	40 mg QD	GLE	300 mg, single dose	12	0.36 [0.21, 0.59]	0.49 [0.35, 0.68]	-
		PIB	120 mg, single dose	12	0.85 [0.70, 1.03]	1.15 [0.94, 1.40]	-
Tacrolimus	1 mg Single dose	GLE	300 mg QD	10	1.07 [0.94, 1.21]	1.01 [0.94, 1.08]	0.89 [0.78, 1.02]
		PIB	120 mg QD	10	0.98 [0.87, 1.11]	1.01 [0.93, 1.10]	1.00 [0.92, 1.09]
Raltegravir	400 mg BID	GLE	300 mg QD	12	0.94 [0.78, 1.12]	0.93 [0.84, 1.03]	1.02 [0.88, 1.18]
		PIB	120 mg QD	12	1.01 [0.94, 1.07]	0.99 [0.92, 1.07]	0.97 [0.90, 1.04]
Rilpivirine	25 mg QD	GLE	300 mg QD	11	0.87 [0.74, 1.03]	0.90 [0.79, 1.02]	-
		PIB	120 mg QD	11	0.97 [0.89, 1.05]	0.96 [0.89, 1.05]	-

Concomitant drug	Dosage regimen			Number of subjects	Geometric least squares mean ratio [90% CI]		
	Concomitant drug	Study population			C_{max}	AUC[a)]	C_{trough} or C_{24}
Darunavir/ritonavir	800/100 mg QD	GLE	300 mg QD	8	3.09 [2.26, 4.20]	4.97 [3.62, 6.84]	-
		PIB	120 mg QD	8	0.85 [0.75, 0.96]	1.16 [0.98, 1.36]	-
Lopinavir/ritonavir	400/100 mg BID	GLE	300 mg QD	9	2.55 [1.84, 3.52]	4.38 [3.02, 6.36]	-
		PIB	120 mg QD	9	1.40 [1.17, 1.67]	2.46 [2.07, 2.92]	-
Atazanavir/ritonavir	300/100 mg , single dose	GLE	300 mg QD	12	4.06 [3.15, 5.23]	6.53 [5.24, 8.14]	-
		PIB	120 mg QD	12	1.29 [1.15, 1.45]	1.64 [1.48, 1.82]	-
elvitegravir/cobicistat/ emtricitabine/ tenofovir alafenamide	150/150/200/ 10 mg QD	GLE	300 mg QD	11	2.50 [2.08, 3.00]	3.05 [2.55, 3.64]	4.58 [3.15, 6.65]
		PIB	120 mg QD	11	1.24 [1.11, 1.39]	1.57 [1.39, 1.76]	1.89 [1.63, 2.19]
Abacavir/dolutegravir/ lamivudine	600/50/ 300 mg QD	GLE	300 mg QD	12	0.74 [0.64, 0.86]	0.75 [0.69, 0.83]	0.82 [0.72, 0.94]
		PIB	120 mg QD	12	0.74 [0.66, 0.83]	0.72 [0.65, 0.79]	0.73 [0.65, 0.82]
Sofosbuvir	400 mg QD	GLE	400 mg QD	8	0.98 [0.75, 1.29]	0.99 [0.80, 1.24]	1.11 [0.83, 1.49]
		PIB	120 mg QD	8	0.99 [0.82, 1.20]	1.04 [0.89, 1.22]	1.16 [1.00, 1.35]

-, Not investigated
a) AUC_{inf} following the single dose, AUC_{0-24} following the multiple doses, b) Single dose of GLE and PIB 24 hours after the final dose of rifampicin

Table 30. Effects of GLE and PIB on PK parameter values of concomitant drugs

Drug or analyte	Dosage regimen			Number of subjects	Geometric least squares mean ratio [90% CI]		
	Concomitant drug	GLE	PIB		C_{max}	AUC[a)]	C_{trough} or C_{24}
Cyclosporine	400 mg, single dose	300 mg, single dose	120 mg, single dose	11	0.94 [0.82, 1.08]	1.01 [0.95, 1.09]	-
Caffeine	Caffeine/tolbutamide/omeprazole/ midazolam/ dextromethorphan hydrobromide, 100/500/20/1/ 30 mg, single dose	300 mg, single dose	120 mg, single dose	12	1.02 [0.97, 1.70]	1.35 [1.23, 1.48]	-
Paraxanthine				12	0.93 [0.88, 0.98]	1.10 [1.03, 1.18]	-
Tolbutamide				12	0.92 [0.87, 0.97]	1.03 [0.99, 1.07]	-
Omeprazole				12	0.57 [0.43, 0.75]	0.79 [0.70, 0.90][b)]	-
5-Hydroxyomeprazole				9	0.61 [0.46, 0.81]	0.84 [0.75, 0.94][b)]	-
Midazolam				12	1.03 [0.91, 1.17]	1.27 [1.11, 1.45]	-
1-Hydroxymidazolam				12	1.11 [0.92, 1.32]	1.34 [1.21, 1.48]	-
Dextromethorphan				12	0.70 [0.61, 0.81]	0.75 [0.66, 0.85]	-
Dextrorphan				12	1.10 [0.96, 1.25]	1.32 [1.21, 1.44]	-
Digoxin	0.5 mg, single dose	400 mg QD	120 mg QD	12	1.72 [1.45, 2.04]	1.48 [1.40, 1.57]	-
Dabigatran	150 mg[c)], single dose	300 mg QD	120 mg QD	11	2.05 [1.72, 2.44]	2.38 [2.11, 2.70]	-
Lamotrigine	50 mg, single dose	300 mg QD	120 mg QD	12	0.98 [0.94, 1.02]	0.96 [0.88, 1.04]	-
Carbamazepine	Carbamazepine, 200 mg BID	300 mg, single dose	120 mg, single dose	10	0.98 [0.95, 1.02]	1.02 [0.99, 1.05]	1.03 [1.00, 1.07]
Carbamazepine-10,11-epoxide				10	1.04 [0.98, 1.10]	1.05 [1.03, 1.07]	1.07 [1.04, 1.10]
Rifampicin	600 mg QD	300 mg, single dose	120 mg, single dose	12	1.18 [1.05, 1.32]	1.13 [1.05, 1.21]	-
Felodipine	2.5 mg, single dose	300 mg QD	120 mg QD	11	1.31 [1.05, 1.62]	1.31 [1.08, 1.58]	-
Amlodipine	5 mg, single dose	300 mg QD	120 mg QD	12	1.22 [1.07, 1.39]	1.21 [1.09, 1.34]	-
Losartan	Losartan, 50 mg, single dose	300 mg QD	120 mg QD	12	2.51 [2.00, 3.15]	1.56 [1.28, 1.89]	-
Losartan carboxylic acid				12	2.18 [1.88, 2.53]	1.14 [1.04, 1.25]	-
Valsartan	80 mg, single dose	300 mg QD	120 mg QD	12	1.36 [1.17, 1.58]	1.31 [1.16, 1.49]	-

Drug or analyte	Dosage regimen			Number of subjects	Geometric least squares mean ratio [90% CI]		
	Concomitant drug	GLE	PIB		C_{max}	AUC[a)]	C_{trough} or C_{24}
Ethinyl estradiol	Ethinyl estradiol/ norgestimate, 35/250 µg QD	300 mg QD	120 mg QD	11	1.31 [1.24, 1.38]	1.28 [1.23, 1.32]	1.38 [1.25, 1.52]
Norgestrel				11	1.54 [1.34, 1.76]	1.63 [1.50, 1.76]	1.75 [1.62, 1.89]
Norelgestromin				11	1.24 [1.08, 1.41]	1.44 [1.34, 1.54]	1.45 [1.33, 1.58]
Norethisterone	0.35 mg QD	300 mg QD	120 mg QD	12	0.83 [0.74, 0.95]	0.94 [0.84, 1.04]	0.91 [0.80, 1.04]
Ethinyl estradiol	Ethinyl estradiol/ levonorgestrel, 20/100 µg QD	300 mg QD	120 mg QD	12	1.30 [1.18, 1.44]	1.40 [1.33, 1.48]	1.56 [1.41, 1.72]
Norgestrel				12	1.37 [1.23, 1.52]	1.68 [1.57, 1.80]	1.77 [1.58, 1.98]
Pravastatin	10 mg QD	400 mg QD	120 mg QD	12	2.23 [1.87, 2.65]	2.30 [1.91, 2.76]	-
Rosuvastatin	5 mg QD	400 mg QD	120 mg QD	11	5.62 [4.80, 6.59]	2.15 [1.88, 2.46]	-
Atorvastatin	10 mg QD	400 mg QD	120 mg QD	11	22.0 [16.4, 29.6]	8.28 [6.06, 11.3]	-
Simvastatin	Simvastatin, 5 mg QD	300 mg QD	120 mg QD	12	1.99 [1.60, 2.48]	2.32[1.93, 2.79]	-
Simvastatinhydroxy acid				12	10.7 [7.88, 14.6]	4.48 [3.11, 6.46]	-
Lovastatin	Lovastatin, 10 mg QD	300 mg QD	120 mg QD	12	1.17 [0.97, 1.42]	1.70 [1.40, 2.06]	-
Lovastatin acid				12	5.73 [4.65, 7.07]	4.10 [3.45, 4.87]	-
(*R*)-Methadone	Methadone, 20-120 mg QD[d)]	300 mg QD	120 mg QD	11	0.96 [0.91, 1.02]	1.02 [0.98, 1.06]	0.98 [0.93, 1.04]
(*S*)-Methadone				11	0.98 [0.93, 1.03]	1.05 [1.01, 1.09]	1.02 [0.96, 1.08]
Buprenorphine	Buprenorphine/ naloxone, maximum 6/24 mg QD[d)]	300 mg QD	120 mg QD	12	1.08 [0.97, 1.19]	1.17 [1.08, 1.27]	1.24 [1.09, 1.40]
Naloxone				12	0.88 [0.74, 1.06]	1.07 [0.90, 1.28]	-
Norbuprenorphine				12	1.25 [1.17, 1.34]	1.30 [1.19, 1.42]	1.21 [1.06, 1.39]
Tacrolimus	1 mg, single dose	300 mg QD	120 mg QD	12[e)]	1.50 [1.25, 1.82]	1.45 [1.24, 1.70]	-
Raltegravir	400 mg BID	300 mg QD	120 mg QD	12	1.34 [0.89, 1.98]	1.47 [1.15, 1.87]	2.64 [1.42, 4.91]
Rilpivirine	25 mg QD	300 mg QD	120 mg QD	12	2.05 [1.73, 2.43]	1.84 [1.72, 1.98]	1.77 [1.59, 1.96]
Darunavir	Darunavir/ ritonavir, 800/100 mg QD	300 mg QD	120 mg QD	12	1.30 [1.21, 1.40]	1.29 [1.18, 1.42]	0.92 [0.81, 1.04]
Ritonavir				12	2.03 [1.78, 2.32]	1.87 [1.74, 2.02]	0.82 [0.64, 1.05]
Lopinavir	Lopinavir/ ritonavir, 400/100 mg BID	300 mg QD	120 mg QD	9	1.11 [1.01, 1.23]	1.24 [1.14, 1.34]	1.47 [1.37, 1.58]
Ritonavir				9	1.17 [0.95, 1.45]	1.23 [1.10, 1.38]	1.38 [1.21, 1.59]
Atazanavir	Atazanavir/ ritonavir, 300/100 mg QD	300 mg QD	120 mg QD	11	1.00 [0.90, 1.10]	1.11[1.03, 1.19]	1.16 [1.07, 1.25]
Ritonavir				11	1.21 [1.05, 1.38]	1.30 [1.21, 1.40]	1.26 [1.12, 1.42]
Efavirenz	Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate, 600/200/ 300 mg QD	300 mg QD	120 mg QD	12	1.06 [0.97, 1.14]	1.03 [0.99, 1.06]	1.01 [0.96, 1.06]
Emtricitabine				12	1.04 [0.95, 1.14]	1.07 [1.02, 1.12]	1.13 [1.05, 1.21]
Tenofovir				12	1.22 [1.08, 1.38]	1.29 [1.23, 1.35]	1.38 [1.31, 1.46]
Elvitegravir	Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide, 150/150/200/ 10 mg QD	300 mg QD	120 mg QD	12	1.36 [1.24, 1.49]	1.47 [1.37, 1.57]	1.71 [1.50, 1.95]
Cobicistat				12	1.29 [1.22, 1.38]	1.42 [1.32, 1.52]	1.72 [1.32, 2.25]
Emtricitabine				12	1.07 [1.00, 1.14]	1.12 [1.09, 1.16]	1.18 [1.10, 1.27]
Tenofovir				12	1.04 [0.99, 1.09]	1.06 [0.99, 1.13]	1.25 [1.16, 1.36]

Drug or analyte	Dosage regimen			Number of subjects	Geometric least squares mean ratio [90% CI]		
	Concomitant drug	GLE	PIB		C_{max}	AUC[a)]	C_{trough} or C_{24}
Abacavir	Abacavir/ dolutegravir/ lamivudine, 600/50/ 300 mg QD	300 mg QD	120 mg QD	12	0.96 [0.89, 1.05]	1.05 [0.99, 1.10]	1.31 [1.05, 1.63]
Dolutegravir				12	1.10 [1.01, 1.19]	1.13 [1.05, 1.21]	1.22 [1.11, 1.35]
Lamivudine				12	0.99 [0.90, 1.10]	1.03 [0.97, 1.09]	0.95 [0.90, 1.01]
Sofosbuvir	Sofosbuvir, 400 mg QD	400 mg QD	120 mg QD	8	1.66 [1.23, 2.22]	2.25 [1.86, 2.72]	-
GS-331007				8	0.85 [0.76, 0.96]	1.21 [1.13, 1.29]	1.85 [1.67, 2.04]

-, Not investigated
a) AUC_{inf} following the single dose, AUC_{0-24} following the multiple doses, b) Area under plasma concentration-time curve up to t hours (AUC_{0-t}), c) As dabigatran etexilate, d) Maintenance dose prescribed for patients on a maintenance therapy by a physician, e) 10 subjects in concomitant use

6.2.5 QT/QTc study (CTD 5.3.4.1-1, Study M15-543 [May 2016 to August 2016])

A four-treatment four-period crossover study was conducted to investigate effects of GLE and PIB on QT/corrected QT (QTc) interval in 48 non-Japanese healthy subjects (12 per group). In this study, subjects orally received moxifloxacin at 400 mg as the positive control, or the placebo or GLE and PIB (GLE/PIB 400/120 mg or 600/240 mg) concomitantly as a single dose under fed conditions[42)]. In subjects who received GLE/PIB at 600/240 mg, a change in QT interval corrected for heart rate according to Fridericia's formula from baseline reached the maximum at 5 hours post-dose. The difference from the placebo group was 3.1 ms, and the upper limit of 95% CI was 5.1 ms. Because the upper limit of 95% CI was below 10 ms, the applicant explained that QTc interval is not prolonged in the dose range of GLE/PIB up to 600/240 mg. In subjects who received GLE/PIB at 600/240 mg, C_{max} and AUC_{inf} of GLE were 4430 ng/mL and 13,600 ng·h/mL, respectively, and those of PIB were 323 ng/mL and 2390 ng·h/mL, respectively.

6.2.6 Exposure-response analysis (CTD 5.3.3.5-4, 5.3.3.5-6, 5.3.3.5-7)

Relationships of C_{max} and AUC_{0-24} of GLE and PIB with virologic therapeutic effects were investigated using data from Japanese phase III studies (Studies M15-594 and M15-828). In patients with virologic failure, C_{max} and AUC_{0-24} of GLE were 1700 ng/mL and 16,600 ng·h/mL, respectively, and those of PIB were 181 ng/mL and 2740 ng·h/mL, respectively. In patients with sustained viral response (SVR), C_{max} and AUC_{0-24} of GLE were 1400 ng/mL and 14,100 ng·h/mL, respectively, and those of PIB were 171 ng/mL and 2670 ng·h/mL, respectively. Relationships of AUC_{0-24} of GLE and PIB with the SVR12 rate were investigated using data from foreign phase II studies and foreign phase III studies.[43)] No clear relationship of AUC_{0-24} of GLE with the SVR12 rate was observed, but a decrease in AUC_{0-24} of PIB by 50% was suggested to decrease the SVR12 rate in patients with the genotype 1, 2, 4, 5, or 6 by 0.83% and in patients with the genotype 3 by 3.3%.

Relationships of AUC_{0-24} of GLE and PIB with the safety (adverse events observed with drugs in the same class)[44)] were investigated using data from Japanese phase III studies (Studies M15-594 and M15-828). As a result, the incidence of Grade ≥2 total bilirubin increased was found related to AUC_{0-24} of GLE.

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42) A washout period for at least 10 days was placed between treatment periods.
43) Studies M14-867, M14-868, M15-410, M13-590, M15-464, M13-594, M13-583, M14-172, and M15-462
44) Grade ≥2 ALT increased and total bilirubin increased as well as Grade ≥2 rash, pruritus, haemoglobin decreased, and creatinine clearance decreased for which a causal relationship to GLE or PIB could not be ruled out

6.R Outline of the review conducted by PMDA

6.R.1 Differences in PK of GLE and PIB between Japanese and non-Japanese patients

The applicant's explanation about effects of ethnic factors on PK of GLE and PIB:

Based on the PK data of GLE and PIB in healthy subjects who orally received GLE + PIB (GLE/PIB 300/120 mg) QD under fed conditions in a phase I study (Study M[redacted]-432) [see Section "6.2.1.1 Phase I study"], effects of ethnic factors on PK of GLE and PIB were investigated. As a result, no clear differences were observed in C_{max} or AUC_{0-24} of GLE or PIB among different ethnic groups.

As shown in Table 31, on the other hand, C_{max} and AUC_{0-24} of GLE and PIB in Japanese patients were higher than those in non-Japanese patients. Table 31 shows estimated PK parameter values of oral administration of GLE and PIB at 300/120 mg under fed conditions according to simulation using the PPK models based on data from Japanese phase III studies (Studies M15-594 and M15-828) and on data from foreign clinical studies.[45)]

Table 31. PK parameter values of GLE and PIB in Japanese and non-Japanese patients

Study population	Ethnic group	C_{max} (ng/mL)		AUC_{0-24} (ng·h/mL)		C_{trough} (ng/mL)	
		Chronic hepatitis C	Compensated cirrhosis type C	Chronic hepatitis C	Compensated cirrhosis type C	Chronic hepatitis C	Compensated cirrhosis type C
GLE	Japanese	1170 (124)	2810 (60)	11,600 (154)	30,400 (73)	33.7 (361)	118 (173)
	Non-Japanese	597 (150)	1110 (78)	4800 (198)	10,500 (93)	13.0 (475)	45.1 (188)
PIB	Japanese	165 (40)	193 (34)	2560 (48)	3100 (40)	41.3 (75)	55.0 (62)
	Non-Japanese	110 (49)	111 (44)	1430 (63)	1530 (54)	18.9 (110)	22.7 (83)

Geometric mean (CV%)

The above higher values in Japanese patients were considered attributable to differences in distribution of body weight and age of the subjects between Japanese phase III studies and foreign clinical studies,[46)] because the PPK analysis suggested that the body weight and age affected the PK of GLE and PIB [see Section "6.2.2.1 PPK analysis"]. The safety of GLE/PIB in Japanese patients with chronic hepatitis C or compensated cirrhosis type C has been confirmed in Japanese studies, and the difference in exposure to GLE and PIB among ethnic groups is considered clinically insignificant.

PMDA confirmed that the exposure to GLE and PIB in patients with chronic hepatitis C or compensated cirrhosis type C was higher in Japanese patients than in non-Japanese patients. The safety of GLE/PIB in Japanese is discussed in Section "7.R.4 Safety."

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

The applicant submitted evaluation data on the efficacy and safety of GLE/PIB from 3 studies and reference data from 8 studies in this application. Summary of the major clinical studies is as shown in

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45) Studies M13-583, M13-590, M13-594, M14-172, M15-462, M15-464, M14-868, and M15-410

46) Age (median [range]), 62 [21-86] years in patients with chronic hepatitis C and 72 [44-85] years in patients with compensated cirrhosis type C in Japanese phase III studies
53 [19-84] years in patients with chronic hepatitis C and 59 [26-88] years in patients with compensated cirrhosis type C in foreign clinical studies
Body weight (median [range]), 58 [31-97] kg in patients with chronic hepatitis C and 58 [31-97] kg in patients with compensated cirrhosis type C in Japanese phase III studies
74 [40-179] kg in patients with chronic hepatitis C and 84 [49-170] kg in patients with compensated cirrhosis type C in foreign clinical studies

Table 32. The safety was evaluated on adverse events observed until Week 4 of administration of the study drug.

Table 32. Summary of major clinical studies for efficacy and safety of GLE/PIB

Study No. (phase)	Study population	Dosage regimen	Number of subjects
Evaluation study			
M15-594 (Japanese phase III)	Study 1 part: DAA-naive patients with chronic hepatitis C (genotype 1)[b] and without severe renal impairment[a]	GLE/PIB, 300/120 mg QD (8 weeks) Control, OBV/PTV/r 25/150/100 mg QD (12 weeks)	GLE/PIB, n = 106[c] Control, n = 52
	Study 2 part: GLE/PIB for 8 weeks: Patients with chronic hepatitis C (genotype 1 or 2) and with severe renal impairment[a] GLE/PIB for 12 weeks: · DAA-treated patients with chronic hepatitis C (genotype 1 or 2) · Patients with compensated cirrhosis type C (genotype 1 or 2) · Patients with chronic hepatitis C or compensated cirrhosis type C (genotype 3, 4, 5, or 6)	GLE/PIB 300/120 mg QD (8 or 12 weeks)	8-week treatment, n = 10 12-week treatment, n = 103
M15-828 (Japanese phase III)	DAA-naive patients with chronic hepatitis C (genotype 2) and without severe renal impairment[a]	GLE/PIB, 300/120 mg QD (8 weeks) Control, SOF 400 mg QD and RBV in combination (12 weeks)	GLE/PIB, n = 90 Control, n = 46
M13-583 (foreign phase III)	Patients with chronic hepatitis C (genotype 4, 5, or 6) who did not receive any therapy or had a history of prior treatment with IFN products or SOF/RBV	GLE/PIB 300/120 mg QD (12 weeks)	n = 121

a) Severe renal impairment, eGFR <30 mL/min/1.73 m^2. Subjects on dialysis included. b) At the screening, presence or absence of Y93H mutation in the NS5A region was checked. All the patients with Y93H mutation received GLE/PIB, while patients without Y93H mutation were randomized (allocation ratio of GLE/PIB and control, 2:1). c) Patients without Y93H mutation in the NS5A region. A total of 23 patients were found positive for Y93H mutation in the NS5A region.

7.1 Phase III studies

7.1.1 Japanese study (CTD 5.3.5.1-1, Study M15-594 [February 2016 to April 2017])

Study M15-594 consisting of 2 parts (Study 1 Part and Study 2 Part) was conducted to investigate the efficacy and safety of GLE/PIB at 62 study sites in Japan.

[Study 1 Part]

Study 1 Part was conducted in DAA-naive[47] patients with chronic hepatitis C (genotype 1) and without severe renal impairment[48] (target sample size, 170 subjects [120 in the GLE/PIB group, 50 in the control group]) using OBV/PTV/r (brand name, Viekirax Combination Tablets) as the control as a randomized, open-label, parallel group study. At the screening, Y93H mutation in the NS5A region was checked. All the patients with Y93H mutation received GLE/PIB, while patients without Y93H mutation were randomized[49] (allocation ratio of GLE/PIB and control, 2:1).

Subjects treated with GLE/PIB were to orally receive 3 GLE/PIB (300/120 mg) tablets QD under fed conditions for 8 weeks, and subjects in the OBV/PTV/r group were to orally receive 2 OBV/PTV/r QD (25/150/100 mg) tablets QD under fed conditions for 12 weeks in accordance with the dosage and

47) Absence of a history of prior treatment with DAA-contained regimen (regardless of a history of prior IFN treatment)
48) eGFR <30 mL/min/1.73 m^2
49) Prior IFN treatment (naïve or treated) and HCV RNA load at the screening (<6,000,000 IU/mL or ≥6,000,000 IU/mL) were defined as the stratification factors.

administration approved in Japan [see Section "7.R.7.1 Dosage and administration, and treatment duration"].

The primary endpoint was the percentage of patients in whom a negative state for blood HCV (HCV RNA below the lower limit of quantitation) was sustained from the end of the study treatment to 12 weeks after the final dose (SVR12 rate).

A total of 181 subjects who received the study drug at least once (129 treated with GLE/PIB [including 106 randomized subjects in the GLE/PIB group], 52 in the OBV/PTV/r group) were included in the intention-to-treat (ITT) population and also in the safety analysis set. Of subjects in the ITT population, 158 subjects who were tested negative for Y93H mutation at the screening and then randomized (106 in the GLE/PIB group, 52 in the OBV/PTV/r group) were included in the major efficacy analysis set.

The SVR12 rate in the major efficacy analysis set was 99.1% (105 of 106) of subjects in the GLE/PIB group and 100% (52 of 52) of subjects in the OBV/PTV/r group with the intergroup difference [95% CI] of −0.9% [−2.8%, 0.9%]. Because the lower limit of 95% CI was above the pre-determined non-inferiority margin (−10%), non-inferiority of GLE/PIB to OBV/PTV/r was verified. In addition, the SVR12 rate in 23 subjects treated with GLE/PIB who were tested positive for Y93H mutation at the screening and thus not randomized was 100%.

In terms of the safety, adverse events (including abnormal changes in laboratory test) occurred in 57.4% (74 of 129) of subjects treated with GLE/PIB and 67.3% (35 of 52) of subjects in the OBV/PTV/r group, and adverse drug reactions[50] occurred in 23.3% (30 of 129) of subjects treated with GLE/PIB and 26.9% (14 of 52) of subjects in the OBV/PTV/r group. Adverse events and adverse drug reactions with an incidence of ≥5% in any population are as shown in Table 33.

Table 33. Adverse events and adverse drug reactions reported by ≥5% of subjects in any population (Study 1 Part, safety analysis set)

Event	Adverse events		Adverse drug reactions	
	Subjects treated with GLE/PIB (n = 129)	OBV/PTV/r (n = 52)	Subjects treated with GLE/PIB (n = 129)	OBV/PTV/r (n = 52)
Overall	74 (57.4)	35 (67.3)	30 (23.3)	14 (26.9)
Pyrexia	0	3 (5.8)	0	2 (3.8)
Cystitis	1 (0.8)	3 (5.8)	0	0
Nasopharyngitis	20 (15.5)	7 (13.5)	3 (2.3)	0
Blood bilirubin increased	3 (2.3)	3 (5.8)	3 (2.3)	3 (5.8)
Headache	6 (4.7)	5 (9.6)	3 (2.3)	1 (1.9)
Pruritus	8 (6.2)	5 (9.6)	6 (4.7)	1 (1.9)
Rash	3 (2.3)	3 (5.8)	2 (1.6)	1 (1.9)
Hypertension	4 (3.1)	4 (7.7)	1 (0.8)	2 (3.8)

Number of subjects (%)

No deaths occurred.

[50] Adverse events assessed as "related to the study drug" (assessment result for a causal relationship to the study drug is described as "related" or "unrelated")

In the subjects treated with GLE/PIB, neither serious adverse events nor adverse events leading to discontinuation occurred. In the OBV/PTV/r group, serious adverse events occurred in 3 subjects (ligament sprain, sternal fracture, angioedema, decreased appetite, constipation, and cholangitis acute in 1 subject each [including duplicate counting]), and adverse events leading to discontinuation occurred in 1 subject (decreased appetite, constipation, and cholangitis acute in 1 subject each [including duplicate counting]).

[Study 2 Part]
Study 2 Part was conducted in the following patients (target sample size, 75 subjects) as an open-label uncontrolled study:

- DAA-naive[48)] patients with compensated cirrhosis type C (genotype 1 or 2) (50 subjects)
- DAA-treated patients with chronic hepatitis C or compensated cirrhosis type C (genotype 1 or 2) (10 subjects)
- Patients with chronic hepatitis C or compensated cirrhosis type C (genotype 1 or 2) and with severe renal impairment (regardless of a history of prior DAA treatment) (10 subjects)
- DAA-naive [48)] patients with chronic hepatitis C or compensated cirrhosis type C (genotype 3, 4, 5, or 6) (5 subjects)

Subjects were to orally receive 3 GLE/PIB (300/120 mg) tablets QD under fed conditions, and the treatment duration was 8 weeks for patients with chronic hepatitis C (genotype 1 or 2) and with severe renal impairment, and 12 weeks for the other patients.

The primary endpoint was SVR12 rate as with Study 1 Part.

All of the 113 subjects who received the study drug at least once were included in the ITT population and also in the safety analysis set, and the ITT population was used for the efficacy analysis.

In terms of the efficacy, the SVR12 rate in each subgroup is as shown in Table 34. Patients with genotype 4, 5, or 6 were not enrolled.

Table 34. SVR12 rate in each subgroup (Study 2 Part, ITT population)

		Overall	Chronic hepatitis C		Compensated cirrhosis type C	
			DAA-naive	DAA-treated	DAA-naive	DAA-treated
GLE/PIB for 12 weeks	Genotype 1	97.1 (68/70)		96.4 (27/28)	100 (38/38)	75.0 (3/4)
	Genotype 2	100 (21/21)		100 (1/1)	100 (20/20)[a)]	-
	Genotype 3	83.3 (10/12)	80.0 (8/10)	-	100 (2/2)	-
GLE/PIB for 8 weeks (with severe renal impairment)	Genotype 1	100 (3/3)	100 (3/3)			
	Genotype 2	100 (7/7)	100 (7/7)			

% (Number of subjects)
-, Applicable subjects were not enrolled.
a) Including 2 subjects with severe renal impairment

In terms of the safety, adverse events (including abnormal changes in laboratory test) and adverse drug reactions[50)] occurred in 66.0% (68 of 103) and 29.1% (30 of 103), respectively, of subjects treated with GLE/PIB for 12 weeks. Adverse events (adverse drug reactions) with an incidence of ≥5% included

pruritus (12.6%, 13 of 103 subjects) (7.8% [8 subjects]), nasopharyngitis (8.7%, 9 of 103) (1.0% [1 subject]), headache (6.8%, 7 of 103 subjects) (5.8% [6 subjects]), malaise at (5.8%, 6 of 103 subjects) (2.9% [3 subjects]), rash at (5.8%, 6 of 103 subjects) (1.9% [2 subjects]).

Of patients with chronic hepatitis C and with severe renal impairment who were treated with GLE/PIB for 8 weeks, adverse events (including abnormal changes in laboratory test) were reported by 80.0% (8 of 10) of subjects and adverse drug reactions[50)] were reported by 40.0% (4 of 10) of subjects. Adverse events reported by ≥2 subjects included blood creatinine increased and arthralgia (2 subjects each), both of which relationships to GLE/PIB were ruled out.

No deaths occurred in any subgroup.

A serious adverse event occurred in 1 subject (fluid overload) treated with GLE/PIB for 8 weeks (patient with chronic hepatitis C and with severe renal impairment), but a relationship of this event to GLE/PIB was ruled out, and it resolved.

Adverse events leading to discontinuation occurred in 2 subjects (drug eruption in both) treated with GLE/PIB for 12 weeks (patients with compensated cirrhosis type C). Although the events in both subjects were assessed as "related to GLE/PIB," they were at Grade 2[51)] and resolved.

7.1.2 Japanese study (CTD 5.3.5.1-2, Study M15-828 [April 2016 to ongoing]) (data cut-off, January 2017)

A randomized, open-label, parallel group study was conducted to investigate the efficacy and safety of GLE/PIB in DAA-naive[48)] patients with chronic hepatitis C (genotype 2) (target sample size, 120 subjects [80 in the GLE/PIB group, 40 in the control group]) at 56 study sites in Japan, using the combination regimen with SOF product (brand name, Sovaldi Tablets 400 mg) and RBV product (brand name, Rebetol Capsules 200 mg) as the control. Patients with creatinine clearance ≤50 mL/min were excluded from this study, because the SOF product, used as the control drug, is contraindicated in "patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or renal failure requiring dialysis," and the RBV product is contraindicated in "patients with chronic renal failure or renal impairment due to creatinine clearance ≤50 mL/min."

In the GLE/PIB group, subjects were to orally receive 3 GLE/PIB tablets (300/120 mg) QD under fed conditions for 8 weeks, and subjects in the SOF/RBV group were to orally receive SOF 400 mg QD and RBV (2 divided doses of the daily dose specified according to the body weight [600-1000 mg/day]) for 12 weeks in accordance with the dosage regimen approved in Japan.

The primary endpoint was SVR12 rate as with Study M15-594.

51) NCI CTCAE ver. 4.0

A total of 136 subjects (90 in the GLE/PIB group, 46 in the SOF/RBV group) who were randomized and then received the study drug at least once were included in the ITT population and also in the safety analysis set, and the ITT population was used for the efficacy analysis.

The SVR12 rate, the efficacy primary endpoint, was 97.8% (88 of 90) of subjects in the GLE/PIB group and 93.5% (43 of 46) of subjects in the SOF/RBV group with the intergroup difference [95% CI] of 4.3% [−3.5%, 12.1%]. Because the lower limit of 95% CI was above the pre-determined non-inferiority margin (−10%), non-inferiority of GLE/PIB to SOF/RBV was verified.

In terms of the safety, adverse events (including abnormal changes in laboratory test) occurred in 47.8% (43 of 90) of subjects in the GLE/PIB group and 76.1% (35 of 46) of subjects in the SOF/RBV group, and adverse drug reactions[50)] occurred in 17.8% (16 of 90) of subjects in the GLE/PIB group and 50.0% (23 of 46) of subjects in the SOF/RBV group. Table 35 shows adverse events and adverse drug reactions with an incidence of ≥5% in any group.

Table 35. Adverse events and adverse drug reactions with an incidence of ≥5% in any group (safety analysis set)

Event	Adverse events		Adverse drug reactions	
	GLE/PIB (n = 90)	SOF/RBV (n = 46)	GLE/PIB (n = 90)	SOF/RBV (n = 46)
Overall	43 (47.8)	35 (76.1)	16 (17.8)	23 (50.0)
Anaemia	0	16 (34.8)	0	16 (34.8)
Nausea	3 (3.3)	3 (6.5)	2 (2.2)	1 (2.2)
Stomatitis	1 (1.1)	3 (6.5)	1 (1.1)	1 (2.2)
Malaise	5 (5.6)	4 (8.7)	4 (4.4)	2 (4.3)
Nasopharyngitis	9 (10.0)	4 (8.7)	2 (2.2)	1 (2.2)
Blood bilirubin increased	1 (1.1)	7 (15.2)	1 (1.1)	7 (15.2)
Hyperuricaemia	0	3 (6.5)	0	2 (4.3)
Headache	6 (6.7)	1 (2.2)	4 (4.4)	0

Number of subjects (%)

No deaths occurred.

Serious adverse events occurred in 1 subject in the GLE/PIB group (pneumothorax spontaneous) and in 1 subject in the SOF/RBV group (pneumonia), but relationships of both events to the study drug were ruled out, and both resolved.

Adverse events leading to discontinuation occurred in 1 subject in the GLE/PIB group (nausea and vomiting) and in 1 subject in the SOF/RBV group (malaise), and these events were assessed as "related to the study drug," but they were at Grade ≤2.[51)] In terms of their outcome, malaise in the SOF/RBV group did not resolve, but nausea and vomiting in the GLE/PIB group resolved.

7.1.3 Foreign study (CTD 5.3.5.2-2, Study M13-583 [November 2015 to November 2016])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of GLE/PIB in treatment-naive[52)] and treated[53)] patients with chronic hepatitis C (genotype 4, 5, or 6) (target sample

[52)] No history of treatment for HCV

[53)] Patients who did not respond to prior treatment with IFN products (irrespective of concomitant use with RBV products) or prior treatment with SOF/RBV combination regimen (irrespective of concomitant use with IFN products)

size, 130 subjects [70 with genotype 4, 30 with genotype 5, 30 with genotype 6]) at 31 study sites in 8 foreign countries including Belgium, Canada, and France.

Subjects were to orally receive 3 GLE/PIB tablets (300/120 mg) QD with a meal for 12 weeks.

The primary endpoint was SVR12 rate as with Study M15-594.

A total of 121 subjects (76 with genotype 4, 26 with genotype 5, 19 with genotype 6) who received the study drug at least once were included in the ITT population and also in the safety analysis set, and the ITT population was used for the efficacy analysis.

The SVR12 rate, the efficacy primary endpoint, was 99.2% (120 of 121 subjects) (98.7% [75 of 76] of subjects with genotype 4, 100% [26 of 26] of subjects with genotype 5, 100% [19 of 19] of subjects with genotype 6).

In terms of the safety, adverse events (including abnormal changes in laboratory test) occurred in 68.6% (83 of 121) of subjects and adverse drug reactions[50)] occurred in 50.4% (61 of 121) of subjects. Adverse events (incidence of adverse drug reactions) with incidence of ≥5% included headache (20.7%, 25 of 121 subjects) (12.4% [15 subjects]), fatigue (17.4%, 21 of 121 subjects) (14.0% [17 subjects]), nausea (9.9%, 12 of 121 subjects) (8.3% [10 subjects]), asthenia (9.1%, 11 of 121 subjects) (9.1% [11 subjects]), pruritus (8.3%, 10 of 121 subjects) (6.6% [8 subjects]), and diarrhoea (6.6%, 8 of 121 subjects) (3.3% [4 subjects]).

No deaths occurred.

A serious adverse event occurred in 1 subject (transient ischaemic attack), and this event was assessed as "related to the study drug," but it resolved.

Adverse events leading to discontinuation occurred in 3 subjects (transient ischaemic attack, dyspepsia, and anxiety in 1 subject each). These events except for anxiety were assessed as "related to the study drug," but they were at Grade 2[51)] and resolved.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA's view on data for review in this marketing application:

This marketing application was submitted with the indication of "improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C" for all the HCV genotypes. For the Japanese phase III study (Study 2 Part of Study M15-594), patients with genotype 3, 4, 5 or 6 were also to be included, but patients with genotype 3, 4, 5, or 6 were extremely limited in Japan (*Hepatology.* 2015;61:77-87). Consequently, only 12 subjects with genotype 3 were included, and subjects with genotype 4, 5, or 6 were not enrolled. The efficacy and safety of GLE/PIB in patients with chronic hepatitis C or compensated cirrhosis type C of genotype 3, 4, 5, or 6 may be evaluated based on data including foreign study data for the following reasons:

- No clear differences were observed in PK of GLE/PIB among ethnic groups [see Section "6.R.1 Differences in PK of GLE and PIB between Japanese and non-Japanese patients"].
- The Japanese phase III studies (Study 1 Part of Study M15-594 and Study M15-828) verified non-inferiority of GLE/PIB to the conventional therapeutic drugs in DAA-naive patients with chronic hepatitis C of genotype 1 or 2 [see Sections "7.1.1 Japanese study" and "7.1.2 Japanese study"]. In addition, although information in patients with genotype 3 obtained from the Japanese phase III study (Study 2 Part of Study M15-594) is limited, the SVR12 rate in these subjects was 83.3% (10 of 12) of subjects, demonstrating the certain efficacy [see Section "7.1.1 Japanese study"].
- The non-clinical pharmacology study results have demonstrated antiviral activity of GLE against genotype 1 to 4 and 6 and that of PIB against genotype 1 to 6. The antiviral activity of GLE against genotype 5 was investigated only in 1 cell line of genotype 5a replicon cells in which amino acid sequence in the NS3 region derived from a patient with genotype 5a was integrated, but results from this investigation did not deny the antiviral activity of GLE [see Section "3.R.1 Antiviral activity of GLE and PIB"].
- The SVR12 rate in patients with chronic hepatitis C in the foreign study (Study M13-583) was 98.7% (75 of 76) subjects with genotype 4, 100% (26 of 26) of subjects with genotype 5, and 100% (19 of 19) of subjects with genotype 6, demonstrating the certain efficacy against any genotype [see Section "7.1.3 Foreign study"].
- The safety of GLE/PIB in Japanese patients with HCV for up to 12 weeks in accordance with the proposed dosage regimen for patients with genotype 3, 4, 5, or 6 (3 GLE/PIB [300/120 mg] tablets are orally administered QD under fed conditions for 12 weeks) was investigated in the Japanese study (Study 2 Part of Study M15-594) [see Section"7.1.1 Japanese study"].

As of June 2017, GLE/PIB has been under review in Europe and the US. The recommended treatment duration of GLE/PIB in the application submitted in foreign countries is 16 weeks for a part of the patients.[54)] Because GLE/PIB has not been administered in Japanese subjects for 16 weeks, the safety of GLE/PIB for 16 weeks in Japanese patients with HCV is unknown. In this review, accordingly, the efficacy and safety of oral administration of GLE/PIB (300 mg/120 mg) QD for 8 or 12 weeks in accordance with the proposed dosage regimen were evaluated.

7.R.2 Rationale for combination

The applicant's explanation about rationale for combination of GLE/PIB:

GLE and PIB are NS3/4A protease inhibitor and NS5A inhibitor, respectively, having different mechanisms of actions and resistance profiles. Even if resistance mutation to either drug develops in HCV, the other drug is expected to avoid treatment failure by exerting the antiviral activity. Effects of concomitant use of GLE and PIB have been confirmed *in vitro* [see Section "3.8 Effects of concomitant use of GLE and PIB"]. In addition, these drugs have been shown to be complementary to each other in overcoming drug resistance in the NS5A or NS3 region [see Sections "3.1.3.3.1 Antiviral activity of GLE against HCV replicon cells with resistance mutations in the NS5A or NS5B region" and "3.5.2.3.1 Antiviral activity of PIB against HCV with resistance mutations in the NS3 or NS5B region"]. In

54) Treated patients with genotype 3 and NS5A-inhibitor-treated patients with genotypes 1, 2 and 4 to 6

addition, in clinical studies, the efficacy and safety of Maviret, combination product of GLE and PIB, have been confirmed.

Because combination products containing multiple drugs are known to improve medication adherence in HIV-infected patients, this combination product is expected to improve medication adherence in HCV-infected patients as well. Furthermore, improved adherence to anti-HCV therapy has been reported to facilitate SVR achievement (*Aliment Pharmacol Ther.* 2013;38:16-27). Therefore, supply of the combination of GLE and PIB has a clinical significance.

PMDA's view:
Whether a combination product containing multiple active ingredients improves adherence to medication against HCV infection remains unknown in daily clinical practice in Japan. Concomitant use of GLE and PIB, however, is possibly deemed to have a certain rationality, in consideration that the applicant explained that the concomitant use of GLE and PIB has a pharmacological significance; and that regimens using combination products containing multiple active ingredients with different mechanisms have been already approved.

7.R.3 Efficacy

7.R.3.1 Efficacy in patients with chronic hepatitis C or compensated cirrhosis type C

As a result of the following investigations, PMDA has concluded that the efficacy of GLE/PIB is expected in DAA-naive patients with chronic hepatitis C (genotype 1 or 2) when treated for 8 weeks as well as DAA-treated patients with chronic hepatitis C (genotype 1 or 2), patients with compensated cirrhosis type C (genotype 1 or 2), and patients with chronic hepatitis C or compensated cirrhosis type C (genotype 3, 4, 5, or 6) when treated for 12 weeks. However, use experience with GLE/PIB in Japanese patients with chronic hepatitis C or compensated cirrhosis type C is limited, especially, in patients infected with HCV genotype 3, 4, 5, or 6 and patients who have a history of prior treatment with NS3/4A protease inhibitors, NS5A inhibitors, or NS5B polymerase inhibitors. The applicant, therefore, is required to continue collecting information about use experiences in these patients even after the market launch and to provide the information to healthcare professionals, appropriately.

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

7.R.3.1.1 Efficacy in patients with genotype 1 or 2

The applicant's explanation about the efficacy of GLE/PIB in patients with chronic hepatitis C or compensated cirrhosis type C of HCV genotype 1 or 2:

(a) DAA-naive patients

Table 36 shows the SVR12 rate in DAA-naive patients with chronic hepatitis C or compensated cirrhosis type C.

Table 36. SVR12 rate in DAA-naive subjects (Studies M15-594 and M15-828)

			Chronic hepatitis C			Compensated cirrhosis type C
			GLE/PIB for 8 weeks	Comparator	Intergroup difference [95% CI]	GLE/PIB for 12 weeks
Genotype 1[a)]	Without severe renal impairment	Without Y93H mutation	99.1 (105/106)	OBV/PTV/r 100 (52/52)	−0.9% [−2.8%, 0.9%]	100 (38/38)
		With Y93H mutation	100 (23/23)			
	With severe renal impairment		100 (3/3)			
Genotype 2[b)]	Without severe renal impairment		97.8 (88/90)	SOF/RBV 93.5 (43/46)	4.3% [−3.5%, 12.1%]	100 (20/20)
	With severe renal impairment		100 (7/7)			

% (Number of subjects)
a) Study M15-594, b) Without severe renal impairment in Study M15-828, with severe renal impairment in Study M15-594

With respect to the SVR12 rate in DAA-naive patients with chronic hepatitis C and without severe renal impairment, the lower limit of 95% CI of the intergroup difference between the GLE/PIB group and the comparator group was above the non-inferiority margin (−10%) both in patients with genotype 1 (without Y93H mutation) (Study 1 Part of Study M15-594) and in patients with genotype 2 (Study M15-828), verifying non-inferiority of GLE/PIB to the respective comparators. In addition, of patients with chronic hepatitis C and with severe renal impairment and patients with chronic hepatitis C of genotype 1 with Y93H mutation detected before randomization who received GLE/PIB for 8 weeks as well as patients with compensated cirrhosis type C who received GLE/PIB for 12 weeks, all achieved the SVR12. Of subjects who achieved the SVR12, 5 subjects were not confirmed to achieve the SVR24 due to missing data on SVR24 (3 DAA-naive patients with chronic hepatitis C [genotype 2] and without severe renal impairment, 1 DAA-naive patient with chronic hepatitis C [genotype 1 without Y93H mutation] and without severe renal impairment, and 1 patient with compensated cirrhosis type C [genotype 2]), but the others achieved the SVR24.

Based on the above, the applicant considers that the efficacy of GLE/PIB in DAA-naive patients with chronic hepatitis C or compensated cirrhosis type C (genotype 1 or 2) has been demonstrated.

(b) DAA-treated patients

In Japan, DAA drugs approved for treatment for HCV included NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors, which are indicated for both genotypes 1 and 2 (as of June 2017).

The SVR12 rate in DAA-treated subjects included in Study 2 Part of Study M15-594 is as shown in Table 37, and similar results were also obtained for the SVR24 rate. Table 38 shows the SVR12 rate in DAA-treated subjects who received GLE/PIB (or concomitant use of GLE and PIB) for 12 weeks according to the mechanism of action of the prior drug. Based on these results, the applicant considered that the efficacy of treatment with GLE/PIB for 12 weeks is expected in DAA-treated patients with genotype 1 or 2 irrespective of class of the prior drug.

Table 37. SVR12 rate in DAA-treated subjects (Study 2 Part of Study M15-594)

		GLE/PIB for 12 weeks	
		Genotype 1	Genotype 2
DAA-treated overall		93.8 (30/32)[a)]	100 (1/1)
Mechanism of action of the prior drug	NS3/4A protease inhibitor	93.8 (30/32)[b)]	-
	NS5A inhibitor	93.3 (28/30)	-
	NS5B polymerase inhibitor	-	100 (1/1)

% (Number of subjects)
a) 96.4% (27 of 28) of subjects with chronic hepatitis C, 75.0% (3 of 4) of subjects with compensated cirrhosis type C
b) Including 2 subjects who had received combination regimen of NS3/4A protease inhibitor and peginterferon (PegIFN) with RBV

Table 38. SVR12 rate in DAA-treated subjects with genotype 1 or 2 (foreign clinical study)

	Mechanism of action of the prior drug	Study (phase)	SVR12 rate	
			Chronic hepatitis C	Compensated cirrhosis type C
Genotype 1	NS3/4A protease inhibitor and NS5A inhibitor	M15-410 (II)[a)]	75.0 (9/12)	100 (1/1)
			85.7 (6/7)	-
	NS3/4A protease inhibitor (no history of treatment with NS5A inhibitors)		100 (7/7)	100 (7/7)
			81.8 (9/11)	-
	NS5A inhibitor (no history of treatment with NS3/4A protease inhibitors)		88.9 (8/9)	85.7 (6/7)
			100 (4/4)	-
	NS5B polymerase inhibitor	M13-590 (III)[b)]	100 (2/2)	-
		M14-172 (III)[c)]	-	100 (4/4)
		M15-462 (III)[d)]	100 (1/1)	100 (1/1)
		M15-464 (III)[e)]	100 (1/1)	-
Genotype 2	NS5B polymerase inhibitor	M14-172 (III)[c)]	-	100 (6/6)
		M15-464 (III)[e)]	100 (5/5)	-

% (Number of subjects)
-, No applicable subjects
a) Reference data CTD 5.3.5.2-6, b) Reference data CTD 5.3.5.2-3, c) Reference data CTD 5.3.5.2-4, d) Reference data CTD 5.3.5.2-5, e) Reference data CTD 5.3.5.1-3

Based on (a) and (b), the applicant considered that the efficacy of GLE/PIB is shown in DAA-naive or treated patients with chronic hepatitis C or compensated cirrhosis type C (genotype 1 or 2) treated for 8 weeks (DAA-naive patients with chronic hepatitis C) or for 12 weeks (DAA-treated patients with chronic hepatitis C and patients with compensated cirrhosis type C).

Based on results from Japanese Phase III studies (Studies M15-594 and M15-828), PMDA has concluded that the efficacy of GLE/PIB is expected in DAA-naive patients with chronic hepatitis C or compensated cirrhosis type C when treated for 8 or 12 weeks.

In DAA-treated patients with chronic hepatitis C or compensated cirrhosis type C, on the other hand, information about the efficacy according to the mechanism of action of the prior drug is limited, even if results from foreign studies are included. Especially, for genotype 2, there is no information about the efficacy of GLE/PIB in patients who have a history of prior treatment with NS3/4A protease inhibitors and NS5A inhibitors.

Based on the following points, PMDA has concluded that as a therapeutic option, 12-week treatment with GLE/PIB may be offered to patients who have a history of prior treatment with the other NS3/4A protease inhibitors, NS5A inhibitors, or NS5B polymerase inhibitors according to results from preceding detailed investigation into the resistance mutations:

- Resistance profiles developed in response to use of various NS3/4A protease inhibitors or NS5A inhibitors are not necessarily identical. The non-clinical pharmacology studies indicated that some of the mutations in NS3 and NS5A regions by which HCV acquired resistance to the other drugs

failed to render resistance to GLE or PIB to HCV. GLE and PIB exerted antiviral activities against HCV with major resistance mutations in the NS5B region [see Sections "3.1.3.3 Cross resistance" and "3.5.2.3 Cross resistance"].

- Japanese and foreign clinical studies showed that many of the patients with genotype 1 who had a history of prior treatment with NS3/4A protease inhibitors, NS5A inhibitors, or NS5B polymerase inhibitors achieved the SVR12.

- In Japanese phase III studies (Studies M15-594 and M15-828), the efficacy of GLE/PIB has been confirmed in patients who had resistance mutations in the NS3 or NS5A region before the first dose or at baseline, except for patients who had P32 deletion at baseline [see Section "7.R.3.2 Resistance mutations in virus"].

For patients who have a history of prior treatment with NS3/4A protease inhibitors, NS5A inhibitors, or NS5B polymerase inhibitors, however, GLE/PIB should be carefully indicated by a physician with sufficient knowledge and experience in treatment for viral hepatic diseases on the basis of the patient's conditions including presence or absence of resistance mutations. Furthermore, the applicant is required to provide the currently available information about resistance mutations to GLE or PIB to healthcare professionals, and then to collect information about the resistance mutation, efficacy and safety of GLE/PIB, etc. in patients who have a history of prior treatment with NS3/4A protease inhibitors, NS5A inhibitors, or NS5B polymerase inhibitors through post-marketing surveillance and to provide the obtained results to healthcare professionals, appropriately.

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

7.R.3.1.2 Efficacy in patients with genotype 3, 4, 5, or 6

The applicant's explanation about the efficacy of GLE/PIB in patients with chronic hepatitis C or compensated cirrhosis type C of HCV genotype 3, 4, 5, or 6 when treated for 12 weeks:
In the Japanese phase III study (Study 2 Part of Study M15-594), the SVR12 rate in patients with chronic hepatitis C and patients with compensated cirrhosis type C[55)] of genotype 3 was 80.0% (8 of 10) and 100% (2 of 2) of patients, respectively. Similar results were also obtained for the SVR24 rate. Patients with genotype 4, 5, or 6 were not included.

Table 39 shows the SVR12 rate in patients with chronic hepatitis C or compensated cirrhosis type C of genotype 3, 4, 5, or 6 who received GLE/PIB (or concomitant use of GLE and PIB) for 12 weeks in foreign clinical studies. The efficacy of treatment with GLE/PIB for 12 weeks has been confirmed for any genotype. No patients with chronic hepatitis C or compensated cirrhosis type C of genotype 5 or 6 who has a history of prior DAA treatment with were included.

[55)] Because there were no approved DAA drugs potentially indicated for genotype 3 in Japan when Study M15-594, all the patients included were DAA-naïve.

Table 39. SVR12 rate in patients with chronic hepatitis C or compensated cirrhosis type C (genotype 3, 4, 5, or 6) (foreign clinical studies)

Genotype	Study (phase)	History of prior DAA treatment	SVR12 rate	
			Chronic hepatitis C	Compensated cirrhosis type C
3	M13-594 (III)[a)]	Naïve	95.3 (222/233)	-
	M14-868 (II)[b)]	Naïve	93.3 (28/30)	-
		Naïve	91.7 (22/24)	-
		Naïve	-	100 (24/24)
		Naïve	85.7 (12/14)	97.5 (39/40)
		Treated[h)]	100 (8/8)	-
	M15-462 (III)[c)]	Naïve	100 (10/10)	100 (1/1)
4	M13-583 (III)[d)]	Naïve	98.7 (75/76)	-
	M14-172 (III)[e)]	Naïve	-	100 (15/15)
		Treated[h)]	-	100 (1/1)
	M14-867 (II)[f)]	Naïve	100 (20/20)	-
	M15-410 (II)[g)]	Treated[i)]	100 (1/1)	-
	M15-462 (III)[c)]	Naïve	100 (16/16)	100 (4/4)
5	M13-583 (III)[d)]	Naïve	100 (26/26)	-
	M14-172 (III)[e)]	Naïve	-	100 (2/2)
	M14-867 (II)[f)]	Naïve	100 (1/1)	-
	M15-462 (III)[c)]	Naïve	100 (1/1)	-
6	M13-583 (III)[d)]	Naïve	100 (19/19)	-
	M14-172 (III)[e)]	Naïve	-	100 (7/7)
	M14-867 (II)[f)]	Naïve	100 (11/11)	-
	M15-462 (III)[c)]	Naïve	100 (1/1)	-

% (Number of subjects)
-, No applicable subjects; a) Reference data CTD 5.3.5.1-4; b) Reference data CTD 5.3.5.2-1; c) Reference data CTD 5.3.5.2-5; d) see Section "7.1.3 Foreign study"; e) Reference data CTD 5.3.5.2-4; f) Reference data CTD 5.3.5.2-7; g) Reference data CTD 5.3.5.2-6; h) Prior treatment with NS5B polymerase inhibitors, i) Prior treatment with NS3/4A protease inhibitors and NS5A inhibitors

PMDA's view:

In patients with chronic hepatitis C or compensated cirrhosis type C of genotype 3, 4, 5, or 6, the certain efficacy of treatment with GLE/PIB for 12 weeks is expected, because the efficacy data obtained from patients with genotype 3, 4, 5, or 6 in Japanese and foreign clinical studies presented the acceptable SVR12 rate for any genotype, although information especially in patients with genotypes 5 and 6 is limited; and non-clinical pharmacology studies presented supportive data on the antiviral activity of GLE and PIB.

In Japan, DAA-treatment potentially indicated for patients infected with HCV genotype 3, 4, 5, or 6 is only a RBV combination regimen including SOF, an NS5B polymerase inhibitor. Only several DAA-treated patients with genotypes 3 and 4 received GLE/PIB for 12 weeks in clinical studies. However, all the DAA-treated patients with genotypes 3 and 4 achieved the SVR12 when treated with GLE/PIB for 12 weeks in foreign clinical studies; the certain efficacy is expected in naïve patients with genotype 3, 4, 5, or 6; and therapeutic options available for patients infected with HCV genotype 3, 4, 5, or 6 are limited. Taking account of the above, PMDA considered it certainly rationale to make GLE/PIB available for patients with a history of prior treatment with NS5B polymerase inhibitors on the precondition that the use of GLE/PIB are carefully considered by physicians with sufficient knowledge and experience in treatment for viral hepatic diseases on the basis of the patient's conditions including presence or absence of resistance mutations.

The use experience with GLE/PIB in patients with chronic hepatitis C and compensated cirrhosis type C of genotype 3, 4, 5, or 6 is limited, and post-marketing information about the efficacy in these patients should be collected and the obtained information should be provided to healthcare professionals, appropriately.

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

7.R.3.2 Resistance mutations in virus

The applicant's explanation about development of GLE/PIB-resistant virus and influences of the resistant virus on the efficacy of GLE/PIB:

Table 40 shows the SVR12 rate in GLE/PIB-treated subjects[56)] in Japanese phase III studies (Studies M15-594 and M15-828) according to presence or absence of resistance mutations[3),4)] in the NS3 and NS5A regions at baseline. Treatment with GLE/PIB resulted in a virologic failure in 2 patients with chronic hepatitis C of genotype 1b in which P32 deletion was found in the NS5A region before the first dose of GLE/PIB or at baseline. Both of them had a history of prior treatment with combination regimen of daclatasvir hydrochloride and asunaprevir. The SVR12 rate in subjects without P32 deletion, on the other hand, was 100% (30 of 30) of subjects, suggesting that the mutation in question possibly affects the efficacy of GLE/PIB. The SVR12 rate was not affected by presence or absence of the other mutations in patients with genotype 1 or 2. With respect to the efficacy in patients with genotype 3, although treatment with GLE/PIB resulted in a virologic failure in 1 of 3 patients with chronic hepatitis C of genotype 3b in which V31M was detected in the NS5A region at baseline, and 1 of 1 patient with chronic hepatitis C of genotype 3k in which G92E was detected in the NS5A region at baseline, the SVR12 was achieved in the other patients with genotype 3, irrespective of amino acid mutation at baseline.

[56)] Of the subject population excluding subjects who did not achieve SVR12 for reasons other than virologic failure (modified intention-to-treat [mITT] population), subjects with the relevant amino acid sequence available were included in the analysis.

Table 40. SVR12 rate according to presence or absence of amino acid mutation in the NS3 or NS5A regions at baseline

Genotype	Region	Mutation at baseline	Chronic hepatitis C				Compensated cirrhosis type C	
			GLE/PIB for 8 weeks		GLE/PIB for 12 weeks[a)]		GLE/PIB for 12 weeks	
			Positive for mutation	Negative for mutation	Positive for mutation	Negative for mutation	Positive for mutation	Negative for mutation
1a	NS3	Q80K/L	100 (2/2)	100 (2/2)	-	-	-	-
		S122G	100 (1/1)	100 (3/3)	-	-	-	-
		Any	100 (2/2)	100 (2/2)	-	-	-	-
	NS5A	M28V	100 (1/1)	100 (3/3)	-	-	-	-
		Q30H	100 (1/1)	100 (3/3)	-	-	-	-
		Y93F	100 (1/1)	100 (3/3)	-	-	-	-
		Any	100 (2/2)	100 (2/2)	-	-	-	-
1b	NS3	V36L	-	-	-	-	100 (1/1)	100 (37/37)
		T54S	100 (4/4)	100 (119/119)	-	-	100 (1/1)	100 (37/37)
		V55I	100 (1/1)	100 (122/122)	-	-	100 (2/2)	100 (36/36)
		Y56F	100 (50/50)	100 (73/73)	83.3 (5/6)	96.0 (24/25)	100 (13/13)	100 (25/25)
		Q80K/L/R	100 (23/23)	100 (100/100)	90.9 (10/11)	95.0 (19/20)	100 (7/7)	100 (31/31)
		V107I	100 (1/1)	100 (122/122)	100 (1/1)	93.3 (28/30)	-	-
		S122C/G/N/T	100 (45/45)	100 (78/78)	100 (13/13)	88.9 (16/18)	100 (13/13)	100 (25/25)
		D168E/T/V	100 (1/1)	100 (122/122)	93.3 (14/15)	93.8 (15/16)	100 (1/1)	100 (37/37)
		V170I	100 (61/61)	100 (62/62)	93.3 (14/15)	93.8 (15/16)	100 (24/24)	100 (14/14)
		Any	100 (98/98)	100 (25/25)	92.6 (25/27)	100 (4/4)	100 (33/33)	100 (5/5)
	NS5A	Q24K/R	100 (8/8)	100 (114/114)	100 (8/8)	91.7 (22/24)	100 (5/5)	100 (33/33)
		L28M/I/T/V	100 (8/8)	100 (114/114)	100 (8/8)	91.7 (22/24)	100 (5/5)	100 (33/33)
		R30H/Q/L/M	100 (14/14)	100 (108/108)	100 (11/11)	90.5 (19/21)	100 (5/5)	100 (33/33)
		L31M/F/I/V	100 (4/4)	100 (118/118)	96.2 (25/26)	83.3 (5/6)	100 (2/2)	100 (36/36)
		P32 deletion	-	-	0 (0/2)	100 (30/30)	-	-
		Q54C/E/G/H/L/Y	100 (43/43)	100 (79/79)	100 (9/9)	91.3 (21/23)	100 (17/17)	100 (21/21)
		P58Q/R/S/T/L	100 (11/11)	100 (111/111)	100 (2/2)	93.3 (28/30)	100 (1/1)	100 (37/37)
		Q62E/G/H/K/L/ N/P/R/S	100 (16/16)	100 (106/106)	100 (3/3)	93.1 (27/29)	100 (6/6)	100 (32/32)
		A92E/P/T/K	100 (9/9)	100 (113/113)	100 (5/5)	92.6 (25/27)	100 (4/4)	100 (34/34)
		Y93H/F/S	100 (23/23)	100 (99/99)	100 (21/21)	81.8 (9/11)	100 (6/6)	100 (32/32)
		Any	100 (76/76)	100 (46/46)	93.5 (29/31)	100 (1/1)	100 (29/29)	100 (9/9)
2a	NS3	L36I/M	100 (2/2)	100 (61/61)	-	-	-	-
		Y56F	100 (2/2)	100 (61/61)	-	-	100 (1/1)	100 (6/6)
		D168E	100 (1/1)	100 (62/62)	-	-	-	-
		Any	100 (5/5)	100 (58/58)	-	100 (1/1)	100 (1/1)	100 (6/6)
	NS5A	T24A/S	100 (3/3)	100 (63/63)	-	-	100 (2/2)	100 (8/8)
		T24A	-	-	100 (1/1)	-	-	-
		F28C/L	100 (2/2)	100 (64/64)	-	-	-	-
		L31M	100 (63/63)	100 (3/3)	100 (1/1)	-	100 (8/8)	100 (2/2)
		P58S	100 (4/4)	100 (62/62)	-	-	100 (2/2)	100 (8/8)
		C92N/S	100 (3/3)	100 (63/63)	-	-	-	-
		Any	100 (65/65)	100 (1/1)	100 (1/1)	-	100 (8/8)	100 (2/2)
2b	NS3	Y56F	100 (1/1)	100 (25/25)	-	-	100 (1/1)	100 (9/9)
		Any	100 (1/1)	100 (25/25)	-	-	100 (1/1)	100 (9/9)
	NS5A	L28F	100 (3/3)	100 (24/24)	-	-	100 (3/3)	100 (7/7)
		M31I/L/V	100 (6/6)	100 (21/21)	-	-	-	-
		P58S	100 (1/1)	100 (26/26)	-	-	100 (1/1)	100 (9/9)
		Any	100 (9/9)	100 (18/18)	-	-	100 (4/4)	100 (6/6)
3a	NS3	A166S/T	-	-	100 (2/2)	100 (4/4)	-	100 (1/1)
		Any	-	-	100 (2/2)	100 (4/4)	-	100 (1/1)
	NS5A	A30K	-	-	100 (1/1)	100 (5/5)	-	100 (1/1)
		Y93H	-	-	100 (1/1)	100 (5/5)	-	100 (1/1)
		Any	-	-	100 (2/2)	100 (4/4)	-	100 (1/1)
3b	NS3	Any	-	-	-	-	-	-

Table 40. SVR12 rate according to presence or absence of amino acid mutation in the NS3 or NS5A regions at baseline

Genotype	Region	Mutation at baseline	Chronic hepatitis C				Compensated cirrhosis type C	
			GLE/PIB for 8 weeks		GLE/PIB for 12 weeks[a)]		GLE/PIB for 12 weeks	
			Positive for mutation	Negative for mutation	Positive for mutation	Negative for mutation	Positive for mutation	Negative for mutation
	NS5A	V31M	-	-	66.7 (2/3)	-	100 (1/1)	-
		Any	-	-	66.7 (2/3)	-	100 (1/1)	-
3k	NS3	Any	-	-	-	-	-	-
	NS5A	G92E	-	-	0 (0/1)	-	-	-
		Any	-	-	0 (0/1)	-	-	-

% (Number of subjects)
-, Not applicable
a) Patients with genotype 1 or 2 were DAA-treated

The resistance analysis[57)] using data from foreign clinical studies indicated that A30K mutation in the NS5A region at baseline was related to the decreased SVR12 rate in patients with genotype 3,[58)] but did not identify resistance mutations at baseline that would affect the efficacy of GLE/PIB in patients with genotype 1, 2, 4, 5, or 6.

Table 41 shows resistance mutations in the NS3 and NS5A regions detected in 4 subjects with virologic failure in the Japanese phase III studies (Studies M15-594 and M15-828) at baseline and at the time of virologic failure.

Table 41. Resistance mutations in the NS3 and NS5A regions in subject with virologic failures

Subject	Subtype	Chronic hepatitis/hepatic cirrhosis	Prior treatment	NS3 region			NS5A region		
				Resistance mutation at baseline	At the time of virologic failure		Resistance mutation at baseline	At the time of virologic failure	
					Resistance mutation	Change in susceptibility[a)]		Resistance mutation	Change in susceptibility[a)]
A	1b	Hepatic cirrhosis	PegIFN/RBV DCV/ASV	Y56F S122G D168V	D168V	3.2	P32L P32 deletion	P32 deletion	1036
					A156V	1786			
					A156D	-			
B	1b	Chronic hepatitis	PegIFN/RBV DCV/ASV	Y56F Q80L V170I	Y56F	-	P32 deletion L31F	P32 deletion	1036
					Q80L	0.6		L31F	1.2
					V170I	-			
C	3b	Chronic hepatitis	PegIFN/RBV	None	None	-	V31M	V31M	-
								Y93H	-
D	3k	Chronic hepatitis	None	None	None	-	G92E	L28F	-
								G92E	-
								Y93H	-

-, Not calculated or non-applicable; DCV, Daclatasvir hydrochloride; ASV, Asunaprevir
a) EC_{50} for mutant replicon/EC_{50} for wild-type replicon [see Sections "3.1.3.2 Antiviral activity of GLE against mutants" and "3.5.2.2 Antiviral activity of PIB against mutants"]

PMDA's view:
Japanese phase III studies have shown that P32 deletion potentially affects the efficacy of GLE/PIB in patients infected with HCV genotype 1, because both subjects with genotype 1b in which P32 deletion in the NS5A region was detected at baseline virologically failed to respond to GLE/PIB, and the same mutation was detected at the time of virologic failure as well. The analysis using data from foreign

57) Pooled analysis using data from Studies M14-867, M14-868, M13-594, M13-583, M14-172, and M15-462
58) The SVR12 rate differed depending on presence or absence of A30K mutation: When GLE/PIB was administered to naïve patients for 8 weeks, the rate was 77.8% (14 of 18) of patients with A30K mutation and 98.8% (161 of 163) of patients without A30K mutation; when GLE/PIB was administered to treated patients for 12 weeks, the rate was 25.0% (1 of 4) of patients with A30K mutation and 95.6% (43 of 45) of patients without A30K mutation. In the *in vitro* investigation using HCV genotype 3a replicon cells [see Section "3.5.2.2 Antiviral activity of PIB against mutants"], single A30K or Y93H mutation in the NS5A region did not affect the antiviral activity of PIB, but double A30K and Y93H mutations decreased the antiviral activity of PIB to approximately 1/69 of the original activity.

clinical studies has shown that A30K mutation in the NS5A region at baseline potentially affects the efficacy of GLE/PIB in patients infected with HCV genotype 3. Although resistance mutations in the NS3 or NS5A region detected at baseline or at the time of virologic failure were also analyzed, available information about the relationship of resistance mutations with the efficacy of GLE/PIB in clinical studies is limited. The applicant, therefore, is required to collect post-marketing information about resistance mutations at baseline and those in patients who have received GLE/PIB but failed to achieve SVR, including published literature, and then to provide the obtained findings to healthcare professionals.

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

7.R.4 Safety

Based on the following investigations, PMDA has concluded that the safety of GLE/PIB is acceptable in Japanese patients with chronic hepatitis C or compensated cirrhosis type C when treated for 8 or 12 weeks.

Use experience with GLE/PIB in elderly patients is limited, thus, the applicant is required to continue collecting information about the safety in these patients even after the market launch and to provide the obtained information to healthcare professionals, appropriately. In addition, the applicant is required to continue collecting information about skin-related events such as rash even after the market launch.

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

7.R.4.1 Safety profile

The applicant's explanation about the safety of GLE/PIB in patients with chronic hepatitis C or compensated cirrhosis type C:

Table 42 shows a summary of the safety in Japanese phase III studies (pooled data from Studies M15-594 and M15-828). Adverse events and adverse drug reactions with an incidence of ≥5% in any GLE/PIB-treated population are as shown in Table 43.

Table 42. Summary of the safety in Japanese phase III studies (pooled data from Studies M15-594 and M15-828)

	Chronic hepatitis C				Compensated cirrhosis type C
	GLE/PIB for 8 weeks (n = 229)	GLE/PIB for 12 weeks (n = 39)	OBV/PTV/r (n = 52)	SOF/RBV (n = 46)	GLE/PIB for 12 weeks (n = 64)
Adverse events	125 (54.6)	28 (71.8)	35 (67.3)	35 (76.1)	40 (62.5)
Adverse drug reactions[a)]	50 (21.8)	14 (35.9)	14 (26.9)	23 (50.0)	16 (25.0)
Grade ≥3 adverse events[b)]	7 (3.1)	0	4 (7.7)	2 (4.3)	1 (1.6)
Serious adverse events	3 (1.3)[c)]	0	3 (5.8)	2 (4.3)[d)]	0
Adverse events leading to discontinuation	1 (0.4)	0	1 (1.9)	1 (2.2)	2 (3.1)
Adverse events resulting in death	0	0	0	0	0

Number of subjects (%)

a) Adverse events assessed as "related to the study drug"; b) NCI CTCAE ver. 4.0; c) 1 subject experienced the event (angina unstable) after the end of the study treatment; d) 1 subject experienced the event (Castleman's disease) after the end of the study treatment

Table 43. Adverse events and adverse drug reactions with an incidence of ≥5% in subjects treated with GLE/PIB

Event (PT)	Chronic hepatitis C				Compensated cirrhosis type C	
	GLE/PIB for 8 weeks (n = 229)		GLE/PIB for 12 weeks (n = 39)		GLE/PIB for 12 weeks (n = 64)	
	Adverse events	Adverse drug reactions[a)]	Adverse events	Adverse drug reactions[a)]	Adverse events	Adverse drug reactions[a)]
Nasopharyngitis	30 (13.1)	5 (2.2)	3 (7.7)	0	6 (9.4)	1 (1.6)
Pruritus	11 (4.8)	8 (3.5)	5 (12.8)	4 (10.3)	8 (12.5)	4 (6.3)
Headache	13 (5.7)	8 (3.5)	6 (15.4)	6 (15.4)	1 (1.6)	0
Malaise	8 (3.5)	7 (3.1)	1 (2.6)	1 (2.6)	5 (7.8)	2 (3.1)
Rash	5 (2.2)	2 (0.9)	3 (7.7)	1 (2.6)	3 (4.7)	1 (1.6)
Stomatitis	1 (0.4)	1 (0.4)	2 (5.1)	1 (2.6)	1 (1.6)	0
Abdominal distension	1 (0.4)	0	2 (5.1)	2 (5.1)	0	0
Decreased appetite	1 (0.4)	1 (0.4)	2 (5.1)	1 (2.6)	0	0

Number of subjects (%)
a) Adverse events assessed as "related to the study drug"

In subjects treated with GLE/PIB, Grade ≥3 adverse events occurred in 7 subjects treated for 8 weeks (patients with chronic hepatitis C) (hypertension in 3 subjects, and depression, blood creatinine increased, fluid overload, and protein urine present in 1 subject each) and 1 subject treated for 12 weeks (patient with compensated cirrhosis type C) (hypertension), and protein urine present in 1 subject was assessed as "related to GLE/PIB." The subject in question had renal impairment, and protein urine present was observed even at baseline.

Serious adverse events occurred in 3 subjects treated with GLE/PIB for 8 weeks (patients with chronic hepatitis C) (fluid overload, pneumothorax spontaneous, and angina unstable in 1 subject each), but all of them were assessed as "unrelated to GLE/PIB."

Adverse events leading to discontinuation occurred in 1 subject treated with GLE/PIB for 8 weeks (patient with chronic hepatitis C) (nausea and vomiting) and 2 subject treated with GLE/PIB for 12 weeks (patients with compensated cirrhosis type C) (drug eruption in 2 subjects). The events in both events in 2 subjects were assessed as "related to GLE/PIB," but were at Grade 2.

The summary of the safety of GLE/PIB in patients with chronic hepatitis C when treated for 8 or 12 weeks was found to have no particular problems compared with the safety of the comparators. In addition, no remarkable differences were observed in the safety profile of GLE/PIB between patients with chronic hepatitis C treated for 8 weeks and patients with chronic hepatitis C or compensated cirrhosis type C treated for 12 weeks.

PMDA's view:
Based on the incidence of adverse events in subjects treated with GLE/PIB for 8 or 12 weeks in Japanese phase III studies (Studies M15-594 and M15-828), the safety of treatment with GLE/PIB for 8 or 12 weeks is considered acceptable as long as GLE/PIB is used under supervision of a physician with sufficient knowledge and experience in treatment for viral hepatic diseases. The following sections describe PMDA's views on safety concerns already reported for drugs in the same class, such as anaemia-related events, skin-related events (rash, etc.), hepatic function disorders including blood bilirubin increased, and hepatocellular carcinoma as well as the safety in patients with renal impairment and elderly patients in details. The safety in patients with compensated cirrhosis type C is described in Section "7.R.6.2 Use of GLE/PIB in patients with compensated cirrhosis type C."

7.R.4.2 Anaemia-related events

The applicant's explanation about anaemia-related events associated with GLE/PIB:

In Japanese phase III studies (Studies M15-594 and M15-828), anaemia and haemoglobin decreased, anaemia-related events, occurred in 0.6% (2 of 332) and 0.9% (3 of 332), respectively, of subjects treated with GLE/PIB, but no Grade ≥3 abnormal haemoglobin values (<8 g/dL) occurred, and none of them discontinued GLE/PIB. In the Japanese phase III study (Study M15-828), on the other hand, anaemia occurred in 34.8% (16 of 46) of subjects in the SOF/RBV group. In addition, no events such as serious anaemia occurred in foreign clinical studies either.

Based on the above, anaemia-related events are unlikely to raise clinical concerns in patients receiving GLE/PIB.

Based on the incidence of anaemia-related events in Japanese phase III studies (Studies M15-594 and M15-828), PMDA considers the applicant's explanation acceptable in which these events are unlikely to raise clinical concerns in patients receiving GLE/PIB.

7.R.4.3 Skin-related events (rash, etc.)

The applicant's explanation about skin-related events such as rash associated with GLE/PIB:

Skin-related events[59)] reported by ≥2 subjects treated with GLE/PIB in Japanese phase III studies (Studies M15-594 and M15-828) included pruritus in 7.2% (24 of 332) of subjects, rash in 3.3% (11 of 332) of subjects, drug eruption and eczema in 0.9% each (3 of 332 for each) of subjects, pruritus generalised, dry skin, miliaria, and dermal cyst in 0.6% each (2 of 332 for each) of subjects. The events assessed as "related to GLE/PIB" included pruritus in 16 subjects, rash in 4 subjects, drug eruption in 3 subjects, and pruritus generalised, erythema, and alopecia in 1 subject each. Although drug eruption in 2 subjects led to discontinuation, the events in both were at Grade 2 and resolved. For others, no serious events or Grade ≥3 events occurred. In foreign clinical studies, Grade 3 pruritus occurred in 2 subjects, but both of them had severe renal impairment, and pruritus is a commonly observed event in patients with renal impairment (*Semin Nephrol.* 2015;35:383-91). No serious rash, etc. occurred, either.

Based on the above, skin-related events such as rash are unlikely to raise clinical concerns in patients receiving GLE/PIB.

PMDA's view:

Although events such as serious rash have not occurred in Japanese and foreign clinical studies at present, the applicant is required to provide cautions for rash, drug eruption, etc., skin-related events reported in clinical studies, because the events of drug eruption led to discontinuation in the Japanese phase III studies, and drug eruption potentially results in serious outcome. In addition, the applicant is required to continue collecting information about skin-related events such as rash even after the market launch.

[59)] Event classified into "Skin and subcutaneous tissue disorders" under System Organ Class of Medical Dictionary for Regulatory Activities (MedDRA)

7.R.4.4 Effects on hepatic function

The applicant's explanation about effects of GLE/PIB on hepatic function:
Of 332 subjects treated with GLE/PIB in Japanese phase III studies (Studies M15-594 and M15-828), blood bilirubin increased occurred in 8 subjects (5 patients with chronic hepatitis C and 3 patients with compensated cirrhosis type C) and ALT increased occurred in 2 subjects (1 patient with chronic hepatitis C and 1 patient with compensated cirrhosis type C). Although all the events were assessed as "related to GLE/PIB," they were non-serious and at Grade ≤2, and did not lead to discontinuation.

Of clinical laboratory values (mean), the total bilirubin value increased in patients with either chronic hepatitis C or compensated cirrhosis type C following administration of GLE/PIB, but returned to the baseline value until 4 weeks after the end of treatment. The ALT value decreased to below the baseline value following administration of GLE/PIB in patients with either chronic hepatitis C or compensated cirrhosis type C, suggesting that the change in question is possibly affected by the therapeutic effect of GLE/PIB against HCV infection.

Based on the above, the effect of GLE/PIB on hepatic function is unlikely to raise clinically critical concerns.

PMDA's view:
Because all the events of blood bilirubin increased and ALT increased in Japanese phase III studies (Studies M15-594 and M15-828) were non-serious and at Grade ≤2; the increase in total bilirubin value during treatment with GLE/PIB was transient; and changes in ALT value do not raise particular concerns, the applicant's explanation is acceptable in which the effect of GLE/PIB on hepatic function is unlikely to raise clinically critical concerns at present.

7.R.4.5 Hepatocellular carcinoma

The applicant's explanation about hepatocellular carcinoma following administration of GLE/PIB:
Table 44 shows a summary of hepatocellular carcinoma developed following administration of GLE/PIB in the Japanese phase III study (Studies M15-594 and M15-828, 332 subjects treated with GLE/PIB) or foreign clinical studies (2369 subjects treated with GLE/PIB). All the events were assessed as "unrelated to GLE/PIB," hepatocellular carcinoma is considered related to HCV infection, the underlying disease. Patients with a history of hepatocellular carcinoma were excluded from the clinical studies, and all the subjects experienced a new lesion of hepatocellular carcinoma.

Table 44. Patients with hepatocellular carcinoma following administration of GLE/PIB

Study	Age Sex	Treatment duration	Patient characteristics	Genotype	Prior treatment	Adverse events	Date of onset (after the end of treatment)	Relation to GLE/PIB	Outcome
Japan	7[redacted] years old Female[a)]	12 weeks	Hepatic cirrhosis	1b	Naïve	Hepatocellular carcinoma	Day 169 (85 days)	None	Resolved[c)]
Foreign	6[redacted] years old Female	16 weeks	Hepatic cirrhosis, hepatic nodule	3b	PegIFN, RBV	Hepatic neoplasm	Day 85 (1 day)	None	Resolved[c)]
	5[redacted] years old Male	12 weeks	Hepatic cirrhosis	1b	Naïve	Hepatocellular carcinoma	Day 92 (8 days)	None	Resolved[c)]
	5[redacted] years old Female	12 weeks[b)]	Hepatic cirrhosis	1b	Naïve	Hepatocellular carcinoma	Day 40	None	Continuing
	6[redacted] years old Female	12 weeks	Non-hepatic cirrhosis	1a	PegIFN, RBV, TVR	Hepatic cancer metastatic	Day 156 (71 days)	None	Death
	5[redacted] years old Male	12 weeks	Hepatic cirrhosis, Benign hepatic nodule	1a	RBV, DCV, SMV, SOF	Hepatocellular carcinoma	Day 122 (37 days)	None	Continuing
	5[redacted] years old Female	12 weeks	Hepatic cirrhosis	1b	LDV, SOF, RBV	Hepatic cancer	Day 189 (105 days)	None	Continuing

TVR, Telaprevir; DCV, Daclatasvir hydrochloride; SMV, Simeprevir; LDV, Ledipasvir; a) Reported after lock of Study M15-594 database; b) GLE/PIB discontinued on Day 50 for the other reason; c) Subject who underwent hepatectomy

Increased incidences of development or recurrence of hepatocellular carcinoma in DAA-treated patients infected with HCV were reported (*J Hepatol*. 2016;65:719-26). Information about a risk of hepatocellular carcinoma in DAA-treated patients, however, is limited, and the relationship remains unclear. The applicant therefore considers it difficult to determine the relationship of DAA treatment with development of hepatocellular carcinoma at present.

PMDA's view:

The applicant's explanation is acceptable in which it is difficult to conclude the relationship of DAA treatment with development of hepatocellular carcinoma because information about long-term prognosis for DAA-treated patients infected with HCV is limited at present. The applicant is thus required to continue collecting information about the relationship of DAA treatment with development of hepatocellular carcinoma in Japan and foreign countries, and then, if a new finding become available, to provide the information to healthcare professionals, appropriately.

7.R.4.6 Use in patients with severe renal impairment

The applicant's explanation about the safety of GLE/PIB in patients with chronic hepatitis C or compensated cirrhosis type and with severe renal impairment:

In patients with chronic hepatitis C and patients with compensated cirrhosis type C who were undergoing blood dialysis and included in the Japanese phase III study (Study M15-594), the incidence of adverse events was 80.0% (8 of 10) and 100% (2 of 2), respectively, of patients and the incidence of adverse drug reactions was 40.0% (4 of 10) and 50.0% (1 of 2), respectively, of patients. No serious adverse events assessed as "related to GLE/PIB" occurred, and a Grade ≥3 adverse event assessed as "related to GLE/PIB" occurred in 1 subject (protein urine present). Neither deaths nor adverse events leading to

discontinuation occurred. In addition, in terms of clinical laboratory values, Grade ≥3 decreased creatinine clearance occurred in 1 subject who was undergoing blood dialysis, but the difference from the baseline value was not observed. No Grade ≥3 blood creatinine increased occurred.

In the foreign phase III study (Study M15-462) in patients with chronic hepatitis C and patients with compensated cirrhosis type C who had severe renal impairment, including patients undergoing blood dialysis, the incidence of adverse events was 64.3% (54 of 84) and 100% (20 of 20), respectively, of subjects, and the incidence of adverse drug reactions was 46.4% (39 of 84) and 60.0% (12 of 20), respectively, of subjects. Adverse events reported by ≥10% of the subjects included pruritus, fatigue, and nausea. Neither deaths assessed as "related to GLE/PIB" nor serious adverse events occurred. Grade ≥3 adverse events assessed as "related to GLE/PIB" and adverse events leading to discontinuation occurred in 5 subjects (pruritus in 2 subjects, anaemia, asthenia, and diarrhea in 1 subject each) and 2 subjects (diarrhoea and pruritus in 1 subject each), respectively. In terms of clinical laboratory values, Grade ≥3 blood creatinine increased or creatinine clearance decreased occurred in 22 and 15 subjects, respectively. These laboratory values, however, may greatly vary in patients undergoing blood dialysis, and actually many of the subjects with the above changes were undergoing blood dialysis (18 of 22 subjects and 10 of 15 subjects, respectively). In addition, Grade ≥3 blood creatinine increased and creatinine clearance decreased occurred in 4 and 5 subjects not undergoing blood dialysis, respectively, and these events were also considered attributable to changes or progression of the underlying renal impairment.

Based on the above, there are no specific concerns about the safety of GLE/PIB in patients with severe renal impairment.

PMDA's view:
The safety of GLE/PIB in patients with chronic hepatitis C or compensated cirrhosis type C and with severe renal impairment is acceptable, taking into account that no specific concerns about the safety of GLE/PIB in patients with severe renal impairment were raised in Japanese and foreign clinical studies; and PK data following administration of GLE/PIB in subjects with renal impairment were supportive [see Section "6.2.3.2 Foreign study in subjects with renal impairment"].

7.R.4.7 Use in elderly patients

The applicant's explanation about the safety of GLE/PIB in the elderly:
Table 45 shows a summary of the safety in subjects without severe renal impairment in Japanese phase III studies (Studies M15-594 and M15-828) according to age stratification.

Table 45. Summary of the safety according to age stratification (in subjects without severe renal impairment) (pooled data from Studies M15-594 and M15-828)

	GLE/PIB for 8 weeks			GLE/PIB for 12 weeks		
	<65 years	≥65 and <75 years	≥75 years	<65 years	≥65 and <75 years	≥75 years
Number of subjects	127	56	36	33	41	27
Adverse events	71 (55.9)	29 (51.8)	17 (47.2)	20 (60.6)	28 (68.3)	18 (66.7)
Adverse drug reactions[a)]	28 (22.0)	12 (21.4)	6 (16.7)	9 (27.3)	13 (31.7)	7 (25.9)
Grade ≥3 adverse events[b)]	2 (1.6)	2 (3.6)	0	0	1 (2.4)	0
Serious adverse events	0	2 (3.6)	0	0	0	0
Adverse events leading to discontinuation	1 (0.8)	0	0	0	1 (2.4)	1 (3.7)
Adverse events resulting in death	0	0	0	0	0	0

Number of subjects (%)
a) Adverse events assessed as "related to the study drug"; b) NCI CTCAE ver. 4.0

Adverse events with a ≥5% higher incidence in the subgroup aged ≥65 and <75 years or subgroup aged ≥75 years than in the subgroup aged <65 years included blood bilirubin increased in subjects treated with GLE/PIB for 8 weeks (0 of 127 subjects aged <65 years, 5.4% [3 of 56] of subjects aged ≥65 and <75 years, 2.8% [1 of 36] of subjects aged ≥75 years); in subjects treated with GLE/PIB for 12 weeks, pruritus (3.0% [1 of 33] of subjects aged <65 years, 14.6% [6 of 41] of subjects aged ≥65 and <75 years, 14.8% [4 of 27] of subjects aged ≥75 years) and malaise (0 of 33 subjects aged <65 years, 12.2% [5 of 41] of subjects aged ≥65 and <75 years, 3.7% [1 of 27] of subjects aged ≥75 years). All of these events were non-serious, and none of them were at Grade ≥3 or led to discontinuation.

PMDA's view:
Although there were some adverse events with a higher incidence in subjects aged ≥65 years than in subjects aged <65 years in Japanese phase III studies (Studies M15-594 and M15-828), all of these events were non-serious, and none of them were at Grade ≥3 or led to discontinuation, and thus no clinical concerns specific to patients aged ≥65 years have been raised at present. Use experience with GLE/PIB in elderly patients, however, is limited, and in general a possibility of adverse events cannot be ruled out in the elderly due to decreased physiological functions. The applicant, therefore, is required to continue collecting information about the safety of GLE/PIB in elderly patients even after the market launch.

7.R.5 Clinical positioning

The applicant's explanation about clinical positioning of GLE/PIB in patients with chronic hepatitis C or compensated cirrhosis type C:
At present, the first-line therapy for patients with chronic hepatitis C or compensated cirrhosis type C recommended in Japan is IFN-free DAA regimens (Table 46, JSH Guidelines for the Management of Hepatitis C Virus Infection Version 5.4).

Table 46. DAA therapy regimens recommended for patients with chronic hepatitis C or compensated cirrhosis type C in Japan

Genotype	Therapeutic regimen
Genotype 1	• Concomitant use of daclatasvir hydrochloride with asunaprevir • Ledipasvir acetonate/SOF combination drug • OBV/PTV/r • Concomitant use of elbasvir with grazoprevir • Daclatasvir hydrochloride/asunaprevir/beclabuvir hydrochloride combination drug
Genotype 2	• Concomitant use of SOF and RBV • Concomitant use of OBV/PTV/r with RBV[a)]
Genotype 3, 4, 5, 6	• Concomitant use of SOF with RBV

a) Indicated for chronic hepatitis C only

For patients who have failed to eliminate HCV with these DAA regimens, however, the standard therapy has not been established. In addition, because DAA regimens approved for treatment in patients infected with HCV genotype 2, or genotype 3, 4, 5 or 6 require concomitant use of RBV products, there are no regimens available for patients with renal impairment in whom RBV products are contraindicated or patients who cannot tolerate RBV products due to adverse drug reactions such as anaemia.

GLE/PIB is potentially used as a new therapeutic option for patients with chronic hepatitis C or compensated cirrhosis type C (genotype 1, 2, 3, 4, 5, or 6) irrespective of a history of prior DAA treatment, for the following reasons: (1) The certain SVR12 rate was obtained from patients with chronic hepatitis C or compensated cirrhosis type C of genotype 1 or 2 who received GLE/PIB in Japanese phase III studies (Studies M15-594 and M15-828), irrespective of a history of prior DAA treatment, or severe renal impairment, and the efficacy in patients with chronic hepatitis C or compensated cirrhosis type C of genotype 3, 4, 5, or 6 was also confirmed in foreign clinical studies [see Section "7.R.3 Efficacy"]; and (2) the safety in patients with chronic hepatitis C or compensated cirrhosis type C was confirmed to be favorable irrespective of severe renal impairment [see Section "7.R.4 Safety"].

PMDA's view:
Based on the reviews in Sections "7.R.3 Efficacy" and "7.R.4 Safety," GLE/PIB has a potential to be used as a therapeutic option for patients with chronic hepatitis C or compensated cirrhosis type C (genotype 1, 2, 3, 4, 5, or 6) irrespective of a history of prior DAA treatment, although information about the efficacy of GLE/PIB in DAA-treated patients is limited, as long as the use of GLE/PIB are carefully considered by physicians with sufficient knowledge and experience in treatment for viral hepatic diseases on the basis of the patient's conditions including presence or absence of resistance mutations, and appropriate measures for adverse events are taken.

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

7.R.6 Indication

Based on the reviews in Sections "7.R.3 Efficacy" and "7.R.4 Safety" and the following reviews, PMDA has concluded that the indication of GLE/PIB is "improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C" as proposed.

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

7.R.6.1 Genotype

The applicant's explanation about the efficacy of GLE/PIB according to subtype:

In Japanese phase III studies (Studies M15-594 and M15-828), the SVR12 rate in DAA-naïve patients with chronic hepatitis C of genotype 1 or 2 who received GLE/PIB for 8 weeks was 100% (4 of 4) of subjects with genotype 1a, 99.2% (127 of 128) of subjects with genotype 1b, 97.1% (66 of 68) of subjects with genotype 2a, and 100% (27 of 27) of subjects with genotype 2b. In addition, the SVR12 rate in patients with chronic hepatitis C of genotype 3 who received GLE/PIB for 12 weeks was 100% (6 of 6) of subjects with genotype 3a, 66.7% (2 of 3) of subjects with genotype 3b, and 0% (0 of 1) of subject with genotype 3k.

Although data according to subtype obtained from Japanese phase III studies are limited, pooled analysis on data from foreign clinical studies covered patients with genotype 1 including 1a, 1b, and 1g as well as patients with genotype 2 including 2a, 2a/2c, 2b, 2c, and 2q. In patients with any subtype, high SVR12 rates (93.1%-100%) were obtained when GLE/PIB was administered for 8 weeks. In addition, data were obtained from patients with genotype 3 including 3a, 3b, and 3i, genotype 4 including 4a, 4a/4c/4d, 4c, 4d, 4f, 4g, 4g/4k, 4h, 4k, 4m, 4n, 4o, 4q, 4r, and 4t, genotype 5 such as 5a, and genotype 6 including 6a, 6c, 6e, 6h, 6p, 6q, 6r, and 6t. Except for the patients with chronic hepatitis C of genotype 3b which was 50.0% (1 of 2) of subjects, the certain SVR12 rates were presented in patients with the other subtypes who received GLE/PIB for 12 weeks (94.8%-100%).

PMDA confirmed that the certain SVR12 rate was presented in patients with genotype 1a or 1b, or genotype 2a or 2b in Japanese phase III studies; and no particular problems were observed for the efficacy according to the subtype (genotype 1 or 2) in foreign clinical studies. Although only a limited number of subjects were included in evaluation on the efficacy according to the subtype of genotype 3, 4, 5, or 6, the available data at least demonstrated the certain efficacy.

7.R.6.2 Use of GLE/PIB in patients with compensated cirrhosis type C

The applicant's explanation about the efficacy and safety of GLE/PIB in patients with compensated cirrhosis type C:

In Japanese phase III studies (Studies M15-594 and M15-828), the SVR12 rate in DAA-naïve patients with compensated cirrhosis type C who received GLE/PIB for 12 weeks was 100% (38 of 38) of subjects with genotype 1, 100% (20 of 20) of subjects with genotype 2, and 100% (2 of 2) of subjects with genotype 3 [see Section "7.R.3.1.1 Efficacy in patients with chronic hepatitis C or compensated cirrhosis type C" and "7.R.3.1.2 Efficacy in patients with genotype 3, 4, 5, or 6"]. In foreign clinical studies, the SVR12 rate in patients with compensated cirrhosis type C who received GLE/PIB for 12 weeks was ≥97.5% for any of genotypes 3, 4, 5, and 6 [see Section "7.R.3.1.2 Efficacy in patients with genotype 3, 4, 5, or 6"].

The SVR12 rate in DAA-treated patients with compensated cirrhosis type C who received GLE/PIB for 12 weeks was 75% (3 of 4) of subjects with genotype 1 in Japanese phase III studies (Studies M15-594 and M15-828), and the certain SVR12 rate was presented in patients with any of genotypes 1, 2, and 4 in foreign clinical studies as well [see Sections "7.R.3.1.1 Efficacy in patients with genotype 1 or 2" and "7.R.3.1.2 Efficacy in patients with genotype 3, 4, 5, or 6"].

In addition, Table 47 shows a summary of the safety in patients with chronic hepatitis C or compensated cirrhosis type C, and no particular differences were observed between both of them.

Based on the above, the efficacy of the treatment with GLE/PIB for 12 weeks in patients with compensated cirrhosis type C has been demonstrated, and no particular concerns about the safety have not been raised.

Table 47. Summary of the safety in patients with chronic hepatitis C or compensated cirrhosis type C (pooled data from Studies M15-594 and M15-828)

	Chronic hepatitis C		Compensated cirrhosis type C
	GLE/PIB for 8 weeks (n = 229)	GLE/PIB for 12 weeks (n = 39)	GLE/PIB for 12 weeks (n = 64)
Adverse events	125 (54.6)	28 (71.8)	40 (62.5)
Adverse drug reactions[a)]	50 (21.8)	14 (35.9)	16 (25.0)
Grade ≥3 adverse events[b)]	7 (3.1)	0	1 (1.6)
Serious adverse events	3 (1.3)	0	0
Adverse events leading to discontinuation	1 (0.4)	0	2 (3.1)
Adverse events resulting in death	0	0	0

Number of subjects (%)
a) Adverse events assessed as "related to the study drug"; b) NCI CTCAE ver. 4.0

PMDA's view:
Based on results from Japanese and foreign clinical studies, the efficacy of GLE/PIB is expected in DAA-naive patients with compensated cirrhosis type C. Although information obtained from DAA-treated patients with compensated cirrhosis type C is limited, the treatment with GLE/PIB for 12 weeks has a potential to be used as a therapeutic option even in DAA-treated patients with compensated cirrhosis type C, because the SVR12 rate in DAA-naive patients with compensated cirrhosis type C was comparable to that in patients with chronic hepatitis C.

In addition, the safety of the treatment with GLE/PIB for 12 weeks in patients with compensated cirrhosis type C is acceptable as long as appropriate measures such as monitoring and controlling of adverse events, and interruption and discontinuation of treatment are taken by physicians with sufficient knowledge and experience in treatment for viral hepatic diseases, because no clear differences were observed in the safety profile between patients with chronic hepatitis C and patients with compensated cirrhosis type C in Japanese phase III studies (Studies M15-594 and M15-828).

Because use experience with GLE/PIB in Japanese patients with compensated cirrhosis type C is limited, information about the safety and efficacy of GLE/PIB in these patients should be collected through post-marketing surveillance, if new information becomes available, the information should be provided to healthcare professionals, appropriately.

7.R.7 Dosage and administration

Based on the reviews in Sections "7.R.3 Efficacy" and "7.R.4 Safety," the following reviews, and descriptions for the other drugs in the same class, PMDA has concluded that the dosage and administration of GLE/PIB should be specified shown below. In addition, the package insert should include the statement that patients with chronic hepatitis C who had a history of prior treatment with NS3/4A protease inhibitors, NS5A inhibitors, or NS5B polymerase inhibitors received GLE/PIB for 12 weeks in Japanese clinical studies.

- Serogroup 1 (genotype 1) or serogroup 2 (genotype 2) chronic hepatitis C virus infection

The usual adult dosage is 3 tablets (300 mg of glecaprevir and 120 mg of pibrentasvir) orally administered once daily after a meal. The duration of treatment is 8 weeks. It may be extended to 12 weeks depending on the history of previous treatment for chronic hepatitis C.

- Serogroup 1 (genotype 1) or serogroup 2 (genotype 2) compensated cirrhosis type C, and non-serogroup 1 (-genotype 1) or non-serogroup 2 (-genotype 2) chronic hepatitis C or compensated cirrhosis type C

  The usual adult dosage is 3 tablets (300 mg of glecaprevir and 120 mg of pibrentasvir) orally administered once daily after a meal. The duration of treatment is 12 weeks.

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

7.R.7.1 Dosage and administration, and treatment duration

The applicant's explanation about dosage regimens and treatment duration:

In Japanese and foreign phased III studies, doses of GLE/PIB were selected at GLE 300 mg and PIB 120 mg, which were to be administered QD, based on the following points:

- In a foreign phase II study (Study M13-595), untreated patients with chronic hepatitis C or compensated cirrhosis type C (genotype 1) orally received GLE at 100 to 700 mg QD or PIB at 15 to 400 mg QD for 3 days. The same reduction in RNA load was achieved at the GLE dose of ≥100 mg QD or PIB dose of ≥40 mg QD.
- In multiple foreign phase II studies, doses of GLE and PIB and necessity of concomitant use of RBV were investigated. As a result, concomitant use of GLE and PIB at 300 mg and 120 mg, respectively, presented the favorable efficacy, and concomitant RBV was confirmed to be unnecessary (Table 48). In addition, both GLE and PIB were well tolerated.

Table 48. SVR12 rate in foreign phase II studies

Study	Study population			Dosage regimen				SVR12 rate % (Number of subjects)
	History of prior treatment	Genotype	Chronic hepatitis/ compensated cirrhosis	GLE	PIB	Concomitant use of RBV	Treatment duration	
M14-867[a)]	Naive or PegIFN/RBV treated (no response)	1	Chronic hepatitis	200 mg QD	120 mg QD	No	12 weeks	100 (40/40)
				200 mg QD	40 mg QD	No	12 weeks	97.4 (38/39)
	Naive or PegIFN/RBV treated (virologic failure or relapse during treatment)	1	Chronic hepatitis	300 mg QD	120 mg QD	No	8 weeks	97.1 (33/34)
			Compensated cirrhosis	200 mg QD	120 mg QD	No	12 weeks	96.3 (26/27)
		4, 5, 6	Chronic hepatitis	300 mg QD	120 mg QD	No	12 weeks	100 (34/34)
M14-868[b)]	Naive or PegIFN/RBV treated	2	Chronic hepatitis	300 mg QD	120 mg QD	No	12 weeks	96.0 (24/25)
				200 mg QD	120 mg QD	No	12 weeks	100 (24/24)
				200 mg QD	120 mg QD	Yes	12 weeks	100 (25/25)
		3		300 mg QD	120 mg QD	No	12 weeks	93.3 (28/30)
				200 mg QD	120 mg QD	No	12 weeks	93.3 (28/30)
				200 mg QD	120 mg QD	Yes	12 weeks	93.5 (29/31)
				200 mg QD	40 mg QD	No	12 weeks	83.3 (25/30)
		2	Chronic hepatitis	300 mg QD	120 mg QD	No	8 weeks	98.1 (53/54)
		3		300 mg QD	120 mg QD	No	Naive: 8 weeks Treated: 12 weeks	Naive: 96.6 (28/29) Treated: 91.7 (22/24)
		3	Compensated cirrhosis	300 mg QD	120 mg QD	No	Naive: 12 weeks Treated: 16 weeks	Naive: 100 (24/24) Treated: 75.0 (3/4)
				300 mg QD	120 mg QD	Yes	12 weeks	100 (27/27)
	Naïve	3	Compensated cirrhosis	300 mg QD	120 mg QD	No	12 weeks	97.5 (39/40)
	Treated with regimens including IFN product or SOF		Chronic hepatitis	300 mg QD	120 mg QD	No	12 weeks	90.9 (20/22)
				300 mg QD	120 mg QD	No	16 weeks	95.5 (21/22)
			Compensated cirrhosis	300 mg QD	120 mg QD	No	16 weeks	95.7 (45/47)
	Naive or treated with regimens including IFN product or SOF	2	Chronic hepatitis	300 mg QD	120 mg QD	No	8 weeks	97.9 (142/145)
		4						93.5 (43/46)
		5						100 (2/2)
		6						90.0 (9/10)
M15-410[c)]	DAA-treated (virologic failure or relapse during treatment)	1	Chronic hepatitis	200 mg QD	80 mg QD	No	12 weeks	100 (6/6)
				300 mg QD	120 mg QD	Yes	12 weeks	95.5 (21/22)
				300 mg QD	120 mg QD	No	12 weeks	86.4 (19/22)
		1, 4, 5, 6	Chronic hepatitis or compensated cirrhosis	300 mg QD	120 mg QD	No	12 weeks	88.6 (39/44)
				300 mg QD	120 mg QD	No	16 weeks	91.5 (43/47)

a) Reference data CTD 5.3.5.2-7, b) Reference data CTD 5.3.5.2-1, c) Reference data CTD 5.3.5.2-6

Based on results from foreign phase II studies, the treatment duration in Japanese phase III studies (Studies M15-594 and M15-828) was as follows: DAA-naive patients with chronic hepatitis C (genotype 1 or 2) were to receive GLE/PIB for 8 weeks; and DAA-treated patients with chronic hepatitis C (genotype 1 or 2), patients with compensated cirrhosis type C (genotype 1 or 2), and patients with chronic hepatitis C or compensated cirrhosis type C (genotype 3, 4, 5, or 6) were to receive GLE/PIB for 12 weeks.

In Japanese phase III studies in which subjects received GLE 300 mg and PIB 120 mg for 8 or 12 weeks, the favorable efficacy and safety were confirmed in patients with chronic hepatitis C or compensated cirrhosis type C [see Sections “7.R.3 Efficacy,” “7.R.4 Safety,” and “7.R.6.2 Use of GLE/PIB in patients with compensated cirrhosis type C”]. In addition, in foreign clinical studies, the certain efficacy of treatment with GLE/PIB (GLE 300 mg and PIB 120 mg) for 12 weeks was confirmed in DAA-treated patients and patients with genotype 3, 4, 5, or 6, from whom data were not sufficiently collected in Japanese clinical studies.

Based on the above, the applicant considers it meaningful to administer GLE/PIB (GLE 300 mg and PIB 120 mg) to patients with chronic hepatitis C or compensated cirrhosis type C for 8 or 12 weeks.

Based on the reviews in Sections "7.R.3 Efficacy" and "7.R.4 Safety," and results from Japanese and foreign clinical studies, PMDA has concluded that the following dosage regimens are acceptable: 3 GLE/PIB tablets (GLE 300 mg and PIB 120 mg) are orally administered once daily under fed conditions; and the treatment duration is 8 weeks or 12 weeks for patients with chronic hepatitis C of genotype 1 or 2 according to a history of prior treatment, and 12 weeks for patients with compensated cirrhosis type C of genotype 1 or 2, and patients with chronic hepatitis C or compensated cirrhosis type C of genotype 3, 4, 5, or 6.

7.R.8 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance plan for GLE/PIB:
[Use-results surveys]

- Objective: To collect information about the safety and efficacy of GLE/PIB in patients with chronic hepatitis C or compensated cirrhosis type C of genotypes 1 to 6 in routine clinical use
- Target sample size: 1000
  [Rationale for setting] The target sample size of 1000 is considered sufficient for evaluation of the safety at a certain precision
- Observation period: 32 weeks or 36 weeks (treatment duration of 8 weeks or 12 weeks, and follow-up period of 24 weeks)
- Survey period: 27 months from date of initial marketing (registration period of 18 months)

PMDA considers it necessary to collect information about the following points after the market launch:

- Safety and efficacy in patients with genotype 3, 4, 5, or 6
- Resistance mutations in response to GLE/PIB and the efficacy of GLE/PIB in patients previously treated with an NS3/4A protease inhibitor, NS5A inhibitor, or NS5B polymerase inhibitor
- Relationship between the efficacy of GLE/PIB and resistance mutations identified before the start of treatment or after treatment failure
- Safety and efficacy in elderly patients and patients with compensated cirrhosis type C
- Skin-related events (drug eruption)

The following information should be collected even from published literature, then, if a new finding becomes available, the information should be provided to healthcare professionals, immediately:

- Resistance mutations before and after the start of GLE/PIB
- Relationship of DAA treatment with development of hepatocellular carcinoma

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

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

At present, the assessment is ongoing, and the results and PMDA's conclusion are reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that efficacy of GLE/PIB has efficacy in the treatment of chronic hepatitis C or compensated cirrhosis type C and acceptable safety in view of its benefits.

PMDA has concluded that Maviret may be approved if Maviret is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 10, 2017

Product Submitted for Approval

Brand Name	Maviret Combination Tablets
Non-proprietary Name	Glecaprevir Hydrate/Pibrentasvir
Applicant	AbbVie GK
Date of Application	February 14, 2017

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

PMDA's conclusions on issues presented in the Review Report (1) [Sections "7.R.3 Efficacy," "7.R.4 Safety," "7.R.5 Clinical positioning," "7.R.6 Indication," "7.R.7 Dosage and administration," and "7.R.8 Post-marketing investigations"] were supported by expert advisors.

PMDA discussed the following additional matters and took necessary actions.

1.1 Efficacy and post-marketing investigations

At the Expert Discussion, PMDA's conclusions on the efficacy [Sections "7.R.3 Efficacy" and "7.R.8 Post-marketing investigations"] were supported, and the following comments were raised from the expert advisors:

- GLE/PIB has promising efficacy in patients with chronic hepatitis C or compensated cirrhosis type C (genotypes 1 to 6). However, the clinical studies yielded only limited data from patients treated with direct-acting antiviral (DAA) and patients with genotypes 3 to 6. Relevant data should be continuously collected in the post-marketing setting.

- Japanese clinical studies revealed virologic failure in 2 patients with chronic hepatitis C of genotype 1b having P32 deletion in NS5A. The information about resistance mutations in response to GLE/PIB should be provided to healthcare professionals and relevant data should be further collected in the post-marketing setting.

PMDA instructed the applicant to provide currently available information about resistance mutations to healthcare professionals, and the applicant agreed to take actions appropriately. Actions on post-marketing investigations are described in Section "1.2 Risk management plan (draft)."

1.2 Risk management plan (draft)

Based on the reviews in Section "7.R.8 Post-marketing investigations" of the Review Report (1) and comments from expert advisors at the Expert Discussion, PMDA considers that the following data should be collected through the post-marketing surveillance, and any new findings should be provided to healthcare professionals appropriately:

- Safety and efficacy in patients with genotype 3, 4, 5, or 6
- Resistance mutations in response to GLE/PIB and the efficacy of GLE/PIB in patients previously treated with an NS3/4A protease inhibitor, NS5A inhibitor, or NS5B polymerase inhibitor
- Relationship between the efficacy of GLE/PIB and resistance mutation identified before the start of treatment or after treatment failure
- Safety and efficacy in elderly patients and patients with compensated cirrhosis type C
- Skin-related events (drug eruption)

In addition, the following information should be sourced from published literature as well. New findings should be communicated to healthcare professionals appropriately.

- Resistance mutation occurring before or after the start of GLE/PIB treatment
- Relationship between DAA treatment and the development of hepatocellular carcinoma

PMDA requested the applicant to investigate the above points, and the applicant accepted.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for GLE/PIB should include the safety and efficacy specifications presented in Table 49, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 50. PMDA thus accepted the outline of the use-results survey (draft) presented in Table 51.

Table 49. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Reactivation of hepatitis B virus	Not applicable	Not applicable
Efficacy specification		
• Efficacy in routine clinical use • Drug resistance		

Table 50. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results surveys	• Provision of information obtained from early post-marketing phase vigilance

Table 51. Outline of use-results survey (draft)

Objective	Collection of information about the safety and efficacy of GLE/PIB in routine clinical use
Survey method	Central registration system
Population	Patients with chronic hepatitis C or compensated cirrhosis type C (genotypes 1 to 6)
Observation period	32 or 36 weeks (treatment duration of 8 or 12 weeks and follow-up period of 24 weeks)
Planned sample size	1000 patients (680 with genotype 1 [including 48 with compensated cirrhosis type C], 290 with genotype 2 [including 21 with compensated cirrhosis type C], 30 with genotypes 3 to 6)
Main survey items	Patient characteristics, history of treatment for chronic hepatitis C (drugs used, therapeutic effects, etc.), use status of GLE/PIB, HCV-RNA test, acquired drug-resistance mutations, clinical laboratory values, and adverse events

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, CTD 5.3.5.1-2, CTD 5.3.5.1-2-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved for the proposed indication and the dosage and administration modified as shown below, with the following condition of approval. Maviret is a drug with new active ingredients and is a new combination drug. Thus the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product, and neither the drug product nor its drug substances, glecaprevir hydrate and pibrentasvir, is classified as a poisonous drug or a powerful drug.

Indication

Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C

Dosage and administration

(The underlined words are added to the proposed text, and strikethrough words were deleted from the proposed text.)

- Serogroup 1 (genotype 1) or serogroup 2 (genotype 2) chronic hepatitis C virus infection

  The usual adult dosage is 3 tablets (300 mg of glecaprevir and 120 mg of pibrentasvir) orally administered once daily after a meal. ~~The treatment duration is as follows:~~ The duration of treatment

is 8 weeks. It may be extended to 12 weeks depending on the history of previous treatment for chronic hepatitis C.

- Serogroup 1 (genotype 1) or serogroup 2 (genotype 2) compensated cirrhosis type C
- Non-serogroup 1 (-genotype 1) or non-serogroup 2 (-genotype 2) chronic hepatitis C or compensated cirrhosis type C

  The usual adult dosage is 3 tablets (300 mg of glecaprevir and 120 mg of pibrentasvir) orally administered once daily after a meal. The duration of treatment is 12 weeks.
- ~~Patients with serogroup 1 or 2 (genotype 1 or 2) chronic hepatitis C who have not received direct-acting antiviral therapy: 8 weeks~~
- ~~Patients other than the above: 12 weeks~~

Condition of Approval

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