








## RESEARCH ARTICLE

# Safety and efficacy of glecaprevir and pibrentasvir in north Tohoku Japanese patients with genotype 1/2 hepatitis C virus infection

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## Abstract

**Background and aims:** To assess the efficacy and safety of treatment with glecaprevir/pibrentasvir in Japanese patients with genotype (GT) 1/2 hepatitis C virus (HCV) infection in a real-world clinical setting.

**Methods:** A total of 230 patients from 12 centers in northern Tohoku Japan with chronic hepatitis (CH) or compensated liver cirrhosis (LC) and GT1/2 HCV infection were treated with glecaprevir/pibrentasvir and followed up for 12 weeks after treatment completion. Those patients were evaluated by dividing them into the following three groups: CH GT1/2 HCV-infected, direct-acting antiviral agents (DAA)-naive patients received 8 weeks of treatment (8-week initial treatment group), compensated LC GT1/2 HCV-infected, DAA-naive patients received 12 weeks of treatment (12-week initial treatment group), and GT1/2 HCV-infected patients with previous failed DAA treatment were assigned to 12-week treatment (12-week re-treatment group).

**Results:** The overall sustained virologic response (SVR) rate in the modified intention-to-treat population was 99% (222/225). The SVR rate in 8-week initial treatment group, 12-week initial treatment group, and 12-week re-treatment group were 99% (118/119), 98% (104/106), and 97% (56/58), respectively. SVR rates based on chronic kidney disease (CKD) stage were 99% in stage 1/2, 96% in stage 3, and 100% in stage 4/5 patients. SVR rate among the three treatment groups was not influenced by CKD stage. Furthermore, all 18 patients (six in the 8-week initial treatment group, 12 in 12-week initial treatment group) who underwent hemodialysis attained SVR. Serious treatment-associated adverse events (grade  $\geq$  3) occurred in 12 patients (5.2%). Five patients (2.2%) discontinued treatment because of adverse events; however, three of these patients achieved SVR.

**Conclusion:** Primary treatment and re-treatment with glecaprevir/pibrentasvir are effective and safe for patients without decompensated LC and GT1/2 HCV infection in a real-world clinical setting. Furthermore, the SVR rate was not influenced by CKD stage.

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## KEYWORDS

antiviral agent, chronic kidney disease, hepatitis C virus, sustained virologic response

## 1 | INTRODUCTION

Hepatitis C virus (HCV) is a leading cause of hepatic cirrhosis, hepatocellular carcinoma, and end-stage liver disease.<sup>1,2</sup> Therefore, early detection and treatment are crucial. Direct-acting antiviral agents (DAAs) have become the first-line treatment for chronic HCV infection and are often used in combination with NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors. In 2014, combined use of asunaprevir (ASV) and daclatasvir (DCV) became the first approved interferon (IFN)-free treatment for genotype (GT) 1 HCV infection in Japan. Thereafter, DAAs for GT1 and GT2 were launched in succession. Several oral regimens combining DAAs with different modes of action, such as NS3/4A protease inhibitors plus NS5A inhibitors and NS5A inhibitors plus NS5B polymerase inhibitors, are available now.<sup>3</sup> All of these treatments show high efficacy and safety, with >90% patients attaining sustained virologic response (SVR), described as the absence of HCV at 12 weeks after treatment completion.

A combination of glecaprevir (GLE; NS3/4A protease inhibitor)/pibrentasvir (PIB; NS5A inhibitor) for chronic hepatitis (CH) and compensated liver cirrhosis (LC) was approved for use in Japan in 2017 and shown to be pangenotypic, as demonstrated by SVR rates in clinical trials.<sup>4-6</sup> GLE/PIB is highly effective for patients with NS5A resistance-associated substitutions (RASs),<sup>7</sup> has fewer adverse events (AEs), such as elevation of alanine aminotransferase (ALT) and/or total bilirubin levels, and shows minimal drug-drug interactions.<sup>8</sup> Furthermore, GLE/PIB undergoes metabolism in the liver and is eliminated via the bile duct, indicating minimal effect on kidney function.<sup>9,10</sup>

This study evaluated the efficacy and safety of GLE/PIB treatment in patients with chronic HCV infection in a real-world setting. We also aimed to identify laboratory abnormalities during GLE/PIB treatment.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

This prospective cohort study enrolled 230 consecutive patients with chronic HCV infection who were treated with GLE/PIB for either 8 or 12 weeks between December 2017 and March 2021 at 12 viral treatment centers in northern Tohoku Japan. Enrollment criteria consisted of age of  $\geq 18$  years, serum HCV RNA levels of  $>1.2$  log IU/mL at the time of screening, and confirmation of chronic GT1/2 HCV infection before treatment. The presence of LC was determined at screening by physicians based on one or more of the following: (a) liver biopsy findings,<sup>11</sup> (b) fibrosis-4 (Fib-4) index  $\geq 3.25$ ,<sup>12</sup> (c) discriminant score  $> 0$ ,<sup>13</sup> (d) serum markers of fibrosis (platelet count  $<10 \times 10^4/\text{mm}^3$ , serum WFA[+]-M2BP levels  $>3.67$ ),<sup>14</sup> (e) transient elastography ( $>9.6$  kPa),<sup>15</sup> and (f) liver imaging examination (ultrasonography,

computed tomography, or magnetic resonance imaging) that revealed signs of cirrhosis combined with clinical state. Patients with HCV infection with GT other than 1/2, decompensated liver disease (Child-Pugh grade B or C), other causes of liver disease, hepatitis B infection, or human immunodeficiency virus infection were excluded.

The study was carried out in accordance with the Declaration of Helsinki and approved by the ethics committee of our institution (approval number H29-170) and the relevant committees at the treatment sites. All patients provided written informed consent before the start of the study procedures.

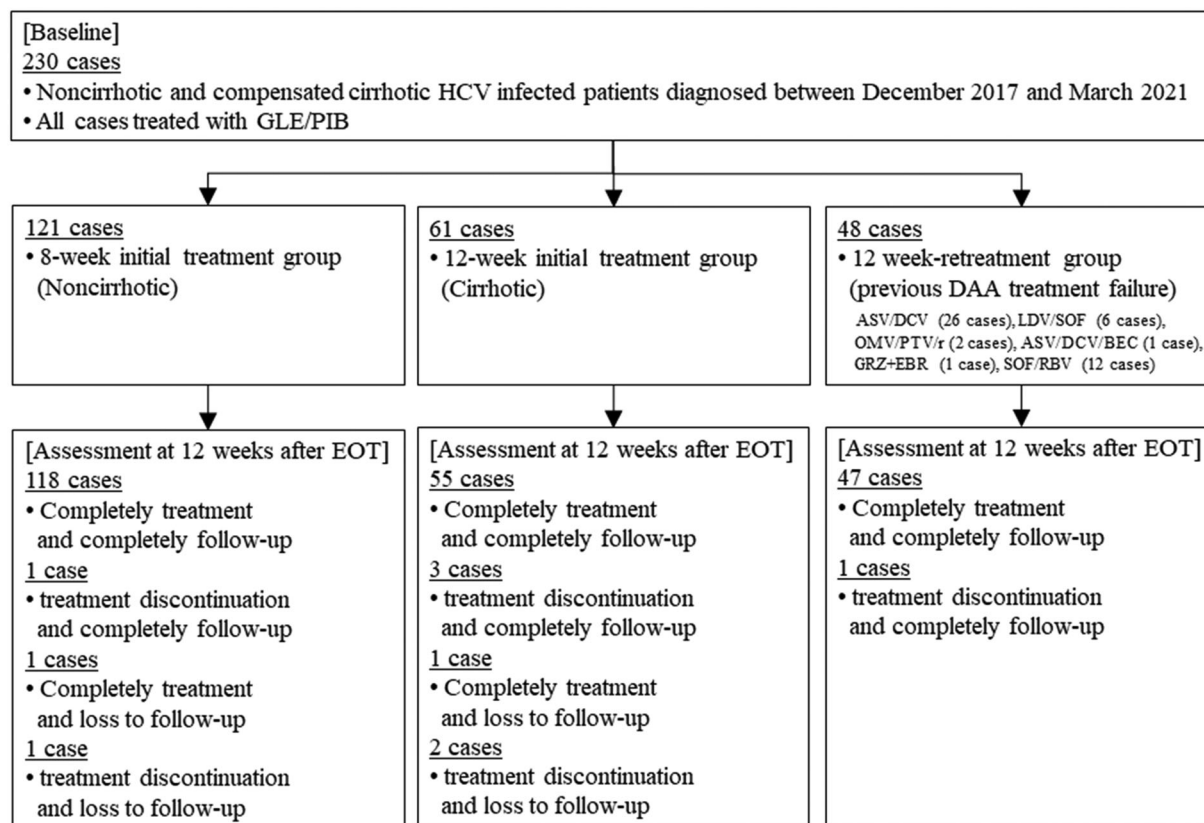
### 2.2 | Treatment protocol and laboratory tests

Patients received an oral dose of 300 mg of GLE and 120 mg of PIB (Maviret, AbbVie Inc., North Chicago, Illinois) once daily for either 8 or 12 weeks. Noncirrhotic GT1/2 HCV-infected, DAA-naïve patients received 8 weeks of GLE/PIB treatment (8-week initial treatment group), and compensated cirrhotic GT1/2 HCV-infected, DAA-naïve patients were assigned to 12 weeks of GLE/PIB treatment (12-week initial treatment group). GT1/2 HCV-infected patients with previous failed DAA treatment were assigned to 12-week GLE/PIB treatment (12-week re-treatment group) (Figure 1). The final decision to lower the dose or discontinue treatment was made by a physician.

Peripheral blood samples were obtained at baseline and at 4 weeks after the first administration of GLE/PIB and then every 4 weeks thereafter for 20 and 24 weeks for the 8-week and 12-week treatment groups, respectively. Serum HCV RNA levels were measured using a COBA TaqMan HCV quantitation assay (Roche Diagnostics, Tokyo, Japan), with a detection range of 15 to  $6.9 \times 10^7$  IU/mL ( $1.2$ - $7.8$  log IU/mL), and undetectable HCV RNA was defined as negative. HCV GT was determined by polymerase chain reaction (PCR) as previously defined by Okamoto et al.<sup>16</sup>

NS5A amino acids at positions 31 and 93 were measured by direct sequencing, and NS5A Y93 mutations were measured using Cycleave PCR (SRL Laboratory, Tokyo, Japan)<sup>17</sup> or the PCR-Invader method (BML Inc., Tokyo, Japan)<sup>18</sup> to determine the effect of baseline NS5A RAS in patients with GT1 HCV. In naïve patients with HCV GT 1 infection, the decision to check for NS5A RAS was made by a physician. On the other hand, samples from patients with previous DAA failure were tested for RAS at the NS5A region using direct sequencing (LSI Medicine Inc., Tokyo, Japan) before starting GLE/PIB.

Hyperbilirubinemia was characterized as total bilirubin levels  $>1.2$  mg/dL. ALT levels  $<30$  U/L were considered normal. Fib-4 index were calculated based on following formula: Fib-4 index = (aspartate aminotransferase [AST] [U/L]  $\times$  Age [years]) / (Platelet [ $\times 10^4/\text{mm}^3$ ])  $\times \sqrt{\text{ALT [U/L]}}$ . The estimated glomerular filtration rate (eGFR) was calculated using the formula  $\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{creatinine}$



**FIGURE 1** Flowchart depicting the selection of participant and assessment. HCV, hepatitis C virus; GLE, glecaprevir; PIB, pibrentasvir; DAAs, direct-acting antiviral agent; EOT, end of treatment; ASV, asunaprevir; DCV, daclatasvir; LDV, ledipasvir; SOF, sofosbuvir; OMV, ombitasvir; PTV, paritaprevir; r, ritonavir; BEC, beclabuvir; GRZ, grazoprevir; EBR, elbasvir; RBV, ribavirin

$(\text{mg/dL})^{-1.094} \times \text{age (years)}^{-0.287} (\times 0.739, \text{ if female})$ . eGFR was used as a surrogate marker of creatinine clearance. The chronic kidney disease (CKD) stage was classified according to the kidney disease: Improving Global Outcomes Clinical Practice Guideline for CKD.<sup>19</sup> Patients were divided into three groups at baseline according to stage: stage 1/2, eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>; stage 3,  $60$  mL/min/1.73 m<sup>2</sup>  $>$  eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup>; and stage 4/5, eGFR  $< 30$  mL/min/1.73 m<sup>2</sup>.

### 2.3 | Treatment efficacy and safety assessment

SVR was defined as undetectable HCV RNA at 12 weeks after treatment completion, whereas non-SVR was described as detectable HCV RNA at treatment completion or undetectable HCV RNA at treatment completion but detectable HCV RNA after 12 weeks. The primary efficacy endpoint was the percentage of patients who achieved an SVR in the intention-to-treat (ITT) and modified ITT (mITT) analyses. All patients who received at least one dose of the study drug (including cases of nonvirological failure, for example, loss to follow-up or early discontinuation) formed the ITT population. mITT analysis was also conducted, excluding all nonvirological failure.

Treatment-associated AEs, including all clinical, biochemical, and hematological abnormalities, were reported and documented. The frequency of GLE/PIB-associated AEs was computed. AEs were graded according to the

National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.<sup>20</sup> The primary safety endpoint was frequency of AEs.

### 2.4 | Statistical analysis

Treatment results were examined according to ITT and mITT. A 95% confidence interval (CI) was calculated for the SVR rate. Categorical variables were analyzed using the Chi-square test and Fisher's exact test and continuous variables using the paired Mann-Whitney *U* test to compare clinical parameters among the groups. The Friedman test was used to compare two or more paired groups, followed by a Bonferroni's multiple-comparison post hoc test. *P* values  $< .05$  (determined by two-tailed test) were considered statistically significant. All statistical analyses were conducted using SPSS software (SPSS Statistics for Windows, SPSS Inc., Chicago, Illinois).

## 3 | RESULTS

### 3.1 | Patients' characteristics

A total of 230 patients with chronic HCV infection were enrolled, comprising 121 participants (49 males, 72 females) in the 8-week

initial treatment group and 61 (32 males, 29 females) in the 12-week initial treatment group. A total of 48 (25 males, 23 females) re-treatment patients were included in the 12-week group (Table 1). The median age was 68 (range, 26-88) years in the 8-week initial treatment group, 70 (range, 36-88) years in the 12-week initial treatment group, and 71 (range, 44-85) years in the 12-week re-treatment group. The baseline characteristics of the patients in the study are shown in Table 1.

Of the 230 patients, 21% (48/230) experienced a previous IFN-free DAA treatment failure. Previous DAA treatments for GT1 HCV patients included ASV + DCV in 26 patients, LDV/SOF in five, OMV/PTV/r in two, ASV/DCV/BEC in one, and GRZ + EBR in one patient. Of the GT2 HCV-infected patients, 12 had previously received SOF + RBV treatment and one had received LDV/SOF.

The presence of NS5A Y93 RAS and NS5A L31 RAS at baseline is shown in Table 1. Double mutation of NS5A Y93 and L31 was detected in 82.4% (28/34) of patients with previous DAA failure. P32 deletion in NS5A was not detected among DAA-experienced GT1 HCV patients. Moreover, NS5A A92 RAS was detected in 9.4% (3/32) of patients with a previous DAA failure.

### 3.2 | Efficacy

The overall SVR rate in the mITT population was 99% (222/225). Among patients who received treatment for 8 weeks, the SVR rate was 99% (118/119; mITT analysis excluding 2 patients lost to

**TABLE 1** Baseline characteristics of the study patients

Variable	8-Week initial treatment n = 121	12-Week initial treatment n = 61	12-Week re-treatment n = 48
Sex (male/female)	49/72	32/29	25/23
Age (years) <sup>a</sup>	68 (26-88)	70 (36-88)	71 (44-85)
WBC (/mm <sup>3</sup> ) <sup>a</sup>	5140 (1970-13 800)	4640 (1800-8930)	4400 (1680-11 160)
Hemoglobin (g/dL) <sup>a</sup>	13.4 (8.6-16.8)	12.6 (6.0-15.9)	13.3 (9.6-16.4)
Platelets ( $\times 10^4$ /mm <sup>3</sup> ) <sup>a</sup>	19.3 (5.7-41.8)	12.5 (5.7-33.0)	14.1 (4.7-35.3)
Total bilirubin (mg/dL)	0.5 (0.2-1.8)	0.6 (0.1-2.1)	0.6 (0.2-2.1)
AST (IU/L) <sup>a</sup>	29 (12-527)	45 (9-189)	35 (14-182)
ALT (IU/L) <sup>a</sup>	28 (8-740)	41 (9-220)	30 (7-264)
Serum albumin (g/dL) <sup>a</sup>	4.2 (2.7-6.3)	3.9 (2.9-4.6)	4.2 (2.9-6.4)
eGFR (mL/min/1.73 m <sup>2</sup> ) <sup>a</sup>	70.6 (5.4-114.2)	64.0 (3.7-112.1)	69.5 (5.0-112.1)
CKD stage 1 <sup>b</sup>	22	7	9
CKD stage 2 <sup>c</sup>	59	28	26
CKD stage 3 <sup>d</sup>	28	11	11
CKD stage 4 <sup>e</sup>	4	1	1
CKD stage 5 <sup>f</sup>	6	14	1
CKD on HD state	6	12	0
Noncirrhosis/cirrhosis	120/1	5/56	33/15
Fib-4 index (<3.25/ $\geq$ 3.25)	95/22	20/36	24/24
WFA(+)-M2BP (COI) <sup>a</sup>	1.29 (0.15-8.20)	3.53 (0.50-15.70)	2.59 (0.45-12.32)
AFP (ng/mL) <sup>a</sup>	3.4 (0.9-81.3)	6.1 (1.1-255.9)	3.6 (1.2-33.5)
HCV RNA (log IU/mL) <sup>a</sup>	6.3 (2.1-7.3)	6.1 (3.5-7.6)	6.5 (5.0-7.4)
HCV genotype (1/2)	75/46	32/29	35/13
NS5A L31 RAS (absent/present/unknown)	38/4/33	15/2/15	5/29/1
NS5A Y93 RAS (absent/present/unknown)	32/10/33	15/3/14	3/31/1
History of prior interferon-free DAA treatment (absent/present/unknown)	121/0/0	61/0/0	0/48/0

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; COI, cutoff index; DAAs, direct-acting antiviral agents; eGFR, estimated glomerular filtration rate; Fib-4, Fibrosis-4; HCV, hepatitis C virus; HD, hemodialysis; RAS, resistance-associated substitution; WBC, white blood cell; WFA(+)-M2BP, Wisteria floribunda agglutinin-positive human Mac-2-binding protein.

<sup>a</sup>Median (range).

<sup>b</sup>eGFR level  $\geq$  90 mL/min/1.73 m<sup>2</sup>.

<sup>c</sup>90 mL/min/1.73 m<sup>2</sup> > eGFR level  $\geq$  60 mL/min/1.73 m<sup>2</sup>.

<sup>d</sup>60 mL/min/1.73 m<sup>2</sup> > eGFR level  $\geq$  30 mL/min/1.73 m<sup>2</sup>.

<sup>e</sup>30 mL/min/1.73 m<sup>2</sup> > eGFR level  $\geq$  15 mL/min/1.73 m<sup>2</sup>.

<sup>f</sup>eGFR level < 15 mL/min/1.73 m<sup>2</sup>.

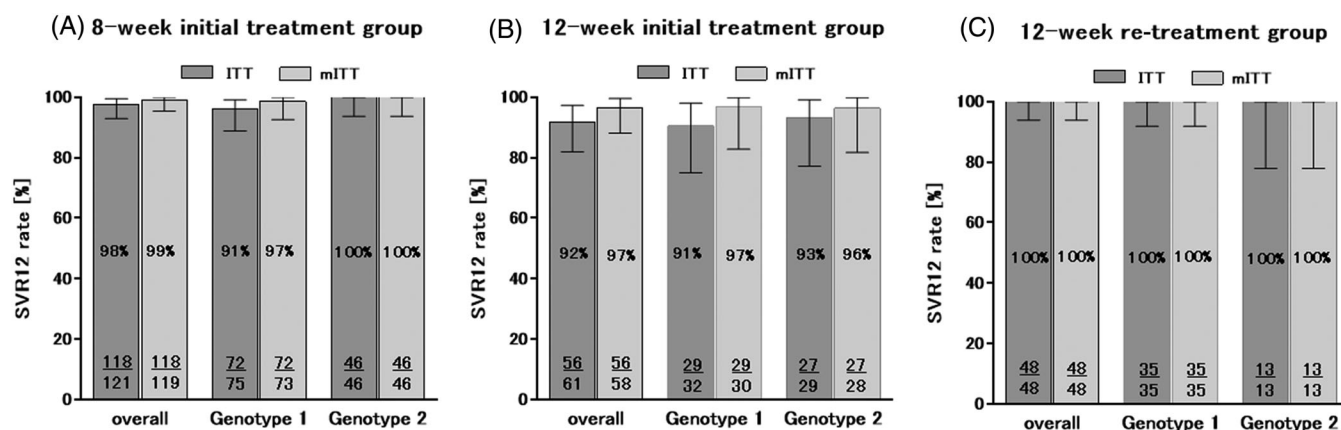
follow-up) (Figure 2A). In patients with GT1 and GT2 HCV infection, the SVR rates were 99% (72/73) and 100% (46/46), respectively. Among the patients receiving the 12-week treatment, the SVR rate was 97% (56/58; mITT analysis excluding three patients lost to follow-up) for DAA-naïve patients with LC and 100% (48/48; mITT analysis) for IFN-free DAA-experienced patients (Figure 2B,C). The SVR rates in DAA-experienced patients without and with LC were 100%.

In naïve patients with HCV genotype 1 infection for whom RAS were measured, the SVR rate was 100% regardless of whether it was Y93RAS or L31RAS in both the 8-week initial treatment group [Y93RAS(-) (31/31), Y93RAS(+) (10/10), L31RAS(-) (37/37), RAS(+)] (4/4) and 12-week initial treatment group [Y93RAS(-) (15/15), Y93RAS(+) (1/1), L31RAS(-) (14/14), RAS(+) (2/2)].

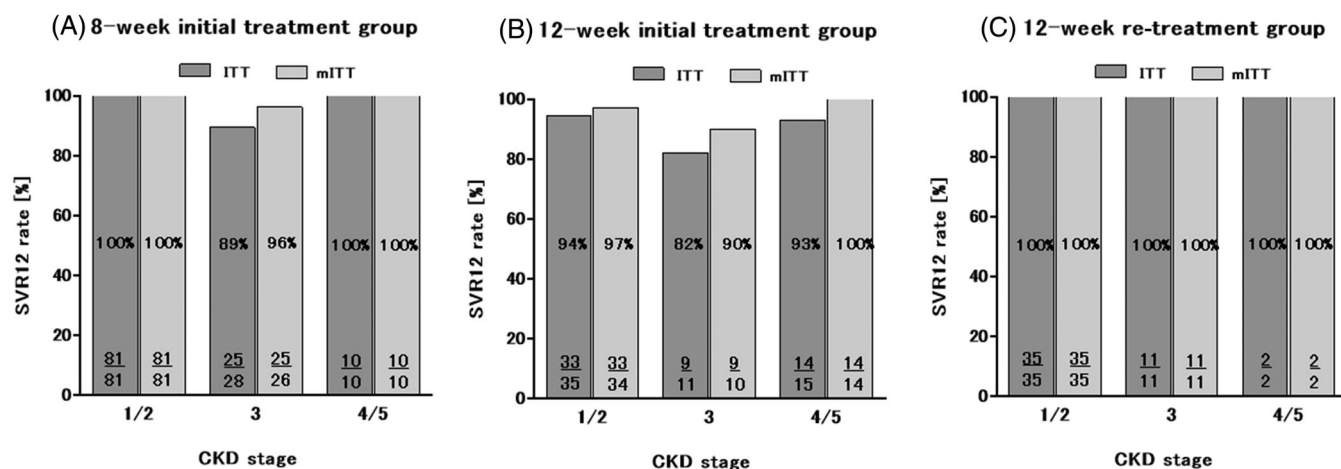
mITT analysis showed that, according to the CKD stage, SVR rates were 99% (149/150) for stage 1/2, 96% (45/47) for stage 3, and

100% (26/26) for stage 4/5. SVR rates for patients receiving 8-week initial treatment according to the CKD stage were 100% (81/81) for stage 1/2, 96% (25/26) for stage 3, and 100% (10/10) for stage 4/5 (Figure 3A), whereas SVR rates for patients receiving 12-week initial treatment according to CKD stage were 97% (33/34) for stage 1/2, 90% (9/10) for stage 3, and 100% (14/14) for stage 4/5 (Figure 3B). Moreover, SVR rates for patients receiving 12-week re-treatment according to CKD stage were 100% in all stages (Figure 3C). Therefore, the SVR rate was not influenced by the CKD stage. In particular, SVR was achieved in all 18 patients (six receiving 8-week initial treatment and 12 receiving 12-week initial treatment) who underwent hemodialysis. One patient treated for 8 weeks and nine patients treated for 12 weeks had GT2 HCV infection.

The baseline characteristics of patients who failed the GLE/PIB treatment are shown in Table 2. The baseline patient characteristics



**FIGURE 2** SVR12 rate following GLE/PIB treatment. Percentages of patients in whom hepatitis C virus RNA was undetectable at 12 weeks after treatment. (A) 8-week initial treatment group, (B) 12-week initial treatment group, (C) 12-week re-treatment group. SVR12, sustained virologic response at 12 weeks after end of treatment; ITT, intention-to-treat; mITT, modified intention-to-treat



**FIGURE 3** SVR12 rates according to CKD stage. (A) 8-week initial treatment group, (B) 12-week initial treatment group, (C) 12-week re-treatment group. SVR12, sustained virologic response at 12 weeks after end of treatment; CKD, chronic kidney disease; ITT, intention-to-treat; mITT, modified intention-to-treat

of all groups to determine whether any features were associated with the achievement of SVR. Table 3 illustrates the SVR rates for the mITT analysis according to various features. Although the cases of

treatment cessation were few, results revealed that discontinuation of treatment resulted in a significantly lower SVR compared with other factors (60.0% [3/5]; 95% CI, 14.7-94.7;  $P = .00118$ ).

**TABLE 2** Baseline characteristics of patients who failed GLE/PIB treatment

Case	Age (years)	Sex	Liver status	Fib-4 index	GT	HCV RNA (logIU/mL)	NS5A L31 RAS	NS5A Y93 RAS	CKD stage	Treatment discontinuation
1	73	Female	CH	3.11	1	5.9	Not tested	Not tested	3	Yes
2	81	Female	LC	3.47	2	6.5	-	-	3	Yes
3	58	Male	LC	12.70	1	6.4	Not tested	Not tested	1	No

Abbreviations: CH, chronic hepatitis; CKD, chronic kidney disease; Fib-4 index, fibrosis-4 index; GT, genotype; HCV, hepatitis C virus; LC, liver cirrhosis; NS, nonstructural protein; RAS, resistance-associated substitutions.

	n/N	SVR12 (%)	95% CI	P value
Sex				
Male	103/104	99.0	94.8-100	1.000
Female	119/121	98.3	94.2-99.8	
Age				
<70 years	117/118	99.2	95.4-100	.606
≥70 years	105/107	98.1	93.4-99.8	
Fibrosis				
CH	154/155	99.4	96.5-100	.241
LC	68/70	97.0	90.1-99.7	
Fib-4 index				
<3.25	135/136	99.3	96.0-100	.292
≥3.25	74/76	97.4	90.8-99.7	
Treatment duration				
8 weeks	118/119	99.2	95.4-100	.603
12 weeks	104/106	98.1	93.4-99.8	
Previous DAA treatment				
No (initial treatment)	174/177	99.4	96.9-100	1.000
Yes (re-treatment)	48/48	100	93.9-100	
Tx discontinuation				
No	219/220	99.5	97.5-100	.00118
Yes	3/5	60.0	14.7-94.7	
HCV genotype				
GT 1	136/138	98.6	94.9-99.8	1.000
GT 2	86/87	98.9	93.8-100	
HCV RNA				
<6 Log IU/mL	71/72	98.6	92.5-100	1.000
≥6 Log IU/mL	145/147	98.6	95.2-99.8	
CKD stage				
1/2	139/140	99.1	96.1-100	.163
3	45/47	95.7	85.5-99.5	
4/5	26/26	100	89.1-100	

**TABLE 3** SVR rate according to the initial patient characteristics

Abbreviations: CH, chronic hepatitis; CI, confidence interval; CKD, chronic kidney disease; DAA, direct-acting antiviral agent; GT, genotype; HCV, hepatitis C virus; LC, liver cirrhosis; SVR12, sustained virologic response at 12 weeks after end of treatment; Tx, treatment.



### 3.3 | Biochemistry abnormalities

Changes in mean Fib-4 index, AST, ALT, and platelet counts are shown in Table 4. The Fib-4 index, AST and ALT levels showed statistically significant improvement from baseline to 12 weeks post-treatment in all three groups ( $P < .05$ ). Conversely, platelet counts indicated no statistically significant improvement from baseline to 12 weeks post-treatment in the 8-week initial treatment group and 12-week re-treatment group, but did significantly improve in the 12-week initial treatment group ( $P < .05$ ). Change in mean eGFR according to CKD stage are shown in Figure 4. No significant changes

were seen in eGFR according to CKD stage from baseline to end of treatment (post-treatment week 12) in any group.

### 3.4 | Safety

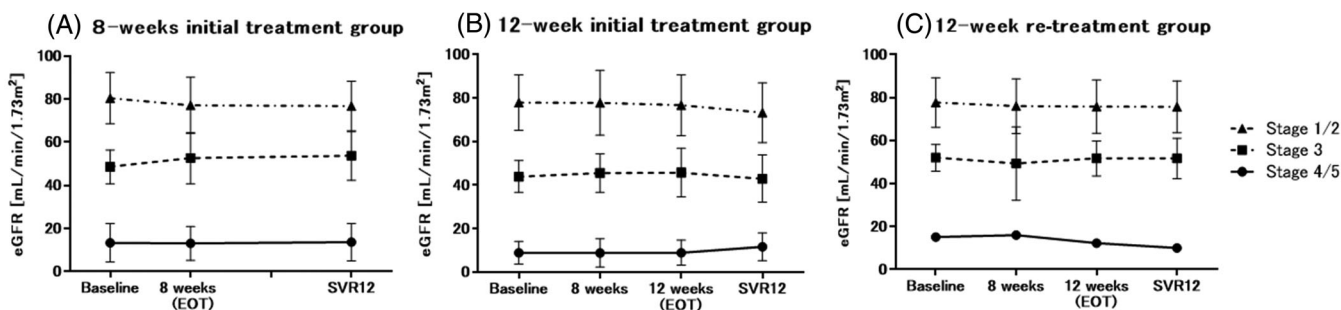
Seven patients discontinued treatment, and two patients died during treatment (chronic renal failure and cerebral hemorrhage) but did not demonstrate a causal relationship with the drug. Treatment was discontinued in five patients because of treatment-associated AEs. One patient in the 8-week initial treatment group and one in the 12-week initial treatment group discontinued treatment because of pruritus. Thereafter, they did not achieve SVR. One patient stopped because of

**TABLE 4** Changes in mean fibrosis-4 index, AST, ALT, and platelet count

A. 8-week initial treatment group				
	Baseline	8 weeks (EOT)	-	SVR 12
Fib-4 index	2.40 ± 1.65	1.94 ± 1.02*	-	2.08 ± 1.24*
AST (IU/L)	49 ± 67	20 ± 6*	-	23 ± 12*
ALT (IU/L)	55 ± 95	15 ± 8*	-	16 ± 12*
Platelets ( $\times 10^4/\text{mm}^3$ )	20.7 ± 6.7	20.7 ± 6.6	-	20.7 ± 6.7
B. 12-week initial treatment group				
	Baseline	8 weeks	12 weeks (EOT)	SVR 12
Fib-4 index	4.44 ± 2.93	2.92 ± 1.50*	3.00 ± 1.61*	2.88 ± 1.35*
AST (IU/L)	58 ± 44	23 ± 11*	24 ± 11*	25 ± 10*
ALT (IU/L)	57 ± 51	17 ± 11*	20 ± 18*	20 ± 11*
Platelets ( $\times 10^4/\text{mm}^3$ )	13.9 ± 5.0	15.0 ± 5.7*	15.2 ± 5.4*	15.8 ± 5.2*
C. 12-week re-treatment group				
	Baseline	8 weeks	12 weeks (EOT)	SVR 12
Fib-4 index	3.77 ± 2.43	3.19 ± 1.92*	2.96 ± 1.68*	3.02 ± 1.76*
AST (IU/L)	41 ± 28	25 ± 13*	24 ± 10*	25 ± 9*
ALT (IU/L)	42 ± 41	18 ± 13*	18 ± 11*	20 ± 13*
Platelets ( $\times 10^4/\text{mm}^3$ )	15.3 ± 6.6	16.2 ± 7.4	16.4 ± 7.2	16.7 ± 7.3

Note: Data are expressed as the average ± SD, \* $P < .05$  in the Friedman test when compared with the baseline level.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of treatment; Fib-4 index, fibrosis-4 index; SVR 12, sustained virologic response at 12 weeks after end of treatment.



**FIGURE 4** Changes in eGFR according to CKD stage from baseline to 12 weeks post-treatment. (A) 8-week initial treatment group, (B) 12-week initial treatment group, (C) 12-week re-treatment group. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; EOT, end of treatment; SVR, sustained virologic response

**TABLE 5** Adverse events

	Total (n = 230)
Treatment discontinued because of AEs	5 (2.2%)
Serious treatment-related AEs (≥grade 3)	
Pruritus	2 (0.9%)
Increased AST/ALT	2 (0.9%)
Increased total bilirubin	7 (3.0%)
Decreased platelet count	1 (0.4%)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

elevated total bilirubin levels (6.8 g/dL), one patient ceased because of elevated ALT levels (116 U/L), and one patient withdrew because of a decline in platelet count ( $5.0 \times 10^4/\text{mm}^3$ ) 2 weeks after starting the treatment; however, these three patients achieved SVR.

Serious AEs (≥ grade 3) occurred in 5.2% (12/230) of patients, ALT elevation occurred in two patients, hyperbilirubinemia occurred in seven patients, a decline in platelet count occurred in one patient, and pruritus occurred in two patients (Table 5).

## 4 | DISCUSSION

Our study of patients treated with GLE/PIB in a real-world clinical setting for 8 to 12 weeks found excellent SVR rates with a small number of AEs. The total SVR rate in patients without cirrhosis and with GT1/2 HCV infection was 99% (mITT) in the 8-week initial GLE/PIB treatment group. SVR rates of GLE/PIB treatment among IFN-free DAA-naive patients with GT1/2 HCV infection were extremely high. Also, in a clinical trial comparing 8 weeks of GLE/PIB treatment with 12 weeks of GLE/PIB treatment in naive patients with CH and HCV GT2 infection, the treatment efficacy and safety were equal.<sup>21</sup> Considering these results, it is beneficial for patients without cirrhosis to obtain a high SVR rate following short-term GLE/PIB treatment. Therefore, distinguishing between noncirrhosis and cirrhosis using methods such as liver biopsy, fibro index score, aminotransferase to platelet ratio index, Fib-4 index, discriminate score, serum markers of fibrosis, and transient elastography is important.

Results collected after 12 weeks of treatment for compensated cirrhosis receiving initial treatment with GLE/PIB were excellent, and the treatment efficacy and safety were as good as those from the clinical trials.<sup>4,5,22</sup> However, discontinuation of treatment yielded a low SVR12 in the 8- and 12-week initial treatment groups.

SVR rates of patients receiving re-treatment for previous DAA failure were also excellent. SVR rates of experienced ASV + DCV, SOF/LDV, OMV/PTV/r, EBR + GRZ, and ASV/DCV/BEC patients with GT1 HCV infection were all 100%. A Japanese clinical trial (CERATAIN-1) revealed that two patients with GT1b HCV infection and GLE/PIB treatment failure harbored a P32 deletion in the NS5A region at baseline, which greatly reduces susceptibility to PIB.<sup>23</sup>

However, in this study, a P32 deletion in NS5A was not determined among the DAA-experienced GT1 HCV patients. Moreover, a lower SVR rate has been reported in patients with an A92 substitution in NS5A at baseline compared with those without this substitution as well as a lower SVR rate in those with several RASs at Q24, L28, R30, or Q54 in NS5A than in those without these RASs among the GLE/PIB re-treatment groups.<sup>24</sup> In this study, 9.4% of patients with previous DAA failure had A92 RAS in NS5A, and those patients achieved SVR. SVR may be influenced by not only A92 RAS but also multiple substitutions including RASs at Q24, L28, R30, Q54, and A92.<sup>25</sup> In addition, compared with DAA-naive patients, the prevalence of double mutations in NS5A Y93 and L31 was higher in those with a previous DAA failure, but SVR rates in patients with double mutations treated with GLE/PIB were high. Moreover, the SVR rate in experienced SOF + RBV GT2 HCV patients was 100%. Therefore, 12-week treatment with GLE/PIB shows high efficacy in patients with a previous SOF + RBV treatment failure.

The efficacy and safety of several IFN-free DAA combination regimens for GT1, such as DCV + ASV, OMV/PTV/r, and EBR + GRZ, in patients with CKD, including those undergoing hemodialysis, have been demonstrated.<sup>26-28</sup> In this study, 18 patients with GT1/2 HCV underwent dialysis. Among these, 12 cirrhotic DAA-naive patients received the 12-week treatment, and six DAA-naive patients without LC received the 8-week treatment. All patients achieved SVR, and AEs were not observed. Therefore, GLE/PIB therapy is applicable for HCV-GT1/2-infected patients, including those without cirrhosis and with compensated cirrhosis receiving hemodialysis. Furthermore, GLE/PIB treatment is expected to show high SVR rates in HCV-infected patients without cirrhosis receiving hemodialysis after treatment for 8 weeks.

The GLE/PIB treatment was well tolerated in all three groups. Serious treatment-related AEs (Grade ≥ 3) occurred in 12 patients (5.2%), and five of them discontinued the treatment. The observed ALT elevation, hyperbilirubinemia, decline in platelet count, and pruritus improved with cessation of treatment.

Fib-4 index, a noninvasive measurement, is used as a marker of liver fibrosis in HCV-infected patients.<sup>11</sup> In our study, Fib-4 index was significantly reduced at 12 weeks after the end of treatment compared with baseline. Supposedly, this short-term change after DAA treatment can reflect reduced inflammatory activity rather than improvement of fibrosis, because a remarkable decrease in aminotransferase was observed rather than an increase in platelet count. However, it is necessary to carefully monitor the Fib-4 index to provide prognostic information, such as long-term improvement in fibrosis and liver-related event.

This real-world study has some limitations. First, this study was conducted at multiple centers. Consequently, the methods of data collection and assessment of cirrhosis might vary among centers. Second, the NS5A RAS data from the GT1 HCV patients were insufficient and only available for approximately 69% of these patients. However, data from DAA-experienced GT1 HCV patients were almost complete. Third, in this study, minor AEs may have been missed as the physicians might not have recorded them.



In conclusion, primary treatment and re-treatment with GLE/PIB for patients with chronic hepatitis or compensated hepatic cirrhosis and GT1/2 HCV infection in a real-world clinical setting is effective and safe. Moreover, the SVR rate was not influenced by CKD stage.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest directly relevant to the content of this article.

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All authors have read and approved the final version of the manuscript.

Akio Miyasaka had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

## TRANSPARENCY STATEMENT

Akio Miyasaka affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

## INFORMED CONSENT

Written informed consent was obtained from each patient before treatment.

## DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

## ETHICS STATEMENT

The study was approved by the Ethics Committee of Iwate Medical University (approval number H29-170) and the respective committees at each treatment site.

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