



# Efficacy and Safety of Glecaprevir/Pibrentasvir in Korean Patients with Chronic Hepatitis C: A Pooled Analysis of Five Phase II/III Trials

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**Background/Aims:** Glecaprevir/pibrentasvir (G/P) is the first pan-genotypic direct-acting antiviral combination therapy approved in Korea. An integrated analysis of five phase II and III trials was conducted to evaluate the efficacy and safety of G/P in Korean patients with chronic hepatitis C virus (HCV) infection.

**Methods:** The study analyzed pooled data on Korean patients with HCV infection enrolled in the ENDURANCE 1 and 2, SURVEYOR II part 4 and VOYAGE I and II trials, which evaluated the efficacy and safety of 8 or 12 weeks of G/P treatment. The patients were either treatment-naïve or had received sofosbuvir or interferon-based treatment. Efficacy was evaluated by assessing the rate of sustained virologic response at 12 weeks posttreatment (SVR12). Safety was evaluated by monitoring adverse events (AEs) and laboratory assessments.

**Results:** The analysis included 265 patients; 179 (67.5%) were HCV treatment-naïve, and most patients were either subgenotype 1B (48.7%) or 2A (44.5%). In the intention-to-treat population, 262 patients (98.9%) achieved SVR12. Three patients did not achieve SVR12: one had virologic failure and two had non-virologic failures. Most AEs were grade 1/2; eight patients (3.0%) experienced at least one grade  $\geq 3$  AE. No serious AEs related to G/P treatment were reported, and grade  $\geq 3$  hepatic laboratory abnormalities were rare (0.8%).

**Conclusions:** G/P therapy was highly efficacious and well tolerated in Korean patients with HCV infection, with most patients achieving SVR12. The safety profile was comparable to that observed in a pooled analysis of a global pan-genotypic population of patients with HCV infection who received G/P. (*Gut Liver* 2021;15:895-903)

**Key Words:** Glecaprevir and pibrentasvir; Pan-genotypic antivirals; Hepatitis C virus; Korea

## INTRODUCTION

Hepatitis C virus (HCV) infection affects up to 71 million individuals worldwide and causes substantial morbidity and mortality.<sup>1,2</sup> Patients who do not receive antiviral

treatment are at high risk of serious long-term hepatic complications which include cirrhosis, decompensation, hepatocellular cancer and death.<sup>1,3-5</sup> Among Korean patients with advanced liver diseases including liver cirrhosis and hepatocellular carcinoma, 11% to 17% present with

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HCV infection.<sup>6</sup> The estimated seroprevalence of anti-HCV antibodies in Korean adults is 0.8% (about 300,000 individuals), which increases steeply with age to 2.3% in individuals aged  $\geq 70$  years.<sup>7,8</sup> Among patients with chronic HCV infection in South Korea, virus genotypes (GTs) 1 and 2 collectively account for the vast majority (99%) and the most common subtypes are GT1B (45% to 59%) and GT2A (26% to 51%).<sup>6,9</sup>

With the advances in antiviral treatment, a cure to the HCV infection is achievable, which is defined as a sustained reduction in HCV RNA levels below the lower limit of quantification (LLOQ; 15 IU/mL) at 12 or 24 weeks after completion of treatment (referred to as sustained virologic response [SVR]; SVR12 or SVR24, respectively).<sup>2</sup> Patients who achieve SVR have a very low risk of late relapse, indicating long-term control of the infection.<sup>2,10</sup> Until recently, the choice of treatment was based on previous treatment status, presence of cirrhosis and comorbidities, and genotyping and resistance profiles.<sup>11,12</sup> However, the introduction of pan-genotypic combination direct-acting antiviral (DAA) regimens, using drugs with different modes of action, has simplified the care pathway for patients with HCV infection.<sup>3,11,13</sup>

Glecaprevir/pibrentasvir (G/P), a fixed-dose combination of two DAAs, is the first pan-genotypic, once-daily treatment regimen approved in South Korea for patients with chronic HCV infection regardless of genotypes.<sup>14,15</sup> The international and Korean guidelines recommend the use of G/P therapy for both treatment-naïve and treatment-experienced patients.<sup>2,11,12</sup>

G/P therapy is also approved for a shortened 8-week treatment regimen. An integrated analysis of nine phase II and III global clinical trials, including treatment-naïve and treatment-experienced patients with chronic HCV GT1-6 infection without cirrhosis ( $n=2,041$ ), demonstrated high rates of SVR with the G/P regimen regardless of 8-week (98%) or 12-week (99%) therapy.<sup>16</sup> In another study enrolling 343 treatment-naïve patients with chronic HCV GT1-6 infection and compensated cirrhosis, 97.7% of patients achieved SVR12 with 8-week G/P therapy.<sup>17</sup>

Several regional and country-level differences exist in the disease characteristics of patients with HCV infection. The screening practices, care pathways and treatment access also differ across countries.<sup>18</sup> Hence, local data on clinical characteristics and treatment efficacy and tolerability is highly desirable, particularly in Asian countries that are generally under-represented in global clinical trials. A pooled analysis of data from six phase II and III clinical trials demonstrated high SVR12 rates with 8-week G/P therapy in Japanese and international patients with non-cirrhotic chronic HCV GT1-2 infection ( $n=899$ ).<sup>19</sup>

However, there are currently no data on the efficacy and safety of the G/P regimen in Korean subjects with HCV infection. Five phase II and III clinical trials of G/P therapy, including three global trials (ENDURANCE 1<sup>20</sup> and 2<sup>21</sup> and SURVEYOR II [part 4]<sup>21</sup>) and two Asian clinical trials (VOYAGE I<sup>22</sup> and II<sup>22</sup>), enrolled patients from South Korea. Therefore, using pooled data from these five clinical trials, this analysis aimed to evaluate the efficacy and safety of G/P in Korean patients with GT1 or GT2 HCV infection with or without compensated cirrhosis.

## MATERIALS AND METHODS

### 1. Study design and population

An integrated analysis was conducted using data from Korean patients with HCV GT1 or GT2 infection enrolled in five phase II and III trials evaluating the efficacy and safety of G/P therapy. In all five trials, patients received oral G/P therapy (300 mg/120 mg), administered as three 100/40 mg tablets once daily with food, for either 8 or 12 weeks. The detailed study methodology and primary outcomes of the following registrational clinical trials have been published: ENDURANCE 1 (NCT02604017),<sup>20</sup> ENDURANCE 2 (NCT02640482),<sup>21</sup> SURVEYOR II part 4 (NCT02243293),<sup>21</sup> VOYAGE I (NCT03222583)<sup>22</sup> and VOYAGE II (NCT03235349)<sup>22</sup> (Supplementary Table 1). All the trials required a written informed consent from enrolled patients and were designed and conducted in accordance with the ethical principles laid down in the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulations and were approved by independent ethics or institutional review committees.

A comparison of the inclusion and exclusion criteria across studies is described in Supplementary Table 2. For all the five trials, eligible patients were adults aged  $\geq 18$  years with chronic HCV GT1 or GT2 infection (confirmed by HCV RNA  $\geq 1,000$  IU/mL at screening; chronic HCV infection was confirmed by anti-HCV seropositivity or plasma HCV RNA  $\geq 6$  months prior to screening or liver biopsy). In addition, eligible patients were non-cirrhotic (except for VOYAGE II trial), treatment naïve or previously treated for HCV (interferon $\pm$ ribavirin or sofosbuvir+ribavirin $\pm$ interferon). Patients with prior treatment experience were required to have completed their previous HCV treatment at least 8 weeks prior to screening. The absence of cirrhosis was documented by screening FibroTest<sup>®</sup>  $\leq 0.48$ , and aspartate aminotransferase platelet ratio index  $< 1$ , or FibroScan<sup>®</sup>  $< 12.5$  kPa, or liver biopsy at screening. Patients with documented compensated cirrhosis were included only in the VOYAGE II trial. ENDURANCE 1, VOYAGE

I and II allowed patients with HCV/human immunodeficiency virus (HIV) coinfection, defined as positive test result for HIV antibody at screening (HIV-1 RNA <1,000 copies/mL for treatment naïve or HIV-1 RNA <LLOQ for those receiving antiretroviral treatment regimen)—however none of the patients enrolled in the VOYAGE trials had HIV coinfection. Hepatitis B coinfection was exclusionary for all clinical trials.

In the ENDURANCE-1 trial, patients were randomized to receive either 8-week or 12-week treatment with G/P, whereas in the SURVEYOR II part 4 and VOYAGE I trials, patients received G/P treatment for 8 weeks. In the ENDURANCE-2 and VOYAGE II (which included patients with compensated cirrhosis), patients with GT1 or GT2 HCV infection received 12-week G/P therapy.

## 2. Assessments

For the assessment of baseline viral load and SVR12, plasma HCV RNA was quantified for each sample using COBAS AmpliPrep/TaqMan real-time reverse-transcriptase polymerase chain reaction assay (version 2.0; Roche Molecular Diagnostics, Rotkreuz, Switzerland), which has a LLOQ of 15 IU/mL. HCV genotyping was done at screening using LiPA assay (Versant HCV Genotype 2.0 Assay; Siemens Healthcare Diagnostics, Erlangen, Germany) or a Sanger sequencing assay (if the LiPA assay failed) and was confirmed by phylogenetic analysis. For patients who experienced virologic failure, HCV resistance analysis to check for NS3 and NS5A polymorphisms was done at baseline and at the time of virologic failure using next-generation sequencing (detection limit: 2%).

Adverse events (AEs) and abnormalities in physical examinations and laboratory test assessments were monitored in all five studies; the causal relationship with the study treatment (G/P) was assessed by the study investigator.

## 3. Endpoints

The primary outcome of this analysis was the efficacy of G/P therapy in Korean patients with HCV infection as assessed by SVR12, which is defined as achieving an HCV RNA level below the LLOQ (15 IU/mL) 12 weeks after the last dose of G/P. Safety evaluations included treatment-emergent AEs (occurring from day 1 of dosing until 30 days after the last dose of G/P) and laboratory abnormalities occurring during treatment. Secondary outcomes included incidence of on-treatment virologic failure and posttreatment relapse. On-treatment virologic failure was defined as a confirmed increase in HCV RNA of: >1 log<sub>10</sub> IU/mL above nadir or ≥100 IU/mL after achieving HCV RNA level <LLOQ during treatment; or HCV RNA

≥LLOQ at the end of treatment with ≥6 weeks of treatment. Posttreatment relapse was assessed in patients who completed treatment as planned and achieved an HCV RNA <LLOQ at the end of treatment, and was defined as a confirmed HCV RNA ≥LLOQ between the last dose of G/P and 12 weeks thereafter. A summary of AEs and laboratory abnormalities from a previously reported pooled analysis of a global population of patients with non-cirrhotic pan-genotypic HCV infection treated with G/P (n=2,041) is also presented.<sup>16</sup>

## 4. Statistical analysis methods

Efficacy and safety outcomes were analyzed for the intention-to-treat population, defined as patients receiving ≥1 dose of G/P (300/120 mg). The SVR12 rates and two-sided 95% confidence intervals (CI; using Wilson score method) were calculated for the overall population and for subgroups based on genotype (GT1 or GT2), subgenotype (1A, 1B, 2, 2A, 2A/2C, or 2B), cirrhosis status (no cirrhosis or compensated cirrhosis), and treatment duration (8 weeks and 12 weeks). Secondary efficacy and safety endpoints were summarized with numbers and percentages of patients.

# RESULTS

## 1. Baseline patient demographics and disease characteristics

This pooled analysis of data from five phase II or III clinical trials included 265 South Korean patients with chronic HCV infection who received 8-week or 12-week G/P treatment. Of these, 133 (50.2%) were GT1-infected and 132 (49.8%) were GT2-infected, and the most common subtypes were 1B (48.7%, 129/265) and 2A (44.5%, 118/265). The baseline patient demographics and disease characteristics are described in Table 1. The median age was 60 years (range, 21 to 87 years) and 46.4% of the study population were male; the median HCV RNA level at baseline was 6.3 log<sub>10</sub> IU/mL (range, 2.5 to 7.7 log<sub>10</sub> IU/mL). Most patients were HCV treatment naïve (67.5%, 179/265), without cirrhosis (86.0%, 228/265), and not using injection drugs (94.3%, 250/265); more than half of the study population received 8-week G/P treatment (57.7%, 153/265). The analysis population included 101 (38.1%) patients with cardiovascular disease, 92 (34.7%) patients with hypertension, 41 (15.5%) patients with diabetes, and 35 (13.2%) patients with HIV coinfection.

## 2. Efficacy outcomes

Overall, 98.9% of patients achieved SVR12 (262/265;

**Table 1.** Demographics and Disease Characteristics at Baseline in the Intention-to-Treat Population

Characteristic	GT1 (n=133)	GT2 (n=132)	Overall (n=265)
Male sex	63 (47.4)	60 (45.5)	123 (46.4)
Age, yr	59 [21–85]	62 [25–87]	60 [21–87]
BMI, kg/m <sup>2</sup>	23.8 (17.9–36.7)	24.3 (17.9–33.9)	24.2 (17.9–36.7)
HCV treatment experience			
Naive	93 (69.9)	86 (65.2)	179 (67.5)
IFN based	39 (29.3)	42 (31.8)	81 (30.6)
SOF based	1 (0.8)	4 (3.0)	5 (1.9)
Enrolled study			
M13-590 (ENDURANCE 1)	35 (26.3)	0	35 (13.2)
M15-464 (ENDURANCE 2)*	1 (0.8)	63 (47.7)	64 (24.2)
M14-868 (SURVEYOR II part 4)	0	5 (3.8)	5 (1.9)
M15-592 (VOYAGE I)*	74 (55.6)	50 (37.9)	124 (46.8)
M15-593 (VOYAGE II)	23 (17.3)	14 (10.6)	37 (14.0)
HCV subgenotype			
1A	4 (3.0)	0	4 (1.5)
1B	129 (97.0)	0	129 (48.7)
2	0	3 (2.3)	3 (1.1)
2A	0	118 (89.4)	118 (44.5)
2A/2C	0	3 (2.3)	3 (1.1)
2B	0	8 (6.1)	8 (3.0)
Cirrhosis status			
No cirrhosis	110 (82.7)	118 (89.4)	228 (86.0)
Compensated cirrhosis	23 (17.3)	14 (10.6)	37 (14.0)
Baseline HCV RNA level, IU/mL			
<1.0×10 <sup>6</sup>	123 (92.5)	118 (89.4)	241 (90.9)
≥1.0×10 <sup>6</sup>	10 (7.5)	14 (10.6)	24 (9.1)
Baseline HCV RNA level, log <sub>10</sub> IU/mL	6.4 [2.5–7.7]	6.2 [2.5–7.3]	6.3 [2.5–7.7]
IL28B			
CC	99 (74.4)	105 (79.5)	204 (77.0)
Non-CC	34 (25.6)	27 (20.5)	61 (23.0)
History of disorders			
Diabetes	23 (17.3)	18 (13.6)	41 (15.5)
Depression or bipolar disorder	6 (4.5)	7 (5.3)	13 (4.9)
Bleeding disorder	1 (0.8)	1 (0.8)	2 (0.8)
Hypertension	48 (36.1)	44 (33.3)	92 (34.7)
Cardiovascular disease	51 (38.3)	50 (37.9)	101 (38.1)
HIV coinfection	35 (26.3)	0	35 (13.2)
G/P treatment duration			
8 Weeks	98 (73.7)	55 (41.7)	153 (57.7)
12 Weeks	35 (26.3)	77 (58.3)	112 (42.3)
History of injection drug use			
Yes	7 (5.3)	8 (6.1)	15 (5.7)
No	126 (94.7)	124 (93.9)	250 (94.3)

Data are presented as number [%] or median [range].

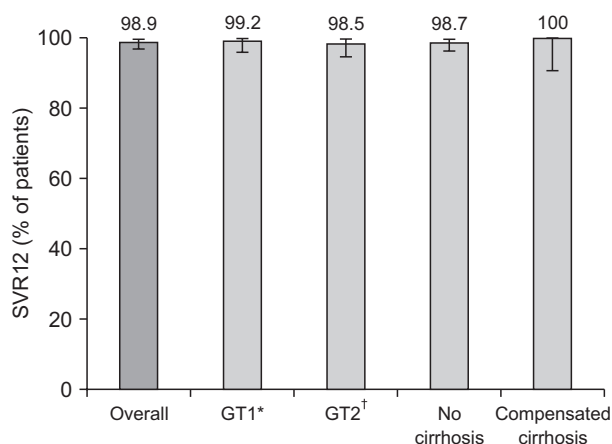
GT, genotype; BMI, body mass index; HCV, hepatitis C virus; IFN, interferon; SOF, sofosbuvir; IL28B, interleukin 28B; HIV, human immunodeficiency virus; G/P, glecaprevir/pibrentasvir.

\*Including patients who received placebo during the double-blind treatment period followed by G/P during the open-label treatment period.

95% CI, 96.7 to 99.6) (Fig. 1). The proportions of patients with GT1 and GT2 achieving SVR12 were 99.2% (132/133; 95% CI, 95.9 to 99.9), and 98.5% (130/132; 95% CI, 94.6 to 99.6), respectively. All patients with compensated cirrhosis (included in VOYAGE II trial and received 12-week G/P therapy) achieved SVR12 (100%, 37/37); among patients without cirrhosis, 98.7% (225/228; 95% CI, 96.2 to 99.6)

achieved SVR12 (Table 2). All patients with subgenotypes 1A, 2, 2A/2C and 2B (Fig. 2A), and with a 12-week treatment duration achieved SVR12, whereas, 98.0% (150/153; 95% CI, 94.4 to 99.3) of subjects with 8-week treatment duration achieved SVR12 (Fig. 2B).

A total of three patients did not achieve SVR12, including one virologic failure and two non-virologic failures



**Fig. 1.** Number and percentage of Korean subjects with SVR12 in the intention-to-treat population. Rates of SVR12 by genotype, cirrhosis status and treatment duration (8 or 12 weeks). Error bars represent 95% confidence intervals.

GT, genotype; SVR12, sustained virologic response at 12 weeks posttreatment. \*4 Patients were GT1A and 129 patients were GT1B; †118 Patients were GT2A, 8 were GT2B, 3 were GT2A/2C, and 3 had unknown subtype.

(Table 3). Two patients with GT2A infection did not achieve SVR12; one patient experienced virologic failure due to posttreatment relapse at 12 weeks, and another patient was missing HCV RNA data in the SVR12 analysis window. One patient with GT1B infection experienced hyperbilirubinemia leading to premature discontinuation of G/P treatment, which was assessed as not related to the treatment by the study investigators. All three patients who did not achieve SVR12 were non-cirrhotic, had no HIV coinfection, and received 8-week G/P therapy.

We also analyzed the long-term follow-up data (as of date/month/year) available from the included trials for the incidence of relapse or reinfections. None of the Korean patients included in the trials experience relapse or reinfections. Overall, there was only one case of reinfection in SURVEYOR II part 4 study in a non-Korean participant.

### 3. Safety outcomes

Overall, 119 patients (44.9%) experienced an AE, with

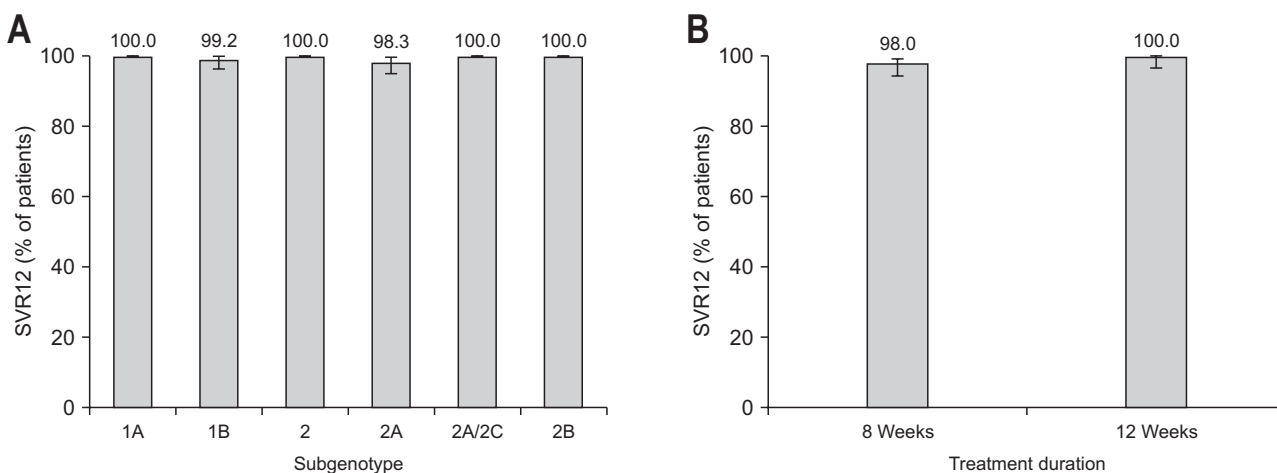
**Table 2.** Primary (SVR12) and Secondary (on-Treatment Virologic Failure and Posttreatment Relapse) Outcomes in the Intention-to-Treat Population

Outcome	No cirrhosis (n=228)			Compensated cirrhosis (VOYAGE II) (n=37)			Overall (n=265)
	All patients (n=228)	GT1 (n=110)	GT2 (n=118)	All patients (n=37)	GT1 (n=23)	GT2 (n=14)	
SVR12	225 (98.7)	109 (99.1)	116 (98.3)	37 (100)	23 (100)	14 (100)	262 (98.9)
Virologic failure							
On-treatment	0	0	0	0	0	0	0
Relapse*	1 (0.4)	0	1 (0.8)	0	0	0	1 (0.4)
Non-virologic failure							
Premature G/P discontinuation	1 (0.4)	1 (0.9)	0	0	0	0	1 (0.4)
Missing SVR12 data	1 (0.4)	0	1 (0.8)	0	0	0	1 (0.4)

Data are presented as number (%).

SVR12, sustained virologic response at 12 weeks posttreatment; GT, genotype; G/P, glecaprevir/pibrentasvir.

\*Among patients who completed treatment as planned and achieved an hepatitis C virus RNA level less than lower limit of quantification at final treatment visit and had posttreatment data (n=262).



**Fig. 2.** Number and percentage of Korean subjects with SVR12 by subgroup in the intention-to-treat population. Rates of SVR12 by (A) subgenotype (1A, 1B, 2, 2A, 2A/2C, and 2B) and (B) G/P treatment duration (8 weeks and 12 weeks). Error bars represent 95% confidence intervals.

SVR12, sustained virologic response at 12 weeks posttreatment; G/P, glecaprevir/pibrentasvir.



**Table 3.** Characteristics of Patients Experiencing Virologic and Non-Virologic Failure at Baseline and the Time of Failure from the VOYAGE I Clinical Trial

Characteristic	Patient 1	Patient 2	Patient 3
Reason for nonresponse	Relapse	Missing SVR12 data*	Premature G/P discontinuation
Sex/age, yr	Male/66	Female/74	Female/77
Treatment history	SOF-experienced	Naïve	Naïve
HCV subtype	2A	2A	1B
Compensated cirrhosis	No	No	No
Baseline HCV RNA level, IU/mL	8.6×10 <sup>6</sup>	21×10 <sup>6</sup>	13.1×10 <sup>6</sup>
IL28B subtype	CC	CC	CC
Treatment duration, wk	8	8	8
HIV coinfection	No	No	No
NS3 variants <sup>†</sup>			
Baseline	None	None	S122T, V170I
At failure	None	NA	NA
NS5A variants <sup>‡</sup>			
Baseline	L31M	T24A, L31M	Q54Y, Q62D, Y93H
At failure	L31M, C92S	NA	NA

HCV, hepatitis C virus; IL28B, interleukin 28B; HIV, human immunodeficiency virus; NS, nonstructural protein; SVR12, sustained virologic response at 12 weeks posttreatment; G/P, glecaprevir/pibrentasvir; SOF, sofosbuvir; NA, not available.

\*No detectable HCV RNA at last visit (posttreatment week 4, posttreatment day 27); did not return for SVR12 visit. Baseline polymorphisms and treatment-emergent substitutions at signature amino acid positions: <sup>†</sup>NS3 (36, 43, 54, 55, 56, 80, 107, 122, 155, 156, 158, 168, 170, 175) and <sup>‡</sup>NS5A (24, 28, 29, 30, 31, 32, 54, 58, 62, 92, 93) at 2% detection threshold.

**Table 4.** Overview of AEs and Laboratory Abnormalities in the Intention-to-Treat Population

AE	Korean population (n=265)	Pooled analysis of global phase II&III <sup>‡</sup> (n=2,041)
Any AE	119 (44.9)	1,343 (65.8)
Serious AE	7 (2.6)*	42 (2.1)
G/P-related AE	30 (11.3)	NA
G/P-related serious AE	0	1 (<0.1)
AE leading to G/P discontinuation	1 (0.4)	10 (0.5)
AEs in ≥10% of all patients	0 <sup>†</sup>	
Headache		344 (16.9)
Fatigue		281 (13.8)
Laboratory abnormalities		
ALT, grade ≥3 (>5×ULN)	1 (0.4)	1 (<0.1)
AST, grade ≥3 (>5×ULN)	0	7 (0.3)
Total bilirubin, grade ≥3 (>3×ULN)	1 (0.4)	7 (0.3)

Data are presented as number (%). This table is presenting “data in perspective” from two separate analyses.<sup>16</sup>

AE, adverse event; G/P, glecaprevir/pibrentasvir; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; NA, not available.

\*Bile duct stone (n=2), followed by urinary tract infection, radius fracture, ligament rupture, papillary thyroid cancer, and depression (n=1 each);

<sup>†</sup>Five most frequent AEs: upper respiratory tract infection (7.2%), fatigue (4.2%), diarrhea (3.0%), headache (2.6%), and pruritus (2.3%); <sup>‡</sup>This is not a comparison performed in the current study of Korean patients.

most being grade 1 or 2; eight patients (3.0%) reported at least one AE of grade 3 or higher severity (Table 4). AEs related to study treatment were reported in 30 patients (11.3%); none of these AEs were of grade 3 or higher severity. Serious AEs occurred in seven patients (2.6%) and were unlikely to be related to G/P therapy as assessed by the investigator: bile duct stone (0.8%), urinary tract infection (0.4%), radius fracture (0.4%), ligament rupture (0.4%), papillary thyroid cancer (0.4%), and depression (0.4%). The most commonly reported AEs were upper respiratory tract infection (7.2%), fatigue (4.2%), diarrhea (3.0%) headache (2.6%), and pruritus (2.3%). Only one

patient (0.4%) experienced an AE which led to treatment discontinuation (blood bilirubin increased); this AE was considered not related to G/P. The incidence of laboratory abnormalities of grade ≥3 severity was rare and none of the patients experienced grade ≥3 abnormalities in aspartate aminotransferase levels. Only two patients experienced grade 3 abnormalities in bilirubin and alanine aminotransferase, respectively.

The safety profile of G/P therapy in the Korean population was comparable with that observed in the integrated analysis of nine global phase II and III clinical trials in which patients with non-cirrhotic HCV GT1-6

infection were treated with G/P therapy (Table 4).<sup>16</sup> The incidence of AEs was slightly lower in the Korean population (44.9%, 119/265) than in the global pooled analysis (65.8%, 1,343/2,041). Serious AEs were reported in 2.6% (7/265), and 2.1% (42/2,041) of patients in the Korean and global pooled analyses, respectively. Serious AEs related to treatment occurred only in one patient in the global pooled analysis. AEs leading to drug discontinuation were reported in 0.4% (1/265), and 0.5% (10/2,041) of patients in the Korean and global pooled analyses, respectively. Among the Korean population, no AEs occurred in  $\geq 10\%$  of the subjects whereas in the global pooled analysis, the most common AEs were headache (16.9%), and fatigue (13.8%). Incidence of grade 3 or higher hepatic laboratory abnormalities was low in both Korean and global analyses (alanine aminotransferase 0.4% and  $<0.1\%$ ; aspartate aminotransferase 0% and 0.3%; and total bilirubin 0.4% and 0.3%, respectively).

## DISCUSSION

The findings from this pooled analysis demonstrated high efficacy of 8-week or 12-week G/P therapy in Korean patients with HCV infection, regardless of genotype, sub-genotype, presence of cirrhosis, and treatment duration. As in the global integrated analysis, G/P therapy was well tolerated in Korean patients with HCV infection, with low incidence of serious AEs or AEs leading to treatment discontinuation. Findings from this analysis of Korean patients also indicate that the study population and disease characteristics were representative of Korean patients with HCV; for instance, genotypes GT1B and GT2A were the most common subtypes, accounting for 93% of all patients.<sup>9</sup>

This is the first analysis evaluating the efficacy and safety of G/P in Korean HCV GT1- or GT2-infected patients with or without compensated cirrhosis. HCV genotypes appear to be a key predictive factor of liver disease severity and treatment response, with a distinct geographical distribution. Among the Korean population GT1 and GT2 account for 99% of HCV infection.<sup>6</sup> Previous studies investigating treatment response in Korean patients with HCV infection have shown high therapeutic efficacy in this population, even before the introduction of new pan-genotypic DAA agents. For example, results from a retrospective study evaluating the efficacy of pegylated interferon and ribavirin therapy in Korean patients with chronic HCV infection showed a superior therapeutic efficacy of this regimen in Koreans as compared with Caucasians, with overall SVR rates ranging between 63% and 81%.<sup>23</sup> Even though

the evidence on the efficacy of first-generation DAA in Korean patients with HCV infection is very limited,<sup>11</sup> data from a real-world study conducted in Korean patients demonstrated high SVR12 rates of 93% with the first-generation DAA treatment combination daclatasvir plus asunaprevir.<sup>24</sup> Another study comparing the efficacy of several DAA regimens in Asian patients with HCV showed SVR12 rates of 99.2%, and a significant improvement in quality of life with ledipasvir/sofosbuvir combination, the previous standard treatment for HCV GT1A infection.<sup>25</sup> Furthermore, a retrospective study evaluating sofosbuvir-based therapy showed an SVR12 rate as high as 100% in Korean patients with HCV infection.<sup>26</sup>

Results from the current study demonstrated high efficacy of an 8-week regimen of the pan-genotypic G/P therapy, which can have significant implications on the treatment burden and care pathway for patients with HCV. For example, the G/P regimen as first-line therapy would reduce the treatment duration without compromising efficacy. Shortened treatment duration also implies less on-treatment monitoring and physician visits, enabling cost-reductions in terms of reduced number of diagnostic procedures and clinic visits, thus improving the accessibility of treatment for a larger number of patients. In addition, as G/P is effective across all genotypes, use of this regimen may preclude baseline assessments, such as genotyping. The promotion of a simplified pretreatment evaluation in patients with HCV GT1 or GT2 infection receiving the G/P pan-genotypic regimen would help prevent liver disease complications and further HCV transmission; thereby contributing towards HCV elimination.<sup>27</sup> However, genotyping is still considered as an essential component of HCV diagnosis in South Korea.<sup>9</sup>

The incidence of AEs was slightly lower in the Korean population than in the global integrated analysis, 44.9% (119/265) versus 65.8% (1,343/2,041); however, statistical analysis of this difference was not performed.<sup>16</sup>

Limitations of this pooled analysis include small sample size ( $n=265$ ) as compared with the global integrated analysis ( $n=2,041$ ).<sup>16</sup> Additionally, when comparing the AE pattern with the global pooled population, no differentiation between genotypes was considered, and data from all genotypes (GT1-6) were included. Furthermore, the present analysis in the Korean population included a small number of high-risk patients such as previous injection drug users (IDU; 5.7%), those with sofosbuvir-based treatment-experience (1.9%), compensated cirrhosis (14.0%), HIV coinfection (13.2%), and non-CC interleukin 28B subtype (23.0%). Most of the population were not previous IDUs (94.3%, 250/265), which may have resulted in better treatment adherence and compliance than in the global

integrated analysis (61%, 1,243/2,041).<sup>16</sup> Nevertheless, a recent pooled analysis of seven phase III trials evaluating efficacy and safety of 8-week or 12-week G/P treatment demonstrated that treatment adherence and compliance in recent IDUs were high despite enduring concerns.<sup>28</sup> The current international guidelines (European Association for the Study of the Liver<sup>2</sup> and American Association for the Study of Liver Diseases<sup>12</sup>) emphasize that treatment response among IDUs is similar to that in non-IDU populations. Moreover, this high-risk group could benefit from a shorter treatment duration (8 weeks).<sup>28</sup> Interleukin 28B CC genotype, which is estimated to be present in around 90% of the Korean population, has been strongly associated with spontaneous viral clearance and favorable clinical outcomes.<sup>29</sup> However, it is still unclear whether Interleukin 28B genotype has a strong influence on the effects of DAAs, or which DAAs are best for people with non-CC genotypes.

In conclusion, results from this analysis indicate that treatment with G/P combination therapy for 8 or 12 weeks is highly efficacious and well tolerated in Korean patients with HCV GT1 or GT2 infections, supporting the current Korean Association for the Study of the Liver recommendation.<sup>11</sup>

## CONFLICTS OF INTEREST

Y.S.L. is an advisory board member of Bayer Healthcare and Gilead Sciences. E.D.C., L.M.F., and N.N.A. are employees of AbbVie, Inc. and may hold stock or stock options. A.A. and D.H.K. are former employees of AbbVie, Inc. and may hold stock or stock options. Other authors have no conflicts of interest to declare.

Y.J.K. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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