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ORIGINAL RESEARCH

# Observational, Post-marketing Surveillance of Safety and Effectiveness of Glecaprevir/Pibrentasvir in Korean Patients with Chronic Hepatitis C

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## ABSTRACT

***Introduction***: Glecaprevir/pibrentasvir (G/P) is a pan-genotypic, interferon-free, direct-acting antiviral regimen approved for chronic hepatitis C (CHC) treatment. While clinical trials have demonstrated its efficacy and safety, real-world data in the Korean population remain limited. This post-marketing surveillance study aimed to evaluate the safety and effectiveness of G/P in Korean patients with CHC in routine clinical practice.

***Methods***: A prospective, multicenter observational study was conducted across 56 institutions in Korea from January 2018 to January 2024. Adult and adolescent patients (aged ≥ 12 years) with CHC receiving G/P were enrolled. Safety outcomes evaluated adverse events (AEs), including serious AEs (SAEs), and treatment-related AEs. Effectiveness was assessed by sustained virologic response at 12 weeks post-treatment (SVR12) in evaluable patients.

***Results***: Of 3061 patients enrolled, 51.1% were female and 18.6% had cirrhosis. AEs were reported in 9.7% of patients, with pruritus (2.0%) and headache (1.0%) being most common. SAEs occurred in 1.2% of patients, and 0.3% discontinued treatment due to AEs. No new safety signals were identified. SVR12 was

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achieved in 98.2% of the effectiveness population ($n = 2434$). Among patients whose hepatitis C virus RNA was monitored during therapy, on-treatment virologic failure occurred in 1.3%, while post-treatment relapse was observed in 1.2%.

***Conclusions***: G/P therapy demonstrated a manageable safety profile and high effectiveness in Korean patients with CHC in real-world settings, supporting its continued use and coverage under national health programs.

***Clinical Trials Registration***: ClinicalTrials.gov (NCT03740230).

**Keywords:** Glecaprevir/pibrentasvir; Chronic hepatitis C; Real-world evidence; Post-marketing surveillance; Korean population; Direct-acting antivirals

**Key Summary Points**

| *Why carry out this study?* |
|---|
| Real-world data on the safety and effectiveness of glecaprevir/pibrentasvir (G/P) therapy in the Korean population are limited. |
| This post-marketing surveillance study aimed to evaluate the safety and effectiveness of G/P in Korean patients with chronic hepatitis C (CHC) in real-world settings. |
| *What was learned from the study?* |
| Adverse events (AEs) were reported in 9.7% of patients, and 0.3% discontinued treatment due to AEs; no new safety signals were identified. |
| Sustained virologic response at 12 weeks post-treatment was achieved by 98.2% of patients in the effectiveness population, and efficacy was maintained across hepatitis C virus genotypes. |
| G/P therapy demonstrated a manageable safety profile and high effectiveness in Korean patients with CHC in routine clinical practice. |

## INTRODUCTION

Among patients with liver cirrhosis and hepatocellular carcinoma in Korea, about 16–24% are infected with hepatitis C virus (HCV) [1]. HCV demonstrates a high degree of genetic variability and has been classified into seven major genotypes and several subtypes [2]. The prevalence of each genotype and subtype varies widely among different countries [3]. In Korea, HCV genotypes 1 and 2 are the most prevalent (99%) among patients with chronic HCV, and genotypes 1B (45–58%) and 2A (32–51%) are the most common subtypes [3, 4].

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Globally, approximately 55–85% of people infected with HCV do not clear the infection and develop chronic hepatitis C (CHC) [5]. CHC is a leading cause of chronic liver disease, liver cirrhosis, and hepatocellular carcinoma (HCC), and is the most common indication for liver transplantation [6]. Currently, about 50 million people have CHC worldwide, which causes more than 242,000 deaths annually [5]. In approximately 30% of people with CHC, progressive hepatic fibrosis, which leads to liver cirrhosis, can occur within 3 years [7]. Among patients with liver cirrhosis, approximately 6% develop hepatic decompensation, 3% develop HCC, and 4–5% require liver transplantation or die annually [8].

The progression of advanced liver disease as a result of CHC may be accelerated by various factors, including the patient's age, gender, duration of HCV infection, alcohol consumption, obesity, metabolic syndromes, and coinfection with other viruses such as hepatitis B virus and human immunodeficiency virus (HIV) [9–11]. Comorbidity can also impact CHC treatment eligibility, safety, tolerability, and effectiveness [12].

Previously, HCV treatment options were dependent on patients' HCV genotypes and subtypes, previous treatment status, presence of liver cirrhosis and comorbidities, and resistance-associated substitutions [13, 14]. The recent introduction of pan-genotypic, interferon (IFN)-free, direct-acting antiviral (DAA) therapies have simplified and shortened the treatment for patients with HCV infection [14–17]. The Korean Association for the Study of the Liver recommends two pan-genotypic DAAs, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir (G/P), as part of a simplified HCV treatment strategy [4]. G/P therapy was approved in 2018 and is currently the only pan-genotypic DAA therapy that is approved by the Korean Ministry of Food and Drug Safety and covered by the Korean National Health Insurance Service [18–20]. G/P is a combination of two DAAs with different modes of action: glecaprevir inhibits HCV NS3/4A protease and pibrentasvir inhibits HCV NS5A [21]. International guidelines recommend three oral tablets (100 mg glecaprevir and 40 mg pibrentasvir per tablet) once per day with food for 8, 12, or 16 weeks on the basis of the HCV genotype, previous treatment, and presence of liver cirrhosis [22, 23].

Previous clinical trials demonstrated that G/P treatment is effective and well tolerated among patients with CHC regardless of genotype, subgenotype, presence of cirrhosis, and prior treatment experience [24–27]. Phase 2 and 3 clinical trials globally reported that 8-week, 12-week, and 16-week G/P treatment led to sustained virologic response at 12 weeks post-treatment (SVR12) in most (83–100%) patients regardless of HCV genotype [25–27]. Few (< 1%) patients discontinued treatment due to adverse events (AEs) and most AEs were mild in severity [25–27]. Notably, G/P treatment was also highly efficacious and well tolerated among most (96–98%) treatment-naïve or treatment-experienced patients with cirrhosis [27]. Similarly, a pooled analysis of global phase 2 and 3 clinical trials (ENDURANCE 1 [NCT02604017] [26], ENDURANCE 2 [NCT02640482] [28], SURVEYOR II part 4 [NCT02243293] [28], VOYAGE I [NCT03222583] [29], and VOYAGE II [NCT03235349] [29]) reported that most (98.9%) of the Korean patients enrolled who received 8-week or 12-week G/P treatment achieved SVR12 [24]. AEs related to G/P treatment were reported in 11.3% of the Korean patients, and all AEs were grade ≤ 3 [24].

G/P was highly efficacious and well tolerated in clinical trials, which have strict inclusion and exclusion criteria under tightly controlled conditions [24–27]. However, there are limited data on the effectiveness and safety of the G/P regimen in Korean patients with HCV infection in real-world clinical settings. In general, patients with CHC in daily clinical practice are typically older, have comorbidities, advanced hepatic fibrosis and concurrent malignancy, and often take multiple medications, which may influence G/P treatment effectiveness and safety in real-world clinical settings [30, 31]. Furthermore, large international cohorts may not fully reflect the patient and disease characteristics of the Korean population, and thus, findings may not be generalizable to the Korean population. Hence, the Korea Institute of Drug Safety and Risk Management requires thorough post-marketing surveillance of new therapies to ensure

the safety and effectiveness of medications in real-world settings [32].

This observational study aimed to evaluate the safety and effectiveness of the G/P regimen among a variety of patient populations with CHC in clinical practice in Korea to support its continued use in this population.

# METHODS

### Study Design

This prospective, multicenter observational study evaluated the safety and effectiveness of the G/P regimen in Korean patients (ClinicalTrials.gov Identifier: NCT03740230). The post-marketing surveillance study examined patients with CHC who received the G/P regimen from 12 January 2018 to 11 January 2024 at 56 institutions in the Republic of Korea. The study protocol was conducted in accordance with the Declaration of Helsinki, approved by Institutional Review Board at each site (IRB names [IRB numbers]): IRB of Inha University Hospital [PMS2019-001], Severance Hospital Yonsei university health system Institutional Review Board [4–2018-0824], Yeungnam University Hospital Institutional Review Board [PMS2018-030], Ajou University Hospital Institutional Review Board [MED-PMS-18–362], Pusan National University Yangsan Hospital Institutional Review Board [06–2019-014], Kyungpook national University Hospital Institutional Review Board [PMS2018-015], Dong-a University hospital Institutional Review Board [DAUHIRB-18–185], Seoul National University Hospital Institutional Review Board [1901–121-1005], The Catholic University of Korea Daejeon St. Mary's Hospital Institutional Review Board [DC19MODP0083], Korea University Anam Hospital IRB [2019AN0017], and Institutional Review Board Pusan National University Hospital [H-1809–005-084]; Supplementary Table 1, and in compliance with Korean regulatory laws. All patients provided written, informed consent prior to being enrolled in the study.

### Patient Inclusion Criteria

Patients were enrolled in the study once they were given their first dose of the G/P regimen. Adult and adolescent patients aged 12 years or older with CHC and HCV genotypes 1–6, who were prescribed the G/P regimen at the discretion of the physician according to approved local labels, were included in the study. Patients with contraindications listed in the approved local labels were excluded (Supplementary Sect. 1).

### Assessments

Patients were administered the G/P regimen in accordance with the approved label of the regimen, receiving 300 mg glecaprevir and 120 mg pibrentasvir once a day (taken as three tablets of 100 mg glecaprevir and 40 mg pibrentasvir). For patients without previous HCV treatment experience, the recommended treatment duration was 8 weeks. Depending on previous treatment experience, HCV genotype, and presence of liver cirrhosis, the recommended treatment duration was 8, 12, or 16 weeks (Supplementary Sect. 2). HCV RNA levels were assessed during treatment, at the end of the treatment (EoT), and at 12 weeks (≥ 70 days) following EoT. Patients were observed during the treatment period and followed up until 12 weeks (≥ 70 days) after EoT.

### Outcomes

Safety outcomes included: the percentage of patients with serious AEs (SAEs) or serious treatment-related AEs (TRAEs) during the study; the percentage of patients with any unexpected AEs or unexpected TRAEs not indicated in the approved label during the study; the percentage of patients with any AEs stratified by treatment duration and patient characteristics (e.g., liver cirrhosis status); the percentage of patients who experienced post-baseline shifts in clinical laboratory values from low/normal to high and high/normal to low during treatment on the basis of the reference range; and occurrence of HCC and hepatic decompensation (i.e., ascites,

variceal bleeding, or hepatic encephalopathy). The AEs were categorized according to the System Organ Class and Preferred Term coded by the Medical Dictionary for Regulatory Activities (MedDRA).

All AEs, deaths, and clinical laboratory abnormalities that occurred during the study period until 30 days after the last dose of the G/P regimen were recorded, regardless of causality with the regimen. SAEs were defined as any AE that was life-threatening; or resulted in death, hospitalization, prolongation of hospitalization, congenital malformation, or significant disability; or required medical or surgical intervention to prevent the above outcomes.

The primary effectiveness outcome was the percentage of patients who achieved SVR12, which was defined as a plasma HCV RNA concentration below the lower limit of quantification (LLOQ) 12 weeks (≥ 70 days) after EoT. Secondary effectiveness outcomes included: the percentage of patients with on-treatment virologic failure, which was defined as confirmed HCV RNA concentration ≥ LLOQ after HCV RNA concentration < LLOQ during treatment, confirmed HCV RNA concentration increase of > 1 $\log_{10}$ IU/mL above the lowest post-baseline concentration during treatment, or HCV RNA concentration ≥ LLOQ persistently during the treatment period; and the percentage of patients with post-treatment relapse, which was defined as confirmed HCV RNA concentration ≥ LLOQ between EoT and 12 weeks after EoT among patients who achieved EoT response (ETR), defined as patients who completed the treatment and had HCV RNA concentration < LLOQ at EoT. SVR12 and virologic failures were also assessed in patient subpopulations on the basis of their HCV genotypes and subgenotypes, age, cirrhosis status, prior treatment with pegylated IFN (pegIFN) or IFN, and/or ribavirin and/or sofosbuvir (PRS).

### Statistical Analyses

No data imputation was conducted and statistical analysis for each endpoint was based on available data at each visit. Descriptive statistical measures for the safety and effectiveness parameters were described in the periodic updates. The safety population was defined as all patients enrolled in the study who had been administered at least one dose of the G/P regimen and had been followed up at least once for safety. Safety analysis was performed on the safety population and all safety variables were summarized using descriptive statistical methods for the safety population, stratified by scheduled treatment duration (i.e., 8, 12, or 16 weeks). All AEs were coded using MedDRA version 25.0.

Mean changes in clinical laboratory parameters between baseline and each visit were summarized descriptively. The effectiveness population consisted of all patients in the safety population who had completed the G/P regimen according to the prescribed duration consistent with the approved label and had sufficient follow-up, including SVR12 data, and excluded patients without HCV RNA evaluation 12 weeks post-treatment due to reasons not related to safety and effectiveness. The intent-to-treat (ITT) population included all patients in the effectiveness population and patients who were lost to follow-up. Patients lost to follow-up were counted as treatment failures in the ITT population.

The effectiveness analysis was performed for the overall effectiveness population, the ITT population, and subpopulations of interest. Response rates, including SVR12 rates, on-treatment virologic failure rates, and post-treatment virologic failure, were assessed. All baseline and disease characteristics were summarized for the safety and effectiveness populations stratified by HCV genotype/subtypes, cirrhosis status, prior PRS treatment, and scheduled treatment duration. The 95% confidence intervals for all AE occurrence rates and response rates were determined using the Wilson's score method.

The effectiveness population was also analyzed for relapse rates and on-treatment virologic failure rates. The relapse rates were estimated in patients with EoT response and sufficient HCV RNA measurements post-treatment. On-treatment virologic failure rates were estimated in patients who had at least one undetectable HCV RNA measurement during treatment and at least one on-treatment or EoT measurement thereafter or confirmed increase from nadir in

HCV RNA concentration (defined as HCV RNA concentration > 1 $\log_{10}$ IU/mL above nadir) at any timepoint during treatment, or HCV RNA concentration persistently ≥ LLOQ during the treatment period.

## RESULTS

### Study Population

Patient-level data were collected from 56 institutions in Korea. Overall, 3061 patients received at least 1 dose of the G/P regimen (Fig. 1). Among these patients, 51.1% were female, with a median age of 59 years (range 18–93 years; Table 1). The proportion of patients with a prior medical condition was 67.0%; the most prevalent conditions were hypertension (27.3%), hepatic cirrhosis (18.5%), and diabetes mellitus (14.7%; Supplementary Table 2). A total of 14 patients (0.5%) were infected with human HIV. The proportion of patients with hepatic impairment was 27.5%, while 8.0% had renal impairment; 0.2%, 0.4%, and 2.6% received liver transplantation, kidney transplantation, and dialysis, respectively. Patients were most commonly infected with HCV genotype 2 (55.8%), followed by genotype 1 (42.5%). None of the patients had genotype 5. The duration of HCV infection was confirmed among 2615 patients, with a mean of 2.8 years. Among these patients, 227 (7.4%) had received prior HCV treatment: 98 received pegIFN, 73 received IFN, and 42 received sofosbuvir. At baseline, among patients with known liver fibrosis stage, 62.9% had liver fibrosis (F1–F4) and 27.1% had cirrhosis (F4). Around half of the patients (50.1%) had Child–Pugh score A, while the Child–Pugh score was unknown in 48.6%. Three patients (0.1%) had liver cancer occurrence or recurrence.

The mean (standard deviation [SD]) administration period of the G/P regimen was 57.8 (±10.7) days, ranging from 1 to 112 days: 9.5%, 82.4%, and 8.1% of patients took G/P for less

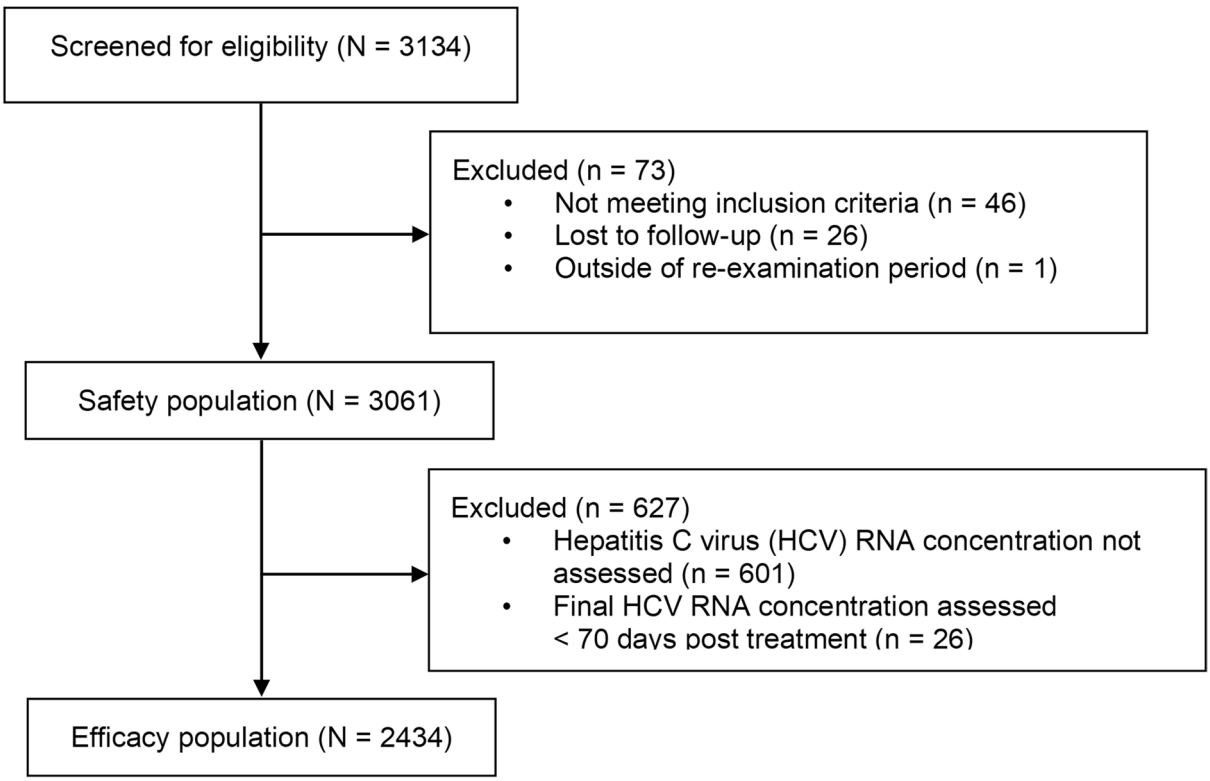


**Fig. 1** CONSORT flow diagram of patient disposition. *HCV* hepatitis C virus, *RNA* ribonucleic acid

**Table 1** Baseline demographics and clinical characteristics of all patients

| | **All patients (*N* = 3061)** |
|---|---|
| Female, *n* (%) | 1564 (51.1) |
| Age (years), median (range) | 59.00 (18.0–93.0) |
| ≥ 65 years, *n* (%) | 990 (32.3) |
| Height (cm), *n* | 2088 |
| Median (range) | 162.00 (133.0–190.0) |
| Weight (kg), *n* | 2234 |
| Median (range) | 62.00 (29.0–115.0) |
| Pregnant, *n* (%) | 0 (0.0) |
| Hepatitis C family history, *n* (%) | 58 (1.9) |
| Allergy history, *n* (%) | 46 (1.5) |
| Duration of hepatitis C virus (HCV) infection,[†] *n* | 2615 |
| Duration (years), mean (standard deviation [SD]) | 2.78 (5.7) |
| HCV genotype, [‡] *n* (%) | |
| 1 | 1300 (42.5) |
| 2 | 1709 (55.8) |
| 3 | 37 (1.2) |
| 4 | 11 (0.4) |
| 5 | 0 (0.0) |
| 6 | 5 (0.2) |
| C hild–Pugh score, *n* (%) | |
| A | 1565 (51.1) |
| B[§] | 8 (0.3) |
| C | 0 (0.0) |
| Unknown | 1488 (48.6) |
| Known history of liver cirrhosis,[¶] *n* (%) | 568 (18.6) |
| Liver fibrosis stage, *n* (%) | |
| Known | 1758 (57.4) |
| F0 | 653 (37.1)[††] |
| F1 | 318 (18.1)[††] |
| F2 | 171 (9.7)[††] |

**Table 1** continued

| | **All patients (*N* = 3061)** |
|---|---|
| F3 | 140 (8.0)[††] |
| F4 (cirrhosis) | 476 (27.1)[††] |
| Unknown | 1303 (42.6) |
| Prior chronic hepatitis C (CHC) treatment status, *n* (%) | |
| CHC treatment naïve | 2778 (90.8) |
| CHC treatment experienced | 227 (7.4) |
| CHC treatment type[‡] | |
| Interferon (IFN) | 73 (2.4) |
| Pegylated IFN (pegIFN) | 98 (3.2) |
| Sofosbuvir | 42 (1.4) |
| NS5A inhibitor alone | 4 (0.1) |
| NS3/4A protease inhibitor only | 2 (0.1) |
| Combination of NS5 inhibitor and sofosbuvir | 9 (0.3) |
| Others[‡‡] | 9 (0.3) |
| Human immunodeficiency virus (HIV) infection, *n* (%) | 14 (0.5) |
| Liver transplant, *n* (%) | 7 (0.2) |
| Kidney transplant, *n* (%) | 13 (0.4) |
| Dialysis, *n* (%) | 78 (2.5) |
| Resolved or ongoing medical condition, *n* (%) | 2052 (67.0) |
| Liver impairment, *n* (%) | 843 (27.5) |
| Renal impairment, *n* (%) | 244 (8.0) |
| Liver cancer occurrence/recurrence, *n* (%) | 3 (0.1) |

*CHC* chronic hepatitis C, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *IFN* interferon, *pegIFN* pegylated interferon, *SD* standard deviation

[†]Duration of hepatitis C infection (years) = (date of first administration of this drug − date of hepatitis C diagnosis + 1)/365.25, duration unknown: 446 patients

[‡]Duplicate counting

[§]Subjects registered before the change in precautions for use of this product (31 July 2020)

[¶]A total of 568 patients with liver cirrhosis were identified as 2 in liver fibrosis stage F0, 8 in F1, 10 in F2, 15 in F3, 445 in F4 (cirrhosis), and 88 in unknown

[††]Percentage calculated as a percentage of patients with known liver fibrosis stage

[‡‡]Other drugs: unknown (seven cases), injectable (one case), clinical trial drug (one case)

than 8 weeks, 8–12 weeks, and more than 12 weeks, respectively (Supplementary Table 3). The mean (SD) total dose of G/P received was 173.5 (±32.1) tablets. Most patients (95.9%) completed the G/P regimen prescribed. Of the 126 patients who discontinued treatment, 10 (7.9%) were due to AEs, 2 (1.6%) due to lack of effectiveness, and 114 (90.5%) discontinued for other reasons, the most common reasons being loss to follow-up (75/114) and completion of the study (17/114; Supplementary Table 4).

Patient baseline characteristics stratified by treatment duration were also analyzed (Supplementary Table 5). Patients who received less than 8 weeks and 8–12 weeks of treatment were more likely to be CHC treatment naïve and less likely to have liver impairment compared with patients who received more than 12 weeks of treatment. Despite this, most patients with prior treatment still received more than 8 weeks of treatment.

**Table 2** Overall summary of adverse events (AEs) and treatment-related AEs (TRAEs)

| Types of AEs | Safety population ($N = 3061$) *n* (%) | 95% confidence interval (CI) |
|---|---|---|
| Overall AEs | 298 (9.7) | 8.74, 10.84 |
| Overall TRAEs | 168 (5.5) | 4.74, 6.35 |
| Serious AEs (SAEs) | 37 (1.2) | 0.88, 1.66 |
| Serious TRAEs | 5 (0.2) | 0.07, 0.38 |
| Unexpected AEs | 198 (6.5) | 5.65, 7.40 |
| Unexpected SAEs | 35 (1.1) | 0.82, 1.59 |
| Unexpected TRAEs | 91 (3.0) | 2.43, 3.64 |
| AEs that led to treatment discontinuation | 10 (0.3) | 0.18, 0.60 |
| AEs that led to death | 1 (0.03) | 0.01, 0.18 |

*AE* adverse event, *CI* confidence interval, *SAE* serious adverse event, *TRAE* treatment-related adverse event

## Safety

Safety evaluation was performed on 3061 patients who completed the study. Overall, a total of 390 AEs were reported in 298 patients (9.7%) (Table 2). The most common AEs were pruritus in 61 patients (2.0%), headache in 29 patients (1.0%), and fatigue in 22 patients (0.7%) (Supplementary Table 6). Among the 390 AEs, 333 (85.4%) were mild, 47 (12.1%) were moderate, and 10 (2.6%) were severe (Supplementary Table 7). Overall, 333 (85.4%) of the AE cases were resolved, 35 (9.0%) were resolving, two (0.5%) were not resolved, one (0.3%) recovered with sequelae, and one (0.3%) was fatal (Supplementary Table 8). TRAEs were reported in 168 patients (5.5%) (Table 2), most commonly pruritus in 49 patients (1.6%), headache in 21 patients (0.7%), and fatigue in 18 patients (0.6%) (Supplementary Table 6).

A total of 45 SAEs occurred in 37 patients (1.2%), of which 39 cases (86.7%) resulted in hospitalization (Supplementary Table 9). The most common SAEs were hepatocellular carcinoma, pneumonia, and nausea (Supplementary Table 9). Among them, five patients (0.2%) had serious TRAEs (Table 2), which were determined to be one case each of dyspepsia, vomiting, headache, paraparesis, blood bilirubin increase, and jaundice (Supplementary Table 6).

Unexpected AEs that were not listed in the local label were reported in 198 patients (6.5%) (Table 2). Among them, 91 patients (3.0%) had unexpected TRAEs (Table 2). The most common unexpected TRAEs were dizziness in 13 patients (0.4%), dyspepsia in 12 patients (0.4%), and rash in 7 patients (0.2%) (Supplementary Table 6). Unexpected SAEs were reported in 35 patients (1.1%) (Table 2). The most common unexpected SAEs were hepatocellular carcinoma in six patients (0.2%) and pneumonia in two patients (0.1%) (Supplementary Table 6).

Of the 390 AEs, 368 (94.4%) did not result in any changes to the treatment regimen. Nine events (2.3%) led to transient discontinuation of treatment; the AEs were two cases of pruritus and one case each of nausea, gastrointestinal disorder, duodenal ulcer, tongue discoloration, vomiting, headache, and jaundice. Thirteen AEs (3.3%) led to permanent discontinuation of treatment—by overlapping

counts, there were two cases of dizziness and one case each of nausea, cerebellar infarction, paraparesis, asthenia, pneumonia, hepatic cancer, decreased appetite, depression, blood creatinine increase, blood bilirubin increase, and palpitations. One AE (chronic kidney disease) resulted in death (Supplementary Table 8).

## Effectiveness

### *Primary Effectiveness Outcome*

A total of 2434 patients were evaluated in the effectiveness population, which excluded 601 patients who did not undergo HCV RNA evaluation and 26 patients whose final HCV RNA evaluation was less than 70 days post-treatment (Fig. 1). Overall, 98.2% of patients achieved SVR12 (Table 3). An analysis of SVR12 was conducted for 2460 subjects in the ITT population (Supplementary Table 10). Since all patients lost to follow-up received less than 8 weeks of treatment, SVR12 rates for this treatment duration in the ITT population was lower than that of the effectiveness population (80.1% and 95.0%, respectively; Supplementary Table 11), while SVR12 rates for those receiving 8–12 weeks and more than 12 weeks of treatment were the same (98.3% and 99.5%, respectively) for both the ITT and effectiveness populations. Similar trends were observed when evaluating SVR12 rates by treatment duration within HCV genotype subpopulations in both the ITT and effectiveness populations (Supplementary Tables 12 and 13). The overall SVR12 for the ITT population was 97.2%, which is 1% lower than that of the effectiveness population.

### *Secondary Effectiveness Outcomes*

Of 2248 patients with HCV RNA concentration assessed during treatment, 28 (1.3%) had virologic failure during treatment (Table 3). Most had no history of cirrhosis, had prior treatment experience, and were under 65 years of age (Supplementary Table 14). Of 2217 patients (98.1%) who achieved an ETR, 27 (1.2%) had virologic relapse after EoT (Table 3). Subgroup analyses were performed on the basis of HCV RNA genotype, liver cirrhosis status, prior HCV treatment history, age group, hepatic impairment status, and renal impairment status (Fig. 2; Supplementary Table 15). Among 14 patients with HIV co-infection, 10 had evaluable SVR12 and the SVR12 response rate was 100%. Among the 3061 patients with confirmed HCV genotype, SVR12 was achieved by 99.5% of patients with genotype 1, 97.3% of patients with genotype 2, 95.0% of patients with genotype 3, and 100.0% of patients with genotype 4 or 6. None of the patients in this study had HCV genotype 5.

SVR12 was achieved by 98.0% of patients with liver cirrhosis and 98.2% of those without. Similarly, 98.5% of patients with liver impairment and 98.1% of those without achieved SVR12. Among patients with confirmed CHC treatment history, SVR12 was achieved in 96.5% of treatment-experienced patients and 98.3% treatment-naïve patients. SVR12 was achieved

**Table 3** Overall response rates

| | *N* | *n* (%) | 95% CI |
|---|---|---|---|
| SVR12 | 2434 | 2390 (98.2) | 97.58, 98.65 |
| End-of-treatment response (ETR) achieved | 2261 | 2217 (98.1) | 97.40, 98.55 |
| Virologic failure during treatment | 2248 | 28 (1.2) | 0.86, 1.78 |
| Virologic relapse after end of treatment (EoT) | 2217 | 27 (1.2) | 0.84, 1.77 |

*CI* confidence interval, *EoT* end of treatment, *ETR* end-of-treatment response, *SVR12* sustained virologic response at 12 weeks post-treatment

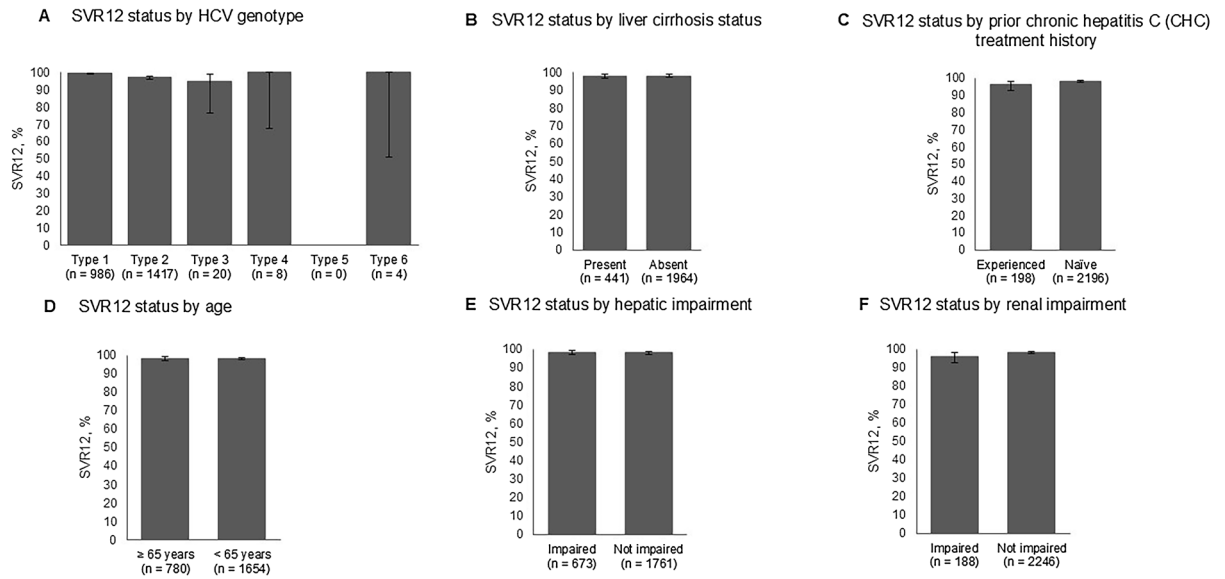


**Fig. 2** Sustained virologic response at 12 weeks post-treatment (SVR 12) in patient subpopulations. *CHC* chronic hepatitis C, *HCV* hepatitis C virus, *SVR12* sustained virologic response at 12 weeks post-treatment

in 98.2% of patients 65 years or older and 98.2% of patients younger than 65 years. Finally, 96.3% of patients with renal impairment and 98.4% of patients without renal impairment achieved SVR12.

## DISCUSSION

This post-marketing surveillance study described the tolerability and effectiveness of G/P treatment in real-world clinical settings across Korea.

### Safety

The study demonstrated that G/P treatment is well tolerated in real-world settings. Safety data for G/P treatment have previously been reported in clinical trials. A pooled analysis of five phase 2 and 3 trials previously found that AEs and TRAEs were reported by 44.9% and 11.3% of Korean patients, respectively [24]. In this study, AEs and TRAEs were reported in 9.7% and 5.5% of patients, respectively, which is slightly lower than findings from clinical trials [24]. However, statistical analysis of the differences was not performed. Consistent with the pooled analysis of five clinical trials, no single AE occurred in ≥ 10% of patients in this study [24]. The most common AEs reported here were pruritus (2.0%), headache (1.0%), nausea (0.7%), and fatigue (0.7%). In the pooled analysis, upper respiratory tract infection (7.2%), fatigue (4.2%), diarrhea (3.0%), headache (2.6%), and pruritus (2.3%) were the most common [24]. The current study recorded SAEs in 37 patients (1.2%) compared with 2.6% in the pooled analysis [24].

Real-world safety data of G/P treatment have also been reported in previous studies. A meta-analysis of 18 real-world studies summarized the safety data for 7199 patients with HCV infection across 8 cohorts and found that AEs were reported in 17.7% of patients, which is slightly higher than the 9.7% reported in this study [33]. However, statistical analysis of the difference was not performed. Commonly reported AEs in the meta-analysis were similar to those recorded in this study, with the most frequent being pruritus (4.7%), fatigue (4.2%), and headache (2.7%) [33]. The meta-analysis also reported that, across 6 cohorts involving 5595 patients, 0.6% of patients discontinued G/P treatment because of an AE [33]. Similarly,

10 of the 3061 patients (0.3%) in this study discontinued treatment due to AEs. No new safety signals were observed.

### Effectiveness

The effectiveness of G/P therapy in the Korean population demonstrated in this study is comparable to that observed in clinical trials and real-world studies. Overall, 98.2% of patients in this study achieved SVR12, consistent with previous reports. When classifying patients lost to follow-up as treatment failures, SVR12 decreased by 1%, which demonstrates minimal impact on the primary outcome. A pooled analysis of five phase 2 and 3 trials previously reported an overall efficacy of 98.9%, while a meta-analysis of 18 real-world studies found an overall SVR12 of 96.7% [24, 33]. Furthermore, subgroup analyses of SVR12 confirmed that G/P therapy in Korean patients with HCV is effective regardless of HCV genotype, previous CHC treatment experience, presence of liver cirrhosis, age group, and hepatic and renal impairment status. These findings support the evidence from earlier clinical and real-world studies [24, 33].

The pooled analysis of five clinical trials conducted by Heo et al. found that SVR12 was achieved in 99.2% and 98.5% of patients with HCV genotype 1 and 2, respectively [24]. In the same pooled analysis, SVR12 was achieved in 100% and 98.7% of patients with compensated cirrhosis and without cirrhosis, respectively [24]. A pooled analysis of nine phase 2 and 3 clinical studies found similar SVR12 of 97.9% and 97.3% in patients aged ≥ 65 years and < 65 years, respectively [34]. The meta-analysis of 18 real-world studies by Lampertico et al. found G/P treatment to be effective across all HCV genotypes and patient subgroups studied, with SVR12 of ≥ 95% across genotypes and in populations of interest such as treatment-experienced patients and patients with cirrhosis [33].

### Limitations

A limitation of this study is the lack of participants with HCV genotype 5, and the relatively few participants with genotypes 3, 4, and 6, limiting SVR12 comparison across all genotypes. Nonetheless, this distribution is representative of the prevalence of each genotype in the Republic of Korea, where genotypes 1 and 2 account for a large majority of infections [3, 35]. Secondly, due to the observational nature of this study, collection of Child–Pugh scores was not mandatory, which resulted in a substantial proportion of patients with missing data. Thirdly, although AEs that occurred during treatment were systematically collected in accordance with the study protocol, AEs appeared to be underreported in this study compared with clinical trials. Fourthly, 601 patients did not undergo HCV RNA testing following G/P treatment. The reasons for missing this assessment are unclear, but it is possible that these individuals may represent a subgroup with suboptimal adherence to follow-up procedures. It should be noted that HCV RNA data collection was not mandated in this study, reflecting the real-world nature of the protocol. The primary objective was to evaluate adverse events rather than efficacy outcomes. Finally, although all patients who were prescribed G/P were approached for participation in the study, prescription was at the discretion of the physician and selection bias cannot be excluded. Thus, the study population may not comprehensively reflect the overall population of Korean patients with HCV, and may explain the low proportion of patients with liver cancer in this study.

## CONCLUSIONS

This large, prospective, post-marketing surveillance study provides real-world data that affirms the tolerability and effectiveness of G/P in accordance with criteria set out by the Ministry of Food and Drug Safety in Korea for the reexamination of new drugs.

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Jeong (previously Immunology Medical, AbbVie, Seoul, Republic of Korea at the time of the study) has changed after completion of the manuscript and is now MSc in Global Healthcare Leadership at Nuffield Department of Primary Care Health Sciences & Saïd Business School, University of Oxford.

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***Data Availability.*** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## *Declarations*

***Conflict of Interest.*** Ji Young Jeong was employed by AbbVie at the time of initiation of the manuscript, and contributed to the study conception and design, as well as reviewed and commented on the manuscript. Jeong Heo has received grant support from Gilead and Roche; consultant fees from Roche; lecture fees from AbbVie Korea, Roche, Yuhan Korea, Oncolys, and Gilead; and is a member of an AstraZeneca steering committee. Jin-Woo Lee, Sang Hoon Ahn, Jeong Gil Park, Jae Youn Jeong, Ki Tae Yoon, Won Young Tak, Yang Hyun Baek, Su Jong Yu, Myeong Jun Song, and Yeon Seok Seo declare no conflicts of interest.

***Ethical Approval.*** The study protocol was conducted in accordance with the Declaration of Helsinki, approved by Institutional Review Board at each site (IRB names [IRB numbers]): IRB of Inha University Hospital [PMS2019-001], Severance Hospital Yonsei university health system Institutional Review Board [4–2018-0824], Yeungnam University Hospital Institutional Review Board [PMS2018-030], Ajou University Hospital Institutional Review Board [MED-PMS-18–362], Pusan National University Yangsan Hospital Institutional Review Board [06–2019-014], Kyungpook national University Hospital Institutional Review Board [PMS2018-015], Dong-a University hospital Institutional Review Board [DAUHIRB-18–185], Seoul National University Hospital Institutional Review Board [1901–121-1005], The Catholic University of Korea Daejeon St. Mary's Hospital Institutional Review Board [DC19MODP0083], Korea University Anam Hospital IRB [2019AN0017], and Institutional Review Board Pusan National University Hospital [H-1809–005-084]; Supplementary Table 1, and in compliance with Korean regulatory laws. All patients provided written, informed consent prior to being enrolled in the study.

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