# Real-World Effectiveness and Safety of Glecaprevir Plus Pibrentasvir in HCV: A Multi-Country Analysis of Post-Marketing Observational Studies

THU-151

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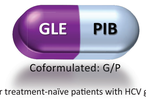
**Presented at the European Association for the Study of the Liver's 54th Annual International Liver Congress, 10–14 April 2019, Vienna, Austria**

## BACKGROUND

- For patients with chronic hepatitis C virus (HCV) infection, significant heterogeneity exists in access to direct-acting antiviral (DAA) drugs and treatment patterns across different countries
- It is therefore crucial to evaluate the effectiveness and safety of the most recently approved pangenotypic DAAs in real-world populations
- Glecaprevir/pibrentasvir (G/P), an interferon-free, ribavirin-free, fixed-dose DAA combination, was approved in the United States and Europe in 2017 for the treatment of patients chronically infected with HCV genotype (GT) 1–6[1]

### G/P is Approved for Patients With HCV GT1–6 Infection

**Glecaprevir**
pangenotypic NS3/4A protease inhibitor




**Pibrentasvir**
pangenotypic NS5A inhibitor

- 8-week duration approved for treatment-naïve patients with HCV genotype (GT) 1–6 infection and without cirrhosis[1]
- Pangenotypic SVR12 rate of 98% in more than 2200 patients in registrational studies
- Potent against common polymorphisms (eg, Y93H in NS5A and Q80K in NS3)
- Favorable safety profile irrespective of baseline factors
- Recent real-world results demonstrate that G/P achieved high SVR12 rates consistent with those observed in clinical trials[2,3]

G/P dosed as 3 pills taken once daily with food for a total dose of 300 mg/120 mg.
Glecaprevir was identified by AbbVie and Enanta.

## OBJECTIVE

- This pooled analysis aims to evaluate the real-world effectiveness and safety of G/P in patients with chronic HCV infection in ongoing post-marketing observational studies (PMOS)

## METHODS

### STUDY DESIGN

- Data were pooled from 8 countries currently participating in the PMOS: Austria, Belgium, France, Greece, Israel, Italy, Poland, and Switzerland
- Data were collected from 13 November 2017 to 1 February 2019
- Patients with chronic HCV GT1–6 infection were eligible for the PMOS if they were receiving G/P at the treating physician's discretion according to local label, national or international recommendations, and/or local clinical practice
- Eligible patients were HCV treatment-naïve or interferon-, ribavirin-, and/or sofosbuvir-experienced, and were without cirrhosis or with compensated cirrhosis
  - Cirrhosis status was most often assessed using transient elastography

## DISCLOSURES

**Pietro Lampertico:** Speaker bureau and/or advisory board: Bristol-Myers Squibb, Roche, Gilead, GSK, AbbVie, MSD, Arrowhead, Alnylam, and Janssen. **Markus Peck-Radosavljevic:** Consultant: AbbVie, Bristol-Myers Squibb, Gilead, and MSD; Speaker: AbbVie, Gilead, and MSD. **Yves Horsmans:** Consultant: AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Merck. **Nasser Semmo:** Advisory board: Gilead and MSD; Speaker: AbbVie. **Ella Veitsman:** Nothing to disclose. **Konstantinos Mimidis:** Advisory boards/lectures: AbbVie. **Mark Bondin, Sadhana Sonparote, Zhenzhen Zhang,** and **Ariel Porcalla:** Employees of AbbVie Inc. and may hold stock or stock options. **Robert Flisiak:** Grants, advisory boards and honoraria: AbbVie, Gilead, Merck, and Roche. **Dominique Thabut:** Speaker: AbbVie, MSD, Gilead, Gore, and Alfasigma.

AbbVie sponsored the study; contributed to its design; and participated in the collection, analysis, and interpretation of the data and in the writing, reviewing, and approval of the presentation. All authors had access to relevant data, and participated in the writing, review, and approval of the presentation.

## METHODS (CONTINUED)

### DATA ANALYSIS

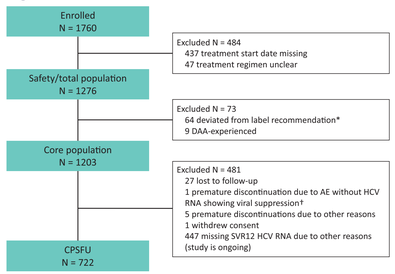
- Demographics and clinical characteristics at baseline and safety data were summarized for all patients who received ≥1 dose of G/P (safety/total population)
- Effectiveness was evaluated using the core population with sufficient follow-up (CPSFU), defined as:
  - Patients treated according to the label with known drug start date, excluding patients who did not have an HCV ribonucleic acid (RNA) evaluation after post-treatment Day 70 due to reasons not related to effectiveness or safety (lost to follow-up or unavailable HCV RNA data)
  - To be included in the CPSFU, a patient had to have 1 of the following:
    - HCV RNA data after post-treatment Day 70 (not included if the drug end date is unknown)
    - Virologic failure (on-treatment virologic failure or post-treatment relapse)
    - Discontinued the study due to an adverse event (AE) and had HCV RNA <50 IU/mL at the last measurement
- Effectiveness was measured as sustained virologic response at post-treatment Week 12 (SVR12), defined as HCV RNA below the lower limit of quantification (LLOQ, <50 IU/mL) at ≥70 days after the last dose of G/P
- Treatment adherence was calculated as the percentage of tablets taken relative to the total tablets expected to be taken
- Safety was assessed by monitoring AEs and laboratory abnormalities

## RESULTS

### STUDY POPULATION

- As of 1 February 2019, 1760 patients were enrolled: 1276 in the safety population; 1203 in the core population; 722 in the CPSFU **(Figure 1)**

### Figure 1. Patient Selection




*Deviations included 7 patients with cirrhosis who were treated for 8 weeks (to date, 3 of these patients have achieved SVR12).
†Patients with premature discontinuation due to AE and last HCV RNA <50 IU/mL were included in the CPSFU.
AE, adverse event; CPSFU, core population with sufficient follow-up; DAA, direct-acting antiviral; HCV, hepatitis C virus; RNA, ribonucleic acid; SVR12, sustained virologic response at post-treatment Week 12.

- Of 1276 patients who received ≥1 dose of G/P, 1143 (89.6%) were non-cirrhotic and 1083 (85.1%) were HCV treatment-naïve **(Table 1)**
- As a result, 1096 patients (85.9%) were assigned to G/P for 8 weeks, whereas 165 (12.9%) and 15 (1.2%) of patients were assigned to G/P for 12 and 16 weeks, respectively **(Table 1)**
- The mean ± standard deviation (SD) time since diagnosis of HCV infection was 11.6 ± 9.5 years
- In 1153 patients with available data, adherence to treatment was >99% (mean ± SD, 99.7% ± 2.3%)

## RESULTS (CONTINUED)

### Table 1. Demographics and Clinical Characteristics at Baseline

| Characteristic | Total population N = 1276 |
|---|---|
| Male | 690 (54.1) |
| Age, median (range), years | 53 (18–88) |
| HCV GT | |
| 1 | 707 (56.2) |
| 2 | 157 (12.5) |
| 3 | 265 (21.0) |
| 4 | 119 (9.5) |
| 5 | 7 (<1.0) |
| 6 | 4 (<1.0) |
| Missing | 17 |
| Mode of HCV infection | |
| Contaminated needle or IV drug use | 382 (30.4) |
| Blood product transfusion | 197 (15.7) |
| Vertical transmission (mother to child) | 22 (1.8) |
| Contact with infected individual (other than transmission) | 62 (4.9) |
| Surgery/operation | 72 (5.7) |
| Occupational exposure | 13 (1.0) |
| Unknown | 508 (40.4) |
| Missing | 20 |
| Referral source (>3%) | |
| General practitioner | 411 (45.9) |
| Hepatologist | 233 (26.0) |
| Gastroenterologist | 81 (9.1) |
| Infectious disease specialist | 52 (5.8) |
| Addiction center | 30 (3.4) |
| Missing | 381 |
| Fibrosis stage | |
| F0–F1 | 593 (78.8) |
| F2 | 44 (5.8) |
| F3 | 52 (6.9) |
| F4 | 64 (8.5) |
| Missing | 523 |
| Fibrosis staging technique | |
| FibroScan™ | 703 (93.4) |
| Biopsy | 41 (5.4) |
| FibroTest™ | 8 (1.1) |
| ARFI | 1 (<1.0) |
| Missing | 523 |
| APRI score | |
| ≤1 | 714 (77.9) |
| >1 | 202 (22.1) |
| Missing | 360 |
| No cirrhosis* | 1143 (89.6) |
| Prior HCV treatment | |
| Naïve | 1083 (85.1) |
| Experienced | 189 (14.9) |
| Sofosbuvir-based | 6 (<1.0) |
| Interferon-based | 165 (13.0) |
| Missing | 4 |
| HCV RNA, median (range), $Log_{10}$ IU/mL | 6.1 (0.7–8.4) |
| G/P treatment duration | |
| 8 weeks | 1096 (85.9) |
| 12 weeks | 165 (12.9) |
| 16 weeks | 15 (1.2) |

Data are n (%) unless stated otherwise; percentages are calculated from non-missing values.
*Cirrhosis was defined as METAVIR, Batts and Ludwig, Knodell, IASL, Scheuer, or Laennec stage 4, ISHAK stage ≥5, FibroScan ≥12.5 kPa, FibroTest ≥0.75, or ARFI ≥2.31.
APRI, aspartate aminotransferase-to-platelet ratio index; ARFI, acoustic radiation force impulse elastography; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; IV, intravenous; RNA, ribonucleic acid.

- Approximately one-third of the population reported current (<6 months) or prior (>6 months) recreational drug use and 131 (10.8%) were on stable opioid substitution therapy **(Table 2)**
- A minority of patients were coinfected with human immunodeficiency virus (n = 54; 4.2%) or hepatitis B virus (n = 18; 1.4%) **(Table 2)**

### Table 2. Comorbidities at Baseline

| Comorbidity, n (%) | Total population N = 1276 |
|---|---|
| Recreational drug use* | 426 (34.2) |
| Current or within 6 months prior to screening | 103 (8.3) |
| 6 to 12 months prior to screening | 9 (<1.0) |
| More than 12 months prior to screening | 311 (25.0) |
| None | 818 (65.8) |
| Missing | 32 |
| On stable opiate substitution therapy | |
| Yes | 131 (10.8) |
| No | 1085 (89.2) |
| Missing | 60 |
| Chronic kidney disease | |
| ≥90 mL/min | 440 (50.9) |
| ≥60–<90 mL/min | 358 (41.4) |
| ≥30–<60 mL/min | 32 (3.7) |
| <30 mL/min | 34 (3.9) |
| Missing | 412 |
| Dialysis treatment | 17 (1.3) |
| HIV coinfection | 54 (4.2) |
| HBV coinfection | 18 (1.4) |
| History of depression or bipolar disorder | 88 (6.9) |
| History of cardiovascular disease | 307 (24.1) |
| History of diabetes | 92 (7.2) |

Percentages are calculated from non-missing values.
*Of 426 patients with recreational drug use, type of illicit drug was: heroin, 58.0%; cocaine, 27.0%; marijuana, 13.8%; hashish, 8.9; opioids, 4.2%; other, 21.4% (patients could report >1 drug type).
HBV, hepatitis B virus; HIV, human immunodeficiency virus.

- More than half of the population (n = 692) were receiving comedications **(Table 3)**
  - The most common comedications (prescribed or non-prescribed) were antithrombotic drugs (n = 113; 8.9%), anxiolytics (n = 112; 8.8%), drugs used in addictive disorders (n = 109; 8.5%), and beta blocking drugs (n = 103; 8.1%) **(Table 3)**

### Table 3. Comedications at Baseline

| Comedication (in >5% of patients), n (%) | Total population N = 1276 |
|---|---|
| Any concomitant medication | 692 (54.2) |
| Antithrombotic drugs | 113 (8.9) |
| Anxiolytics | 112 (8.8) |
| Drugs for addictive disorders | 109 (8.5) |
| Beta blocking drugs | 103 (8.1) |
| Antidepressants | 98 (7.7) |
| Drugs for peptic ulcer and gastro-oesophageal reflux | 82 (6.4) |
| ACE inhibitors | 77 (6.0) |
| Selective calcium channel blockers | 75 (5.9) |

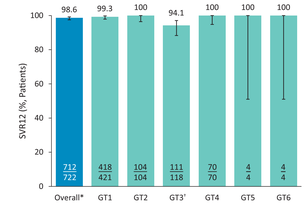
Comedications administered during the treatment period. ATC code 3 used.
ACE, angiotensin converting enzyme.

### EFFECTIVENESS

- Overall, the SVR12 rate was 98.6% (712/722) **(Figure 2A)**
  - There were 8 patients with virologic failure (2 on-treatment virologic failures and 6 relapses), of whom 7 had HCV GT3 infection **(Table 4)**
  - Three patients who had virologic failure were confirmed as having achieved SVR12 on retest after 1 February 2019 (data cut-off date)
- SVR12 rates across HCV GTs **(Figure 2A)** or subgroups of interest **(Figure 2B)** were generally similar

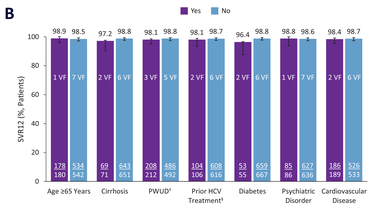
### Figure 2. SVR12 Rates With G/P Treatment (A) Overall and by HCV GT and (B) by Subgroups of Interest (CPSFU)

**A**




| Reason for non-response, n/N (%) | Overall* | GT1 | GT2 | GT3† | GT4 | GT5 | GT6 |
|---|---|---|---|---|---|---|---|
| On-treatment VF | 2/722 (0.3) | 0 | 0 | 2/118 (1.7) | 0 | 0 | 0 |
| Relapse | 6/652 (0.9) | 1/379 (0.3) | 0 | 5/101 (5.0) | 0 | 0 | 0 |
| Premature G/P discontinuation | 1/722 (0.1) | 1/421 (0.2) | 0 | 0 | 0 | 0 | 0 |
| Missing SVR12 data | 1/722 (0.1) | 1/421 (0.2) | 0 | 0 | 0 | 0 | 0 |

**B**




Error bars represent 95% confidence intervals.
*1 patient had unknown GT; this patient achieved SVR12.
†At the time of the data cut and subsequent analysis, two GT3 patients were confirmed as having achieved SVR12 on retest. Post hoc SVR12 rate for GT3 patients would then be 95.8% (113/118).
‡18 patients had unknown PWUD status; all patients achieved SVR12.
¶Prior experience with pegylated interferon (or interferon) and/or ribavirin and/or sofosbuvir; no prior experience with DAAs other than sofosbuvir.
CPSFU, core population with sufficient follow-up; DAA, direct-acting antiviral; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; PWUD, persons who use drugs; SVR12, sustained virologic response at post-treatment Week 12; VF, virologic failure.

### Table 4. Patients With Virologic Failure

| Patient | Country | HCV GT | Cirrhosis status | Prior HCV treatment | G/P treatment duration | G/P treatment completion | Adherent* | PWUD | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Belgium | 3 | NC | TN | 8 weeks | Yes | Yes | No | Relapse |
| 2 | France | 3a | NC | TN | 8 weeks | Yes | Yes | No | Relapse |
| 3 | Poland | 3a | NC | TN | 8 weeks | No | Yes | No | EOT positive† |
| 4 | Poland | 3 | NC | TN | 8 weeks | No | Yes | No | EOT positive† |
| 5 | Switzerland | 3a | NC | TN | 8 weeks | Yes | Yes | Yes | Relapse |
| 6 | Switzerland | 3a | NC | TN | 8 weeks | Yes | Yes | Yes | Relapse |
| 7 | Belgium | 1 | CC | TE‡ | 12 weeks | Yes | Yes | No | Relapse‡ |
| 8 | Italy | 3a | CC | TE§ | 16 weeks | Yes | Yes | Yes | Relapse |

*Patients were 100% adherent; no drug interruption or non-adherence were reported.
†Patient confirmed as having achieved SVR12 on retest.
‡Patient received prior treatment with interferon.
§Patient received prior treatment with pegginterferon plus ribavirin.
CC, compensated cirrhosis; EOT, end of treatment; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; NC, non-cirrhotic; PWUD, persons who use drugs; TE, treatment-experienced; TN, treatment-naïve; VF, virologic failure.

### SAFETY

- Treatment with G/P was well tolerated with no G/P-related serious AEs and a low rate of DAA-related AEs leading to premature G/P discontinuation (n = 5; 0.4%) **(Table 5)**
- The most common AEs were fatigue (n = 36; 2.8%), asthenia (n = 27; 2.1%), headache (n = 25; 2.0%), and nausea (n = 14; 1.1%) **(Table 5)**
- Elevations of alanine aminotransferase were uncommon and did not occur with total bilirubin elevations; no cases consistent with drug-induced liver injury were identified **(Table 5)**
- Elevations of total bilirubin were consistent with the labeled G/P-mediated inhibition of bilirubin transport and metabolism. Bilirubin elevations were not associated with hepatic decompensation **(Table 5)**
- One hepatic decompensation event (ascites) developed in 1 patient with baseline evidence of synthetic dysfunction and risk factor for passive congestion of the liver

### Table 5. AEs and Laboratory Abnormalities With G/P Treatment

| | Total population N = 1276 |
|---|---|
| **AEs** | |
| Any AE | 192 (15.0) |
| DAA-related AEs | 106 (8.3) |
| Serious AEs | 14 (1.1) |
| DAA-related serious AEs | 0 |
| AEs leading to discontinuation of study drug | 7 (0.5) |
| DAA-related AEs leading to discontinuation of study drug* | 5 (0.4) |
| Deaths† | 5 (0.4) |
| Common AEs (occurring in ≥1.0% of patients) | |
| Fatigue | 36 (2.8) |
| Asthenia | 27 (2.1) |
| Headache | 25 (2.0) |
| Nausea | 14 (1.1) |
| **Laboratory abnormalities** | |
| Post-nadir ALT >5 × ULN | 1/732 (0.1) |
| Total bilirubin ≥2 × ULN | 15/732 (2.0) |
| Post-nadir ALT >3 × ULN and total bilirubin >2 × ULN with a direct bilirubin: total bilirubin ratio >0.4 | 0/732 |

Data are n (%) or n/N (%).
*DAA-related AEs leading to discontinuation of study drug: nausea (n = 1); dizziness, nausea, and malaise (n = 1); loss of appetite, fatigue, and muscle cramps (n = 1); high creatinine value (n = 1); ascites (n = 1).
†There were no DAA-related deaths.
AE, adverse event; ALT, alanine aminotransferase; DAA, direct-acting antiviral; G/P, glecaprevir/pibrentasvir; ULN, upper limit of the normal range.

## CONCLUSIONS

- In patients with chronic HCV infection, the effectiveness and safety of G/P in these real-world observational studies were consistent with results seen in registrational trials
- The overall SVR12 rate was 98.6%, which was generally unaffected by HCV GT or subgroups of interest
- Treatment was well-tolerated with no G/P-related serious AEs; laboratory abnormalities and hepatic decompensation events were rare
- Enrollment, treatment, and follow-up are ongoing

## REFERENCES

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2. Wiegand J, et al. *Hepatology.* 2018;68:364A (abstract #611).
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## ACKNOWLEDGMENTS

Medical writing support was provided by Paul MacCallum, PhD, of Fishawack Communications Ltd., funded by AbbVie.

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