# Efficacy and Safety of Glecaprevir/Pibrentasvir in Renally-Impaired Patients With Chronic HCV Genotype 1–6 Infection

THU-363

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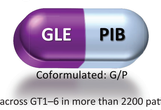
## INTRODUCTION

- Hepatitis C virus (HCV) infection is highly prevalent among patients with chronic kidney disease (CKD) and increases their risk of extra-hepatic complications including progression to end-stage renal disease[1]
- Previously-available direct-acting antiviral (DAA) regimens were not approved for patients with CKD across all HCV genotypes, were recommended for 12 or more weeks of treatment, and required the addition of ribavirin in some patient populations[2]
- Sofosbuvir-based regimens are not recommended in patients with moderate or severe CKD due to the renal excretion of sofosbuvir and its metabolite, GS-331007; when treated with sofosbuvir-based regimens, patients with advanced CKD have shown progressive deterioration of renal function[2,3]

### G/P is Approved for Patients With HCV GT1–6 Infection Including Those With CKD Stage 4/5

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




Coformulated: G/P

**Pibrentasvir**
pangenotypic NS5A inhibitor

- Overall SVR rate of 98% across GT1–6 in more than 2200 patients as well as in 104 patients with CKD stages 4/5 with or without dialysis[4,5]
- 8 week duration approved for all treatment naïve patients without cirrhosis[6]
- Favorable safety profile irrespective of baseline factors such as compensated liver cirrhosis or advanced renal disease, including those on dialysis
- Potent against common polymorphisms (eg, Y93H in NS5A and Q80K in NS3)
- Minimal renal excretion (<1%) of G/P

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

- G/P demonstrated high SVR12 rates (98%) and a favorable safety profile in patients with CKD stage 4 or 5, including those on dialysis, treated for 12 weeks in EXPEDITION-4[4]
- No dosage adjustment of G/P is required in patients with mild, moderate, or severe renal impairment, including those on dialysis
- EXPEDITION-5 is a Phase 3b clinical trial aimed at evaluating efficacy and safety of label-recommended G/P regimen among patients with CKD stage 3b, 4, or 5, including the 8-week G/P treatment duration indicated for patients who are treatment-naïve or PRS-experienced, and non-cirrhotic

## OBJECTIVE

- Evaluate efficacy and safety of G/P at the approved treatment durations among patients with moderate or severe CKD

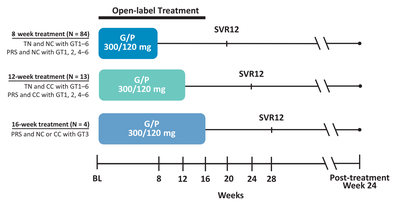
## METHODS

- Phase 3b, open label, non-randomized, multicenter study in HCV GT1-6-infected patients with CKD stage 3b, 4, or 5
  - Data were included for all patients who received at least 1 dose of study drug in an intent-to-treat analysis
  - Patients were enrolled in Canada, Germany, Greece, Italy, South Korea, Poland, Puerto Rico, Spain, Sweden, and the United States

## METHODS (CONTINUED)

- CKD stage was assessed at screening and defined by estimated glomerular filtration rate (eGFR) as follows:
  - CKD stage 3b: eGFR ≥30 to <45 mL/min/1.73 m$^2$
  - CKD stage 4: eGFR ≥15 to <30 mL/min/1.73 m$^2$
  - CKD stage 5: eGFR <15 mL/min/1.73 m$^2$ or dialysis-dependent
- G/P treatment for 8, 12, or 16 weeks based on HCV genotype, cirrhosis status, and prior treatment experience **(Figure 1)**
- G/P administered regardless of timing of either hemodialysis or peritoneal dialysis

### Figure 1. EXPEDITION-5 Study Design




BL, baseline; G/P, glecaprevir/pibrentasvir; SVR12, sustained virologic response at post-treatment Week 12; TN, treatment naive; PRS, experienced with interferon (IFN) or pegIFN ± ribavirin, or sofosbuvir + ribavirin; NC, non-cirrhotic; CC, compensated cirrhotic; GT, genotype.

### KEY INCLUSION CRITERIA

- Adults (≥18 years) with chronic HCV GT 1, 2, 3, 4, 5, or 6 infection (HCV RNA ≥1000 IU/mL)
- eGFR <45 mL/min/1.73 m$^2$ at screening, including patients on dialysis (either hemodialysis or peritoneal dialysis) for at least 1 month prior to treatment
- Patients without cirrhosis or with compensated cirrhosis as assessed by liver biopsy, Fibroscan, or Fibrotest and APRI

### KEY EXCLUSION CRITERIA

- Coinfection with either hepatitis B virus or HIV
- Clinical history of acute renal failure in the 3 months prior to screening
- Prior treatment experience with any investigational or commercial DAA other than sofosbuvir
- Presence of hepatocellular carcinoma (HCC) in an ultrasound, computed tomography, or magnetic resonance imaging within 3 months of screening

### ENDPOINTS AND ANALYSES

- Percentage of patients with SVR12 (HCV RNA <LLOQ 12 weeks after the last dose of study drug) in an intent-to-treat analysis
- Adverse events (AEs), including AEs leading to treatment discontinuations, AEs occurring in ≥5% of patients, serious AEs, DAA-related serious AEs, and laboratory abnormalities
- Renal function as assessed by requirement of dialysis in all patients and/or eGFR before and after G/P treatment in pre-dialysis patients

## PRELIMINARY RESULTS

### PATIENTS

- Among the 101 patients enrolled, 84 (83%) were treatment-naïve or PR-experienced, non-cirrhotic patients receiving G/P for 8-weeks
- Of the remaining patients, 13 (13%) with compensated cirrhosis and 4 (4%) with GT3 infection and prior treatment experience were treated with G/P for 12- and 16-weeks, respectively

### Table 1. Baseline Demographics and Disease Characteristics

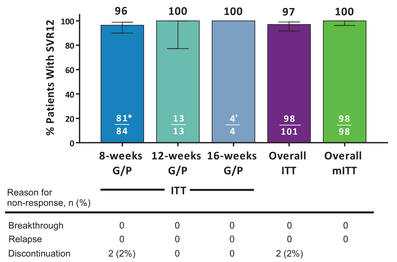
| Characteristic | 8-week G/P N = 84 | 12-week G/P N = 13 | 16-week G/P N = 4 | Overall N = 101 |
|---|---|---|---|---|
| Male, n (%) | 51 (61) | 7 (54) | 2 (50) | 60 (59) |
| Race | | | | |
| White | 62 (74) | 8 (62) | 4 (100) | 74 (73) |
| Black or African American | 11 (13) | 3 (23) | 0 | 14 (14) |
| Asian | 11 (13) | 2 (15) | 0 | 13 (13) |
| Hispanic or Latino ethnic origin | 16 (19) | 1 (8) | 1 (25) | 18 (18) |
| Age, median (range), years | 59 (32–84) | 58 (49–87) | 62 (54–70) | 58 (32–87) |
| BMI, median (range), kg/m$^2$ | 24.9 (16.8–53.5) | 28.7 (17.1–41.1) | 24.3 (17.7–26.8) | 25.2 (16.8–53.5) |
| Baseline HCV RNA level, median (range), $\log_{10}$ IU/mL | 5.9 (3.2–7.2) | 5.6 (4.8–7.2) | 6.6 (5.4–6.9) | 5.9 (3.2–7.2) |
| HCV RNA ≥1 million IU/mL, n (%) | 34 (40) | 5 (38) | 3 (75) | 42 (42) |
| HCV genotype, n (%)* | | | | |
| GT1 | 45 (54) | 9 (69) | 0 | 54 (54) |
| GT2 | 26 (31) | 1 (8) | 0 | 27 (27) |
| GT3 | 9 (11) | 2 (15) | 4 (100) | 15 (15) |
| GT4 | 3 (4) | 1 (8) | 0 | 4 (4) |
| Prior HCV treatment-experience, n (%) | | | | |
| Treatment-naive | 69 (82) | 12 (92) | 0 | 81 (80) |
| Treatment-experienced† | 15 (18) | 1 (8) | 4 (100) | 20 (20) |
| Fibrosis stage, n (%) | | | | |
| F0–1 | 61 (73) | 0 | 4 (100) | 65 (65) |
| F2 | 5 (6) | 0 | 0 | 5 (5) |
| F3 | 16 (19) | 0 | 0 | 16 (16) |
| F4 | 1 (1)‡ | 13 (100) | 0 | 14 (14) |
| Missing | 1 | 0 | 0 | 1 |
| CKD stage, n (%)§ | | | | |
| Stage 3b | 4 (5) | 3 (23) | 0 | 7 (7) |
| Stage 4 | 14 (17) | 2 (15) | 1 (25) | 17 (17) |
| Stage 5 | 66 (79) | 8 (62) | 3 (75) | 77 (76) |
| On dialysis¶ | 66 (79) | 8 (62) | 3 (75) | 77 (76) |
| History of Diabetes | 35 (42) | 6 (46) | 1 (25) | 42 (42) |
| History of Cardiovascular disease | 74 (88) | 12 (92) | 4 (100) | 90 (89) |
| History of Hypertension | 73 (87) | 11 (85) | 4 (100) | 88 (87) |

BMI, body-mass index; HCV, hepatitis C virus; GT, genotype; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
*Although eligible, no GT5- or GT6-infected patients were enrolled in this study.
†All patients with prior treatment-experience had previously received pegIFN ± RBV; no patients had prior experience with a DAA including sofosbuvir.
‡Despite this staging according to Fibrotest, other evidence confirmed the subject was non-cirrhotic.
§CKD stage was determined at screening visit.
¶Four patients (3 from 8-week arm and 1 from 12-week arm) were on peritoneal dialysis. All other patients were on hemodialysis.

### EFFICACY

- Overall SVR12 rate for the ITT population was 97% (95% CI; 91.6–99.0) **(Figure 2)**
  - Of the 3 patients not achieving SVR12, none experienced virologic failure (on-treatment breakthrough or relapse)
  - 2 patients prematurely discontinued due to AEs (pruritus and ileus) and 1 had missing SVR12 data

### Figure 2. Efficacy of G/P in Patients With CKD Stage 3b, 4, or 5 by Treatment Duration




| Reason for non-response, n (%) | | | | | |
|---|---|---|---|---|---|
| Breakthrough | 0 | 0 | 0 | 0 | 0 |
| Relapse | 0 | 0 | 0 | 0 | 0 |
| Discontinuation | 2 (2%) | 0 | 0 | 2 (2%) | |
| Missing $SVR_{12}$ | 1 (1%) | 0 | 0 | 1 (1%) | |

G/P, glecaprevir/pibrentasvir; ITT, intent-to-treat; mITT, modified ITT.
*One patient with NS5A Y93H resistance-associated substitution achieved SVR12.
†95% CI not presented for this treatment arm due to small sample size.

### SAFETY

- Overall, 56 (55%) patients experienced a treatment-emergent AE, of which 13 patients (13%) had a grade 3 or higher AE. All grade 3 or higher AEs were considered not related to G/P by the investigator
- The most common AEs overall by preferred term were pruritus (16%), hypertension (6%), generalized pruritus (6%), and bronchitis (5%)
  - All cases of hypertension occurred in patients with underlying history of hypertension and were considered not related to G/P
- No DAA-related serious AEs were observed
- No grade ≥3 laboratory abnormalities in ALT, AST, or total bilirubin were observed

### Table 2. Adverse Events and Laboratory Abnormalities

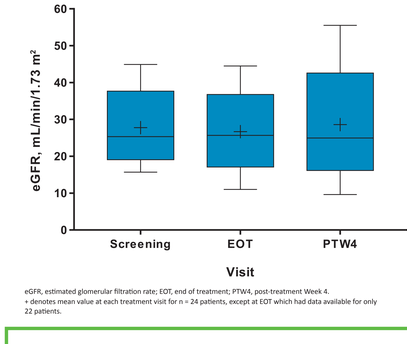
| Event, n (%) | Overall N = 101 |
|---|---|
| Any AE | 56 (55) |
| Grade ≥3 AE | 13 (13)* |
| Serious AE | 12 (12) |
| DAA-related† serious AE | 0 |
| AE leading to study drug discontinuation | 2 (2)‡ |
| AEs occurring in ≥5% of all patients by preferred term | |
| Pruritus§ | 16 (16) |
| Hypertension | 6 (6) |
| Generalized pruritus§ | 6 (6) |
| Bronchitis | 5 (5) |
| Laboratory abnormalities (Grade ≥3) | |
| ALT >5 × ULN¶ | 0 |
| AST >5 × ULN | 0 |
| Total bilirubin >3 × ULN | 0 |
| Deaths | 0 |

AE, adverse event; DAA, direct-acting antiviral; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.
*13 patients experienced 16 Grade ≥3 AEs namely anemia, ileus, bronchitis (n = 2), erysipelas, pneumonia, hyperglycemia, hypokalemia, myelopathy, presyncope, nephrolithiasis, pleural effusion, pulmonary edema, extremity necrosis, peripheral artery stenosis, and venous stenosis; all occurred in 1 patient unless otherwise noted.
†Relatedness of AEs to DAA treatment was determined by study investigator.
‡AEs of ileus and pruritus each occurred in 1 patient; the latter was considered DAA-related and started on Day 5 leading to study drug discontinuation and resolved by Day 18.
§22 (22%) patients reported Pruritus or Generalized pruritus.
¶Post-nadir increase in grade to Grade ≥3.

### RENAL FUNCTION

- Of the 24 patients with CKD Stage 3b or 4 (comprising the pre-dialysis population) and with available results, eGFR (mean ± SD, in mL/min/1.73 m$^2$) remained unchanged from screening (27.1 ± 9.2) to end of treatment (EOT; 26.4 ± 9.8) to post-treatment week 4 (PTW4; 27.4 ± 11.6) **(Figure 3)**
- At the individual patient level, for the 22 out of 24 patients with EOT results, CKD stage remained unchanged in 18 (82%), improved in 2 (9%), and declined in 2 (9%) from screening to EOT
  - Two patients with CKD stage 4 improved to stage 3b by EOT, but 2 declined to stage 5 without dialysis by EOT; no CKD stage 3b patients demonstrated a change in CKD stage
  - No patient experienced an AE of worsening of renal function or started dialysis during the treatment or post-treatment period

### Figure 3. Renal Function in Pre-dialysis Population Before and After G/P Treatment




eGFR, estimated glomerular filtration rate; EOT, end of treatment; PTW4, post-treatment Week 4.
+ denotes mean value at each treatment visit for n = 24 patients, except at EOT which had data available for only 22 patients.

## LIMITATIONS

- EXPEDITION-5 is an open-label study without an active or placebo control; however, the use of objective measures for efficacy, laboratory abnormalities, and renal function mitigates this concern
- The effect of G/P on renal function was only assessed through PTW4, thus no final conclusions can be made about long-term effect
- No patients with GT5 or GT6 infection enrolled in the study

## CONCLUSIONS

- G/P is highly efficacious in patients with CKD stage 3b to 5 treated with the label-recommended treatment durations based on HCV genotype, cirrhosis status, and prior treatment experience
- G/P treatment was well-tolerated with low rates of AEs leading to discontinuation, no DAA-related serious AEs, and no clinically relevant laboratory abnormalities
- The safety profile of G/P in the CKD population is consistent with the known safety profile described in the product information and with pre-existing comorbidities of the CKD population[7,8]
- Overall, renal function remained unchanged after G/P treatment in pre-dialysis patients assessed out to PTW4
- Data corroborate results from registrational studies with G/P demonstrating high efficacy and a favorable safety profile, thereby supporting the label-recommended regimen as a short duration, pangenotypic treatment option for patients with CKD including those on dialysis

## DISCLOSURES

**Marcello Persico:** Speaker: AbbVie, Gilead, BMS, MSD, Janssen.
**Robert Flisiak:** Consultancy/Advisory Board/Speaker: AbbVie, Alfa Wasserman, BMS, Gilead, Janssen, Merck, Roche.
**Meghan Sise:** Investigator in Clinical Trials sponsored by AbbVie, Gilead Sciences, Merck. Scientific Advisory Board Member: AbbVie and Merck. Scientific Consultant: AbbVie.
**Eric Lawitz:** Speaker: Gilead, GSK, Kadmon, Merck, Vertex; Research/Grant Support: AbbVie, Achillion, Boehringer Ingelheim, BMS, Gilead Sciences, GSK, Idenix, Intercept Pharmaceuticals, Janssen, Medtronic, Merck, Novartis, Presidio, Roche, Santaris Pharmaceuticals, Vertex; Advisor: AbbVie, Achillion, BioCryst, Biotica, Enanta, Idenix, Janssen, Merck, Novartis, Santaris, Theravance, Vertex.
**Jun Yong Park:** Investigator in Clinical Trials sponsored by AbbVie, Gilead Sciences, Hanmi, Norvatis.
**Marwan Kaskas:** Principal Investigator in AbbVie study; Speaker: Amgen and Novartis. Investigator: Frenova, Amgen, Akebia, Shield, Chemocentryx, Calipso, Fibrogen, Ironwood.
**Annette Bruchfeld:** Consulting Fees from ChemoCentryx and Merck; Honoraries for Lectures from AbbVie, MSD, Sanofi-Genzyme.
**Marcus-Alexander Wörns:** Advisor: AbbVie, BMS; Speaker: AbbVie, BMS, Gilead, Janssen.
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**Philippe J Zamor:** Grant/Research Funding: AbbVie, Gilead, Bristol-Myers Squibb, Merck; Speaker: Gilead, AbbVie, Janssen; Advisory: AbbVie, Bristol-Myers Squibb.
**Manal Abunimeh, Roger Trinh, Eric Cohen, Ariel Porcalla, Zhenyi Xue, Janean Rullman:** Employees of AbbVie Inc. and may hold stock or stock options.
AbbVie sponsored the study (NCT03069365) contributed to its design, participated in the collection, analysis and interpretation of the data, and in the writing, reviewing, and approval of the abstract. All authors had access to relevant data.

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