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ORIGINAL RESEARCH

Efficacy and Safety of Glecaprevir/Pibrentasvir in Participants with Chronic HCV Infection and Comorbidities or Multiple Concomitant Medications: An Integrated Analysis

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ABSTRACT

***Introduction*:** Glecaprevir/pibrentasvir (G/P) is globally approved for the treatment of chronic hepatitis C virus (HCV) infection and for acute HCV infection in the USA. The efficacy and safety of G/P has been clinically demonstrated in participants with chronic HCV. We used clinical trial data to assess the efficacy, safety, and tolerability of G/P in participants with comorbidities or on multiple concomitant medications with potential for drug–drug interaction with G/P.

***Methods*:** An integrated pooled analysis across 21 randomized, controlled phase 2 and 3 trials of participants who received G/P for 8, 12, or 16 weeks was performed. Participants were stratified by comorbidity or population of interest and by number of concomitant medications received.

***Results*:** This analysis included 6547 participants with chronic HCV infection. Overall, 2068 (31.6%) had cardiovascular disorders, 2031 (31.0%) reported illicit drug use, 1373/4617 (29.7%) reported injection drug use, 1810

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(27.6%) had psychiatric disorders, 1169 (17.9%) had compensated cirrhosis, and 291 (4.4%) had human immunodeficiency virus (HIV)–HCV coinfection. Additionally, 4524 (69.1%) were receiving ≥ 1 concomitant medication. According to the Liverpool HEP Drug Interactions checker, 1357 (20.7%) were receiving a concomitant medication with mechanistic potential or weak potential drug–drug interaction with G/P. Overall, 94.3% (6174/6547) achieved sustained virologic response at 12 weeks post-treatment (SVR12: 98.7% [6174/6257] when excluding non-virologic treatment failure), with consistent rates between subgroups. In total, 3140 (48.0%) of participants experienced an adverse event (AE) and 1638 (25.0%) experienced a treatment-related AE. Serious AEs and treatment-related serious AEs were observed in 165 (2.5%) and 6 (0.1%) participants, respectively. In subgroup analyses, the highest rate of treatment-related serious AEs was observed in participants with HIV–HCV coinfection (0.7%). Mean compliance was 99.6%, which was consistent across subgroups and by number of concomitant medications received.

Conclusions: These pooled data support the efficacy, safety, and tolerability of G/P in participants with chronic HCV infection and comorbidities or who are on multiple concomitant medications.

Keywords: Chronic HCV infection; Glecaprevir; Pibrentasvir; Comorbidity; Concomitant medication; Polypharmacy; Integrated analysis

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Key Summary Points

Why carry out this study?

Many individuals with hepatitis C virus (HCV) can have underlying comorbidities and may be receiving multiple concomitant medications or using illicit drugs.

We used clinical trial data to assess the efficacy, safety, and tolerability of glecaprevir/pibrentasvir (G/P) in participants with comorbidities or on multiple concomitant medications with potential for drug–drug interactions with G/P.

What was learned from the study?

G/P was effective and well tolerated in participants with HCV who had comorbidities or were on multiple concomitant medications.

The high efficacy and low rates of adverse events leading to treatment discontinuation support that potential drug–drug interactions between G/P and antipsychotics, calcium channel blockers, opioids, beta blockers, antihypertensives, and lipid-lowering agents should not be a barrier to treatment initiation.

The G/P regimen is suitable for a wide range of patients with chronic HCV infection and thus has an important role to aid in the elimination of HCV.

INTRODUCTION

Direct-acting antiviral (DAA) therapy is safe, efficacious, and is widely recommended for the treatment and management of individuals with hepatitis C virus (HCV) infection [1]. Compared with the general population, chronic HCV infection is more prevalent in those with comorbidities, notably those with psychiatric disorders and in people with current or former drug use [2–4]. Individuals with chronic HCV and underlying comorbidities may be receiving multiple concomitant medications or using illicit drugs [5–7]. Individuals with comorbidities

often require polypharmacy, increasing the risk of drug–drug interactions (DDIs) [8, 9]. Additionally, these individuals may have a less stable lifestyle and experience socioeconomic disparities, including food and housing insecurity, and lack of connection to the healthcare system, which can contribute to variable adherence to DAA treatment [10–13].

Glecaprevir/pibrentasvir (G/P) is a highly efficacious, pangenotypic, and well-tolerated DAA regimen with a high barrier to resistance, first approved in 2017 and currently approved globally for the treatment of chronic HCV infection; more recently, in June of 2025, G/P was approved by the US Food and Drug Administration (FDA) for the treatment of acute HCV infection [14, 15]. Several phase 2 and 3 clinical trials have demonstrated the efficacy, safety, and tolerability of G/P for the treatment of participants with chronic HCV, including those receiving multiple concomitant medications, with psychiatric or cardiovascular comorbidities, with human immunodeficiency virus (HIV) coinfection, and those with a history of or ongoing illicit drug use [12, 16–24].

Despite G/P having a well-documented safety profile, some potential DDIs between G/P and concomitant medications have been predicted based on enzyme inhibition patterns [14, 25–29]. Drug classes metabolized by pathways impacted by G/P and that are of particular interest are antipsychotics, calcium channel blockers, opioids (cytochrome P450 [CYP] 3A4 substrates), antihypertensives, lipid-lowering agents (organic anion transporting polypeptide 1B1/3 [OATP1B1] substrates), and beta blockers (P-glycoprotein [P-gp] substrates) [14, 26, 30]. These drug classes are of interest as they are frequently administered in populations living with chronic HCV infection and are predicted by the Liverpool HEP Drug Interactions checker to have potential mechanistic interactions with DAAs for treating HCV [31]. Additionally, the ability to manage of some of these drugs, such as antipsychotics and opioids, may be limited by narrow therapeutic drug index windows, constrained by the balance between efficacy and toxicity [32, 33]. Coadministration of G/P with concomitant medications that are substrates of P-gp, breast cancer resistance protein (BCRP), and OATP1B1/3 may result in an increased plasma concentration of these drugs [14]. Additionally, glecaprevir and pibrentasvir are weak inhibitors of CYP3A, CYP1A2, and uridine glucuronosyltransferase 1A1 [14]. Coadministration of G/P with medications that inhibit P-gp, BCRP, or OATP1B1/3 may increase glecaprevir and/or pibrentasvir concentrations. Currently, there are limited data available on coadministration of G/P with these drug classes, demonstrating an unmet need to further characterize the G/P safety profile.

Herein, using data from an integrated analysis of 21 clinical trials in patients with chronic HCV infection, we assess and report the efficacy, safety, tolerability of, and adherence to G/P, in participants with comorbidities, or on multiple concomitant medications. These data will allow us to better understand clinically relevant drug interactions vs purely theoretical ones and will help to further characterize the safety profile of G/P. This will support expansion of the treater pool by enabling non-specialists to provide HCV treatment, and aid in the goal of HCV elimination.

METHODS

Analysis Set

Data were pooled from 6547 participants with chronic HCV genotype 1–6 infection and either without cirrhosis or with compensated cirrhosis across 21 randomized, controlled, phase 2 and phase 3 clinical trials evaluating G/P worldwide (Tables S1 and S2).

This integrated analysis set included all participants who received at least one dose of glecaprevir 300 mg and pibrentasvir 120 mg either as separate tablets (phase 2 formulation) or coformulated tablets dosed orally as three pills for a total 300 mg/120 mg dose (phase 3 formulation). Both formulations were given once daily (with food), as all-oral regimens for 8, 12, or 16 weeks.

This article is based on previously conducted studies. Included studies were performed in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and principles of the Declaration of Helsinki or the laws and regulations of the regions in which the research was done. Studies were approved by the institutional review boards or independent ethics committees of the participating sites. Written informed consent was obtained from all study participants.

Participants

Complete inclusion and exclusion criteria were similar across all clinical trials except for some key trial-specific eligibility criteria. Populations of interest for this study were those with psychiatric disorders, cardiovascular disorders, HIV–HCV coinfection, cirrhosis, and who were ≥ 65 years of age, as well as people who use illicit drugs (PWUD) or inject drugs (PWID). These comorbidities were selected based on their increased prevalence among individuals with HCV infection [2–4]. Determination of the presence of psychiatric disorders, cardiovascular disorders, and HIV–HCV coinfection was based on medical history and/or the receipt of concomitant medication to treat those conditions. Illicit or injection drug use was self-reported by the participant. Participants with a medical history of psychiatric disorders were allowed unless the disorder was uncontrolled and made the participant unsuitable for inclusion in the trial, as assessed by the study investigator. Ongoing drug or alcohol use was allowed unless it could preclude optimal adherence, per study investigator assessment. Among participants with reported drug use, current illicit drug use was defined as use reported ≤ 12 months prior to study enrollment and former illicit drug use was reported > 12 months prior to enrollment.

Concomitant medications of interest, based on the potential for interaction with G/P, were antipsychotics, calcium channel blockers, beta blockers, other antihypertensives, lipid-lowering agents, and opioids.

Procedures

Interaction status between G/P and comedications was determined based on the University of Liverpool HEP Drug Interactions checker, where interaction was classified as no interaction expected (green), potential weak interaction (yellow), potential interaction (orange), or do not coadminister (red) [31].

Efficacy was assessed as sustained virologic response 12 weeks after the end of treatment (SVR12) [34]. For SVR12 assessments, HCV RNA levels were measured using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test (version 2.0; Roche Molecular Systems, Branchburg, NJ, USA), which has a lower limit of quantification and lower limit of detection of 15 IU/mL.

Safety was evaluated by monitoring adverse events (AEs), vital signs, physical examination findings, electrocardiography, and clinical laboratory tests. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and were assessed for their relationship with G/P by study investigators. Liver test abnormalities were assessed and Hy's law criteria were used to detect liver injury signals per FDA guidance [35].

Study drug interruption was defined as a pause in treatment with subsequent restarting. Treatment discontinuation was defined as cessation of treatment without restarting. Treatment adherence was assessed using pill count at visits every 4 weeks during the treatment period including at the end of treatment visit. Adherence was calculated as the percentage of tablets taken vs tablets expected to be taken. Participants were considered adherent if the percentage of tablets taken vs tablets expected was 80–120%.

Statistical Analysis

Statistical summaries were descriptive in nature, and no statistical hypothesis testing was performed. The full analysis set (FAS) was defined as

all participants who received ≥1 G/P dose. The modified FAS (mFAS) was defined as the FAS but excluding those who did not achieve SVR12 for non-virologic reasons.

An analysis of the relationship between interruption of study drug and number of concomitant medications was performed. A logistic regression model was adopted, which used the actual number of concomitant medications as a continuous predictor instead of the eight subgroups defined by number of concomitant medications (i.e., 1–2, 3–4, etc.) used in other analyses.

SAS EG version 8.3 software was used for the statistical analyses.

RESULTS

Baseline Characteristics

This analysis included 6547 participants with chronic HCV infection treated with G/P for 8, 12, or 16 weeks. Overall, 2068 participants (31.6%) had a medical history of a cardiovascular disorder, 1810 (27.6%) had a psychiatric disorder, 1169 (17.9%) had compensated cirrhosis, and 291 (4.4%) had HIV–HCV coinfection; 2031 (31.0%) reported current or former illicit drug use (Table 1). Among participants with injection drug use information ($n=4617$), 1373 (29.7%) reported current or former injection drug use and there were 62 participants (1.3%) who reported current use. Use of illicit or recreational drugs with the potential for interaction with G/P was self-reported by 15 participants (0.2%), all reporting etizolam use. Among those with psychiatric disorders, the most common disorders were depression (43.5%), sleep disorder (23.5%), and anxiety (21.9%) (Table S3).

Overall, 2023 (30.9%) participants were not receiving any concomitant medications, while 4524 (69.1%) were receiving ≥1 concomitant medication (Table 1). Smaller numbers of patients had extreme polypharmacy, with 79 (1.2%) receiving 15–19 concomitant medications and 59 (0.9%) receiving ≥20. Considering specific drug classes with a mechanistic interaction with G/P, 3.5% of overall participants were receiving antihypertensives, 3.4% lipid-lowering agents, 2.1% antipsychotics, 2.0% opioids, 1.4% beta blockers, and 0.7% calcium channel blockers (Table S4).

According to the Liverpool HEP Drug Interactions checker, among all participants in the analysis, most (79.3%) had no potential DDI between G/P and a concomitant medication (Fig. 1). Among comorbidity or subgroups of interest, the proportions of participants with a concomitant medication with a potential weak (yellow) or potential interaction (orange) with G/P ranged from 16.2% to 43.4%.

Efficacy

In the FAS ($N=6547$), 94.3% of participants achieved SVR12 (Fig. 2). In the mFAS ($n=6257$), which excluded participants who did not achieve SVR12 for non-virologic reasons, SVR12 was 98.7%. Among the 83 participants who did not achieve SVR12 in the FAS, 51 were due to relapse, 19 due to on-treatment virologic failure, and 13 due to non-virologic failure (8 due to treatment discontinuation and 5 due to other reasons).

Among comorbidity and subgroups of interest, SVR12 rates in the mFAS ranged from 97.9% to 99.3% (Fig. 2a). The number of concomitant medications did not impact SVR12 rates, as the mFAS SVR12 rates ranged from 98.0% to 100% in subgroups defined by number of concomitant medications (Fig. 2b). Across participants receiving the key concomitant medications of interest, SVR12 rates were ≥93.4% in the FAS and ≥96.9% in the mFAS (Fig. S1).

Safety and Tolerability

The safety and tolerability of G/P in comorbidity and subgroups of interest is shown in Table 2. Overall, 48.0% of participants experienced an AE of any cause and 25.0% experienced a treatment-related AE. By subgroup, the lowest rates of AEs of any cause and treatment-related AEs were in the HIV–HCV coinfection population (41.6% and 22.0%, respectively) and were highest among PWID (70.0% and 42.0%).

Serious AEs (SAEs) and treatment-related SAEs (as assessed by investigators) were observed in

Table 1 Demographics and baseline characteristics of the study participants

Baseline characteristic	G/P 8 weeks (*n* = 4229)	G/P 12 weeks (*n* = 2152)	G/P 16 weeks (*n* = 166)	Overall (*N* = 6547)
Sex at birth, *n* (%)				
Male	2290 (54.1)	1237 (57.5)	119 (71.7)	3646 (55.7)
Female	1939 (45.9)	915 (42.5)	47 (28.3)	2901 (44.3)
Median age (min, max)	53 (18, 88)	56 (20, 88)	56 (25, 77)	54 (18, 88)
Country, *n* (%)				
USA	550 (13.0)	430 (20.0)	62 (37.3)	1042 (15.9)
Outside the USA	3679 (87.0)	1722 (80.0)	104 (62.7)	5505 (84.1)
Race, *n* (%)				
White	3011 (71.2)	1493 (69.5)	137 (82.5)	4641 (70.9)
Asian	986 (23.3)	494 (23.0)	16 (9.6)	1496 (22.9)
Black or African American	204 (4.8)	126 (5.9)	11 (6.6)	341 (5.2)
Native Hawaiian or Pacific Islander	8 (0.2)	12 (0.6)	1 (0.6)	21 (0.3)
American Indian or Alaskan Native	6 (0.1)	6 (0.3)	1 (0.6)	13 (0.2)
Multiple	13 (0.3)	18 (0.8)	0	31 (0.5)
Missing	1	3	0	4
≥ 65 years of age, *n* (%)	700 (16.6)	456 (21.2)	24 (14.5)	1180 (18.0)
Comorbidities, *n* (%)				
Cardiovascular disorder	1111 (26.3)	896 (41.6)	61 (36.7)	2068 (31.6)
PWUD	1256 (29.7)	699 (32.5)	76 (45.8)	2031 (31.0)
Psychiatric disorder	1018 (24.1)	730 (33.9)	62 (37.3)	1810 (27.6)
PWID[a]	709 (27.7)	601 (31.2)	63 (48.5)	1373 (29.7)
Use reported ≤ 12 months prior[b]	34 (1.3)	27 (1.4)	1 (0.8)	62 (1.3)
Use reported > 12 months prior[b]	509 (19.9)	444 (23.1)	6 (4.6)	959 (20.8)
Compensated cirrhosis	343 (8.1)	755 (35.1)	71 (42.8)	1169 (17.9)
HIV–HCV coinfection	248 (5.9)	40 (1.9)	3 (1.8)	291 (4.4)
Number of concomitant medications, *n* (%)				
0	1552 (36.7)	434 (20.2)	37 (22.3)	2023 (30.9)
1–2	1207 (28.5)	541 (25.1)	46 (27.7)	1794 (27.4)
3–4	632 (14.9)	421 (19.6)	21 (12.7)	1074 (16.4)
5–6	379 (9.0)	285 (13.2)	18 (10.8)	682 (10.4)
7–9	268 (6.3)	239 (11.1)	21 (12.7)	528 (8.1)

Table 1 continued

Baseline characteristic	G/P 8 weeks ($n = 4229$)	G/P 12 weeks ($n = 2152$)	G/P 16 weeks ($n = 166$)	Overall ($N = 6547$)
10–14	142 (3.4)	154 (7.2)	12 (7.2)	308 (4.7)
15–19	29 (0.7)	44 (2.0)	6 (3.6)	79 (1.2)
≥ 20	20 (0.5)	34 (1.6)	5 (3.0)	59 (0.9)

G/P glecaprevir/pibrentasvir, *PWID* people who inject drugs, *PWUD* people who use illicit drugs

[a]Data not included for one study where PWID data were not reported (G/P 8 weeks [$n = 2563$]; G/P 12 weeks [$n = 1924$]; G/P 16 weeks [$n = 130$]; Overall [$N = 4617$])

[b]Data not included for four studies where timing of most recent injection drug use was not reported (G/P 8 weeks [$n = 2563$]; G/P 12 weeks [$n = 1924$]; G/P 16 weeks [$n = 130$]; Overall [$N = 4617$])

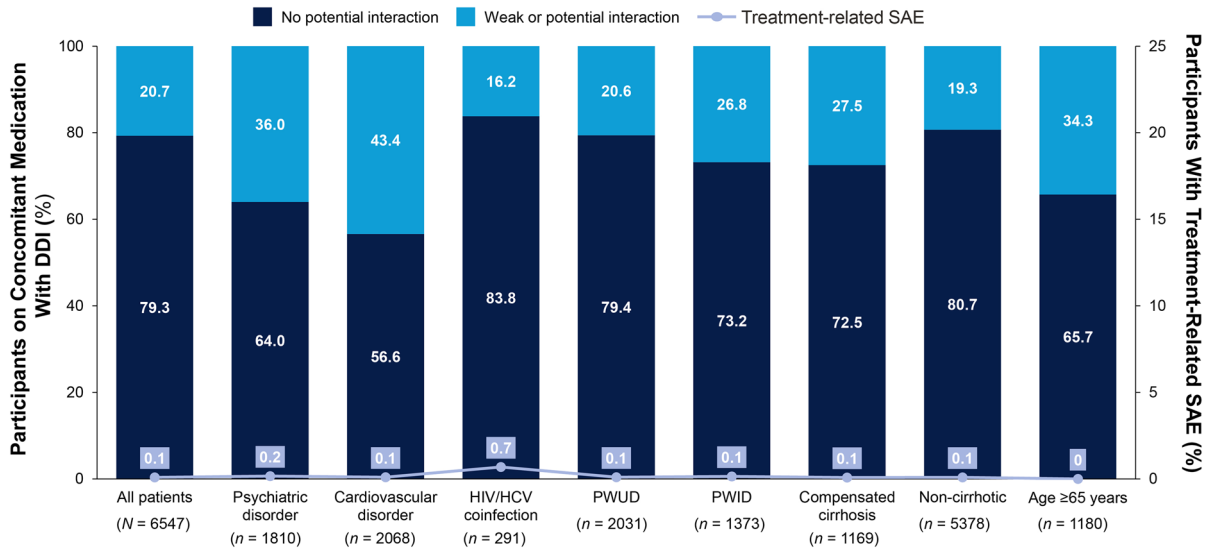

Fig. 1 Participants classified as having potential or weak potential drug–drug interaction according to comorbidity or subgroup of interest. *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *PWID* people who inject drugs, *PWUD* people who use illicit drugs

2.5% and 0.1% of participants, respectively. Treatment-related SAEs included angioedema ($n = 2$), as well as pericarditis, upper gastrointestinal hemorrhage, sinusitis, and transient ischemic attack (all $n = 1$). Among the comorbidity and subgroups of interest, rates of SAEs ranged from 2.2% in non-cirrhotic individuals to 5.0% in participants with cardiovascular disease. The highest rate of treatment-related SAEs was 0.7%, observed in the HIV–HCV coinfection population, where two participants experienced a treatment-related SAE of angioedema. Treatment-related SAEs observed in the PWID population were transient ischemic attack and angioedema. Study drug discontinuations due to AE occurred in 0.5% of participants overall, ranging from 0.4% in PWUD to 1.1% in participants ≥ 65 years of age. Of the 30 study drug discontinuations due AE, 17 were due to treatment-related AEs.

The safety and tolerability of G/P by number of concomitant medications is shown in Table 3. The overall rate of AEs was 21.5% among participants with no concomitant medications, while rates of AEs among participants taking concomitant medications were proportionally

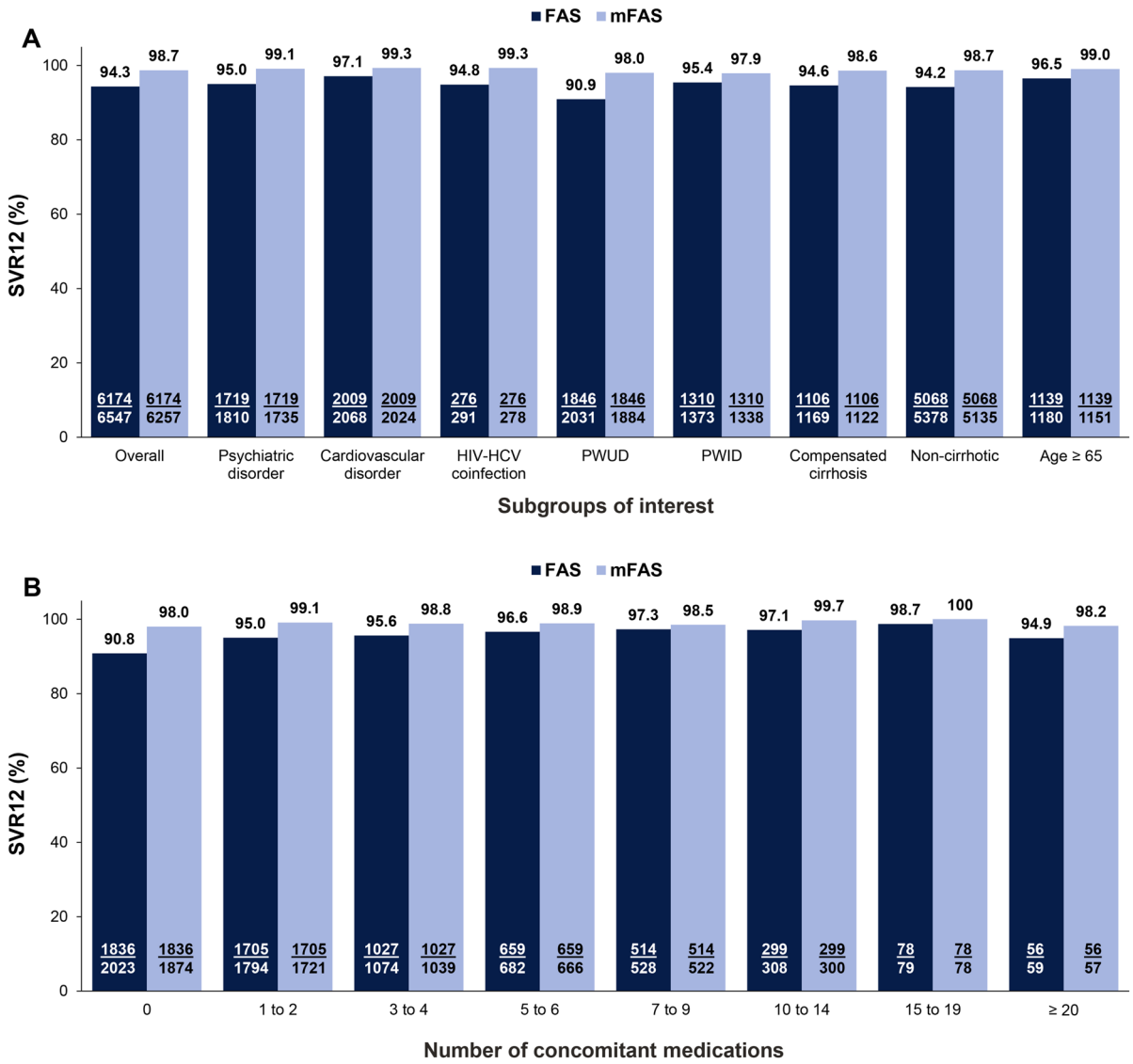

Fig. 2 SVR12 by **a** subgroups of interest and **b** number of concomitant medications. *FAS* final analysis set, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *mFAS* modified final analysis set, *PWID* people who inject drugs, *PWUD* people who use illicit drugs, *SVR12* sustained virologic response 12 weeks after the end of treatment

increased with the number of concomitant medications and ranged from 47.5% (one to two concomitant medications) to 94.9% (≥ 20 concomitant medications). Similar trends were observed with treatment-related AEs (no concomitant medication 10.0% vs a range of 24.6% with 1–2 to 50.8% with ≥ 20) and SAEs (0.5% vs a range of 0.9% with 1–2 to 44.1% with ≥ 20). Treatment-related SAEs were infrequent, with none reported among participants with no concomitant medications and rates ranging from 0% to 0.3% in subgroups defined by number of concomitant medications. Overall, treatment-related SAEs were not observed in participants with potential interactions across antipsychotics, calcium channel blockers, beta blockers, other hypertensives, and lipid-lowering agents in the pooled analysis (Fig. S2). Low rates of

Table 2 Safety, tolerability, and laboratory abnormalities by comorbidity or subgroup of interest

n (%)	Overall (*N* = 6547)	Psychiatric disorder (*n* = 1810)	CV disorder (*n* = 2068)	HIV–HCV coinfection (*n* = 291)	PWUD (*n* = 2031)	PWID (*n* = 1373)	Compensated cirrhosis (*n* = 1169)	Non-cirrhotic (*n* = 5378)	≥ 65 years of age (*n* = 1180)
Any AE	3140 (48.0)	1169 (64.6)	1195 (57.8)	121 (41.6)	1058 (52.1)	961 (70.0)	594 (50.8)	2546 (47.3)	559 (47.4)
TRAE	1638 (25.0)	674 (37.2)	622 (30.1)	64 (22.0)	623 (30.7)	576 (42.0)	306 (26.2)	1332 (24.8)	267 (22.6)
SAE	165 (2.5)	75 (4.1)	104 (5.0)	8 (2.7)	50 (2.5)	38 (2.8)	47 (4.0)	118 (2.2)	50 (4.2)
TRSAE	6 (0.1)	3 (0.2)	2 (0.1)	2 (0.7)	2 (0.1)	2 (0.1)	1 (0.1)	5 (0.1)	0
Study drug D/C due to AE	30 (0.5)	16 (0.9)	18 (0.9)	3 (1.0)	9 (0.4)	8 (0.6)	8 (0.7)	22 (0.4)	13 (1.1)
ALT ≥ 3 × ULN	34 (0.5)	7 (0.4)	10 (0.5)	2 (0.7)	12 (0.6)	11 (0.8)	10 (0.9)	24 (0.4)	2 (0.2)
AST ≥ 3 × ULN	10 (0.2)	2 (0.1)	2 (< 0.1)	1 (0.3)	2 (< 0.1)	2 (0.1)	5 (0.4)	5 (< 0.1)	0
TBL ≥ 3 × ULN	7 (0.1)	2 (0.1)	4 (0.2)	1 (0.3)	1 (< 0.1)	1 (< 0.1)	3 (0.3)	4 (< 0.1)	4 (0.3)
ALT ≥ 3 × ULN + TBL ≥ 2 × ULN	3 (< 0.1)	1 (< 0.1)	0	0	1 (< 0.1)	1 (< 0.1)	0	3 (< 0.1)	0

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CV* cardiovascular, *D/C* discontinuation, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *PWID* people who inject drugs, *PWUD* people who use illicit drugs, *SAE* serious adverse event, *TBL* total bilirubin, *TR* treatment-related, *ULN* upper limit of normal

Table 3 Safety, tolerability, and laboratory abnormalities by number of concomitant medications

n (%)	Number of concomitant medications							
	0 (*n* = 2023)	1–2 (*n* = 1794)	3–4 (*n* = 1074)	5–6 (*n* = 682)	7–9 (*n* = 528)	10–14 (*n* = 308)	15–19 (*n* = 79)	≥ 20 (*n* = 59)
Any AE	434 (21.5)	853 (47.5)	641 (59.7)	457 (67.0)	384 (72.7)	247 (80.2)	68 (86.1)	56 (94.9)
TRAE	202 (10.0)	442 (24.6)	347 (32.3)	228 (33.4)	216 (40.9)	133 (43.2)	40 (50.6)	30 (50.8)
SAE	10 (0.5)	17 (0.9)	20 (1.9)	19 (2.8)	26 (4.9)	32 (10.4)	15 (19.0)	26 (44.1)
TRSAE	0	1 (0.1)	2 (0.2)	1 (0.1)	1 (0.2)	1 (0.3)	0	0
Study drug D/C due to AE	3 (0.1)	5 (0.3)	5 (0.5)	5 (0.7)	4 (0.8)	5 (1.6)	2 (2.5)	1 (1.7)
ALT ≥ 3 × ULN	8 (0.4)	11 (0.6)	6 (0.6)	6 (0.9)	3 (0.6)	0	0	0
AST ≥ 3 × ULN	0	6 (0.3)	3 (0.3)	0	1 (0.2)	0	0	0
TBL ≥ 3 × ULN	1 (< 0.1)	2 (0.1)	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0	0
ALT ≥ 3 × ULN + TBL ≥ 2 × ULN	0	1 (0.1)	2 (0.2)	0	0	0	0	0

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *D/C* discontinuation, *SAE* serious adverse event, *TBL* total bilirubin, *TR* treatment-related, *ULN* upper limit of normal

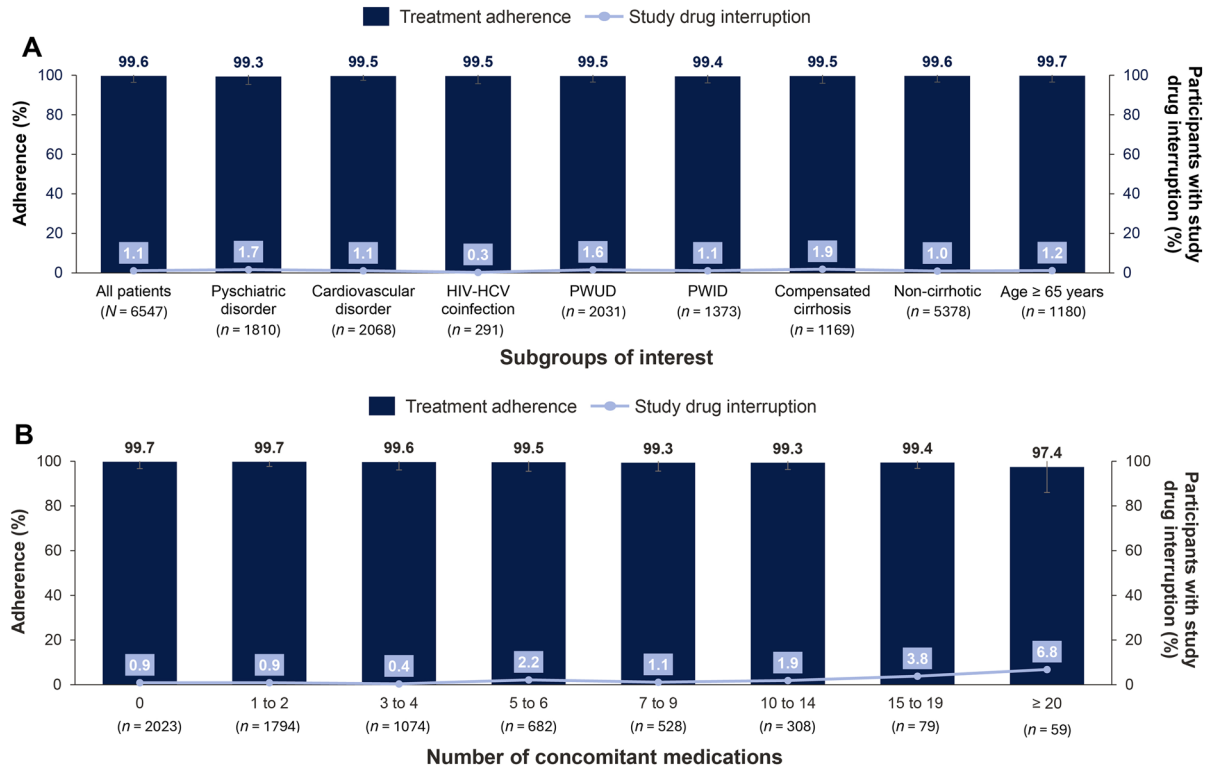

Fig. 3 Treatment adherence and study drug interruptions by **a** subgroups of interest and **b** number of concomitant medications. *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *PWID* people who inject drugs, *PWUD* people who use illicit drugs

treatment-related SAEs were observed in participants on opioids, occurring in 0.8% of participants in this subgroup.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin elevations ≥ 3 × upper limit of normal (ULN) occurred in 0.5%, 0.2%, or 0.1% of participants, respectively, and < 0.1% participants experienced ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (Table 2). ALT, AST, and total bilirubin elevations occurred in < 1% of participants in all subgroups (range, < 0.1% to 0.9%), irrespective of comorbidities or the number of concomitant medications. There were three participants who met the liver test laboratory criteria of ALT ≥ 3 × ULN combined with total bilirubin ≥ 2 × ULN. None of these cases met the criteria for Hy's law.

Adherence and Drug Interruptions

Overall, 94.1% of participants were adherent to G/P therapy and mean adherence was 99.6%. Mean adherence rates were consistent across comorbidity and subgroups of interest (Fig. 3a) and by subgroups defined by number of concomitant medications (Fig. 3b). Among comorbidity and subgroups of interest, the rate of study drug interruptions was consistently low, ranging from 0.3% in participants with HIV–HCV coinfection to 1.9% in participants with compensated cirrhosis (Fig. 3a). Among subgroups defined by the number of concomitant medications, overall the range was 0.9% in participants receiving 0 concomitant medications up to 6.8% of participants receiving ≥ 20

concomitant medications (Fig. 3b). A statistical analysis of the rate of study drug interruptions by number of concomitant medications suggests that the odds of having a study drug interruption increased as the number of concomitant medications increased (odds ratio 1.08; 95% CI 1.05, 1.12). Across subgroups defined by classes of concomitant medications received, mean treatment adherence was high (>98%) and study drug interruptions were low (Fig. S3).

DISCUSSION

There is an aim to treat all individuals with HCV, irrespective of comorbidity, both to ensure equitable care and to meet global HCV elimination goals. Promoting the involvement of non-specialist treaters is a way to expand the treater pool [36]. Simplified DAA regimens with manageable safety profiles are key for expansion of the HCV treater pool, notably for the treatment of individuals with limited exposure to the traditional healthcare system. As a result of the increased prevalence of chronic HCV infection in those with comorbidities compared with the general population, these are key populations of interest for HCV treatment [2–4]. The benefits reported after treatment in these populations include reductions in the number of hospitalizations, and reductions in liver-related morbidity, liver-related mortality, and all-cause mortality [37, 38].

This integrated pooled analysis of participants with HCV confirms that the pangenotypic, once-daily DAA regimen G/P had high efficacy and was well tolerated in those with comorbidities or on multiple comedications. Those with chronic HCV are more likely to be taking multiple medications in addition to DAAs for treating HCV infection [9]. In this study, coadministration of G/P with concomitant antipsychotics, calcium channel blockers, opioids, beta blockers, antihypertensives, and lipid-lowering agents had a favorable risk and tolerability profile. The overall SVR12 rate was 94.3% (98.7% in the mFAS) and rates were similar across comorbidity subgroups, including those with polypharmacy. Treatment-related SAEs and study drug discontinuations due to AEs were infrequent across all subgroups. Mean treatment adherence was 99.6% overall, adherence rates were consistent across subgroups, and study drug interruptions were infrequent.

In this study, 69.1% of participants were receiving ≥1 concomitant medication. Numerically increased rates of treatment-related AEs, SAEs, and study drug interruptions were observed in cases of extreme polypharmacy, such as ≥10 concomitant medications. Although adverse events reported were lowest in participants not receiving any concomitant medications, this finding is not unexpected given that polypharmacy increases risk of adverse events [39]. Notably, study drug interruptions occurred in <2.2% of participants in the subgroups who received <15 concomitant medications. In cases of extreme polypharmacy, side effects from concomitant medications will need to be managed; however, treatment interruption rates were low overall, and polypharmacy did not impact SVR12 rates in this study. Compared with the overall study population, FAS SVR12 rates were numerically lower among patients receiving concomitant antipsychotic medication (93.4%) or opioids (94.0%). However, the most commonly used antipsychotic, quetiapine, as well as opioids, are CYP3A4 substrates and are not expected to affect glecaprevir or pibrentasvir concentrations, suggesting the lower SVR12 rates were not due to DDIs.

This study included a substantial number of participants with psychiatric disorders (27.6%), as well as PWUD (31.0%) and PWID (29.7% among those with data available). Adherence to DAAs among those with psychiatric disorders and PWUD and PWID can be variable due to a range of factors, including less stable lifestyle, socioeconomic disparities, and disconnection from the healthcare system [10–13]. Mean adherence in this analysis was high, likely due to the structure afforded by clinical trial participation and the voluntary exclusion of PWUD and PWID deemed to have a high risk of non-adherence. Additionally, the rates of all-cause and treatment-related AEs were numerically higher in the psychiatric disorder, PWUD, and PWID subgroups compared with the overall

study population. This is consistent with previous analyses of patients treated with G/P in the clinical trial program [11, 23] and real-world data [40, 41], suggesting the increase is primarily driven by the comorbidity.

There were some limitations to this study. Some subgroups, such as those receiving ≥ 20 concomitant medications or those receiving specific concomitant drugs, had small sample sizes. Additionally, these results were based on clinical trial data and may not be representative of real-world data, including in difficult-to-reach populations experiencing housing and other insecurities. Further, there may be confounding variables not accounted for in the analysis, such as sex/gender or age groups other than the 65-year cutoff used in this analysis. Additionally, PWID and PWUD status were not available in some of the trials. Lastly, adherence to concomitant medications was not assessed and could have varied between participants.

CONCLUSION

Overall, this integrated pooled analysis demonstrated that G/P was effective and well tolerated, with high adherence, in participants with HCV who had comorbidities or were on multiple concomitant medications. Additionally, these data provide evidence that certain potential drug–drug interactions do not have clinical significance and should not be a barrier to treatment starts. Overall, these data support that the G/P regimen is suitable for a wide range of patients with chronic HCV infection and thus has an important role to aid in the elimination of HCV.

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Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg., protocols, clinical study reports, synopses, or statistical analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Use Agreement (DUA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. For more information on the process or to submit a request, visit

the following link: https://vivli.org/ourmember/abbvie/ then select "Home".

Declarations

Conflict of Interest. Curtis Cooper: speaker fees from AbbVie and Gilead; advisor for AbbVie and Gilead; unrestricted research and program funding from AbbVie and Gilead. Shweta A. Raina, Lisa Johnson, Liz Uribe, Moming Li, Alexandru Iacob, John Marcinak, and Dimitri Semizarov: employees of AbbVie and may own stock or options. Jordan J. Feld: honoraria/research support from AbbVie, Gilead, and Atea. Ashley Brown: no relevant disclosures. Anthony Martinez: speaking fees from AbbVie, Gilead, Cepheid, Madrigal, Braeburn, and Ipsen; consulting fees from AbbVie, Gilead, Cepheid, Madrigal, Ipsen, Atea, Altimune, and Arbutus; research funding from Cepheid. Brian Conway: speaking fees from AbbVie, AstraZeneca, Gilead, GSK, Indivior Canada, Merck, Moderna, Pfizer Canada, Sanofi Pasteur, Sequiris, and ViiV; consulting for AbbVie, AstraZeneca, Gilead, GSK, Indivior Canada, Merck, Moderna, Sanofi Pasteur, Sequiris, and ViiV; research support from AbbVie, AstraZeneca, Gilead, GSK, Indivior Canada, Merck, Moderna, Sanofi Pasteur, Sequiris, and ViiV. Stuart C. Gordon, Tarik Asselah: honoraria/research support from AbbVie, Gilead, and Atea. Stanislas Pol: speaker, consultant, and advisory board member for Janssen, Gilead, Roche, MSD, AbbVie, Biotest, Shinogi, ViiV, and French laboratory of fractionation and biotechnology (LFB); research support from Gilead, AbbVie, Roche, and MSD.

Ethical Approval. This article is based on previously conducted studies. Included studies were performed in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and principles of the Declaration of Helsinki or the laws and regulations of the regions in which the research was done. Studies were approved by the institutional review boards or independent ethics committees of the participating sites. Written informed consent was obtained from all study participants.

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