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Glecaprevir/pibrentasvir in patients with chronic HCV and recent drug use: An integrated analysis of 7 phase III studies

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ABSTRACT

Background: Injection drug use is the primary mode of transmission for hepatitis C virus (HCV), and treatment guidelines recommend treating HCV-infected people who use drugs; however, concerns about adherence, effectiveness, and reinfection have impeded treatment uptake.

Methods: Data were pooled from seven phase III trials that evaluated the efficacy and safety of 8 or 12 weeks of glecaprevir/pibrentasvir (G/P) in patients chronically infected with HCV genotypes 1–6. Patients had compensated liver disease, with or without cirrhosis, and were HCV treatment-naïve or -experienced with interferon or pegylated interferon ± ribavirin, or sofosbuvir plus ribavirin ± pegylated interferon. Patients were grouped into recent drug users (injection drug use ≤12 months before screening, positive urine drug screen [UDS], and/or drug-related adverse event), former drug users (> 12 months before screening and negative UDS), or non-drug users. Assessments included sustained virologic response at 12 weeks posttreatment (SVR12), treatment adherence, and safety.

Results: Among 1819 patients, 5%, 34%, and 61% were recent, former, and non-drug users, respectively. Treatment adherence and completion were high (≥96%) regardless of drug use status. SVR12 was achieved by 93% (n/N = 91/98), 97% (n/N = 591/610), and > 99% (n/N = 1106/1111) of recent, former, and non-drug users, respectively (intention-to-treat analysis). The overall rates of virologic failure were ≤1.5% across all three subpopulations, with no HCV reinfections among recent drug users. Drug-related serious adverse events and adverse events leading to treatment discontinuation were experienced by ≤1% of patients.

Conclusions: G/P is a well-tolerated and efficacious pangenotypic regimen for chronic HCV-infected people with recent or active drug use.

1. Introduction

People who use drugs (PWUD) are at increased risk for hepatitis C virus (HCV) infection because of high-risk drug use behaviors,(Reed et al., 2016) and injection drug use is now the primary mode of transmission for HCV in many parts of the world. (Hajarizadeh et al., 2013) Anti-HCV seroprevalence is estimated at 52% in injection drug users (IDUs), or approximately 8–10 million people worldwide. (Degenhardt et al., 2017; Larney et al., 2017) Among IDUs, the most common HCV genotype (GT)/subtype is 3a,(Jacka et al., 2014; Morice

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et al., 2006; Salehi Moghadam et al., 2014) and studies have demonstrated that 50–65% of people with GT3 infection have a history of injection drug use. (Ampuero et al., 2014; Gigi et al., 2007; Harder et al., 2004) Advances in direct-acting antiviral (DAA) HCV therapy, (Schinazi and Asselah, 2017) as well as practices like blood product screening, have contributed to the decreased prevalence and transmission of HCV, in general, over the last few decades. In contrast, the prevalence of HCV GT3a infection has increased in IDUs over that same period. (Kalinina et al., 2001; Romano et al., 2010) IDUs often contract HCV infection at a young age, leading to prolonged chronic HCV infection and associated progression to cirrhosis and hepatocellular carcinoma. (Smith et al., 2015; Thomas et al., 2000)

Current guidance for HCV treatment from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommends treating IDUs with chronic HCV infection;(AASLD-IDSA, 2018; EASL, 2018) however, enduring concerns about treatment adherence, poor treatment outcomes, and risk of HCV reinfection have hindered widespread treatment application. (Grebely et al., 2015a) In addition to endorsing treatment, international guidelines highlight that treatment efficacy among IDUs is similar to that in non-IDU populations;(Grebely et al., 2015c) in support of this assertion, studies have demonstrated minimal impact of ongoing drug use, even during anti-HCV therapy, on treatment adherence, completion, or sustained virologic response (SVR) in IDUs. (Aspinall et al., 2013; Dore et al., 2016; Grebely et al., 2015c; Martinello et al., 2017) A safe and effective pangenotypic treatment regimen, particularly with a short duration, could facilitate increased treatment access for PWUDs, a currently underserved patient population. (Grebely et al., 2015b) This could help reduce the global HCV burden by providing an additional treatment option for a patient population at high risk of HCV reinfection. (Jiang and Nwankwo, 2017)

The DAA regimen of glecaprevir (GLE; an NS3/4A protease inhibitor identified by AbbVie and Enanta) and pibrentasvir (PIB; an NS5A inhibitor), coformulated as GLE/PIB (G/P), is approved for the treatment of chronic HCV GT1–6 infection. (MAVIRET [SmPC], 2018; MAVYRET [US package insert], 2018) Both GLE and PIB have a high barrier to resistance, potent pangenotypic antiviral activity,(Ng et al., 2014, 2017) primarily biliary metabolism and clearance, and negligible renal excretion. (Kosloski et al., 2016) G/P demonstrated a 98% rate of SVR at posttreatment week 12 (SVR12) in over 2200 patients in phase II and III clinical trials across all six major HCV genotypes, including patients without cirrhosis or with compensated cirrhosis, prior HCV treatment experience, and severe renal impairment. (Grebely et al., 2017a)

In this integrated analysis, data were pooled from 1819 patients across seven phase III clinical trials that evaluated the efficacy and safety of G/P treatment for 8 or 12 weeks in patients chronically infected with HCV GT1–6, including those with compensated cirrhosis and/or prior HCV treatment experience. Although none of these trials was designed to specifically evaluate HCV-infected PWUD, an integrated analysis of the clinical trial results focused on this subpopulation could be a useful and reliable measure of the efficacy of G/P within this population. To this end, patients were grouped into recent PWUDs, former PWUDs, or non-PWUDs. SVR12, treatment adherence and completion, and safety were compared among the three subpopulations.

2. Methods

2.1. Study oversight

All patients signed informed consent for their respective trial, and the original studies were conducted in accordance with the International Conference on Harmonization guidelines and the ethics set forth by the Declaration of Helsinki. All authors had access to all relevant study data, and reviewed and approved this manuscript for submission.

2.2. Study design

Data were pooled from seven phase III clinical trials: ENDURANCE-1 (NCT02604017), ENDURANCE-2 (NCT02640482), ENDURANCE-3 (NCT02640157), ENDURANCE-4 (NCT02636595), EXPEDITION-1 (NCT02642432), EXPEDITION-2 (NCT02738138), and EXPEDITION-4 (NCT02651194). Patients received coformulated oral G/P 300 mg/120 mg once daily (provided as three 100 mg/40 mg tablets), without ribavirin, for 8 or 12-weeks.

2.3. Patient population

Eligibility criteria were generally similar across the phase III studies; key differences in criteria between studies are shown in Table S1. Briefly, adults at least 18 years old, with chronic HCV GT 1, 2, 3, 4, 5, or 6 infection and compensated liver disease, with or without cirrhosis, were enrolled. HCV subtype was determined by the Versant® HCV Genotype Inno LiPA assay (version 2.0) and subsequently confirmed via phylogenetic analysis of the NS5B region of the viral genome. Determination of the presence or absence of cirrhosis and fibrosis staging are detailed in the Supplementary Material. Patients in ENDURANCE-1 and EXPEDITION-2 could have been coinfected with human immunodeficiency virus (HIV)-1; however, coinfection with multiple HCV genotypes was exclusionary in all studies. Patients with a positive test for hepatitis B surface antigen were also excluded. Patients who were HCV treatment-naïve or had prior experience with interferon or pegylated interferon with or without ribavirin, or sofosbuvir plus ribavirin with or without pegylated interferon, were eligible for enrollment. Ongoing drug use was not exclusionary unless it could preclude protocol adherence, as assessed by the study investigator.

2.4. Definitions of analysis populations

Patients were divided into three subpopulations based on drug use status: recent PWUD, former PWUD, or non-PWUD. Patients considered as having recently used drugs (recent PWUD) were those who self-reported injection drug use within 12 months of screening, had positive urine drug screen results, or both (note: for all studies in this analysis, urine drug screens were only collected at the Screening visit); a positive urine drug screen included a positive test for cocaine, amphetamines, phencyclidine, propoxyphene, heroin, or other opioids that could not be accounted for by prescribed concomitant medications taken for transcribed medical diagnoses (e.g. prescribed methadone or buprenorphine for opioid dependence). Patients who had a treatment-emergent adverse event (AE) consistent with the use of the aforementioned drugs (identified by the Drug Abuse, Dependence and Withdrawal Standardized MedDRA Queries) were also considered recent drug users. Patients with a history of drug use (former PWUD) were those who self-reported injection drug use more than 12-months prior to screening and had a negative urine drug screen. Patients who self-reported never injecting drugs and also had a negative urine drug screen were considered non-drug users (non-PWUD).

2.5. Endpoints

The endpoints of treatment completion, adherence (≥90% of doses), efficacy, and safety were described for the recent PWUD, former PWUD, and non-PWUD subpopulations.

2.5.1. Treatment completion and adherence

Treatment completion was defined as study-site reported completion of the entire scheduled on-treatment procedure, including the end-of-treatment visit. Adherence was calculated as the percentage of tablets taken (determined by tablet counts at study visits from weeks 4, 8, and 12 [where applicable]) relative to the total expected number of tablets. Patients without records for the number of tablets taken at one

Table 1
Patient Demographics and Baseline Characteristics.

Characteristic	Recent PWUD N = 98	Former PWUD N = 610	Non-PWUD N = 1111
Male, n (%)	79 (81)	399 (65)	550 (50)
Race, n (%)			
White	82 (84)	547 (90)	811 (73)
Black or African American	12 (12)	31 (5)	69 (6)
Asian	1 (1)	16 (3)	211 (19)
Age, median years (range)	45 (22–66)	51 (22–76)	54 (19–88)
BMI, median kg/m^2 (range)	24 (18–48)	26 (17–49)	25 (18–55)
HCV RNA, median $\log_{10}$ IU/mL (range)	6.0 (4.1–7.4)	6.2 (1.2–7.5)	6.1 (1.2–7.6)
Category of drug use, n (%)			
Reported recent injection drug use	35 (36)	0	0
Positive urine drug screen[a]	56 (57)	0	0
Both	6 (6)	0	0
Ongoing drug use adverse event	1[b] (1)	0	0
Class of positive urine drug screen[c], n (%)			
Opioids	37 (66)	0	0
Heroin	11 (20)	0	0
Other[d]	26 (46)	0	0
Cocaine	16 (29)	0	0
Amphetamines	16 (29)	0	0
Opioid substitution therapy, n (%)	30 (31)	94 (15)	7 (< 1)
Genotype, n (%)			
GT1	45 (46)	273 (45)	631 (57)
GT2	7 (7)	50 (8)	198 (18)
GT3	38 (39)	245 (40)	144 (13)
GT4–6	8 (8)	42 (7)	138 (12)
Baseline fibrosis stage[e], n (%)			
F0–F2	78 (80)	486 (80)	894 (81)
F3	8 (8)	58 (10)	111 (10)
F4	12 (12)	66 (11)	101 (9)
Compensated cirrhosis, n (%)	12 (12)	66 (11)	104 (9)
Prior HCV treatment-naïve, n (%)	86 (88)	501 (82)	757 (68)
History of depression or bipolar disorder, n (%)	23 (23)	157 (26)	393 (35)
Current alcohol use, n (%)	45 (46)	243 (40)	326 (29)

BMI, body-mass index; GT, genotype; HCV, hepatitis C virus; PWUD, people who use drugs.
Recent PWUD defined as self-reported injection drug use within 12 months prior to screening and/or positive urine drug screen.
Former PWUD defined as self-reported injection drug use more than 12 months prior to screening and negative urine drug screen.
[a] Positive urine drug screens for drugs prescribed for transcribed medical diagnoses (e.g. methadone for drug addiction) were counted as negative.
[b] Patient had serious adverse event of relapse of heroin and amphetamine use during treatment period; patient did not self-report injection drug use and did not have positive urine drug screen at baseline.
[c] Patients could have positive urine drug screen for more than one substance; percentage based on total patients with positive urine drug screen (n = 56).
[d] Opioids detected include: dihydrocodeine, morphine, codeine, and hydromorphone.
[e] Five non-PWUDs had missing fibrosis staging data.

or more of the study visits were treated as having missing adherence data.

2.5.2. Efficacy

The primary efficacy endpoint was the percentage of patients with SVR12, which was defined as an HCV RNA concentration less than the lower limit of quantification (LLOQ) at 12 weeks after the last dose of study drug. For all phase III trials analyzed here, plasma HCV RNA levels were determined using the COBAS® AmpliPrep/COBAS® TaqMan HCV Quantitative Test (v2.0). The lower limits of detection and quantification for this assay are both 15 IU/mL for all HCV genotypes. Efficacy analyses were conducted in the intention-to-treat (ITT) population, which included all patients who received at least one dose of study drug, and in the modified ITT (mITT) population, which excluded patients with non-virologic failure (e.g. SVR12 non-response due to early discontinuation or loss to follow-up). Secondary efficacy endpoints were the percentage of patients in the ITT population with on-treatment virologic failure and post-treatment virologic relapse.

2.5.3. Safety

AEs and laboratory assessments were evaluated. Treatment-emergent AEs were collected from the first administration of study drug until 30 days after study drug discontinuation. Relatedness of AEs to DAA administration was determined by the study investigator.

2.6. Statistical analyses

All statistical tests and confidence intervals (CIs) were 2-sided with an alpha level of 0.05. For analyses of the primary efficacy endpoint of SVR12, two-sided 95% CIs were calculated using the normal approximation to the binomial distribution. If the SVR12 rate was 100%, then the Wilson's score method was used to calculate the CIs. Subgroup efficacy analyses (including stratification by genotype, cirrhosis status, treatment duration received, prior HCV treatment experience, category of drug use, HIV-1 coinfection and opioid substitution therapy [OST]) were performed on the ITT SVR12 endpoint; within each subgroup, the percentage of patients with SVR12 was calculated for the subpopulations of recent PWUDs, former PWUDs, and non-PWUDs, along with corresponding two-sided 95% Wilson score CIs (for a minimum of 10 patients in a given subgroup). Pairwise comparison of the percentages of patients with SVR12 was performed between recent PWUDs versus former PWUDs, and between recent PWUDs versus non-PWUDs, for

each subgroup variable. Pairwise comparisons, by drug use status and by treatment duration, were also performed on the treatment adherence and completion data. Fisher's exact test was used for all pairwise comparisons. Multiple stepwise logistic regression analysis was performed to assess the association between SVR12 and all of the aforementioned subgroup variables, as well as PWUD status (recent PWUDs, former PWUDs, and non-PWUDs). Subgroup variables may have been changed to continuous to prevent separation or quasi-separation. Patients must have completed treatment to be included in the analysis of virologic relapse, where treatment completion was defined as ≥52 days for 8-week G/P treatment and ≥77 days for 12-week treatment. Statistical summaries were performed using SAS® software.

3. Results

3.1. Baseline patient demographics

Among 1819 patients treated, 98 (5%) were recent PWUDs, 610 (34%) were former PWUDs, and 1111 (61%) were non-PWUDs (Table 1). Compared with former PWUDs or non-PWUDs, recent PWUDs were of younger age and had a higher percentage of HCV treatment-naïve patients. Overall, most patients were male, of white race, and had F0–F2 stage fibrosis; 9–12% of patients had compensated cirrhosis across the subpopulations. Consistent with epidemiology, (Ampuero et al., 2014; Gigi et al., 2007; Harder et al., 2004) HCV GT3 infection was more prevalent among recent or former PWUDs than non-PWUDs (40% versus 13%). Among recent and former PWUDs, 31% and 15% of patients, respectively, were receiving OST; less than 1% of non-PWUDs were receiving OST. Among recent PWUDs, 36% (35/98) reported injection drug use within 12 months prior to screening, 57% (56/98) had a positive urine drug screen per analysis-defined criteria, 6% (6/98) had both recent injection drug use within 12 months prior to screening and a positive urine drug screen per analysis-defined criteria, and 1% (1/98) had a treatment-emergent AE consistent with ongoing drug use. Of the patients in the entire analysis set who had a positive urine drug screen at the Screening visit, 42% (56/132) had a positive urine drug screen that satisfied analysis-defined criteria. Among the 56 patients with positive urine drug screen per analysis-defined criteria, the most common drugs were non-prescribed opioids (66%, including 20% positive for heroin), followed by cocaine and amphetamines (both 29%).

3.2. Treatment completion and adherence

For patients with available adherence data, 96% (75/78) of recent PWUDs, 99% (524/528) of former PWUDs, and 99% (1019/1030) of non-PWUDs were ≥90% adherent to treatment. Additionally, 97% (95/98), 98% (599/610), and 99% (1099/1111) of recent, former, and non-PWUDs completed treatment. Pairwise comparison did not demonstrate a strong statistically significant difference between recent PWUDs and former PWUDs (p = 0.049), or between recent PWUDs and non-PWUDs (p = 0.07). Differences between the rates of treatment completion were not significant. Furthermore, there was no statistical association in adherence or completion between 8- and 12-week treatment durations.

3.3. Efficacy

SVR12 in the ITT population was achieved by 93% (91/98; 95% CI 86–97) of recent PWUDs, 97% (591/610; 95% CI 95–98) of former PWUDs, and > 99% (1106/1111; 95% CI 99–100) of non-PWUDs, across both G/P treatment durations (Fig. 1a). SVR12 rates in the ITT population were statistically lower in recent and former PWUDs compared with non PWUDs (p < 0.0001 for both).

The overall rates of virologic failure were ≤1.5% regardless of drug use status, and the rates of non-response due to reasons other than virologic failure were 6%, 2%, and < 1% for recent, former, or non-PWUDs, respectively (Table 2). Excluding patients with nonresponse due to reasons other than virologic failure, the SVR12 rates in the mITT populations of recent, former, and non-PWUDs were 99% (91/92; 95% CI 94–100), 99% (591/600; 95% CI 97–99), and > 99% (1106/1109; 95% CI 99–100), respectively (Fig. 1b). Rates of SVR12 were not statistically different between recent PWUD and non-PWUDs in the mITT population (p = 0.27) but were statistically lower in former PWUDs compared with non-PWUDs (p = 0.0056).

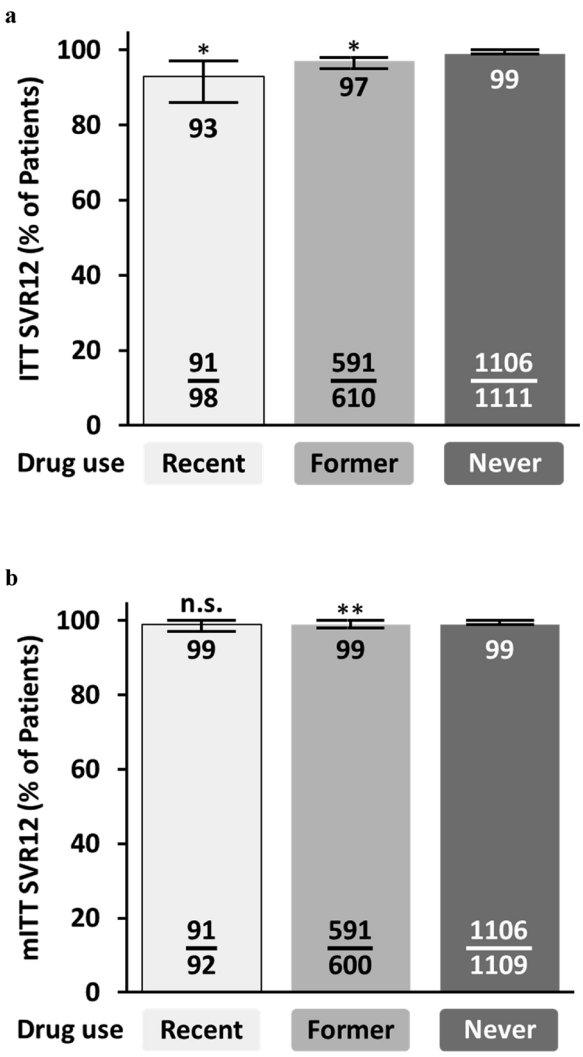

Fig. 1. SVR12 by Drug Use Status. SVR12 rates are shown for the (a) ITT and (b) mITT populations, grouped by drug use status. The mITT population excluded patients with nonresponse due to premature study drug discontinuation or loss to follow-up (missing SVR12 data). Two-sided 95% confidence intervals were calculated using the Wilson score method. Abbreviations: ITT, intention-to-treat; mITT, modified intention-to-treat; SVR12, sustained virologic response at posttreatment week 12. SVR12 vs non-PWUD *p < 0.0001; **p < 0.05; n.s., not significant.

Among recent PWUDs, one out of seven patients who failed to achieve SVR12 had a virologic relapse; this patient had GT3a infection, F0–F1 fibrosis, was HCV treatment naïve, and was treated with G/P for 12-weeks. The other six recent PWUDs with nonresponse were lost to follow-up or had prematurely discontinued study drug. Rates of HCV reinfections through 24 weeks following the end of treatment were < 0.5% for each subpopulation, including no reinfections among recent PWUDs.

Multiple stepwise logistic regression analysis demonstrated that both recent drug use and nonadherence were independent predictors of non-SVR12 (p < 0.05) (Table S2). Subgroup analysis of SVR12 by

Table 2
Summary of Intention-to-treat Efficacy Outcomes.

Outcome, % (n/N)	Recent PWUD N = 98	Former PWUD N = 610	Non-PWUD N = 1111
SVR12	93 (91/98) [95% CI 86–97]	97 (591/610) [95% CI 95–98]	99 (1106/1111) [95% CI 99–100]
Reasons for non-SVR12			
On-treatment virologic failure	0	< 1 (3/610)	< 1 (1/1111)
Virologic relapse	2 (1/64)	1 (6[a]/532)	< 1 (2/1040)
Premature study drug discontinuation	3 (3/98)	< 1 (4/610)	< 1 (1/1111)
Lost to follow-up	3 (3/98)	1 (6/610)	< 1 (1/1111)

PWUD, people who use drugs; SVR12, sustained virologic response at post-treatment week 12.
n = number of patients that achieved SVR12; N = total number of patients with available data.
Virologic relapse was calculated only in patients that completed treatment.
[a] One patient with history of injection drug use had reinfection determined by phylogenetic analysis after posttreatment week 12; no other reinfections were observed across any of the three subpopulations.

Table 3
Intention-to-treat SVR12 by Subgroups (Patient or Viral Characteristics).

Subgroup	Recent PWUD N = 98	Former PWUD N = 610	Non-PWUD N = 1111
	SVR12, % (n/N)		
Treatment duration			
8 weeks	96 (50/52)	97 (230/237)	99 (353/356)
12 weeks	89 (41/46)	97 (361/373)	> 99 (753/755)
Genotype			
1	100 (45/45)	98 (268/273)	> 99 (629/631)
2	86 (6/7)	98 (49/50)	100 (198/198)
3	84 (32/38)	95 (233/245)	98 (141/144)
4–6	100 (8/8)	98 (41/42)	100 (138/138)
Compensated cirrhosis			
Yes	92 (11/12)	95 (63/66)	99 (103/104)
No	93 (80/86)	97 (528/544)	> 99 (1003/1007)
Prior HCV treatment experience			
Yes	92 (11/12)	98 (107/109)	> 99 (353/354)
No	93 (80/86)	97 (484/501)	99 (753/757)
Opioid substitution therapy			
Yes	83 (25/30)	98 (92/94)	100 (7/7)
No	97 (66/68)	97 (499/516)	> 99 (1099/1104)
Type of recent drug use			
Reported injection drug use	91 (32/35)	–	–
Positive urine drug screen	95 (53/56)	–	–
Both of above	83 (5/6)	–	–
Ongoing drug use adverse event	100 (1/1)	–	–
Treatment adherence[a]			
Yes	96 (72/75)	98 (511/524)	> 99 (1015/1019)
No	100 (3/3)	75 (3/4)	91 (10/11)
Depression or bipolar disorder (yes)	91 (30/33)	97 (179/184)	100 (138/138)
Class of recent drug use[b]			
Opioids	89 (33/37)	–	–
Heroin	82 (9/11)	–	–
Other	92 (24/26)	–	–
Cocaine	100 (16/16)	–	–
Amphetamines	94 (15/16)	–	–
HIV-1 coinfection (yes)	95 (35/37)	99 (73/74)	100 (75/75)
Alcohol use			
Current drinker	96 (43/45)	97 (236/243)	99 (324/326)
Former drinker	87 (33/38)	97 (295/305)	99 (226/228)
Non-drinker	100 (15/15)	97 (60/62)	> 99 (551/552)

PWUD, people who use drugs; SVR12, sustained virologic response at post-treatment week 12.
n = number of patients that achieved SVR12; N = total number of patients with available data.
[a] Treatment adherence was defined as ≥90% adherent by tablet counts.
[b] Patients could have positive urine drug screen for more than one substance.

Table 4
Adverse Events and Laboratory Abnormalities.

AE, n (%)	Recent PWUD N = 98	Former PWUD N = 610	Non-PWUD N = 1111
Any AE	82 (84)	431 (71)	695 (63)
Serious AE	3 (3)	20 (3)	38 (3)
Serious AE related to study drugs[a]	0	1 (< 1)	0
AE leading to study drug discontinuation	1 (1)	5 (< 1)	6 (< 1)
AEs occurring in ≥10% of patients			
Headache	14 (14)	131 (21)	166 (15)
Fatigue	17 (17)	97 (16)	129 (12)
Nausea	12 (12)	79 (13)	73 (7)
Death	1[b] (1)	2 (< 1)	1 (< 1)
Laboratory abnormalities[c], n (%)			
Alanine aminotransferase			
Grade 2 (> 3–5 × ULN)	0	0	0
Grade ≥3 (> 5 × ULN)	0	1 (< 1)	0
Aspartate aminotransferase			
Grade ≥3 (> 5 × ULN)	1 (1)	2 (< 1)	1 (< 1)
Total bilirubin			
Grade ≥3 (> 3 × ULN)	3 (3)	0	4 (< 1)
Hemoglobin			
Grade ≥3 (< 8 g/dL)	0	4 (< 1)	2 (< 1)

AE, adverse event; PWUD, people who use drugs; ULN, upper limit of normal. Alanine aminotransferase must have been post nadir increase in grade.
[a] Relation to study drugs as assessed by investigator.
[b] Serious AE of relapse of heroin and amphetamine use during treatment period and subsequently died of heroin overdose at day 77 post treatment.
[c] No grade 4 laboratory abnormalities were observed. N = 608 for former PWUDs.

adherence showed that patients who were treatment adherent (≥90%) had high SVR12 rates (96– > 99%) in all three drug use subpopulations. Among the small number of patients assessed as nonadherent, the SVR12 rates were 100% (3/3), 75% (3/4), and 91% (10/11) for recent, former, and non-PWUDs, respectively (Table 3); for the subpopulation of recent PWUDs, there was no statistically significant association between nonadherence and non-SVR12 ($p > 0.1$).

The complete list of subgroup analyses of the SVR12 rates by patient and viral characteristics in each of the three subpopulations is shown in Table 3. Separated by treatment duration, 96% (50/52; 95% CI 87–99) of recent PWUDs treated with G/P for 8-weeks achieved SVR12, compared with 89% (41/46; 95% CI 77–95) treated for 12 weeks, although the differences were not statistically significant. Among former PWUDs or non-PWUDs, SVR12 rates remained consistent between 8- and 12-week treatment durations at 97% and 99%, respectively. In patients receiving OST, the SVR12 rate in recent PWUDs (83%; 25/30) was statistically significantly lower ($p < 0.05$) than in former PWUDs (98%; 92/94). In patients not receiving OST, the SVR12 rates were

similarly high (≥97%) irrespective of drug use status. No other patient or viral characteristic subgroup demonstrated significantly different rates in SVR12 in recent PWUDs compared with either former or non-PWUDs, including the presence of compensated cirrhosis, genotype, prior HCV treatment experience, or HIV-1 coinfection.

3.4. Safety

AEs were reported in 84% of recent PWUDs compared with 71% of former PWUDs, and 63% of non-PWUDs. AEs occurring in more than 10% of patients were headache, fatigue, and nausea (Table 4). Rates of serious AEs (3%) and discontinuations due to AEs (1%) were similarly low regardless of drug use status. One recent PWUD died in the post-treatment period due to an overdose of alcohol and methadone, an event assessed as not related to study drugs. In general, grade 2 or greater laboratory abnormalities in alanine aminotransferase, aspartate aminotransferase, and hemoglobin occurred in ≤1% of patients, regardless of drug use status; none of the alanine aminotransferase elevations were considered consistent with a drug-induced liver injury. Three recent PWUDs had grade 3 elevations in total bilirubin; all such elevations had indirect predominance, and all three patients had elevated bilirubin at baseline (Table 4).

4. Discussion

PWUDs (including IDUs) are often not treated for HCV infection based on provider concerns about treatment adherence and poor treatment outcome. (Grebely et al., 2015a) Treating people with ongoing injection drug use is further complicated by their high risk for HIV and hepatitis B virus coinfections, or HCV superinfection;(Blackard, 2012; Grebely et al., 2012; Herring et al., 2004) the latter is particularly relevant if the HCV treatment is not pangenotypic and has activity against a narrow range of subtypes. (Abdelrahman et al., 2015; Kohli et al., 2014; McNaughton et al., 2014) Importantly, as prior HCV infection does not result in immunity against reinfection,(Cunningham et al., 2015) the need for therapeutic intervention, combined with a reduction of risk behaviors, is paramount in this vulnerable patient population. A treatment regimen with a reduced duration that is safe and effective in all six major HCV genotypes can facilitate and increase treatment access for PWUDs. In this post-hoc analysis of seven phase III studies, we analyzed the impact of recent drug use on G/P treatment completion and adherence, as well as on the efficacy and safety of G/P, compared with former drug use or no history of drug use. Overall, across all six major HCV genotypes, the treatment completion (97%), adherence (96%), and SVR12 rates (93%) for recent drug users were high and clinically comparable to those of former or non-drug users. G/P was safe and well-tolerated, irrespective of drug use status, with low rates of serious AEs and AEs leading to study drug discontinuation.

Most registrational phase III studies of DAA drugs for HCV treatment have excluded patients with positive urine drug screens or recent drug use,(Grebely et al., 2016a, b; Jacobson et al., 2017) making it difficult to assess the treatment adherence, efficacy, and safety profiles of those DAAs in recent PWUDs. For the seven phase III trials of G/P included in this analysis, positive urine drug screening for non-prescribed drugs (i.e. opiates, cocaine, or amphetamines) and/or self-reported recent injection drug use was not exclusionary, which provided the opportunity to evaluate data in the understudied patient population identified as recent PWUDs. Categorization of patients in this analysis as recent, former, or non-PWUDs was convergent with the higher proportion of patients receiving OST within the subpopulations of recent (31%; 30/98) and former PWUDs (15%; 94/610), compared with non-PWUDs (less than 1%; 7/1111). In this analysis, recent PWUDs were of younger age, mostly treatment-naïve, and with a high percentage of HCV GT3 infection; these demographics are consistent with real-world settings, and such patients are driving emerging trends in the HCV epidemic. (Smith et al., 2015; Thomas et al., 2000)

A statistically lower ITT SVR12 rate was observed in recent PWUDs compared with non-PWUDs; the 6% lower SVR12 rate was driven not by patients with virologic failure, but by patients who prematurely discontinued or were lost to follow-up. Importantly, among recent PWUDs, the SVR12 rate exceeded 90% and noncompletion of study drug impacted a minority of the patients (3%). In addition, although 3% of recent PWUDs had no SVR12 data available (lost to follow-up), these patients were likely to have achieved SVR12 because they completed the planned treatment duration. In this context, the difference in SVR12 rates between recent and non-PWUDs was not of clinical significance.

The HCV reinfection rate through 24 weeks post-treatment was low irrespective of drug use status, including no reinfections among recent PWUDs. One patient with a history of injection drug use, classified as a former PWUD, had reinfection determined by phylogenetic analysis after posttreatment week 12. The natural history of drug use can involve relapses in drug use in some individuals, and this likely explains the recurrent viremia observed in this patient.

Access to HCV therapy, a crucial step in reducing the burden of chronic HCV infection and lowering the rate of HCV transmission, remains poor for IDUs. (Larney et al., 2017) Until recently, the standard-of-care for HCV treatment was at least 12 weeks of therapy, but it has been suggested that reduced treatment duration can improve both access and adherence, particularly in persons who use drugs or receive OST. (Grebely et al., 2013) G/P for 8 weeks was recently approved by the FDA and EMA for treatment-naïve patients without cirrhosis, regardless of HCV genotype; a demographic profile that describes a large majority of the PWUD population. In this analysis, although not statistically significant, the SVR12 rate for recent PWUDs treated for 8 weeks was higher (96% SVR12 [50/52]; 4% rate of non-virologic failure) than those treated for 12 weeks (89% SVR12 [41/46]; 9% rate of non-virologic failure), a trend not observed with either former or non-PWUDs. The higher rate of nonvirologic failure in recent PWUDs treated for 12 weeks suggests that the shorter 8-week treatment duration may help ensure treatment completion and adherence to medical visits. Given the limitations of a post-hoc integrated analysis and the comparatively small sample size of the recent PWUDs cohort, additional controlled studies would be needed to confirm the benefit of shorter G/P treatment durations on adherence and efficacy in recent PWUDs.

Overall, this post-hoc analysis supports current international guidelines advocating the treatment of PWUDs with chronic HCV infection and adds to the accumulating evidence that treatment of this population is safe and efficacious. (Grebely et al., 2017b) Indeed, studies have shown that limited recreational injection drug use, even during treatment for HCV, has minimal impact on adherence, completion, and efficacy in PWUDs. (Aspinall et al., 2013; Grebely et al., 2013, 2015c) This is supported by the results of the current integrated analysis, which showed that 95% (53/56) of patients with a positive urine drug screen achieved SVR12 following treatment with G/P.

This analysis has several limitations. The PWUDs enrolled in these clinical trials likely represent a selected population engaged in their healthcare, and therefore these findings may not be generalizable to other populations of people receiving OST or people who inject drugs. Other limitations that reduce the generalizability of this analysis to the wider population include the exclusion of patients coinfected with hepatitis B virus, which has a high prevalence among IDUs, and the underrepresentation of patients of black race, who may account for the racial majority of PWUD in low socioeconomic regions. A further limitation was the inability to differentiate between injection and non-injection drug users among those patients in the recent PWUD cohort with a positive urine drug screen. (Novak and Kral, 2011) Sample size limitations make it difficult to draw definitive conclusions about factors that may be associated with a reduced rate of SVR12 in the recent/active PWUD cohort. Similarly, the small sample size of nonadherent patients in the entire analysis set (particularly when considering individual drug use groups) and incomplete adherence data make it difficult to draw definitive conclusions about the association of

nonadherence as an independent predictor of non-SVR12; notably, all three recent PWUDs assessed as nonadherent achieved SVR12. Finally, this analysis was post-hoc and not specified prior to the start of the included clinical trials. Additional studies or extensive real-world analyses are needed to better characterize the PWUD population being treated with G/P and to better delineate risk factors that may be associated with treatment failure in this population.

In conclusion, G/P treatment was safe, well tolerated, and demonstrated high rates of SVR12 across patients with HCV GT1–6 infection, irrespective of drug use status. Results of this post-hoc analysis of G/P treatment in chronic HCV-infected persons with recent drug use do not support enduring concerns about poor adherence to, or efficacy of, HCV treatment in this patient population. G/P has pangenotypic efficacy with treatment duration as low as 8-weeks; such treatment could facilitate the simplified care cascade needed to increase HCV treatment uptake in the PWUD population. (Bajis et al., 2017)

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AbbVie sponsored the studies (NCT02604017, NCT02640482, NCT02640157, NCT02636595, NCT02642432, NCT02738138, and NCT02651194), contributed to their design, collection, analysis, and interpretation of the data, and participated in the writing, review, and approval of the content of the manuscript. All authors had access to all relevant data. This manuscript contains information on the investigational use of glecaprevir (GLE; formerly ABT-493) and pibrentasvir (PIB; formerly ABT-530).

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 (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

This 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 and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Contributors

GRF, GJD, JG, SW, AA, FJM were involved in the study concept. Contributors GRF, GJD, JG, SW, JG, KES, AB, BC, DJ, TA, MG, KT, HA, AA participated in the acquisition of data. Contributors GRF, GJD, JG, SW, JG, KES, AB, BC, DJ, TA, MG, KT, HA, AA participated in the analysis and interpretation of data. Critical review and revision of the manuscript by GRF, GJD, SW, JG, KES, AB, BC, DJ, TA, MG, KT, HA, AA, YH, FJM. Statistical analysis completed by YH. All authors approve of this manuscript and its submission for publication.

Conflict of interest

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Appendix A. Supplementary data

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