Safety and Efficacy of Glecaprevir/Pibrentasvir for 8 Weeks for Treatment of Acute Hepatitis C Virus Infection in People Living with HIV

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Kimberly Workowski[1], Barbra Cave[2], Pablo Ryan[3], John Smith[4], Thomas Lutz[5], Patrick Lank[2], Linda M. Fredrick[2], Anne Welhaven[2], Dimitri Semizarov[2], John Marcinak[2], Joseph S. Doyle[6]

[1]Department of Medicine, Division of Infectious Diseases, Emory University, Atlanta, GA, USA; [2]AbbVie Inc., North Chicago, IL, USA; [3] Internal Medicine, Hospital Universitario Infanta Leonor and CIBERINFEC (ISCIII), Madrid, Spain; [4]Digestive & Liver Disease Specialists, Norfolk, VA, USA; [5]Infektiologikum Frankfurt, Frankfurt, Germany; [6]Department of Infectious Diseases, The Alfred and Monash University, Melbourne, Victoria, Australia

BACKGROUND

- Globally there are up to 2.3 million people living with HIV (PLHIV) and hepatitis C virus (HCV) co-infection[1]
- PLHIV and HCV co-infection are at high risk for liver-related morbidity and mortality[2]
- There are currently no approved direct acting antiviral agents for acute HCV infection, however glecaprevir/pibrentasvir (G/P) has been well studied in chronic HCV infection[3]
- Treating acute HCV benefits the individual by reducing the risk of liver-related morbidity and mortality, and may benefit public health by preventing loss of patients to care and reducing onward HCV transmission[4]
- The American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) recommend treatment of acute HCV infection following confirmation of viremia, without waiting for spontaneous resolution[5]
- The objective of this analysis was to examine the safety and efficacy of G/P in PLHIV with acute HCV and to explore the safety of co-administration of HIV therapies with G/P

METHODS

- A phase 3b, multicenter, single-arm, open-label study (NCT04903626) evaluated the safety and efficacy of 8-week G/P (300/120 mg) for acute HCV infection in people who had not previously been treated for current infection
  - A sub-analysis focused on PLHIV and acute HCV
- Efficacy endpoints included achievement of sustained virologic response 12 weeks after the last dose of G/P (SVR12) defined as plasma HCV RNA level below the lower level of quantification 12 weeks after the last G/P dose, evaluated in the intention-to-treat (ITT) set (all participants receiving ≥ 1 dose of G/P) and the modified ITT (mITT) set (excluding those who did not achieve SVR12 for reasons other than virologic failure)
- Safety endpoints evaluated on ITT set included:
  - Changes from baseline in alanine aminotransferase (ALT) during treatment
  - Treatment-emergent (TE) hepatic decompensation
  - TE serious adverse event (TESAE)
  - TEAE leading to G/P discontinuation
- Post-hoc summaries of endpoints by concomitant use of HIV regimens containing dolutegravir, bictegravir and/or NRTI were performed

Key Study Eligibility Criteria

Eligibility Criteria for Acute HCV Infection

Physician diagnosis of acute HCV infection
AND
Quantifiable HCV RNA at Screening
And at least one of
Criterion A: Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 8-month period prior to screening
Criterion B: Negative anti-HCV antibody, HCV RNA, and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 11-month period prior to screening **AND** Risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen
Criterion C: Clinical signs and symptoms compatible with acute hepatitis (ALT >5× ULN and/or jaundice) in the absence of a history of chronic liver disease or other cause of acute hepatitis and positive HCV RNA or HCV core antigen all within an 8-month period prior to screening **AND** Risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen
Criterion D: Negative anti-HCV antibody with a positive HCV RNA or HCV core antigen within a 5-month period prior to screening

ALT, alanine aminotransferase; HCV, hepatitis C virus; RNA, ribonucleic acid; ULN, upper limit of normal.

Key Inclusion Criteria

- Participants with HIV-1 and acute HCV on a stable, qualifying antiretroviral therapy must have had CD4+ count ≥ 200 cells/mm^3

Key Exclusion Criteria

Participant must not have had:

- Cause of liver disease other than HCV infection
- History of liver decompensation
- History of organ transplant
- Uncontrolled diabetes as defined by a glycated hemoglobin (HbA1c) level > 8.5%
- Hepatocellular carcinoma

Prohibited Concomitant Medications

- Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort
- Carbamazepine, phenytoin, pentobarbital phenobarbital, primidone, rifabutin, rifampin
- Atorvastatin, lovastatin, simvastatin
- Astemizole, cisapride, terfenadine
- Atazanavir, efavirenz, oxcarbazepine, pitavastatin

Glecaprevir/Pibrentasvir treatment in people with acute HCV infection living with HIV was safe and effective, and allowed concomitant HIV antiretrovirals to maintain HIV suppression

RESULTS

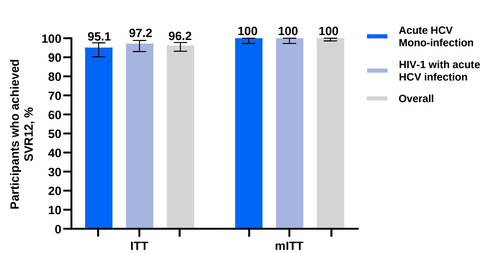
- Of 286 participants, 144 had acute HCV mono-infection and 142 had HIV-1 with acute HCV infection; all participants with HIV-1 and acute HCV were on a stable HIV-1 regimen at G/P start and 124 (87.3%) were suppressed (HIV-1 RNA < 20 copies/mL)
- High SVR12 rates were achieved in both the HCV mono-infection and HIV-1 with acute HCV infection groups, with no virologic failures (on-treatment or relapse) (**Figure 1)**, and one reinfection (0.7%) (**Table 2**)
- No PLHIV and acute HCV experienced on-treatment ALT >3× ULN (≥ Grade 2) that had worsened from baseline **(Figure 3)**, TE hepatic decompensation, a TESAE that was deemed related to G/P, or a TEAE leading to G/P discontinuation (**Table 3**)
- 8 participants had early treatment discontinuation; 5 with HCV mono-infection (AE unrelated to G/P [n=1], lost to follow-up [n=2], non-compliance with G/P [n=2]) and 3 with HIV-1 and acute HCV infection (lost to follow-up [n=1], withdrawal by participant [n=1], non-compliance with G/P [n=1])
- Of PLHIV and acute HCV who were suppressed (HIV-1 RNA < 20 copies/mL) at baseline and had at least one on-treatment HIV-1 RNA, 3.3% (4/123) experienced HIV-1 RNA suppression failure defined as two consecutive on-treatment values ≥ 20 copies/mL

Table 1. Participant Demographic and Baseline Disease Characteristics (ITT Set)

	Acute HCV Mono-infection (N = 144)	HIV-1 with acute HCV infection (N = 142)
Age (years), mean (SD)	41.7 (12.6)	45.7 (10.4)
Sex, n (%)		
Male	116 (80.6)	139 (97.9)
Race, n (%)		
White	125 (86.8)	121 (85.2)
Black or African American	14 (9.7)	16 (11.3)
Asian	5 (3.5)	2 (1.4)
Multiple ethnicity	0 (0)	3 (2.1)
Prior HCV infection, n (%)	4 (2.8)	48 (33.8)
Risk behaviors for acute HCV infection[a], n (%)		
Unprotected sexual activity with other male(s)	74 (51.4)	116 (81.7)
Unprotected sexual activity with multiple partners	79 (54.9)	93 (65.5)
Shared drug-injection equipment	30 (20.8)	24 (16.9)
Shared non-injection drug use equipment	32 (22.2)	21 (14.8)
Shared personal items possible contaminated with blood	12 (8.3)	8 (5.6)
Unregulated tattoos or body piercings	9 (6.3)	2 (1.4)
Healthcare worker with occupational exposure	5 (3.5)	1 (0.7)
Other behavior	16 (11.1)	9 (6.3)
HCV RNA (IU/mL), n (%)		
≥ 1,000,000	40 (27.8)	48 (33.8)
Genotype[b], n (%)		
1	74 (59.2)	91 (68.9)
2	6 (4.8)	5 (3.8)
3	24 (19.2)	9 (6.8)
4	21 (16.8)	27 (20.5)
Missing	19	10
Fibrosis stage, n (%)		
F0-1	113 (81.9)	125 (89.3)
F2	8 (5.8)	7 (5.0)
F3	14 (10.1)	6 (4.3)
F4	3 (2.2)	2 (1.4)
Missing	6	2
CD4+ (cells/mm^3), n (%)		
< 200	N/A	0
≥ 200 to < 350		5 (3.5)
≥ 350 to < 500		28 (19.9)
≥ 500		108 (76.6)
Missing		1
HIV -1 RNA (copies/mL), n (%)		
< 20	N/A	124 (87.3)
≥ 20		18 (12.7)

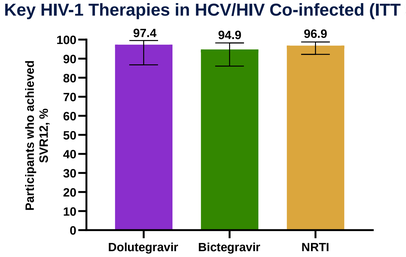
HCV, hepatitis C virus; HIV-1, human immunodeficiency virus; ITT, intention-to-treat; N/A, not applicable; N, number of participants; RNA, ribonucleic acid; SD, standard deviation.
Percentages calculated on non-missing values.
[a]Participants may be counted under more than one behavior.
[b]Final available genotype from phylogenetic analysis or central laboratory if phylogenetic result was not available.

Figure 1. SVR12 Rates (ITT and mITT Sets)



CI, confidence interval; G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus; ITT, intention-to-treat; mITT, modified intention-to-treat; n, number of participants who achieved SVR12; N, number of participants; SVR12, sustained virologic response 12 weeks after the last dose of G/P.
Error bars are 95% CIs.

Figure 2. SVR12 Rates With Co-administration of G/P and Key HIV-1 Therapies in HCV/HIV Co-infected (ITT Set)



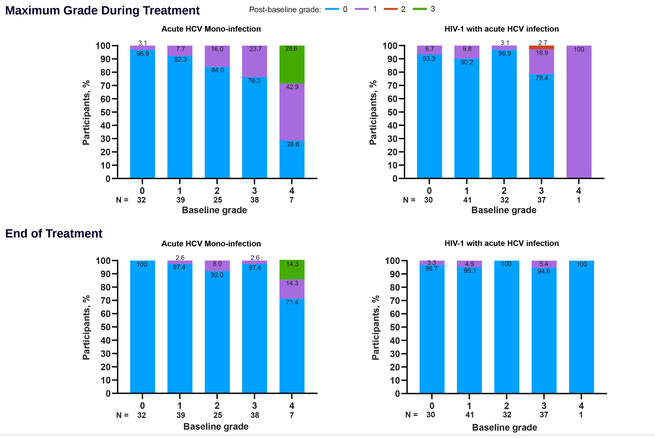
CI, confidence interval; G/P, glecaprevir/pibrentasvir; HIV-1, human immunodeficiency virus; ITT, intention-to-treat; n, number of participants who achieved SVR12; N, number of participants; NRTI, nucleoside reverse transcriptase inhibitor; SVR12, sustained virologic response 12 weeks after the last dose of G/P.
Error bars are 95% CIs.
A participant may be represented in more than one group due to the many possible combinations of HIV antiretroviral therapy.
Rilpivirine (N = 31), Cabotegravir (N = 8), Doravirine (N = 2), Raltegravir (N = 6), Cobicistat (N = 9) not graphed. All participants in these groups achieved SVR12.

Table 2. Reasons for SVR12 Non-Response (ITT Set)

	Acute HCV Mono-infection (N = 144)	HIV-1 with acute HCV infection (N = 142)
On-treatment virologic failure, n (%)	0	0
Virologic relapse, n (%)	0	0
Non-virologic failure		
Premature study drug discontinuation, n (%)	2 (1.4)	3 (2.1)
HCV reinfection, n (%)	1 (0.7)	1 (0.7)
Missing SVR12, n (%)	4 (2.8)	0 (0)

G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus; ITT, intention-to-treat; N, number of participants; SVR12, sustained virologic response 12 weeks after the last dose of G/P.

Figure 3. Shifts in ALT Toxicity Grade From Baseline to Maximum Grade During Treatment and End of Treatment (ITT Set)



ALT, alanine aminotransferase; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus; ITT, intention-to-treat; N, number of participants.
Grades based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Table 3. Safety Overview (ITT Set)

	Acute HCV Mono-infection (N = 144)	HIV-1 with acute HCV infection (N = 142)	Dolutegravir (N = 39)	Bictegravir (N = 59)	NRTI (N = 129)
Any TEAE, n (%)	82 (56.9)	89 (62.7)	21 (53.8)	37 (62.7)	80 (62.0)
TE hepatic decompensation, n (%)	0	0	0	0	0
TESAE, n (%)	4 (2.8)[a]	6 (4.2)[a]	2 (5.1)[a]	3 (5.1)[a]	6 (4.7)[a]
TEAE leading to discontinuation of G/P, n (%)	1 (0.7)[a]	0	0	0	0

G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus; ITT, intention-to-treat; N, number of participants; NRTI, nucleoside reverse transcriptase inhibitor; TEAE, treatment-emergent adverse event; TESAE; treatment-emergent serious adverse event.
Participants are counted no more than once in each row, regardless of the number of events they may have had.
[a]Events were not related to G/P.

CONCLUSIONS

- An 8-week treatment with G/P was safe and well-tolerated in PLHIV and acute HCV and in those with acute HCV mono-infection
- High rates of SVR12 were achieved
- The incidence of adverse events in PLHIV with acute HCV infection was similar to those with acute HCV mono-infection
- Concomitant HIV antiretrovirals maintained HIV suppression and were safe to use with G/P
- New treatment strategies are needed for patients with HIV-1 and acute HCV to enable immediate treatment to prevent loss to care and onward HCV transmission

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