GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Use in Acute HCV Infection

This document is in response to your request for information regarding the use of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) for the treatment of acute HCV infection.

This document includes content from or references to clinical practice guidelines, and inclusion of this information should not be interpreted as a treatment recommendation or an endorsement of the guidelines by Gilead Sciences, Inc.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Summary

Product Labeling[1]

SOF/VEL is currently not indicated for the treatment of acute HCV infection. SOF/VEL is indicated for the treatment of adults and pediatric patients ≥3 years of age with chronic HCV GT 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis, or with decompensated cirrhosis for use in combination with ribavirin.

Clinical Data on the Use of SOF/VEL in Participants With Acute HCV Infection

The REACT study evaluated 6 or 12 weeks of SOF/VEL treatment in participants with recently acquired HCV. SVR12 rates were 81.7% and 90.5% in the 6- and 12-week arms, respectively (*P*=0.08). Safety results are presented below.[2]

The HepNet Acute HCV-V study investigated an 8-week treatment course of SOF/VEL in participants with acute HCV. The SVR12 rates were 90% and 100% in the ITT (N=20) and PP populations (n=18), respectively, and 85% achieved normalized ALT levels (ITT population). Safety results are presented below.[3]

Two case reports summarized the outcomes of SOF/VEL use in male patients who were diagnosed with acute HCV infection. Improvements in serum bilirubin, liver enzymes, and INR were observed in both patients after they initiated treatment with SOF/VEL, and 1 patient achieved SVR12.[4,5]

Clinical Practice Guidelines on the Management of Acute HCV Infection

Please refer to the clinical guidelines for recommendations regarding the treatment of patients with acute HCV infection.

Clinical Data on the Use of SOF/VEL in Participants With Acute HCV Infection

REACT Study in Participants With Recent HCV Infection[2]

Study design and demographics

The REACT study was a National Institutes of Health-funded multicenter, international, open-label, randomized, non-inferiority, phase 4 study that evaluated the efficacy and safety of SOF/VEL for 6 (short arm, n=93) or 12 weeks (standard arm, n=95) in participants with recent HCV infection. At Week 5 or 6 of treatment, participants were randomly assigned to the short or standard arm of treatment, and randomization was stratified according to site and HIV status. The primary outcome was SVR12. The study defined recent primary HCV infection as follows:

- First anti-HCV Ab and/or HCV RNA-positive result within the previous 6 months, as well as one of the following: documented negative anti-HCV Ab result within the 18 months prior to enrollment; acute clinical hepatitis (jaundice or ALT >10 × ULN) within the previous 12 months, excluding other causes of acute hepatitis; or acute asymptomatic hepatitis (acute rise in ALT >5 × ULN) within the previous 12 months, excluding other causes of acute hepatitis.
- For cases of recent HCV reinfection: new positive HCV RNA result within the previous 6 months following previous spontaneous or treatment-induced clearance (previous positive anti-HCV Ab and undetectable HCV RNA on ≥2 occasions).

Initially, the study aimed to enroll 250 participants; however, the study was halted prematurely due to the advice of the data safety and monitoring board. A total of 188 participants (mean age, 43.8 years; 182 males) were included in the primary analysis. Among participants in the short arm, 62.4%, 4.3%, 16.1%, and 16.1% had HCV GT 1a, 1b, 3, and 4, respectively; the median HCV VL was 5.6 $\log_{10}$ IU/mL, and the median ALT was 114 IU/L at baseline. Among participants in the standard arm, 60%, 2.1%, 4%, 17.9%, and 15.8% had HCV GT 1a, 1b, 2, 3, and 4, respectively; the median HCV VL was 5.4 $\log_{10}$ IU/mL, and the median ALT was 128 IU/L at baseline.

Efficacy

The end-of-treatment response in the ITT population was 91.4% (85/93) in the short arm and 91.6% (87/95) in the standard arm. SVR12 was achieved by 81.7% (76/93) in the short arm and by 90.5% (86/95) in the standard arm. The difference in SVR12 between the treatment arms was -8.81% (95% CI: -18.6 to 1), which was below the criterion for non-inferiority (12%) and was nonsignificant (*P*=0.08). Across both treatment arms, 11 participants had virological relapse (short arm, n=9; standard arm, n=2), and 5 participants were reinfected (short arm, n=3; standard arm, n=2). Sixteen participants experienced virological recurrence at or before SVR12 (short arm, n=12; standard arm, n=4).

Safety

Two participants in the short arm died after they achieved sustained virologic response 4 weeks after treatment; neither death was considered treatment related. No participants in the standard arm died. Across both treatment arms, 6 participants discontinued treatment

for non-safety reasons, and 8 participants were LTFU (short arm, n=3; standard arm, n=5). At least one AE was experienced by 55% of participants; 23% experienced a TRAE (short arm, n=22; standard arm, n=21). Most (98%) TRAEs were Grade 1 to 2; 1 TRAE was Grade 3, and none were Grade 4. Fatigue was the most frequently reported AE in the overall study population (11.2%). Six participants (short arm, n=1; standard arm, n=5) experienced an SAE. One SAE of rhabdomyolysis was considered to possibly be treatment related; this occurred 1 week after the participant started treatment, and they were briefly hospitalized. Treatment with SOF/VEL was continued, and the episode spontaneously resolved. No participant discontinued treatment due to AEs.

Adherence

Across both treatment arms, 93% of participants had >80% adherence, and 90% of participants had >95% adherence; adherence was higher in the short arm than the standard arm.

The HepNet Acute HCV-V Study[3]

Study design and demographics

A prospective, open-label, single-arm, multicenter, phase 2 pilot study evaluated the efficacy and safety of an 8-week treatment course of SOF/VEL in participants with acute HCV infection (HCV RNA >10^3 IU/mL). Acute HCV was defined as one of the following criteria being met within 4 months before screening: seroconversion to HCV Ab+, documented conversion to being HCV RNA+, or known or suspected exposure to HCV with an ALT level >10 × ULN. Key exclusion criteria were as follows: cirrhosis, signs of clinical decompensation, solid organ transplantation, co-infection with HIV, uncontrolled drug abuse, or other causes of liver disease. The primary endpoint was SVR12 in the ITT population (defined as participants who received ≥1 dose of study drug). Additional endpoints included virological and biochemical kinetics at baseline and several time points through Week 12, the rate of ALT normalization (defined as ALT <ULN), and the safety and tolerability of SOF/VEL treatment.

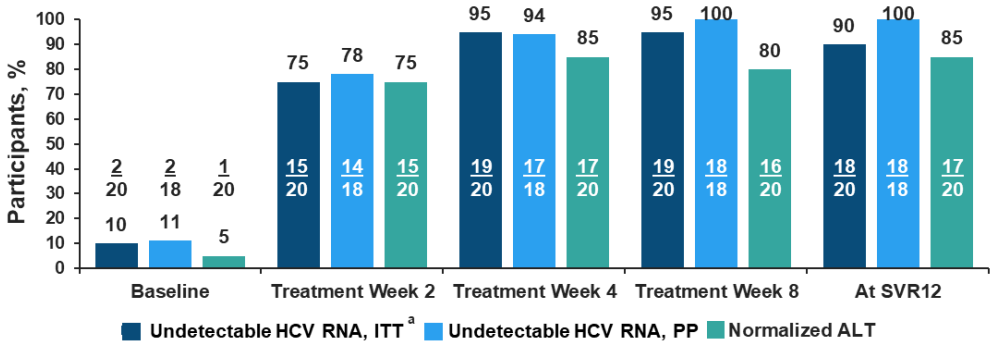
Twenty participants were enrolled and included in the ITT population; the mean age was 37.4 years, and 19 males were included. At baseline, participants had a median (IQR) ALT level of 249 (165–463) U/L and a median (IQR) HCV VL of 104,307 (7842–1,726,734) IU/mL. Two participants (10%) had an HCV RNA <10 IU/mL at baseline, but their HCV RNA VLs were 1426 and 331 IU/mL at screening. Nearly all participants (95%) had primary acute HCV infection; 1 participant (5%) had a confirmed HCV reinfection. Among the enrolled participants, 60% had HCV GT 1a, 5% each had GTs 1b and 2, and 15% each had HCV GTs 3 and 4. Approximately two-thirds of participants were receiving oral HIV pre-exposure prophylaxis with FTC/TDF. The mean ± SD duration of time between diagnosis of acute HCV and initiation of treatment was 43.2±25.6 days.

Efficacy

In the ITT population, the SVR12 rate was 90% (95% CI: 69.9–97.2%; Figure 1); 2 participants were LTFU and were counted as treatment failures. The remaining 18 participants were included in the PP analysis, and 100% (95% CI: 82.41–100%) achieved SVR12. ALT levels normalized in 85% of participants in the ITT population at the SVR12 checkpoint, with a post hoc analysis showing a statistically significant (P<0.001) decline in

ALT concentrations from baseline to Week 4 (Figure 1). One participant had persistently elevated ALT levels throughout the study period (range, 90–131 IU/mL). All 4 participants with a bilirubin level >ULN at baseline had their levels normalize during treatment.

Figure 1. HepNet Acute HCV-V: Participants With HCV RNA VL <10 IU/mL and Normalized ALT[3]



[a]Two participants in the ITT population were LTFU.

Safety

Overall, 28 AEs were reported; there were 6 possible or probable TRAEs, including skin irritations (10%), flatulence (5%), headache (5%), and sleep disorder (5%); all were mild in intensity. There was 1 SAE determined to be unrelated to study drug. There were no significant changes from baseline in CrCl or other laboratory parameters during or after treatment.

Case Reports on the Use of SOF/VEL in Patients With Acute HCV Infection

There are limitations in the interpretation of case reports. Case reports cannot be generalized. Unlike controlled clinical trials, causality cannot be inferred based on uncontrolled observational data. Additionally, incidence or prevalence cannot be estimated due to the lack of a representative population sample. Other limitations of case reports include the retrospective design and publication bias.[6]

Severe acute HCV infection[4]

A 33-year-old male with no remarkable medical history presented to the emergency department with severe malaise and jaundice. The patient was diagnosed with severe acute hepatitis without acute liver failure following laboratory tests that revealed elevated serum ALT (2948 U/L), AST (2618 U/L), alkaline phosphatase (125 U/L), INR (1.6), and bilirubin (110 mmol/L), and a normal serum albumin level. One week after presentation, their HCV VL was 9.12×10^7 IU/mL with GT 1a, despite the patient testing negative twice for anti-HCV Abs. SOF/VEL treatment was immediately initiated, and the patient's condition, serum ALT, AST, alkaline phosphatase, INR, and bilirubin markedly improved after ≥4 days of treatment. Liver enzymes normalized after 40 days of SOF/VEL treatment.

Acute HCV infection in male with IV drug use[5]

A 37-year-old male who was a current user of IV drugs presented to the emergency department with jaundice, lethargy, and malaise. The patient's laboratory profile revealed

elevated levels of bilirubin (103 mcmol/L), ALT (2567 U/L), and INR (1.41), and a normal serum albumin level. On admission, hepatitis A IgM, hepatitis B surface antigen, hepatitis B core IgM Ab, HCV Ab, hepatitis E IgM and IgG, HIV, cytomegalovirus, HBV DNA, and Epstein-Barr virus serology were negative. An ultrasound and CT of the abdomen showed no focal liver abnormalities. An HCV RNA level of 9,520,000 IU/mL confirmed a diagnosis of acute HCV infection with secondary liver injury.

N-acetylcysteine was started immediately; however, the patient's condition deteriorated and was accompanied by further increases in serum bilirubin (244 mcmol/L), ALT (2645 U/L), and INR (1.51). The patient started treatment with SOF/VEL daily, and the patient's clinical condition and serum bilirubin, ALT, and INR improved. By Day 3 of treatment, the HCV RNA level decreased to 224,000 IU/mL and was undetectable at Weeks 6 and 12; SVR12 was achieved.

Clinical Practice Guidelines on the Management of Acute HCV Infection

Please refer to the clinical guidelines for recommendations regarding the treatment of patients with acute HCV infection: www.hcvguidelines.org/unique-populations/acute-infection.

References

1. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Matthews GV, Bhagani S, Van der Valk M, et al. Sofosbuvir/velpatasvir for 12 vs. 6 weeks for the treatment of recently acquired hepatitis C infection. *J Hepatol.* 2021;75(4):829-839.
3. Maasoumy B, Ingiliz P, Spinner CD, et al. Sofosbuvir plus velpatasvir for 8 weeks in patients with acute hepatitis C: The HepNet acute HCV-V study. *JHEP Rep.* 2023;5(3):1-6.
4. Wei S, Bogoch, II, Dhalla IA, Wong DKH. Sexually acquired severe acute hepatitis C infection in men who have sex with men. *CMAJ.* 2022;194(45):E1537-E1540.
5. Micallef S, Gauci J, Gerada J. Acute hepatitis C infection with secondary liver injury successfully treated with sofosbuvir/velpatasvir combination. *Br J Hosp Med (Lond).* 2020;81(8):1-3.
6. Nissen T, Wynn R. The Clinical Case Report: A Review of Its Merits and Limitations. *BMC Res Notes.* 2014;7:264.

Abbreviations

Ab=antibody
AE=adverse event
FTC=emtricitabine
GT=genotype
LTFU=lost to follow-up
PP=per protocol
SAE=serious adverse event
SOF=sofosbuvir
SVR12=sustained virologic response 12 weeks after end of treatment
TDF=tenofovir disoproxil fumarate
TRAE=treatment-related adverse event
ULN=upper limit of normal
VEL=velpatasvir
VL=viral load

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Epclusa US Prescribing Information available at: www.gilead.com/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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