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Epclusa® (sofosbuvir/velpatasvir) Minimal Monitoring Strategies

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

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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]

Test all patients for evidence of current or prior HBV infection before initiating treatment with SOF/VEL. HBV reactivation has been reported in HCV/HBV co-infected patients who were undergoing or had completed treatment with HCV DAAs and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV co-infected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

Clinical Data: Minimal Monitoring With SOF/VEL

In the phase 4 MINMON study, which evaluated the safety and efficacy of 12 weeks of SOF/VEL in TN adults using a simplified approach to monitoring, the SVR rate was 95% (379/399). AEs and SAEs were reported in 6% and 4% of participants, respectively, and 1 participant discontinued due to an AE.[2]

In the TeleHCV, open-label, non-inferiority study, DAA-naive participants with HCV received 12 weeks of SOF/VEL with minimal monitoring, and this approach was inferior to SoC in a historical cohort in the ITT analysis (90.3% [130/144] vs 97%, respectively; $P<0.001$) but non-inferior in the PP analysis (99.2% [130/131]). Most of the AEs (overall, 83 AEs in 54 participants) were managed remotely, and none of the 3 SAEs were due to SOF/VEL.[3]

A phase 3 study evaluated the safety and efficacy of 12 weeks of SOF/VEL in TN and TE adults with chronic HCV using a minimal monitoring approach that consisted of no on-treatment assessments. The SVR12 rate was 93% (120/129). AEs occurred in 15% of participants, 1 SAE was reported, and no discontinuations due to AEs occurred.[4]

In a prospective, multicenter study that evaluated the efficacy and safety of SOF/VEL with simplified monitoring, the SVR12 was 100% (57/57) in the PP analysis and did not differ between those who had ≤3 and ≥4 study visits ($P=1$). AEs occurred in 11.7% of participants, 1 SAE was reported, and no discontinuations due to treatment-related SAEs occurred.[5]

Real-World Data: Minimal Monitoring With SOF/VEL

A single-center, observational study in Singapore evaluated the safety and efficacy of SOF/VEL ± RBV for 12 weeks with simplified (per AASLD/IDSA guidelines) or SoC monitoring. SVR12 rates were 99% in both of the simplified and SoC monitoring groups. In the simplified monitoring group, 1 SAE resulted in the discontinuation of treatment.[6]

Clinical Data: Minimal Monitoring With SOF/VEL

MINMON Study

Study design and demographics[2]

MINMON was a phase 4, open-label, international (Brazil, South Africa, Thailand, Uganda, and US) study that evaluated the safety and efficacy of SOF/VEL for 12 weeks in TN adult participants (N=399) and utilized the MINMON approach (Figure 1). Exclusion criteria included HBV co-infection, decompensated cirrhosis, and pregnancy. The primary outcome was SVR, defined as HCV RNA ≤LLoQ from samples obtained 22 to 76 weeks post treatment initiation.

Figure 1. MINMON Strategy (Solomon et al)[2]

Abbreviation: FIB-4=Fibrosis-4 score.

At baseline, the median (IQR) age was 47 (37–57) years; 65% (n=260) were male; 28% (n=113) were Asian, non-Hispanic; 25% (n=99) were White, non-Hispanic; 24% (n=95) were Hispanic/Latinx, any race; 14% (n=57) were Black, non-Hispanic, and 9% (n=35) reported their race as “other”. Most patients had HCV GT 1 (1a, 44%; 1b, 18%), followed by GT 3 (20%). The median (IQR) HCV RNA was 6.1 (5.6–6.6) log IU/mL; 9% (n=34) had compensated cirrhosis; 42% (n=166) also had HIV; 43% (n=170) reported former substance use; and 14% (n=56) reported current substance use.

Results

The SVR rate was 95% (n/N, 379/399; 95% CI: 92.4–96.7%). Of the 20 participants who did not achieve SVR, 17 were virologic non-responders (including 1 participant who lost their study medication after 6 days), 2 were LTFU, and 1 had a sample that was assessed prior to the SVR visit window.[2]

Among the 18 participants who did not achieve SVR and had ≥1 follow-up, adherence rates were the following: <75%, n=3; 75 to 99%, n=3; and 100%, n=12.[2] In an analysis of self-reported adherence in MINMON, 93% (368/395) reported early optimal adherence (ie, no missed doses at Week 4), and 96.5% of participants (355/368) with early optimal adherence achieved SVR12, compared with 77.8% (21/27) of those with early suboptimal adherence (*P*<0.001). In a multivariate analysis, age (<30 years) and geographic location (US) were factors that were independently associated with early suboptimal adherence.[7]

In terms of the MINMON strategy, remote contact took place for 99% and 84% of participants at Weeks 4 and 22, respectively. Fifteen participants (4%) had 21 unplanned clinic/laboratory visits for the following reasons: abnormal laboratory values at baseline, n=8; non-AE clinical events, n=6; other reasons, n=4; and AEs, n=3. Study drugs were lost

by 3 participants, and 2 received replacement study drug. The third participant did not report their lost medication until 14 days later, which led to premature SOF/VEL discontinuation.[2]

Twenty-eight participants experienced AEs, including 5 study drug-related AEs (diarrhea, n=2; abdominal distension, n=1, fatigue, n=1, and headache, n=1) and 1 discontinuation due to an AE. Fourteen SAEs (4%) were reported, and no drug-related SAEs or discontinuations due to SAEs occurred.[2]

TeleHCV: Minimal Monitoring in Brazil[3]

Study design and demographics

An open-label, single-center, single-arm, non-inferiority study compared efficacy and safety in DAA-naive participants who received SOF/VEL for 12 weeks with minimal monitoring with results from a historical cohort. Eligible participants had chronic HCV, no markers for advanced liver fibrosis, cirrhosis, or portal hypertension, eGFR ≥30 mL/min, no previous solid organ transplantation, and no major drug-drug interactions with SOF/VEL. Eligible participants attended a single study visit that included a presentation on HCV, laboratory sample collection, a pharmacist consultation, and delivery of the 12 weeks of SOF/VEL. There were no study visits during treatment, and participants were responsible to schedule the collection of HCV RNA in 12 weeks and to send the results to the study team.

The primary outcome was SVR12 (HCV RNA <lower limit of detection; ITT), which was compared with the historical cohort's SVR12 rate of 97% (non-inferiority limit, 5%). Secondary endpoints included safety and adherence assessments. Overall, 78 participants (54.2%) were male; the mean ± SD age was 52±12.9 years; and the median (IQR) APRI was 0.49 (0.42). HCV GTs included the following: GT 1a, 22.2%; GT 1b, 10.4%; GT 2, 7%; GT 3, 22.9%; missing, 37.5%. Most participants were low-income (58.1%; 79/136; <2 minimum Brazilian wages) and had ≤5 years of education (62.5%; n=85).

Results

In the ITT analysis, the SVR12 rate was 90.3% (n/N=130/144; 95% CI: 84.2–94.6%), which was statistically inferior to the SVR12 rate of the historical cohort (97%; *P*<0.001). In the PP analysis, the SVR12 rate was 99.2% (n/N=130/131; 95% CI: 95.8–100%), demonstrating non-inferiority to that of the historical cohort. The 1 participant with a positive HCV RNA viral load after end of treatment had HCV GT 3, undiagnosed cirrhosis and a later diagnosis of HCC, self-reported good adherence, and a platelet count >200,000/mL at screening. Of the 123 participants with data, adherence was self-reported as 91.9%, and 10 participants (8.1%) forgot a pill more than once monthly.

Eight participants had thrombocytopenia or APRI scores >2 despite not having a cirrhosis diagnosis at screening; 7 achieved SVR12 and 1 did not have SVR12 testing. Overall, 54 participants reported 83 AEs; most managed remotely via text or phone. Few required in-person care, and 3 SAEs occurred (none were related to SOF/VEL). One death due to lung cancer was reported during follow-up.

Minimal Monitoring in India[4]

Study design and demographics

An open-label, phase 3 study was conducted in India to evaluate the safety and efficacy of SOF/VEL for 12 weeks with minimal monitoring in TN and TE adult participants with chronic

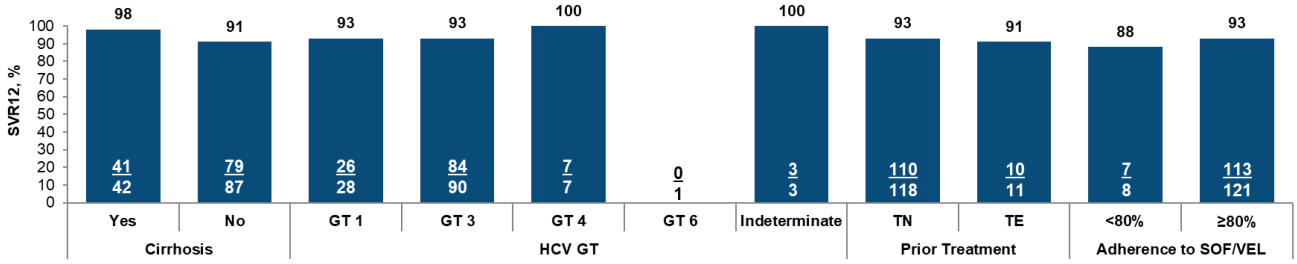
HCV (N=129). Exclusion criteria included platelet count <30,000/mcL, Hgb <8 g/dL, ALT/AST level >10 × upper limit of normal, CrCl <30 mL/min, HIV or HBV co-infection, post liver transplant, HCC, and previous treatment with an NS5A inhibitor. Study visits took place at screening, on Day 1 of therapy, at the EoT, and at Weeks 4 and 12 post therapy. Visits also took place monthly to dispense study drug; however, no on-treatment monitoring was conducted. The primary efficacy endpoint was SVR12, defined as HCV RNA ≤LLoQ 12 weeks after the EoT in participants who took ≥1 dose of study drug.

At baseline, the median (range) age was 42 (19–75) years, 76 participants (59%) were male, 42 (33%) had compensated cirrhosis, 11 (9%) were TE, and the median (range) ALT level was 46 (11–298) U/L. HCV GTs included the following: GT 1, n=28 (22%); GT 3, n=90 (70%); GT 4, n=7 (5%); GT 6, n=1 (1%); and indeterminate GT, n=3 (2%).

Results

The SVR12 rate was 93% (n/N, 120/129; 95% CI: 87–97%). Additional SVR12 rates are presented in Figure 2. Of the 9 participants who did not achieve SVR12, 5 were LTFU, 2 relapsed after therapy, 1 withdrew consent after treatment completion, and 1 experienced virologic failure while on therapy (GT 3 and without cirrhosis). One of the participants who relapsed (GT 3 and had cirrhosis) was TE with an NS5A inhibitor, which was an exclusion criterion, and the other participant (GT 6 and without cirrhosis) was TN. No emergent resistance-associated substitutions were detected in participants who experienced virologic nonresponse.

Figure 2. SVR12 Rates in Subgroups (Sood et al)[4]



Nineteen AEs (15%) were reported, including 1 (1%) Grade 3 to 4 AE and SAE of rectal hemorrhage (not related to SOF/VEL). No AEs led to discontinuation, and there were no deaths. The most common AEs reported by ≥3 participants were headache (3%; n=4), upper abdominal pain (2%; n=3), and pyrexia (2%; n=3).

Simplified Monitoring in Japan[5]

Study design and demographics

A prospective, multicenter study evaluated the efficacy and safety outcomes of SOF/VEL treatment with simplified monitoring (ie, ≤3 outpatient visits) in patients who began treatment after January 2023 and had had ≥24 weeks of follow-up by May 2025 (N=51). The primary endpoints were SVR12, safety, and the association between the number of study visits and treatment outcomes. Participant demographics were as follows (type of statistical measure [ie, mean or median and range or IQR] was not provided): age, 67 (33–93) years; male, 30; HCV RNA, 6.5 (3.3–7.7) log IU/mL; HCV GT 1/2, 19/32; 49 received no prior treatment, while 2 participants had received interferon; ALT, 41 (5–222) IU/L; AST, 43 (15–194) IU/L. The number of outpatient visits from the treatment initiation to SVR12 was 3 (1–8). Baseline

characteristics were not significantly different between those who had ≤3 and ≥4 outpatient visits (each, *P*=not significant), except for the number of outpatient visits (*P*<0.0001).

Results

Of the 49 participants who completed treatment, 19 had ≥4 outpatient visits prior to SVR12, and 30 had ≤3 outpatient visits. In the PP analysis, all participants achieved SVR12 (100%), including the 35 who had ≤3 study visits and the 22 who had ≥4 study visits. In the ITT analysis, 96.7% of the participants achieved SVR12, and the SVR12 rate was similar between those who had ≤3 and ≥4 study visits (97.1% vs 95.8%, respectively).

Safety outcomes were not significantly different between those who had ≤3 and ≥4 study visits (each, *P*=not significant). No Grade 3/4 AEs, Grade 3/4 treatment-related AEs, or treatment-related SAEs that led to discontinuation were reported. Overall, 6 AEs (11.7%; 3 AEs per group), 5 treatment-related AEs (9.8%; ≤3 and ≥4 study visits, n=3 and n=2, respectively), and 1 SAE (1.9%; pregnancy ≥4 study visits group) were reported. One instance each of the following events occurred in the ≤3 study visits group: fever, headache, rash, and serum amylase elevation. In the ≥4 study visits group, an additional event of epigastric tenderness was observed.

Real-World Data: Minimal Monitoring With SOF/VEL

Simplified Monitoring in Singapore[6]

Study design and demographics

A single-center, observational study conducted between January 2019 and November 2021 in Singapore evaluated the safety and efficacy outcomes of SOF/VEL ± RBV for 12 weeks with simplified or SoC monitoring (N=609). Based on AASLD/IDSA guidelines for simplified HCV treatment, patients were eligible for simplified monitoring if they were TN and were either non-cirrhotic or had compensated cirrhosis (Child A). Those ineligible for simplified monitoring were TE or also had HBV/HIV, decompensated cirrhosis, HCC, or eGFR <30 mL/min. In the simplified monitoring group, clinic visits took place at treatment initiation and at SVR12. In the SoC group, clinic visits took place at treatment initiation, several times for monitoring over the course of treatment, and at SVR12. Overall, 561 patients met the criteria for simplified monitoring: 71 received simplified monitoring; 490 received SoC monitoring. The primary outcome was the occurrence of SAEs (ie, AEs that resulted in early discontinuation or hospitalization), and the secondary outcome was SVR12.

Table 1. Baseline Demographics and Disease Characteristics (Koh et al)[6]

Key Demographics and Characteristics	Simplified Monitoring (n=71)	SoC Monitoring (n=490)
Age, mean ± SD, years	52.2±11.2	50.2±9.8
Fibrosis, 0/1/2/3, %	4.2[a]/25.4/7/7	8.6/19.8/15.7/6.1
Cirrhosis Stage 4, n (%)	6 (8.5)	77 (15.7)
HCV GT, 1/2/3/4/6/indeterminate, %	25.4/0/54.9/1.4/0/18.3	20.8/0.8/61.2/0/0.2/16.9

[a]*P*=0.048 for comparison with SoC group.

Results

One SAE of angioedema occurred in the simplified monitoring group; SOF/VEL was discontinued, and the patient recovered. SVR12 rates were 99% in both the simplified monitoring (65/66) and SoC monitoring (448/453) groups.

References

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7. Sowah LA, Smeaton L, Brates I, et al. Perspectives on Adherence From the ACTG 5360 MINMON Trial: A Minimum Monitoring Approach With 12 Weeks of Sofosbuvir/Velpatasvir in Chronic Hepatitis C Treatment. *Clin Infect Dis.* 2023;76(11):1959-1968.

Abbreviations

AASLD=American Association for the Study of Liver Diseases
AE=adverse event
APRI=AST-to-platelets ratio index
DAA=direct-acting antiviral
EoT=end of treatment
GT=genotype
HCC=hepatocellular carcinoma
IDSA=Infectious Diseases of America
LLoQ=lower level of quantification
LTFU=lost to follow-up
NS5A=nonstructural protein 5A
PP=per protocol
RBV=ribavirin
SAE=serious adverse event
SoC=standard of care
SOF=sofosbuvir
SVR=sustained virologic response
SVR12=sustained virologic response 12 weeks after end of treatment
TE=treatment experienced
TN=treatment naive
VEL=velpatasvir

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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