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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 direct-acting antivirals 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 on Minimal Monitoring Strategies With SOF/VEL

The phase 4 MINMON study evaluated the safety and efficacy of 12 weeks of SOF/VEL in TN adults using a simplified but safe approach to HCV therapy monitoring.[2]

- The MINMON approach included no pre-treatment genotyping. All 84 tablets were provided at initiation, no scheduled clinic visits occurred, no laboratory samples were collected during treatment, and remote contact took place at Weeks 4 and 22.[2]
- The SVR rate was 95% (379/399). AEs and SAEs were reported in 6% and 4% of participants, respectively, and 1 discontinuation due to an AE occurred.[2]
- In an analysis of self-reported adherence, 93% reported early optimal adherence (ie, no missed doses at Week 4). Compared with those who had early suboptimal adherence, more participants with early optimal adherence achieved SVR12 (77.8% vs 96.5%; *P*<0.001).[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.[4]

- 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]

Real-World Data on Minimal Monitoring Strategies 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. The SVR12 rates were 99% in each of the simplified and SoC monitoring groups. In the simplified monitoring group, 1 SAE resulted in the discontinuation of treatment.[5]

Clinical Data on Minimal Monitoring Strategies 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), single-arm 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.

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.[2]

Efficacy[2]

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.

Adherence and safety

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.[3]

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]

Safety outcomes are presented in Table 1.

Table 1. MINMON Study: Safety Outcomes[2]

Safety Outcomes, n (%)	SOF/VEL (N=397)
AEs	28
Study drug-related AEs	5[a]
Discontinuation due to AE	1
SAEs	14 (4)
Study drug-related SAE	0
Discontinuation due to SAE	0

[a]Diarrhea (n=2), headache (n=1), fatigue (n=1), and abdominal distension (n=1).

Minimal Monitoring in India[4]

Study design and demographics

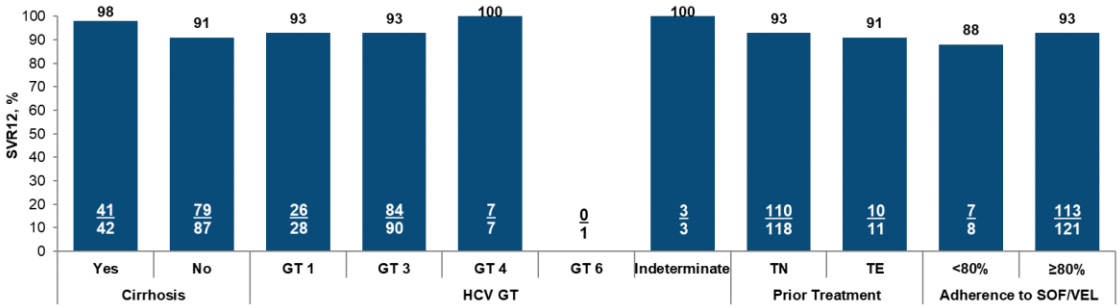
An open-label, phase 3 study was conducted in India to evaluate the safety and efficacy of SOF/VEL for 12 weeks with minimal monitoring in TN and TE adult participants with chronic HCV (N=129). Exclusion criteria included platelet count <30,000/mcL, Hgb <8 g/dL, ALT/AST level >10 × upper limit of normal, 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 end of therapy, 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 end of therapy in participants who took ≥1 dose of study drug.

At baseline, the median (range) age was 42 (19–75) years, 76 (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, 1 withdrew consent after treatment completion, 2 relapsed after therapy, 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 non-response.

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



Safety outcomes are presented in Table 2.

Table 2. Safety Outcomes (Sood et al)[4]

Safety Outcomes, n (%)		SOF/VEL (N=129)
AEs		19 (15)
Grade 3–4 AE		1 (1)[a]
SAEs		1 (1)[a]
Study drug-related SAEs		0
AEs that led to discontinuation		0
Deaths		0
AEs reported by ≥3 participants	Headache	4 (3)
	Upper abdominal pain	3 (2)
	Pyrexia	3 (2)

[a]Rectal hemorrhage.

Real-World Data on Minimal Monitoring Strategies with SOF/VEL

Simplified Monitoring in Singapore[5]

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). Patients were not eligible for simplified monitoring if they 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 check. In the SoC group, clinic visits took place at treatment initiation, several times for monitoring over the course of treatment, and at SVR12. Of the initial 609 patients included in the study, 561 patients met the criteria for simplified monitoring. Of those patients, 71 patients received simplified monitoring and 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 3. Baseline Demographics and Disease Characteristics (Koh et al)[5]

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, n (%)	3 (4.2)[a]/18 (25.4)/5 (7)/5 (7)	42 (8.6)/97 (19.8)/77 (15.7)/30 (6.1)
Cirrhosis Stage 4, n (%)	6 (8.5)	77 (15.7)
HCV GT, 1/2/3/4/6/indeterminate, n (%)	18 (25.4)/0/39 (54.9)/ 1 (1.4)/0/13 (18.3)	102 (20.8)/4 (0.8)/300 (61.2)/ 0/1 (0.2)/83 (16.9)

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

Results

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

References

1. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Solomon SS, Wagner-Cardoso S, Smeaton L, et al. A minimal monitoring approach for the treatment of hepatitis C virus infection (ACTG A5360 [MINMON]): a phase 4, open-label, single-arm trial. *Lancet Gastroenterol Hepatol.* 2022.
3. 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.
4. Sood A, Duseja A, Kabrawala M, et al. Sofosbuvir-velpatasvir single-tablet regimen administered for 12 weeks in a phase 3 study with minimal monitoring in India. *Hepatol Int.* 2019;13(2):173-179.
5. Koh SJ, Teh FKB, Tan YB, et al. Simplified Monitoring is a safe but underutilized strategy for Hepatitis C Virus (HCV) treatment in Singapore [Poster 1297]. Paper presented at: AASLD: The Liver Meeting; 4-8 November, 2022; Washington DC.

Abbreviations

AASLD=American Association for the Study of Liver Diseases
AE=adverse event
GT=genotype
HCC=hepatocellular carcinoma
IDSA=Infectious Diseases of America
LLoQ=lower level of quantification
LTFU=lost to follow-up
NS5A=nonstructural protein 5A
SAE=serious adverse event
SoC=standard of care
SOF=sofosbuvir
SVR=sustained virologic response
SVR12=SVR 12 weeks after end of treatment
TE=treatment experienced
TN=treatment naïve
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

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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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