GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Resistance

This document is in response to your request for information regarding resistance data in participants treated with Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) with or without ribavirin (RBV) for the treatment of 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]

Currently, there are no recommendations in the SOF/VEL product label to conduct baseline resistance testing before using SOF/VEL. Additionally, the length of SOF/VEL therapy is not guided by the presence of baseline RASs.

Clinical Data on Resistance in Participants Treated With SOF/VEL

A resistance analysis of the phase 3 ASTRAL-1, -2, -3, and -4 studies (N=1284) showed that except in those with GT 3, the presence of RASs at baseline did not affect SVR12 rates in participants with or without cirrhosis or decompensated participants treated with SOF/VEL.[2]

Retreatment with SOF/VEL + RBV in a phase 3 study (N=60; GTs 1 and 2) resulted in SVR12 rates of 88% to 100%; the presence of pretreatment RASs did not affect SVR12 rates.[3]

In an open-label pediatric study of SOF/VEL, all of the participants who had baseline RASs achieved SVR12. Of participants aged 6 to 11 years, 10% had NS5A RASs, and none had NS5B RASs; of participants aged 12 to 17 years, 16% had NS5A RASs, and 5% had NS5B RASs. One participant with an NS5A RAS (L31V) experienced nonresponse.[4]

Real-World Data on Resistance in Patients Treated With SOF/VEL

A UK study assessed the effects of RAS on retreatment clinical outcomes in patients who did not respond to previous DAA therapy and were subsequently retreated with SOF/VEL + RBV (24 weeks), SOF/VEL/VOX (8, 12, 16, or 24 weeks), or GLE/PIB (12 or 16 weeks). SVR was achieved by 94% of retreated patients (111/118), and 100% of patients who received SOF/VEL + RBV achieved SVR. The presence of pretreatment RASs did not affect SVR rates.[5,6]

Product Labeling[1]

Currently, there are no recommendations in the SOF/VEL product label to conduct baseline resistance testing before using SOF/VEL. Additionally, the length of SOF/VEL therapy is not guided by the presence of baseline RASs.

Microbiology

Resistance

In cell culture

HCV replicons with reduced susceptibility to SOF have been selected in cell culture for multiple GTs including 1b, 2a, 2b, 3a, 4a, 5a, and 6a. Reduced susceptibility to SOF was associated with the NS5B substitution S282T in all replicon GTs examined. An M289L substitution developed along with the S282T substitution in GT 2a, 5, and 6 replicons. Site-directed mutagenesis of the S282T substitution in replicons of GTs 1 to 6 conferred 2- to 18-fold reduced susceptibility to SOF.

HCV GT 1a, 1b, 2a, 3a, 4a, 5a, and 6a replicon variants with reduced susceptibility to VEL were selected in cell culture. Variants developed amino acid substitutions at NS5A resistance-associated positions 24, 28, 30, 31, 32, 58, 92, and 93. Phenotypic analysis of site-directed mutant replicons of the selected NS5A substitutions showed that single and double combinations of L31V and Y93H/N in GT 1a, the combination of L31V + Y93H in GT 1b, Y93H/S in GT 3a, and L31V and P32A/L/Q/R in GT 6 conferred greater than 100-fold reduction in VEL susceptibility. In the GT 2a replicon, the single mutants F28S and Y93H showed 91-fold and 46-fold reduced susceptibility to VEL, respectively. The single mutant Y93H conferred 3-fold reduced susceptibility to VEL in GT 4a replicons. Combinations of these NS5A substitutions often showed greater reductions in susceptibility to VEL than single substitutions alone.

Persistence of RASs

No data are available on the persistence of SOF or VEL RASs. NS5A RASs observed with administration of other NS5A inhibitors have been found to persist for longer than 1 year in most patients. The long-term clinical impact of the emergence or persistence of virus containing SOF or VEL RASs is unknown.

Cross resistance

Both SOF and VEL were fully active against substitutions associated with resistance to other classes of DAAs with different mechanisms of action, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors. The efficacy of SOF/VEL has not been established in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

Please refer to the full US FDA-approved prescribing information for complete information.

Clinical Data on Resistance in Participants Treated With SOF/VEL

ASTRAL-1, -2, -3, and -4

Study designs[2]

ASTRAL-1, a randomized, double-blind, placebo-controlled study, evaluated treatment with SOF/VEL for 12 weeks in participants with GTs 1, 2, 4, 5, or 6.

ASTRAL-2, a randomized, open-label study, evaluated treatment with SOF/VEL for 12 weeks compared with SOF + RBV in participants with GT 2.

ASTRAL-3, a randomized, open-label study, evaluated treatment with SOF/VEL for 12 weeks compared with SOF + RBV for 24 weeks in participants with GT 3.

ASTRAL-1, -2, and -3 studies included those without cirrhosis or with compensated cirrhosis.

ASTRAL-4, a phase 3, open-label study, evaluated SOF/VEL ± RBV for 12 weeks or SOF/VEL for 24 weeks in TN and TE participants with GTs 1 through 6 who had decompensated cirrhosis (classified as Child-Pugh-Turcotte Class B).

In all studies, treatment duration was not guided by participants' on-treatment HCV RNA levels, and the primary endpoint was SVR12 (lower limit, HCV RNA <15 IU/mL). Participants with 35 of 67 known HCV subtypes were treated with SOF/VEL in these studies, and 13 novel or mixed subtypes were identified in this population.

Relapses in participants treated with SOF/VEL ± RBV[2]

NS5A and NS5B deep sequencing were performed at baseline and at time of VF. NS5A RASs were observed at baseline in 16% to 70% of participants. The S282T NS5B RAS associated with SOF resistance was not detected in the baseline NS5B sequences.

The overall relapse rate was 1% (n=15); most (14/15) had the Y93H/N NS5A RAS at the time of relapse. There were no relapses in participants with GTs 2, 4, 5, or 6 with or without compensated cirrhosis who received SOF/VEL for 12 weeks. For participants with or without compensated cirrhosis, of the 2 participants with GT 1 who experienced VF, 1 participant had emergent NS5A RAS Y93N, and the other had the emergent NS5A RASs Y93H and low-level K24M/T and L31I/V at VF. The latter participant had GT 1c/h at baseline, which harbored NS5A resistance polymorphisms (Q30R, L31M, and H58P) relative to GT 1a.

Of the 10 participants with GT 3a and VF, the NS5A RAS Y93H was observed in all participants at VF. Treatment-emergent SOF NS5B RASs L314F (n=2) and L314I (n=1) were observed at high frequency (≥15%) in the NS5B polymerase in 3 GT 3a participants who relapsed (SOF/VEL, n=1; 24-week SOF + RBV, n=2). In addition, low-frequency (<4%) treatment-emergent L314P was detected in 2 participants with GT 3a who relapsed (24-week SOF + RBV and SOF/VEL groups, n=1 each). The clinical significance of this substitution is unknown.

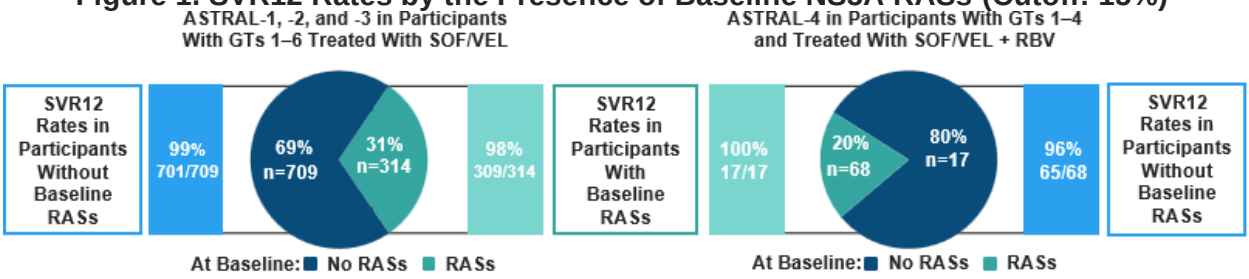
In ASTRAL-4, the participant with GT 1 who relapsed had no NS5A or NS5B RASs at VF. The 2 participants with GT 3a and VF had the NS5A RASs Y93H and either low-level M28V or S38P emerge at the time of VF. One of these participants also developed low levels (<5%) of NS5B nucleoside analog inhibitor RASs N142T and E237G at VF. Two participants

treated with SOF/VEL had emergent SOF NS5B RASs S282T at low levels (<5%), along with L159F.

Treatment response by the absence or presence of RASs

Regardless of the presence of RASs, SVR12 rates were high (Figure 1). Except for those with GT 3, the presence of RASs at baseline did not affect SVR12 rates in participants with or without cirrhosis or in decompensated participants.[2] Among participants with GT 3, a lower SVR12 rate of 88% (38/43) was reported. Of the 25 participants with the Y93H variant at baseline, 21 (84%) achieved SVR12.[2,7]

Figure 1. SVR12 Rates by the Presence of Baseline NS5A RASs (Cutoff: 15%)[2]



Japanese Retreatment Study[3]

Study design and demographics

A phase 3, multicenter, open-label, randomized study analyzed the effect of preexisting RASs in 60 DAA-experienced participants with GT 1 and GT 2 who received SOF/VEL + RBV for 24 weeks. Ninety-three percent of participants had NS5A RASs at baseline, and 83% and 17% of participants with GT 1 and GT 2 had ≥2 RASs, respectively. With or without other RASs, L31 and Y93 (with any amino acid substitution) were the most prevalent NS5A RASs in participants with GT 1 (88% and 81%, respectively; 77% had L31 + Y93 ± another RAS). Among participants with GT 2, L31 (with any amino acid substitution) with or without another RAS was the most prevalent (83%). There were 4 participants with NS5B RASs at baseline and 5 participants with a P32del RAS. Participants with GT 1 (n=48) had previously received DCV (n=36), LDV (n=7), DCV and LDV (n=4), or EBR (n=1). Participants with GT 2 (n=12) had previously received SOF (n=11) or other regimens (n=1).

Results

All participants achieved SVR12 except 1 participant with GT 1 who had ≥2 NS5A RASs at baseline and 1 participant with GT 2 and 1 NS5A RAS at baseline. Among the 2 participants who relapsed, no treatment-induced RASs were noted (GT 1b, L31I/V + P32del; GT 2b, L31M); 4 of the 5 participants with a P32del RAS noted at baseline achieved SVR12. Of participants with GT 1, the following SVR12 rates by baseline NS5A RASs were achieved: any Y93 ± another RAS, 100% (39/39); L31 + Y93 ± another RAS, 100% (37/37); any L31 ± another RAS, 98% (41/42). Ninety percent (9/10) of participants with GT 2 and any L31 ± another RAS achieved SVR12. All 4 participants with NS5B RASs at baseline achieved SVR12 (L159F, n=2; M289I, n=1; and V321I, n=1). These results demonstrate that the presence of RASs (NS5A, NS5B, or P32del) had no impact on treatment outcomes. Safety data were not reported.

Open-Label, Multicenter Study in Pediatric Participants[4]

Study design and demographics

An open-label, multicenter, two-part study evaluated SOF/VEL in TN or TE participants with any GT. The lead-in phase of the study evaluated steady-state pharmacokinetics and confirmed the SOF/VEL dose in three pediatric cohorts with chronic HCV (aged 3−5 years [recruitment ongoing], 6−11 years, and 12−17 years). The treatment phase of the study evaluated the efficacy, safety, and tolerability of 12 weeks of SOF/VEL therapy in two cohorts (6−11 years and 12−17 years). In participants aged 6 to 11 years (n=73) and 12 to 17 years (n=102), the median (range) ages were 8 (6–11) years and 15 (12–71) years, respectively; 48% and 49% were male, 90% and 73% were White, 5% and 22% were TE, and most had GT 1 (90% and 74%).

Results

Overall, SVR12 was achieved by 92% of participants (67/73) aged 6 to 11 years and by 95% of those (97/102) aged 12 to 17 years. All participants who had baseline RASs achieved SVR12. Among participants aged 6 to 11 years and 12 to 17 years, 10% and 16% had NS5A RASs, respectively, and 0% and 5% had NS5B RASs. The 1 participant who experienced nonresponse after 8 weeks of treatment had an NS5A RAS (L31V), and 1 participant who experienced virologic relapse did not develop any RASs.

Treatment with SOF/VEL was well tolerated, and AEs were similar to those seen in adults during phase 3 studies. Grade 3 to 4 AEs occurred in 3 participants: aged 6 to 11 years, n=1 (1%); 12 to 17 years, n=2 (2%). Serious AEs occurred in 2 participants in each age group. Two participants in the 6 to 11 years group discontinued the study due to AEs.

Real-World Data on Resistance in Patients Treated With SOF/VEL

UK Retreatment Study

Study design and demographics[5,6]

A real-world study evaluated the effects of RAS on retreatment outcomes in patients who were retreated with SOF/VEL + RBV (24 weeks), SOF/VEL/VOX (8, 12, 16, or 24 weeks), or GLE/PIB (12 or 16 weeks) after non-response to DAA therapy. Prior to HCV retreatment, whole-genome sequencing was performed on blood samples from 260 patients. Overall, 87% of patients were TE with NS5A inhibitors, 50% were TE with SOF-based treatment (including SOF/VEL + RBV, LDV/SOF, SOF + DCV, and/or SOF), and 30% had previously received protease inhibitors. Pre-retreatment RASs were present in 76% of samples. Of these, 67% had NS5A RASs, 31% had NS3 RASs, and 8% had NS5B RASs. The combination of NS3 and NS5A RASs was present in 23% of the samples. Retreatment outcomes were available for 118 patients (SOF/VEL + RBV, n=11; SOF/VEL/VOX, n=92; GLE/PIB, n=15) with other subtypes within GTs 2, 4, and 6. The most common GT subtypes were 3a (47%; n=56) and 1a (35%; n=41). Known cirrhosis and decompensated cirrhosis were present in 11 and 7 patients, respectively, in the SOF/VEL + RBV group, 42 and 7 patients in the SOF/VEL/VOX group, and 13 and 0 patients in the GLE/PIB group. In the SOF/VEL + RBV, SOF/VEL/VOX, and GLE/PIB groups, 4, 13, and 1 patient, respectively,

had a history of hepatocellular carcinoma; 2, 6, and 1 patient, had a previous liver transplant.

Retreatment outcomes[5]

Overall, SVR was achieved by 94% of retreated patients (111/118). All patients who received SOF/VEL + RBV achieved SVR (100%), and rates were similar between those who were retreated with SOF/VEL/VOX and GLE/PIB (94% and 93%, respectively). The presence of pre-retreatment RASs (no RASs, NS3, NS3 + NS5A, or NS5A) did not affect the achievement of SVR (*P*=0.7).

References

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7. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. *The New England Journal of Medicine.* 2015;373(27):2608-2617.

Abbreviations

AE=adverse event
DAA=direct-acting antiviral
DCV=daclatasvir
EBR=elbasvir
GLE=glecaprevir
GT=genotype
LDV=ledipasvir
NS=non-structural protein
PIB=pibrentasvir
RAS=resistance-associated substitution
RBV=ribavirin
SOF=sofosbuvir
SVR=sustained virologic response
SVR12=sustained virologic response 12 weeks after end of treatment
TE=treatment-experienced
TN=treatment-naive
VEL=velpatasvir
VF=virologic failure
VOX=voxilaprevir

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

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

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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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