GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Use in Patients With Decompensated Cirrhosis

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

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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 indicated for the treatment of adults and pediatric patients 3 years of age and older 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 RBV.

The recommended treatment regimen and duration for TN and TE patients with decompensated cirrhosis (CP Class B or C) is SOF/VEL + RBV for 12 weeks.

No dosage adjustment of SOF/VEL is recommended for patients with mild, moderate, or severe hepatic impairment (CP Class A, B, or C).

Clinical and hepatic laboratory monitoring (including direct bilirubin), as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with SOF/VEL + RBV.

Clinical Studies: SOF/VEL Use in Decompensated Cirrhosis

The phase 3 ASTRAL-4 study evaluated 12 or 24 weeks of SOF/VEL vs 12 weeks of SOF/VEL + RBV in participants with HCV GT 1 to 6 and CPT Class B decompensated cirrhosis. SVR12 was 94% (77/90) in the SOF/VEL + RBV group. The most common AEs in the SOF/VEL + RBV group included fatigue, nausea, anemia, headache, and diarrhea.[2]

In a 12-week multicenter study of SOF/VEL treatment in Japanese participants with decompensated cirrhosis, the SVR rate was 91.3% (188/206). Improvement in liver function was observed, as indicated by an increased proportion of participants with CP Class A at Week 24 after EOT, followed by a gradual decline through Year 5. Liver transplant-free survival rates at 1, 3, and 5 years were 94%, 82.9%, and 69%, respectively. Overall, 43 participants died, and 4 underwent liver transplantation; causes of death included liver failure, non–liver-related conditions, HCC, and variceal rupture.[3]

In a phase 3 study of SOF/VEL vs SOF/VEL + RBV for 12 weeks in Japanese participants with decompensated cirrhosis, SVR12 rates were 92% (47/51) in each group. The most common AEs were nasopharyngitis in the SOF/VEL group and anemia and diarrhea in the SOF/VEL + RBV group.[4]

Real-World Studies: SOF/VEL Use in Decompensated Cirrhosis

In the real-world setting, rates of SVR12 ranged from 86% to 100% in participants with decompensated cirrhosis who were treated with SOF/VEL ± RBV.[5-7]

Clinical Studies: SOF/VEL Use in Decompensated Cirrhosis

ASTRAL-4: SOF/VEL ± RBV for 12 or 24 Weeks in Participants With GT 1 to 6 and Decompensated Cirrhosis

Study design and demographics[2]

ASTRAL-4 was a phase 3, open-label study that evaluated the safety and efficacy (SVR12) of 12 or 24 weeks of SOF/VEL vs 12 weeks of SOF/VEL + RBV in TN and TE participants with HCV GT 1 to 6 and CPT Class B decompensated cirrhosis.

Table 1. ASTRAL-4: Baseline Demographics and Disease Characteristics[2]

Key Demographics and Characteristics	SOF/VEL × 12 Wks (n=90)	SOF/VEL × 24 Wks (n=90)	SOF/VEL + RBV × 12 Wks (n=87)
Race, White/Black, %	88/7	90/7	91/6
HCV GT, 1/2/3/4/5/6, %	76/4/16/4/0/0	79/4/13/2/0/1	78/5/15/2/0/0
MELD score, <10/10–15/≥16, %	40/56/4	29/66/6	33/62/5
TE, n (%)	58 (64)	42 (47)	47 (54)

Efficacy

Overall, SVR12 was achieved by 83% (82/87) and 86% of participants (75/90) in the SOF/VEL 12- and 24-week groups, respectively, and by 94% of participants (77/90) in the SOF/VEL + RBV 12-week group. SVR12 rates by HCV GT are presented in Table 2.[2] SVR12 rates were sustained at the SVR24 check point in all groups except the SOF/VEL 24-week group, which had an SVR24 rate of 88% (79/90).[8]

Table 2. ASTRAL-4: SVR12 Rates by HCV GT[2]

HCV GT, n/N (%)	SOF/VEL × 12 Wks	SOF/VEL × 24 Wks	SOF/VEL + RBV × 12 Wks
1a	44/50 (88)	51/55 (93)	51/54 (94)
1b	16/18 (89)	14/16 (88)	14/14 (100)
2	4/4 (100)	3/4 (75)	4/4 (100)
3	7/14 (50)	6/12 (50)	11/13 (85)
4	4/4 (100)	2/2 (100)	2/2 (100)
6	0	1/1 (100)	0

Twenty-two participants had virologic failure: 12% (11/90) in the SOF/VEL 12-week group, 9% (8/90) in the SOF/VEL 24-week group, and 3% (3/87) in the SOF/VEL + RBV group. Twenty participants relapsed, and 2 participants with GT 3 had virologic breakthrough.[2]

Changes in CPT score from baseline to the 12- and 24-week follow-ups and SVR rates by baseline CPT class are presented in Table 3 and Table 4, respectively.[8]

Table 3. ASTRAL-4: CPT Change From Baseline in Participants Who Achieved SVR[8]

SVR, n (%)	CPT Scores		
	Improved CPT	No Change in CPT	Worsened CPT
SVR12	108 (47)	99 (43)	22 (10)
SVR24	115 (54)	77 (36)	21 (10)

Table 4. ASTRAL-4: SVR Results by Baseline CPT Class[8]

Baseline CPT Class, n/N (%)	SVR12	SVR24
A	4/14 (29)	6/13 (46)
B	98/205 (48)	102/191 (53)
C	6/10 (60)	7/9 (78)

Of the participants who achieved SVR24, 39% of participants (84/213) had an improvement in albumin levels, 16% (35/213) had an improvement in bilirubin levels, 2% (5/213) had an improvement in INR, 15% (32/213) had an improvement in ascites, and 9% (20/213) had an improvement in encephalopathy.[8]

Improvements in MELD score were driven largely by improvements in total bilirubin, and improvements in MELD score at post-treatment Weeks 12 and 24 were more common in participants with higher MELD scores, lower BMI (<30 kg/m^2), or absence of encephalopathy at baseline.[8]

Table 5. ASTRAL-4: Changes in MELD Score in Participants Who Achieved SVR24[8]

Baseline MELD Score, n (%)	MELD Score Results		
	Improved MELD Score	No Change in MELD Score	Worsened MELD Score
<15	92 (49)	47 (25)	49 (26)
≥15	18 (72)	1 (4)	6 (24)

Of the 255 participants for whom pre-treatment NS5A sequencing data were available, 28% (72/255) had pre-treatment NS5A RAVs. Of these participants, 89% (64/72) achieved SVR, compared with 92% of participants (169/183) who did not have pre-treatment NS5A RAVs. Among participants with GT 1 who received SOF/VEL + RBV, the SVR rate in those with NS5A RAVs was 100%, and the rate in participants without such variants was 98%. Among participants with GT 1 in the SOF/VEL groups who had pre-treatment RAVs, the SVR rate was 80% for those who received 12 weeks of treatment and 90% for those who received 24 weeks of treatment. Among those who did not have RAVs, the SVR rates were 96% and 98%, respectively.[2]

Safety[2]

A summary of key safety results is presented in Table 6.

Table 6. ASTRAL-4: Summary of Safety Results[2]

Key Safety Parameters, n (%)		SOF/VEL × 12 Wks (n=90)	SOF/VEL × 24 Wks (n=90)	SOF/VEL + RBV × 12 Wks (n=87)
AEs		73 (81)	73 (81)	79 (91)
AEs occurring in >15% of participants	Fatigue	23 (26)	21 (23)	34 (39)
	Headache	23 (26)	17 (19)	18 (21)
	Nausea	22 (24)	18 (20)	22 (25)
	Diarrhea	6 (7)	7 (8)	18 (21)
	Anemia	4 (4)	3 (3)	27 (31)
SAEs		17 (19)	16 (18)	14 (16)
DCs due to AE		1 (1)	4 (4)	4 (5)

Reductions in Hgb, lymphocytes, and platelets were common in all three groups. Decreases in Hgb to <10 g/dL and <8.5 g/dL occurred in 8% and 1% of participants, respectively, in the SOF/VEL 12-week group, in 9% and 1% in the SOF/VEL 24-week group, and in 23% and 7% in the SOF/VEL + RBV group. Overall, 3 participants in each of the three treatment groups died during the study, most due to complications of end-stage liver disease (ie, liver failure, sepsis, or multiorgan failure); none were considered to be treatment related. Two participants died after discontinuing study treatment, and 7 participants died >30 days after EOT.

Study of Long-term Changes in Liver Function and Prognosis Following SOF/VEL in Japanese Participants With Decompensated Cirrhosis[3]

Study design and demographics

A multicenter study evaluated changes in liver function and liver transplant-free survival following treatment with SOF/VEL in Japanese participants with decompensated cirrhosis, defined as CP Class B or C at enrollment or CP Class A with prior decompensation. A total of 206 participants who received 12 weeks of SOF/VEL between February 2019 and December 2021 were enrolled. Clinical and laboratory data were collected at baseline, EOT, Weeks 12 and 24 after EOT, and every 6 months thereafter. Changes in liver function were evaluated based on the proportion of participants with CP Class A. For the survival analysis, the observation period began on the date of SOF/VEL initiation and ended at the earliest of death, liver transplantation, or last hospital visit.

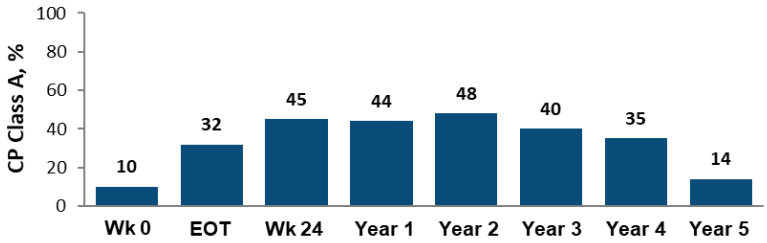
Table 7. Baseline Demographics and Disease Characteristics (Tahata et al)[3]

Key Demographics and Characteristics	SOF/VEL (N=206)
GT, 1/2/3/4/1 + 2/unknown, n	131/71/1/0/1/2
HCV RNA, median (IQR), log IU/mL	5.7 (5.1–6.1)
CP Class, A/B/C, n	20/156/30
MELD score, median (IQR)	11 (9–12)
History of HCC, n (%)	82 (40)
Esophageal gastric varix, absent/F1/F2 or more/history of varix rupture, n	46/74/41/17
Ascites, Grade 1/2/3, n	72/110/24
Encephalopathy, Grade 1/2/3, n	173/33/0
AFP, median (IQR), ng/mL	8.6 (4.4–20.3)

Results

Overall, 91.3% of participants (188/206) achieved SVR in the ITT analysis. Seven participants experienced virologic failure, 2 had missing HCV RNA data, 4 were LTFU, and 5 died prior to SVR confirmation. The proportion of participants who changed to CP Class A increased at Week 24 after EOT, followed by a gradual decline through Year 5 after EOT (Figure 1).

Figure 1. Changes in the Proportion of Participants With CP Class A Through Year 5 After EOT (Tahata et al)[3]



Over the 43.7-month period following SOF/VEL initiation, 43 participants died, and 4 underwent liver transplantation. Causes of death included liver failure (n=19), non–liver-related conditions (n=13), HCC (n=10), and variceal rupture (n=1). The 1-year, 3-year, and 5-year liver transplant-free survival rates were 94%, 82.9%, and 69%, respectively. Liver transplant-free survival rates by virologic outcomes and CP Class at 12 weeks after the EOT are presented in Table 8.

Table 8. Liver Transplant-free Survival Rates by Virologic Outcomes and CP Class at 12 Weeks After the EOT (Tahata et al)[3]

Virologic Outcomes and CP Class at 12 Weeks After EOT, n/N or %	Events[a]	Year 1	Year 3
Virologic failure	3/7	100	50
SVR	38/188	96.2	86.3
CP Class A[b]	6/76	100	91.9
CP Class B[c]	25/97	95.8	86.4
CP Class C	10/18	81.6	46

[a]Died or underwent liver transplantation.
[b]*P*=0.012 vs CP Class B; *P*<0.001 vs CP Class C.
[c]*P*<0.001 vs CP Class C.

Factors associated with liver transplant-free survival were analyzed, excluding 11 participants with non-evaluable SVR data. In the multivariate analysis, virologic response and CP Class B and C at 12 weeks after the EOT were identified as significant factors (*P*=0.04, *P*=0.015, and *P*<0.001, respectively).

Phase 3, Open-Label, Prospective Study of SOF/VEL ± RBV in Japanese Participants With Decompensated Cirrhosis[4]

Study design and demographics

A prospective, phase 3, multicenter, open-label study evaluated the efficacy (SVR12) and safety of SOF/VEL ± RBV in Japanese participants with chronic HCV infection and quantifiable HCV RNA at screening. Participants were randomly assigned to receive 12 weeks of SOF/VEL (n=51) or SOF/VEL + RBV (n=51) and were stratified by GT (GT 1 vs

non-GT 1) and CPT class at screening (CPT Class B vs Class C). At baseline, 77% of participants were CPT Class B (score: 7–9), 20% were CPT Class C (score: 10–12), and 3% were CPT Class A (score: 6). Of the 44 who were TE, all except 1 participant had been treated with an IFN ± RBV, and the remaining participant was treated with simeprevir + pegylated IFNα 2a + RBV for 23 weeks. Of the 100 participants included in the resistance analysis, 41 had baseline NS5A RASs, and none had NS5B RASs.

Table 9. Baseline Demographics and Disease Characteristics (Takehara et al)[4]

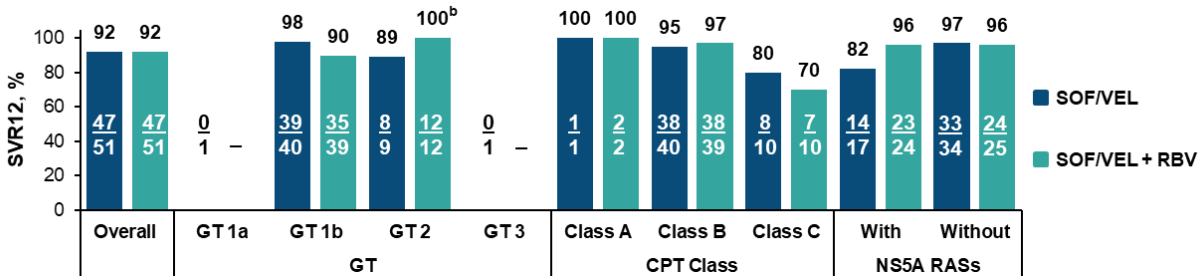
Key Demographics and Characteristics	SOF/VEL (n=51)	SOF/VEL + RBV (n=51)
GT 1/1a/1b, n (%)	41 (80)/1 (2)/40 (78)	39 (76)/0/39 (76)
GT 2/2a/2a-c/2b/no confirmed subtype, n (%)	9 (18)/0/2 (4)/2 (4)/5 (10)	11 (22)/2 (4)[a]/1 (2)/4 (8)/5 (10)
GT 3b, n (%)	1 (2)	0
HCV RNA, mean (range), log_{10} IU/mL	5.7 (3.7–7.1)	5.8 (4.2–7)
TN, n (%)	27 (53)	31 (61)
IL28B CC GT, n (%)	33 (65)	37 (73)
MELD score ≤15, n (%)	46 (90)	48 (94)
Ascites, none/mild or moderate/severe, n (%)	19 (37)/32 (63)/0	16 (31)/33 (65)/2 (4)
Encephalopathy, none/medication controlled, n (%)	23 (45)/28 (55)	22 (43)/29 (57)

[a]One participant who initially had a missing GT was later determined to have GT 2a.

Efficacy

Overall, 100% of participants had undetectable HCV RNA at EOT, and 92% of participants in each group achieved SVR12 (95% CI: 81–98%; Figure 2). Six participants had a virologic relapse, including 4 participants in the SOF/VEL group. Of the 4 participants in the SOF/VEL + RBV group who did not achieve SVR12, 2 had a virologic relapse, and 2 discontinued treatment prematurely and subsequently died. Of the participants with GT 1 who were treated with SOF/VEL, 2 participants relapsed (1 with and 1 without baseline NS5A RASs). Similarly, of those with GT 1 who were treated with SOF/VEL + RBV, 2 participants relapsed (1 with and 1 without baseline NS5A RASs). Four of the 6 participants who experienced virologic relapse had treatment-emergent NS5A RASs; no treatment-emergent NS5B RASs were observed.

Figure 2. SVR12 Rates Overall, by GT, by CPT Class, and by Baseline NS5A (Takehara et al)[4a]



[a]SVR12 data were available for 100 participants who had NS5A RAS data at baseline.
[b]One participant who initially had a missing GT was later determined to have GT 2a.

From baseline to the SVR12 checkpoint among participants who achieved SVR12, 26% of participants (24/91) had an improvement in CPT class, and 2% of participants (2/91) had a worsening in CPT class (Table 10). The improvements in CPT scores were influenced by improvements in albumin levels, as 79% of participants who had increases in CPT scores

also had improvements in albumin levels. MELD scores increased in 27% of participants (25/94) and worsened in 15% (14/94).

Table 10. Changes in CPT Class From Baseline to Post-Treatment Week 12 (Takehara et al)[4]

Post-Treatment Week 12 CPT Class, n (%)	Baseline CPT Class (n=94)		
	CPT Class A (n=3)	CPT Class B (n=76)	CPT Class C (n=15)
CPT Class A (5–6)	3 (100)	19 (25)	0
CPT Class B (7–9)	0	55 (72)	5 (33)
CPT Class C (10–15)	0	2 (3)	10 (67)

Safety

Most AEs were mild to moderate in severity (Table 11). No clinically significant trends in rates of AEs were observed by either age group or CPT class. After treatment completion, 3 participants developed HCC that was considered unrelated to study treatment; none of the participants with a history of HCC experienced a recurrence of HCC. The observed laboratory abnormalities were consistent with those generally observed in participants with decompensated liver disease.

Table 11. AEs and Laboratory Abnormalities by Treatment Group (Takehara et al)[4]

Safety Outcomes, n (%)		SOF/VEL (n=51)	SOF/VEL + RBV (n=51)
Any AE		35 (69)	44 (86)
Nasopharyngitis		7 (14)	3 (6)
Anemia		0	20 (39)
Diarrhea		0	7 (14)
Grade ≥3 AEs		2 (4)	5 (10)
SAEs[a]		4 (8)	7 (14)
AEs that led to DC of SOF/VEL		0	2 (4)
AEs that led to DC of RBV		N/A	9 (18)
AEs that led to alteration in RBV therapy		N/A	18 (35)
Deaths		0	3 (6)[b]
Grade ≥3 laboratory abnormalities	Total bilirubin >2.5 × ULN	6 (12)	12 (24)
	Hyperglycemia >250–500 mg/dL	5 (10)	9 (18)
	Hgb <10 g/dL	2 (4)	7 (14)
	Platelets 25,000–50,000/mm^3	1 (2)	6 (12)
	Lymphocytes <500/mm^3	0	5 (10)

Abbreviation: ULN=upper limit of normal.
[a]SAEs that occurred in >1 participant included hepatic encephalopathy (SOF/VEL, n=1; SOF/VEL + RBV, n=2) and femur fracture (SOF/VEL + RBV, n=2).
[b]All 3 participants had CPT Class C at baseline; all deaths occurred after the completion of treatment and were due to the progression of end-stage liver disease.
Note: Laboratory abnormalities had to increase from baseline by ≥1 toxicity grade. Safety data through 30 days after the last dose of study drug.

Real-World Studies: SOF/VEL Use in Decompensated Cirrhosis

Study of Japanese Participants With Decompensated and Compensated Cirrhosis[5]

Study design and demographics

A real-world, multicenter study compared the efficacy (SVR12) and safety of DAAs, including SOF/VEL ± RBV, in participants with decompensated cirrhosis to the outcomes in those with compensated cirrhosis. Participants with decompensated cirrhosis (n=82; CP Class B/C, a history of decompensation, or the need for SOF/VEL determined by clinicians) were treated with 12 weeks of SOF/VEL. Participants with compensated cirrhosis (n=108) were treated with a 12-week course of LDV/SOF, EBR/GZR, GLE/PIB, or SOF + RBV, or a 24-week course of SOF/VEL + RBV. Eighty-two participants with decompensated cirrhosis received SOF/VEL, and 7 participants with compensated cirrhosis received SOF/VEL + RBV. All patients were treated according to the Japanese guidelines for HCV.

Table 12. Baseline Demographics and Disease Characteristics (Tahata et al)[5]

Key Demographics and Characteristics		Decompensated Cirrhosis (n=82)	Compensated Cirrhosis (n=108)
GT, 1/2/3/4/1 + 2/unknown, n		55/24/1/0/1/1	66/36/4/1/0/1
HCV RNA, median (range), log_{10} IU/mL		5.8 (2.9–7.2)[a]	6.1 (2.2–7.1)
CP score, 5/6/7/8/9/10/11/12/13,[b] n		2/4/26/16/16/8/3/2/1[a]	53/41/6/1/0/0/0/0/0
MELD score, <10/≥10, n		28/50[b]	79/22
Esophageal varices, absent/F1/F2 or more/history of variceal rupture, n		20/36/12/2[a]	39/14/7/0
History of HCC treatment, n		33	37
FIB-4 index, median (range)		7.84 (1.41–33.61)[a]	5.43 (0.69–23.24)
Encephalopathy score,[c] 1/2/3, n		64/18/0[a]	107/1/0
Ascites score,[c] 1/2/3, n		29/41/12	97/10/1
AFP, median (range), ng/mL		9.1 (0.9–5102)	8.3 (1.3–7272.9)
eGFR, median (range), mL/min/1.73 m^2		67.5 (32.5–135.5)	70.1 (4.43–113.8)
Previous treatment, TN/IFN-based/IFN-free, n		62/18/2	85/10/13
DAAs used in study, n	SOF/VEL × 12 wk	82	N/A
	SOF/VEL + RBV × 24 wk	N/A	7
	GLE/PIB × 12 wk	N/A	77
	EBR/GZR × 12 wk	N/A	13
	LDV/SOF × 12 wk	N/A	10
	SOF + RBV × 12 wk	N/A	1

Abbreviation: FIB-4=fibrosis-4.
[a]*P*<0.05 for decompensated vs compensated cirrhosis groups.
[b]Prothrombin data were missing in 4 participants with decompensated cirrhosis (due to concomitant warfarin therapy) and in 7 participants with compensated cirrhosis.
[c]Encephalopathy and ascites scores utilized CP scores.

Efficacy

SVR12 rates were not significantly different between the decompensated (90%; 74/82) and compensated cirrhosis groups (93%; 100/108; *P*=0.564). Among participants with

decompensated cirrhosis, 4 participants relapsed after EOT, 2 were LTFU, and 2 died before the SVR12 time point. Among participants with compensated cirrhosis, 7 were LTFU, and 1 died before the SVR12 time point.

Among participants with decompensated cirrhosis who achieved SVR12, 65% of participants (45/69) had an improvement in CP scores, and 50% (35/70) had an improvement in MELD scores; in the compensated cirrhosis group, 33% (26/80) and 33% (25/76) of participants, respectively, had these outcomes. Changes in CP class from baseline to post-treatment Week 12 are presented in Table 13.

Table 13. Changes in CP Class From Baseline to Post-Treatment Week 12 (Tahata et al)[5a]

CP Class at SVR12, n/N (%)	Decompensated Cirrhosis: Baseline CP Classes			Compensated Cirrhosis: Baseline CP Classes[b]	
	CP Class A (n=6)	CP Class B (n=55[c])	CP Class C (n=13[d])	CP Class A (n=86[e])	CP Class B (n=7[f])
CP Class A	6/6 (100)	26/52 (50)	1/11 (9)	70/74 (95)	4/6 (67)
CP Class B	0/6 (0)	23/52 (44)	3/11 (27)	4/74 (5)	2/6 (33)
CP Class C	0/6 (0)	3/52 (6)	7/11 (64)	0/74 (0)	0/6 (0)

[a]CP Class A=scores 5 to 6; CP Class B=scores 7 to 9; CP Class C=scores 10 to 15.
[b]None of the participants with compensated cirrhosis were CP Class C.
[c]Three participants were receiving warfarin.
[d]Data were missing for 1 participant, and 1 participant was receiving warfarin.
[e]Data were missing for 7 participants, and 5 participants were receiving warfarin.
[f]Data were missing for 1 participant.

Among participants with decompensated and compensated cirrhosis who achieved SVR12, 54% and 27%, respectively, had an improvement in albumin levels. Albumin levels increased significantly from baseline to SVR12 regardless of baseline albumin levels.

Safety

Three participants in the decompensated cirrhosis group discontinued SOF/VEL prematurely (due to variceal bleeding, liver failure, and exacerbation of ascites), and 2 participants died due to liver failure during follow-up. Two participants in the compensated cirrhosis group discontinued DAAs prematurely (due to rupture of cerebral aneurysm and self-suspension), and 1 participant who received GLE/PIB died due to a ruptured cerebral aneurysm during follow-up. Data for AEs that did not result in treatment DC were not collected during this study.

Japanese Study of SOF/VEL for 12 Weeks[6]

Study design and demographics

The efficacy (SVR12) and safety of a 12-week course of SOF/VEL in 72 patients with decompensated cirrhosis (CP Class B or C [score ≥7]) were evaluated in a multicenter, retrospective observational study.

Table 14. Baseline Demographics and Disease Characteristics (Takaoka et al)[6]

Key Demographics and Characteristics	Overall (N=72)	CP Class B (n=59)	CP Class C (n=13)
GT 1 (1a/1b/no confirmed subtype), n	50 (0/41/9)	43 (0/34/9)	7 (0/7/0)
GT 2 (2a/2b/no confirmed subtype), n	22 (11/8/3)	16 (7/7/2)	6 (4/1/1)

Key Demographics and Characteristics	Overall (N=72)	CP Class B (n=59)	CP Class C (n=13)
HCV RNA viral load, median (IQR), log IU/mL	5.7 (5.3–6.1)	5.7 (5.5–6.2)	5.5 (4.6–5.8)
CP score, 7/8/9/10/11/≥12, n	24/16/19/9/4/0	24/16/19/0/0/0	0/0/0/9/4/0
MELD score, <10/10–15/>15, n (%)	44 (61.1)/27 (37.5)/ 1 (1.4)	40 (67.8)/19 (32.2)/ 0	4 (30.8)/8 (61.5)/ 1 (7.7)
TE, n (%)	10 (13.9)[a]	9 (15.3)	1 (7.7)
History of HCC treatment, n (%)	23 (31.9)[b]	20 (33.9)	3 (23.1)
Esophageal varices, n (%)	48 (66.7)	41 (69.5)	7 (53.8)
Ascites present, n (%)	40 (55.6)	31 (52.5)	9 (69.2)
Encephalopathy present, n (%)	14 (19.4)	10 (16.9)	4 (30.8)
eGFR, median (IQR), mL/min/1.73 m^2	64.2 (50.2–78.6)	62.9 (50.2–76.9)	68.9 (50.4–78.5)
Albumin, median (IQR), g/dL	2.9 (2.6–3.2)	3 (2.8–3.2)[c]	2.5 (2.3–2.7)
Prothrombin time, median (IQR), %	61.6 (56–70)	64 (59–74)[c]	51.6 (45–57)
Total bilirubin, median (IQR), mg/dL	1.52 (1.1–2.2)	1.4 (1.1–1.9)[c]	2.6 (2.1–3.1)

[a]Nine patients were TE with IFN, and 1 patient had virologic relapse after previous treatment with SOF + RBV (CP score at baseline: 10).
[b]Median (range) time from previous HCC treatment to SOF/VEL initiation was 8 (0.5–54) months.
[c]*P*<0.01 vs CP Class C.

Efficacy

Seventy patients completed 12 weeks of treatment, including 2 patients who were LTFU. Two patients discontinued treatment due to an AE. Overall, 95.8% of patients (69/72) achieved SVR12; 94.9% of patients (56/59) who had CPT Class B at baseline and 100% of patients (13/13) who had CPT Class C at baseline achieved SVR12.

In the 69 patients who achieved SVR12, albumin levels, prothrombin times, platelet counts, and eGFR increased significantly relative to baseline (*P*<0.05); ALT, AST, and AFP levels decreased significantly relative to baseline (*P*<0.05). The proportion of patients who had ascites at baseline decreased significantly at SVR12 (55.1% vs 26.5%; *P*<0.01); however, the proportion of patients with encephalitis did not decrease (*P*=0.82). Total bilirubin levels did not change significantly over the course of the study period.

In the patients who achieved SVR12 and had CP scores at each time point (n=68), CP scores were improved in 75% of patients, worsened in 5.9%, and unchanged in 19.1%. During the study period, 37.5% of patients (27/72) had an improvement to CP Class A. In a multivariate analysis, the following factors were associated with a lack of improvement in CP score at SVR12 (*P*<0.05): total bilirubin level >2 mg/dL (HR, 3.96; 95% CI: 1–15.7) and a portosystemic shunt diameter >6 mm (HR, 9.81; 95% CI: 1.04–92.2).

Safety

Twenty-two patients (30.6%) reported AEs, most of which were classified as Grade 1 or 2. The most common AEs were hepatic encephalopathy (n=11, 15.3%) and skin symptoms (ie, pruritus and rash; n=7, 9.7%). The incidence of reported AEs was not significantly different between those with CP Class B and those with CP Class C. SAEs occurred in 7 patients and included hepatic encephalopathy (n=3), interstitial pneumonia (n=1), sepsis (n=1), acute kidney injury (n=1), and heart failure (n=1). Two patients discontinued SOF/VEL prematurely due to AEs: 1 at Week 2 (CP score of 9 at baseline) due to Grade 2 encephalopathy, the other at Week 3 (CP score of 10 at baseline) due to Grade 3 interstitial pneumonia. One death occurred 11 weeks after EOT in a 79-year-old patient (baseline CP score: 7; EOT CP score: 6); the death was not considered by the investigator to be related to SOF/VEL.

Nine of the 23 patients who previously had HCC developed recurrent HCC, and 3 patients developed a first occurrence of HCC during the study. Ten of these 12 patients with HCC had radiofrequency ablation and/or transcatheter arterial embolization, including 1 patient who had an improvement from CPT Class C to A and had achieved SVR12. The remaining 2 patients did not receive anticancer treatment due to liver dysfunction and older age. The median (range) time from the beginning of SOF/VEL treatment to new or recurrent HCC was 3.5 (1–7) months.

Five patients underwent treatment for esophageal varices before they began treatment with SOF/VEL, and 1 patient underwent endoscopic variceal ligation during SOF/VEL treatment. No ruptures of esophageal varices occurred during this study.

Japanese Study of SOF/VEL for 12 Weeks in Participants With Decompensated Cirrhosis[7]

Study design and demographics

The KTK49 Liver Study group in Japan conducted a prospective, multicenter real-world study to evaluate the efficacy (SVR12 and undetectable HCV RNA at EOT) and safety of SOF/VEL for 12 weeks in 71 participants with decompensated cirrhosis (CP Class B/C) and HCV GT 1 or 2.

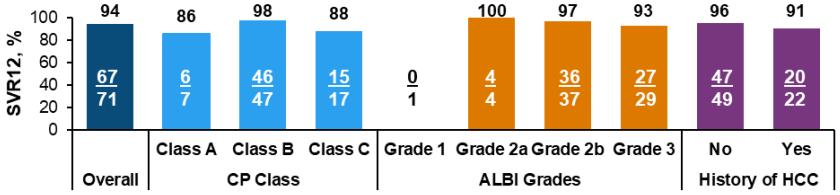
At baseline, 52 participants had GT 1b, 17 had GT 2a, and 2 had GT 2b; 30 participants had mild ascites, and 6 had moderate to severe ascites; 23 participants had mild hepatic encephalopathy; 45 participants had known esophageal varices; 22 participants had a history of HCC treatment; 1 participant had a history of DAA treatment (IFN-free). Seven participants were CP Class A (all had previous decompensation events, were treated with branched-chain amino acids and/or diuretics, and improved to CP Class A), 47 were CP Class B, and 17 were CP Class C. One, 4, 37, and 29 participants had ALBI grades of 1, 2a, 2b, and 3, respectively, and the median (range) ALBI grade was -1.58 (-3.01 to -0.45).

At baseline, the median (range) laboratory values were as follows: HCV RNA, 5.7 (3–7.4) log IU/mL, AFP, 7 (1.3–2031.8) U/L; ALT, 31 (11–119) U/L; AST, 55 (20–152) U/L; albumin, 2.9 (1.9–4.5) g/dL; total bilirubin, 1.5 (0.5–5.2) mg/dL; prothrombin time, 64% (18–110%); Hgb, 11.7 (7.9–16) g/dL; and platelets, 77 (29–186) × 10^3/mm^3.

Efficacy

Sixty-nine participants completed 12 weeks of treatment. The overall SVR12 rate in the ITT population was 94% (Figure 3). Four participants did not achieve SVR12: 2 participants had a virologic relapse, and 2 participants died prior to achieving SVR12 but had undetectable HCV RNA during treatment. Therefore, 71 participants achieved undetectable HCV RNA at EOT, as neither of the 2 participants who died had viremia during treatment (DAA naive, n=70; DAA experienced, n=1 [previously received ASV + DCV]).

Figure 3. SVR12 Rates (ITT Population; Atsukawa et al)[7]



The presence of treatment-related RASs was evaluated in the 2 participants who had virologic relapse (both were DAA naive and had a history of HCC): 1 participant with GT 1b did not have any NS5A RASs at baseline but developed L31V, F37L, and Y93N substitutions at relapse; the other participant had GT 2b with Q30K and L31M substitutions at baseline and had the same NS5A RASs at relapse.

No participants had a reduction in CP class, but 3 participants had a reduction in CP scores after the SVR12 time point. Two participants had a deterioration in mALBI grades, even though both had achieved SVR12 (one from Grade 2b to Grade 3, and the other from Grade 2a to Grade 2b; both received tolvaptan for refractory ascites, and 1 required a transjugular intrahepatic portosystemic shunt procedure). Changes from baseline to SVR12 in CP class and ALBI grades are shown in Table 15.

Table 15. CP Classes and mALBI Grades Among Those Who Achieved SVR12 (Atsukawa et al)[7]

Time Points, n/N (%)	CP Classes			*P*-Value
	CP Class A	CP Class B	CP Class C	
At baseline	6/67 (9)	45/67 (68.6)	15/67 (22.4)	<0.001
At SVR12	25/67 (37.3)	33/67 (49.3)	9/67 (13.4)	
Time Points, n/N (%)	**ALBI Grades**			***P*-Value**
	ALBI Grade 1	ALBI Grade 2a	ALBI Grade 2b	ALBI Grade 3	
At baseline	0	4/67 (6)	36/67 (53.7)	27/67 (40.3)	<0.001
At SVR12	5/67 (7.5)	10/67 (14.9)	40/67 (59.7)	12/67 (17.9)	

Note: *P*-values are for baseline vs SVR12 comparisons.

Safety

AEs and SAEs were reported more frequently in those in the CP Class C subgroup than in those in the CP Class A/B subgroup; these differences, however, were not statistically significant (AEs, *P*=0.08; SAEs, *P*=0.241). Median eGFR levels did not change from baseline to SVR12 (70 mL/min/1.73 m^2 at each time point). Four of the 20 participants with a history of HCC who achieved SVR12 developed recurrent HCC (3 underwent treatment, and 1 was awaiting liver transplantation).

Table 16. Safety Outcomes Overall and By CP Class (Atsukawa et al)[7]

Safety Outcomes, n (%)		Overall (N=71)	CP Class A/B (n=54)	CP Class C (n=17)
Any AE		14 (19.7)	8 (14.8)	6 (35.8)
AEs that occurred in >1 participant overall	Hepatic encephalopathy	2 (2.8)	2 (3.8)	0
	Esophageal varices rupture	2 (2.8)	1 (1.9)	1 (5.9)
	Deterioration of ascites	2 (2.8)	1 (1.9)	1 (5.9)
AEs that led to treatment DC		2 (2.8)[a]	2 (3.8)	0
SAEs (CTCAE Grade ≥4)		4 (5.6)	2 (3.8)	2 (11.8)
Deaths		2 (2.8)[b]	1 (1.9)	1 (5.9)
Laboratory abnormalities, total bilirubin elevation		1 (1.4)[c]	1 (1.9)	0

Abbreviation: CTCAE=Common Terminology Criteria for Adverse Events v4.0.
[a]Acute cholecystitis and esophageal varices rupture (each, n=1).
[b]Sepsis (after acute cholelithiasis; CP Class B) and liver failure (after spontaneous bacterial peritonitis; CP Class C).
[c]Grade 1 elevation from 0.5 mg/dL to 2.3 mg/dL.

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Abbreviations

AE=adverse event
AFP=α-fetoprotein
ALBI=albumin-bilirubin grading system
ASV=asunaprevir
CP=Child-Pugh
CPT=Child-Pugh-Turcotte
DAA=direct-acting antiviral
DC=discontinuation
DCV=daclatasvir
EBR=elbasvir
EOT=end of treatment
GLE=glecaprevir
GT=genotype
GZR=grazoprevir
HCC=hepatocellular carcinoma
HR=hazard ratio
IFN=interferon
LDV=ledipasvir
LTFU=lost to follow-up
mALBI=modified ALBI
MELD=Model for End-Stage Liver Disease
PIB=pibrentasvir
RAS=resistance-associated substitution
RAV=resistance-associated variant
RBV=ribavirin
SAE=serious adverse event
SOF=sofosbuvir
SVR=sustained virologic response
SVR12/24=sustained virologic response 12/24 weeks after end of treatment
TE=treatment-experienced
TN=treatment-naive
VEL=velpatasvir

Product Label

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