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ORIGINAL ARTICLE

The tolerability of sofosbuvir/velpatasvir for 12 weeks in patients treated in the ASTRAL 1, 2 and 3 studies: A pooled safety analysis

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Abstract

To evaluate the safety and tolerability of the fixed-dose, single-tablet regimen sofosbuvir/velpatasvir (SOF/VEL) for the treatment of hepatitis C virus (HCV) infection in three Phase 3 studies in patients with and without compensated cirrhosis. Data from three registrational trials (ASTRAL-1, NCT02201940; ASTRAL-2, NCT02220998; ASTRAL-3, NCT02201953) were pooled by treatment regimen. Researchers assessed treatment-emergent adverse events (TEAEs) and laboratory abnormalities in patients randomized to SOF/VEL or placebo for 12 weeks in ASTRAL-1 and SOF/VEL for 12 weeks in ASTRAL-2 and ASTRAL-3. Overall, 1035 patients were treated with SOF/VEL, and 116 patients received placebo. Rates of any TEAE were generally similar between patients receiving SOF/VEL (79.4%) and those receiving placebo (76.7%). The majority of TEAEs were mild to moderate, with 23 (2.2%) treatment-emergent serious AEs in patients treated with SOF/VEL. Of these treatment-emergent serious AEs, none led to premature study discontinuation, nor were they considered related to treatment. Presence of compensated cirrhosis, greater age and mild renal impairment did not impact incidence or severity of TEAEs with SOF/VEL treatment. The most common TEAEs (incidence ≥10%) were headache, fatigue, nausea and nasopharyngitis in patients receiving SOF/VEL; similar rates were observed in placebo-treated patients. Three deaths (<1%) were reported in patients treated with SOF/VEL, all posttreatment and none assessed as related to study treatment. Similar to that of placebo, SOF/VEL treatment of HCV infection had a safety/tolerability profile that was not affected by baseline factors, such as the presence of compensated cirrhosis, mild renal impairment or advanced age.

KEYWORDS
compensated cirrhosis, hepatitis C, safety, sofosbuvir, velpatasvir

Abbreviations: AE, adverse event; AST, aspartate aminotransferase; CK, creatine kinase; DAA, direct-acting antivirals; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; OST, opioid substitution therapy; PWID, persons who inject drugs; SAE, serious adverse event; SOF/VEL, sofosbuvir/velpatasvir; TEAE, treatment-emergent adverse event.

Clinical trial numbers: NCT02201940; NCT02220998; NCT02201953.

1 | INTRODUCTION

The hepatitis C virus (HCV) is a major health concern: the World Health Organization (WHO) estimates 58 million people have chronic HCV, with 1.5 million new cases occurring annually.[1] The WHO has identified HCV as a major public health threat and has set a target of 2030 for its elimination.[2,3] Direct-acting antivirals (DAAs) have revolutionized HCV treatment with cure rates exceeding 90%.[4] Despite the success of DAA treatments, only 20% of high-income countries are on track to achieve this target.[5]

To drive HCV elimination, several international guidelines (WHO, European Association for the Study of the Liver, and American Association for the Study of Liver Diseases) recommend the use of simple pangenotypic DAA regimens with minimal pretreatment and on-treatment monitoring as part of a global call-to-action initiative among hepatology societies.[3,6–8] The protease inhibitor-free, single-tablet regimen sofosbuvir/velpatasvir (SOF/VEL; nucleotide analogue NS5B polymerase inhibitor plus NS5A inhibitor) was the first approved pangenotypic DAA regimen, allowing for rapid treatment initiation and minimal monitoring.[9,10] As demonstrated in clinical trials and large real-world cohorts, SOF/VEL is highly effective in diverse populations and has a positive impact on patient-reported outcomes.[11–17]

The objective of this paper is to report findings from a retrospective analysis of data pooled across three clinical trials to evaluate the safety of SOF/VEL among patients treated for HCV with and without compensated cirrhosis.

2 | PATIENTS AND METHODS

2.1 | Study design

Patient-level data were pooled from three Phase 3 clinical trials (ASTRAL-1, NCT002201940; ASTRAL-2, NCT02220998; and ASTRAL-3, NCT02201953). Study designs are shown in Figure 1; details of individual study methods have been published previously.[18,19] Data were pooled for the SOF/VEL treatment arms. Eligible patients were 18 years of age or older and had chronic HCV infection with genotype 1, 2, 3, 4, 5 or 6.[18,19] The protocols allowed for up to 20% of patients to show evidence of compensated cirrhosis. Patients could be treatment-naive or treatment-experienced (limited to 20% of the study population; defined as having had prior treatment failure with a regimen containing interferon either with or without ribavirin that was completed at least 8 weeks prior to baseline/Day 1). To ensure that treatment-experienced patients could be accurately characterized as having true virologic failure after prior completed regimens, patients who previously discontinued any HCV treatment because of adverse events (AEs) or who were previously treated with any nucleotide analogue HCV NS5B inhibitor or any NS5A inhibitor were ineligible for enrolment in the ASTRAL trials. Exclusion criteria also included history of, or current, hepatic decompensation or hepatocellular carcinoma. All trials were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice, Declaration of Helsinki guidelines and local regulations. Protocols were approved by relevant institutional review boards or independent ethics committees.

Safety was assessed through treatment-emergent AEs (TEAEs) including AEs leading to treatment discontinuation, serious AEs (SAEs), treatment-related AEs, deaths, AE severity and laboratory abnormalities. A TEAE was defined as any AE, regardless of cause or relation to treatment, that occurred during the period from first dose of study drug through the date of last dose of study drug plus 30 days. Assessment of causality (i.e. whether TEAEs were treatment related) was done by investigators applying clinical judgement. TEAEs were coded and graded according to the Medical Dictionary of Regulatory Activities and the Gilead Sciences, Inc. (GSI) Grading Scale for Severity of Adverse Events and Laboratory Abnormalities. In addition to assessment in the overall study population, safety was also assessed in three patient subgroups: those aged ≥65 years, those with compensated cirrhosis and those with an estimated glomerular

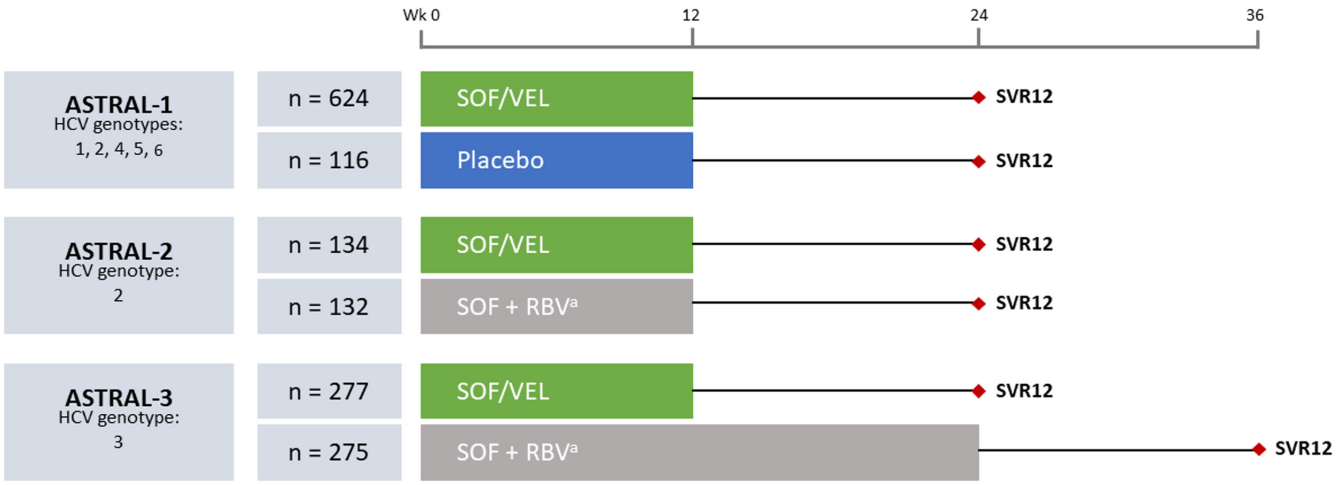

FIGURE 1 Diagram of the overall study design. [a]SOF + RBV data not included as part of this pooled analysis. HCV, hepatitis C virus; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after treatment; VEL, velpatasvir; wk, week.

filtration rate (eGFR) <90 mL/min/1.73 m^2. Results are summarized by descriptive statistics.

3 | RESULTS

The pooled dataset included 1151 patients. Over 12 weeks, 1035 patients received SOF/VEL, and 116 received placebo. Demographics were generally similar across treatment groups. Across datasets, at least 10% of patients were 65 years or older, at least 14% had compensated cirrhosis, and at least 32% had an eGFR value <90 mL/min/1.73 m^2 at baseline (Table 1).

Across treatment groups, the overall rates of TEAEs appeared comparable for SOF/VEL and placebo (Table 2). The most common TEAEs (occurring in >10% of patients) reported by SOF/VEL-treated patients were headache, fatigue, nausea and nasopharyngitis (Table 2); these were also the most commonly reported TEAEs among patients in the placebo group. Diarrhoea was reported in 73 (7.1%) patients receiving SOF/VEL and 8 (6.9%) receiving placebo. Grade 3/4 AEs were relatively rare in the SOF/VEL group (33 patients, 3.2%), with headache and anxiety most common (Table 2). In the SOF/VEL group, there were two cases of acute myocardial infarction, both of which were assessed as not related to treatment by the investigators. No patients experienced serious AEs in the placebo group versus 23 patients (2.2%) in the SOF/VEL group, although none of these SAEs were considered related to treatment nor did they lead to discontinuation of study drug (Table 3).

In the SOF/VEL group, 2 patients (<1%) discontinued treatment due to AEs. One experienced anxiety (assessed as not related to study drug) on Day 4 and discontinued treatment on Day 13. The other experienced disturbance in attention, headache and anxiety after the first dose of study drug, which was assessed as related to treatment, and discontinued study drug the same day. In the placebo group, 2 (2%) patients discontinued treatment due to AEs (elevated liver enzymes). One (<1%) patient receiving SOF/VEL experienced AEs that led to treatment modification/interruption.

Three deaths (<1%) occurred among patients treated with SOF/VEL across the ASTRAL-1, -2 and -3 trials, and none occurred in the placebo arm. One death was treatment-emergent, defined as occurring within 30 days of study completion, and involved a patient in the SOF/VEL group who died in his sleep of undetermined cause on posttreatment Day 8. Two other deaths were not treatment-emergent, occurring more than 30 days after trial completion: one patient was diagnosed with metastatic lung cancer with metastasis to the brain on posttreatment Day 69 and died on posttreatment Day 112. The other had an unwitnessed cardiac arrest at home on posttreatment Day 130 and died on posttreatment Day 131; toxicology reports were positive for opiates, benzodiazepines and ethanol. No deaths were considered related to study treatment.

TABLE 1 Baseline characteristics.

	SOF/VEL, *n* = 1035	Placebo, *n* = 116
Mean age, years	53	53
≥65	123 (12)	12 (10)
≥75	14 (1)	0
Male	630 (61)	68 (59)
Race		
American Indian or Alaskan Native	8 (0.8)	0
Asian	86 (8.3)	11 (9.5)
Black	61 (5.9)	11 (9.5)
White	867 (84)	90 (78)
Ethnicity		
Hispanic or Latino	68 (6.6)	5 (4.3)
Not Hispanic or Latino	959 (92.7)	111 (95.7)
Mean BMI, kg/m^2 (range)	27 (17–57)	26 (18–40)
Compensated cirrhosis	220 (21)	21 (18)
Treatment-experienced[a]	291 (28)	33 (28)
Median eGFR, mL/min/1.73 m^2 (range)	109 (48–244)	108 (55–188)
eGFR < 90 mL/min/1.73 m^2	297 (29)	37 (32)

Note: Data are presented as *n* (%) unless otherwise stated.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.

[a]Patients who had prior treatment failure to a regimen containing interferon either with or without RBV that was completed at least 8 weeks prior to baseline/Day 1.

TABLE 2 Summary of safety and adverse events.

Patients, *n* (%)	SOF/VEL, *n* = 1035	Placebo, *n* = 116
Overall		
TEAE	822 (79)	89 (77)
Grade 3/4 TEAE	33 (3)	1 (<1)
SAE	23 (2)	0
Treatment-related SAE	0	0
AE leading to treatment discontinuation	2 (<1)	2 (2)
Death	3 (<1)	0
Most common TEAEs occurring in >10% of patients in any treatment group		
Headache	296 (29)	33 (28)
Fatigue	217 (21)	23 (20)
Nausea	135 (13)	13 (11)
Nasopharyngitis	121 (12)	12 (10)
Insomnia	87 (8)	11 (10)
Grade 3+ TEAEs in >1 patient		
Headache	5 (<1)	0
Anxiety	3 (<1)	0
Acute myocardial infarction	2 (<1)	0

Abbreviations: AE, adverse event; SAE, serious AE; SOF, sofosbuvir; TEAE, treatment-emergent AE; VEL, velpatasvir.

TABLE 3 Serious adverse events.

Patients, *n* (%)	SOF/VEL, *n* = 1035	Placebo, *n* = 116
Any serious AE[a]	23 (2)	0
Acute myocardial infarction	2 (<1)	0
Palpitations	1 (<1)	0
Abdominal pain	1 (<1)	0
Enteritis	1 (<1)	0
Food poisoning	1 (<1)	0
Hematochezia	1 (<1)	0
Small intestinal obstruction	1 (<1)	0
Sudden death	1 (<1)	0
Cholecystitis acute	1 (<1)	0
Cellulitis	1 (<1)	0
Abscess limb	1 (<1)	0
Appendicitis	1 (<1)	0
Bronchitis	1 (<1)	0
Gastroenteritis	1 (<1)	0
Influenza	1 (<1)	0
Pneumonia	1 (<1)	0
Vestibular neuronitis	1 (<1)	0
Ligament sprain	1 (<1)	0
Upper limb fracture	1 (<1)	0
Rotator cuff syndrome	1 (<1)	0
Lung neoplasm malignant	1 (<1)	0
Epilepsy	1 (<1)	0
Intracranial aneurysm	1 (<1)	0
Mania	1 (<1)	0
Ovarian cyst ruptured	1 (<1)	0
Chronic obstructive pulmonary disease	1 (<1)	0
Extremity necrosis	1 (<1)	0

Abbreviations: AE, adverse event; SOF, sofosbuvir; VEL, velpatasvir.
[a]23 patients had a total of 28 serious adverse events.

Grade 3/4 laboratory abnormalities were reported in the SOF/VEL group (Table 4). Grade 3 hematologic abnormalities reported in >1 patient in the SOF/VEL group were decreased lymphocytes, neutrophils and platelets; none were clinically relevant, and they occurred either as isolated events or in patients with a graded abnormality at baseline. No Grade 3/4 hematologic abnormalities were reported in patients receiving placebo. None of the hematologic abnormalities were considered clinically important.

Among patients treated with SOF/VEL, the most common Grade 3/4 chemistry abnormalities were lipase, glucose and creatine kinase (CK) elevations. Lipase elevations were either single isolated events or intermittent and transient; there were no cases of pancreatitis reported. Within the SOF/VEL group, hyperglycaemia occurred in patients with history of diabetes, on antidiabetic medication, or with elevated haemoglobin A1c at baseline. Reports of CK elevation were associated with exercise or physical exertion and were transient. Elevated aspartate aminotransferase (AST) was reported in three patients treated with SOF/VEL. One patient had an isolated elevation that coincided with an upper respiratory tract infection; two patients had persistently elevated AST (1 associated with high alcohol intake and one in the context of morbid obesity). There were no reports of elevated bilirubin (≥Grade 3) in patients receiving either SOF/VEL or placebo. In patients treated with placebo, elevations in alanine aminotransferase, AST and glucose were most common.

Examining safety by patient subpopulation showed that in patients aged ≥65 years, the rates and severity of AEs were similar across treatment groups and were generally similar to patients aged <65 years (Table 5). In patients with compensated cirrhosis treated with SOF/VEL, 81% reported AEs, and 67% treated with placebo reported AEs (Table 5). In patients without compensated cirrhosis, 79% receiving SOF/VEL reported AEs versus 79% treated with placebo. Grade 3/4 AEs and SAEs were uncommon among patients with compensated cirrhosis, and there were no treatment-related SAEs in any treatment group in patients with or without compensated cirrhosis. In the overall population, change from baseline in eGFR at Week 12 was −0.96 (13.416) for the SOF/VEL group and 1.60 (10.884) for placebo. Among patients with mild renal impairment (eGFR <90 mL/min/1.73 m^2), AEs were reported for 81% of the SOF/VEL group and 78% of the placebo group; these rates were similar to those observed in patients with eGFR ≥90 mL/min/1.73 m^2 (Table 5). In both the eGFR ≥90 mL/min/1.73 m^2 and eGFR <90 mL/min/1.73 m^2 subpopulations, Grade 3/4 AEs and SAEs occurred in 3% and 2% of the SOF/VEL group, respectively; no SAEs in the SOF/VEL group were deemed related to treatment.

4 | DISCUSSION

This pooled analysis of the ASTRAL Phase 3 clinical trials (including 1151 patients) demonstrates that the safety profile of SOF/VEL is similar to that of placebo. Additionally, the safety profile of SOF/VEL was not influenced by older age, presence of compensated cirrhosis or mild renal impairment. Most TEAEs were mild to moderate (Grade 1 or 2), occurring at similar rates across groups, and there were no SAEs assessed as related to treatment. The most common AEs reported in both groups were headache, fatigue, nausea and nasopharyngitis. Treatment discontinuation due to AEs was uncommon (<1%) in the SOF/VEL group. Three deaths occurred in the SOF/VEL group (<1%); none were considered treatment related.

The subpopulation analysis revealed that SOF/VEL was well tolerated by patients aged >65 years, those with compensated cirrhosis and those with mild renal impairment. In all three subpopulations, most AEs were mild to moderate (Grade 1 or 2), SAEs were uncommon (3% in the elderly and 2% each in patients with compensated

TABLE 4 Grade 3/4 laboratory abnormality.

Patients, *n* (%)		SOF/VEL, *n* = 1035	Placebo, *n* = 116
Grade 3/4 haematological abnormalities			
Haemoglobin	<10 g/dL	2 (<1)	0
	<8.5 g/dL	0	0
Lymphocytes	Grade 3: <500/μL	5 (<1)	0
	Grade 4: <350/μL	1 (<1)	0
Neutrophils	Grade 3: <750/μL	4 (<1)	0
	Grade 4: <500/μL	0	0
Platelets	Grade 3: $<50\times10^3$/μL	2 (<1)	0
	Grade 4: $<25\times10^3$/μL	0	0
Grade 3/4 chemistry abnormalities			
ALT	Grade 3: >5 × ULN	1 (<1)	6 (5)
	Grade 4: >10 × ULN	0	2 (2)
AST	Grade 3: >3 × ULN	3 (<1)	2 (2)
	Grade 4: >10 × ULN	0	0
Creatine kinase	Grade 3: ≥10 × ULN	4 (<1)	0
	Grade 4: ≥20 × ULN	4 (<1)	0
Glucose (hyperglycaemia)	Grade 3: >250 mg/dL	20 (2)	5 (4)
	Grade 4: >500 mg/dL	0	0
Lipase	Grade 3: >3 × ULN	28 (3)	1 (<1)
	Grade 4: >5 × ULN	5 (<1)	0
Bilirubin	Grade 3: >3 × ULN	0	0
	Grade 4: >5 × ULN	0	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOF, sofosbuvir; ULN, upper limit of normal; VEL, velpatasvir.

cirrhosis and mild renal impairment), there were no treatment-related SAEs, and only one patient with mild renal impairment discontinued due to AEs.

This safety analysis of SOF/VEL in the controlled clinical trial setting adds to the large body of real-world evidence describing the safety of SOF/VEL in the treatment of chronic HCV infection with minimal treatment discontinuations.[11–13,15–17,20–22] Overall, the safety profile of SOF/VEL allows for the use of this DAA in simplified treatment algorithms, including by nonspecialist providers, with the possibility of rapid treatment initiation after diagnosis and minimal monitoring requirements, as recommended by international guidelines.[3,6–8]

The safe use of SOF/VEL with a simplified treatment paradigm is supported by the results of the MINMON (NCT03512210) trial, in which 400 enrolled patients with HCV received a 12-week course of SOF/VEL without pretreatment genotyping and no scheduled in-person visits or laboratory monitoring while on treatment.[23] The results showed a sustained virologic response rate of 95.0% (95% CI, 92.4–96.7); 4% of patients reported SAEs, none of which were considered related to treatment.[23] Assessing patient and clinician opinions on HCV treatment has shown a clear preference for treatments with minimal pretreatment testing and fewer side effects.[24]

One limitation of this analysis is the small size of the placebo group, which derives from ASTRAL-1 only, and which compromises the ability to determine the relatedness of rare events with treatment. Another potential limitation is that the ASTRAL studies excluded patients with active (within 12 months) drug use, although those on stable opioid substitution therapy (OST) were eligible. Thus, the ASTRAL studies did not fully assess the population of persons who inject drugs (PWID), who are disproportionally affected by HCV. However, SOF/VEL has since been assessed in the PWID population: The SIMPLIFY trial assessed SOF/VEL in patients with active drug use and reported a median adherence rate of 94%; evaluation of safety showed 83% had at least 1 AE, the majority (76%) of which were Grade 1 or 2.[25,26] Analysis of patients who were receiving OST and SOF/VEL therapies in Phase 3 trials showed a similar number of AEs to those who were not receiving OST (73.9% vs. 76.1%, respectively); most AEs in these trials were mild/moderate in severity.[27] The SIMPLIFY trial assessing patients with active drug use, the Phase 3 trials that included patients who were receiving OST, and this pooled analysis of ASTRAL 1, 2 and 3 studies all show similar types, rates and severity of AEs. As such, it does not appear that active drug use or OST affects the safety profile of SOF/VEL.

TABLE 5 Subgroup analysis summary of safety events.

	SOF/VEL	Placebo	SOF/VEL	Placebo
	Aged ≥65 years		Aged <65 years	
	n = 123	*n* = 12	*n* = 912	*n* = 104
TEAE	96 (78)	10 (83)	726 (80)	79 (76)
Grade 3/4 TEAE	4 (3)	0	29 (3)	1 (1)
SAE	4 (3)	0	19 (2)	0
Treatment-related SAE	0	0	0	0
AE leading to treatment discontinuation	0	0	2 (<1)	2 (2)
Death	0	0	3 (<1)	0
	With compensated cirrhosis		No compensated cirrhosis	
	n = 220	*n* = 21	*n* = 813	*n* = 95
TEAE	177 (81)	14 (67)	643 (79)	75 (79)
Grade 3/4 TEAE	8 (4)	0	25 (3)	1 (1)
SAE	4 (2)	0	19 (2)	0
Treatment-related SAE	0	0	0	0
AE leading to treatment discontinuation	0	0	2 (<1)	2 (2)
Death	1 (<1)	0	2 (<1)	0
	With eGFR < 90 mL/min/1.73 m^2		With eGFR ≥ 90 mL/min/1.73 m^2	
	n = 297	*n* = 37	*n* = 738	*n* = 79
TEAE	240 (81)	29 (78)	582 (79)	60 (76)
Grade 3/4 TEAE	8 (3)	0	25 (3)	1 (1)
SAE	7 (2)	0	16 (2)	0
Treatment-related SAE	0	0	0	0
AE leading to treatment discontinuation	1 (<1)	0	1 (<1)	2 (3)
Death	1 (<1)	0	2 (<1)	0

Abbreviations: AE, adverse event; eGFR, estimated glomerular filtration rate; SAE, serious AE; SOF, sofosbuvir; TEAE, treatment- emergent AE; VEL, velpatasvir.

5 | CONCLUSION

Treatment with SOF/VEL for 12 weeks was well tolerated; the types, incidences and severity of AEs were generally similar between patients treated with SOF/VEL or placebo. The safety profile of SOF/VEL was not adversely influenced by older age, compensated cirrhosis or mild renal impairment. These findings suggest that patients treated with SOF/VEL for 12 weeks may only require minimal on-treatment safety monitoring, supporting the use of SOF/VEL in non-specialist settings.

AUTHOR CONTRIBUTIONS

AO, IMJ and GRF were involved in study concept and design. IMJ, SB, PM, PT, SDR, GG and GRF were involved in acquisition of data. AO was involved in analysis of data. All authors were involved in interpretation of data, drafting of the manuscript, critical revision of the manuscript and final approval of the manuscript. SS was involved in administrative, technical and material support.

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CONFLICT OF INTEREST STATEMENT

IMJ reports research funding to his institution from Assembly Biosciences, Bristol-Myers Squibb, Cymabay, Eli Lilly, Enanta, Gilead Sciences, Inc., Intercept, Janssen, Merck, Mirum, and Novo Nordisk; receiving consulting fees from Aligos, Altimmune, Arbutus, Arrowhead, Dynavax, Gilead Sciences, Inc., GSK, Intercept, Janssen, Merck, Roche and Takeda. SB reports receiving consulting fees, honoraria for lectures,

speaker's bureau or educational events and travel support from AbbVie and Gilead Sciences, Inc; and has a leadership role with BeNHSU. PM reports receiving consulting fees, honoraria for lectures, speaker's bureau, or educational events and travel support from Bayer Healthcare, Eisai, Evive Biotech, Gilead Sciences, Inc., Intercept, Ipsen, MSD, Novo Nordisk, Pfizer, Sanofi and Surrozen; and participating on a Data Safety Monitoring Board or Advisory Board for Bayer Healthcare, Eisai, Evive Biotech, Intercept, Ipsen, MSD, Novo Nordisk, Pfizer and Surrozen. PT reports research funding to his institution from Gilead Sciences, Inc.; receiving consulting fees from Mallinkrodt; and honoraria for lectures, speaker's bureau, or educational events from AbbVie and Gilead Sciences, Inc. SDR and GG declare no conflicts of interest. CH, KV, SS, AO and DT are employees of Gilead Sciences, Inc., and may hold Gilead stock or stock options. GRF reports receiving consulting fees from AbbVie, Biomarin, Gilead Sciences, Inc., GSK, MSD and UniQure; receiving honoraria for lectures, speaker's bureau, or educational events from AbbVie, Biomarin, Gilead Sciences, Inc., and MSD; and participates in a Data Safety Monitoring Board or Advisory Board for GSK.

DATA AVAILABILITY STATEMENT

Anonymized individual participant data will be shared upon request for research purposes dependent upon the nature of the request, the merit of the proposed research, the availability of the data, and its intended use. The full data sharing policy for Gilead Sciences, Inc., can be found at https://www.gileadclinicaltrials.com/transparency-policy/.

REFERENCES

1. World Health Organization. Hepatitis C. 2021. Accessed November 11, 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c.
2. World Health Organization. Global health strategy on viral hepatitis, 2016–2021. 2016.
3. World Health Organization. *Guidelines for the Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection*. 2018. World Health Organization.
4. Weisberg IS, Jacobson IM. A pangenotypic, single tablet regimen of sofosbuvir/velpatasvir for the treatment of chronic hepatitis C infection. *Expert Opin Pharmacother*. 2017;18:535-543.
5. Razavi H, Sanchez Gonzalez Y, Yuen C, Cornberg M. Global timing of hepatitis C virus elimination in high-income countries. *Liver Int*. 2020;40:522-529.
6. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update of the series. *J Hepatol*. 2020;73:1-49.
7. Call to action for liver associations to advance progress towards viral hepatits eliminiation: a focus on simplified approaches to HCV testing and cure. 2019. Accessed January 26, 2022. https://www.aasld.org/programs-initiatives/viral-hepatitis-elimination-call-action.
8. Abraham GM, Obley AJ, Humphrey LL, et al. World health organization guidelines on treatment of hepatitis C virus infection: best practice advice from the American College of Physicians. *Ann Intern Med*. 2021;174:98-100.
9. Epclusa (sofosbuvir and velpatasvir) 400 mg/100 mg film-coated tablets. Summary of Product Characteristics. Gilead Sciences Ireland UC. 2020.
10. Chahine EB, Sucher AJ, Hemstreet BA. Sofosbuvir/velpatasvir: the first pangenotypic direct-acting antiviral combination for hepatitis C. *Ann Pharmacother*. 2017;51:44-53.
11. Buggisch P, Wursthorn K, Stoehr A, et al. Real-world effectiveness and safety of sofosbuvir/velpatasvir and ledipasvir/sofosbuvir hepatitis C treatment in a single centre in Germany. *PLoS One*. 2019;14:e0214795.
12. Charatcharoenwitthaya P, Wongpaitoon V, Komolmit P, et al. Real-world effectiveness and safety of sofosbuvir and nonstructural protein 5A inhibitors for chronic hepatitis C genotype 1, 2, 3, 4, or 6: a multicentre cohort study. *BMC Gastroenterol*. 2020;20:47.
13. Huang YT, Hsieh YY, Chen WM, et al. Sofosbuvir/velpatasvir is an effective treatment for patients with hepatitis C and advanced fibrosis or cirrhosis in a real-world setting in Taiwan. *BMC Gastroenterol*. 2021;21:259.
14. Lampertico P, Carrión JA, Curry M, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: a meta-analysis. *J Hepatol*. 2020;72:1112-1121.
15. Liu CH, Chen PY, Chen JJ, et al. Sofosbuvir/velpatasvir for patients with chronic hepatitis C virus infection and compensated liver disease: real-world data in Taiwan. *Hepatol Int*. 2021;15:338-349.
16. Mangia A, Milligan S, Khalili M, et al. Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: analysis of 5552 patients from 12 cohorts. *Liver Int*. 2020;40:1841-1852.
17. Tada T, Kurosaki M, Nakamura S, et al. Real-world clinical outcomes of sofosbuvir and velpatasvir treatment in HCV genotype 1- and 2-infected patients with decompensated cirrhosis: a nationwide multicenter study by the Japanese Red Cross Liver Study Group. *J Med Virol*. 2021;93:6247-6256.
18. Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med*. 2015;373:2599-2607.
19. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med*. 2015;373:2608-2617.
20. Epclusa (sofosbuvir and velpatasvir) tablets for oral use. *Full Prescribing Information*. Gilead Sciences, Inc.; 2021.
21. Wilton J, Wong S, Yu A, et al. Real-world effectiveness of sofosbuvir/velpatasvir for treatment of chronic hepatitis C in British Columbia, Canada: a population-based cohort study. *Open Forum Infect Dis*. 2020;7:ofaa055.
22. Younossi ZM, Stepanova M, Feld J, et al. Sofosbuvir/velpatasvir improves patient-reported outcomes in HCV patients: results from ASTRAL-1 placebo-controlled trial. *J Hepatol*. 2016;65:33-39.
23. 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;7:307-317.
24. Andreoni M, Coppola N, Craxi A, et al. Meet-test-treat for HCV management: patients' and clinicians' preferences in hospital and drug addiction services in Italy. *BMC Infect Dis*. 2022;22:3.
25. Cunningham EB, Amin J, Feld JJ, et al. Adherence to sofosbuvir and velpatasvir among people with chronic HCV infection and recent injection drug use: the SIMPLIFY study. *Int J Drug Policy*. 2018;62:14-23.
26. Grebely J, Dalgard O, Conway B, et al. Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): an open-label, single-arm, phase 4, multicentre trial. *Lancet Gastroenterol Hepatol*. 2018;3:153-161.
27. Grebely J, Feld JJ, Wyles D, et al. Sofosbuvir-based direct-acting antiviral therapies for HCV in people receiving opioid substitution therapy: an analysis of phase 3 studies. *Open Forum Infect Dis*. 2018;5:ofy001.

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