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Efficacy and safety of sofosbuvir–velpatasvir and sofosbuvir–velpatasvir–voxilaprevir for hepatitis C in Korea: a Phase 3b study

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Efficacy and safety of sofosbuvir–velpatasvir and sofosbuvir–velpatasvir–voxilaprevir for hepatitis C in Korea: a Phase 3b study

Phase 3b, multicenter, open-label cohort study

		SVR 12 (HCV RNA <15 IU/mL)	Serious adverse events (None were considered treatment-related)
HCV-infected Korean adults	Cohort 1 N=53 Sofosbuvir–velpatasvir HCV genotype 1 or 2 Treatment-naive or treatment-experienced	98% (52/53)	6% (3/53)
	Cohort 2 N=33 Sofosbuvir–velpatasvir–voxilaprevir HCV genotype 1 Treatment-experienced with NS5A inhibitor	100% (33/33)	3% (1/33)

Conclusion Treatment with sofosbuvir–velpatasvir or sofosbuvir–velpatasvir–voxilaprevir was safe and resulted in high SVR12 rates in Korean HCV patients.

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Background/Aims: Despite the availability of direct-acting antivirals (DAAs) for chronic hepatitis C virus (HCV) infection in Korea, need remains for pangenotypic regimens that can be used in the presence of hepatic impairment, comorbidities, or prior treatment failure. We investigated the efficacy and safety of sofosbuvir–velpatasvir and sofosbuvir–velpatasvir–voxilaprevir for 12 weeks in HCV-infected Korean adults.

Methods: This Phase 3b, multicenter, open-label study included 2 cohorts. In Cohort 1, participants with HCV genotype 1 or 2 and who were treatment-naive or treatment-experienced with interferon-based treatments, received sofosbuvir–velpatasvir 400/100 mg/day. In Cohort 2, HCV genotype 1 infected individuals who previously received an NS5A inhibitor-containing regimen ≥ 4 weeks received sofosbuvir–velpatasvir–voxilaprevir 400/100/100 mg/day. Decompensated cirrhosis was an exclusion criterion. The primary endpoint was SVR12, defined as HCV RNA < 15 IU/mL 12 weeks following treatment.

Results: Of 53 participants receiving sofosbuvir–velpatasvir, 52 (98.1%) achieved SVR12. The single participant who did not achieve SVR12 experienced an asymptomatic Grade 3 ASL/ALT elevation on day 15 and discontinued treatment. The event resolved without intervention. All 33 participants (100%) treated with sofosbuvir–velpatasvir–voxilaprevir achieved SVR 12. Overall, sofosbuvir–velpatasvir and sofosbuvir–velpatasvir–voxilaprevir were safe and well tolerated. Three participants (5.6%) in Cohort 1 and 1 participant (3.0%) in Cohort 2 had serious adverse events, but none were considered treatment-related. No deaths or grade 4 laboratory abnormalities were reported.

Conclusions: Treatment with sofosbuvir–velpatasvir or sofosbuvir–velpatasvir–voxilaprevir was safe and resulted in high SVR12 rates in Korean HCV patients.

Keywords: Direct-acting antiviral; Decompensated cirrhosis; NS5A inhibitor; Polymerase inhibitor; Protease inhibitor

INTRODUCTION

The World Health Organization has set a goal of eliminating hepatitis C as a public health problem by 2030 [1]. Elimination is defined as reducing new infections with hepatitis C virus (HCV) by 90% and resulting deaths by 65%. Globally, multiple countries have initiatives for meeting the 2030 target, and modelling data indicate that 11 countries are on pace to reach this goal [2]. Some countries, such as South Korea, are on pace for elimination by 2040, while many countries are not expected to do so before 2050 [2]. To improve progress, four hepatology societies, including the Asian-Pacific Association for the Study of the Liver, have put forth a call to action describing and emphasizing simplified approaches to HCV testing and cure [3]. The need to evaluate HCV genotype, fibrosis status, and the presence of resistance-associated substitutions (RAS) all slow efforts to begin treatment and complicate on-treatment monitoring [4]. Thus, removing some or all of these steps facilitates cure [4].

As in many regions, in Korea persons aged 60 years or older have the highest prevalence of HCV [5-8]. With longer duration of infection, older generations have a higher risk of advanced liver disease [9,10]. They also are at greater risk for comorbidities [11], including those that can accelerate liver disease progression [12] or whose treatment creates the potential for drug–drug interactions.

Of current direct-acting antiviral (DAA) regimens, several are highly effective and well tolerated [13-15]. However, few are pangenotypic, and several contain protease inhibitors, whose risk for drug-drug interactions limit their use in patients with hepatic impairments. The combination of sofosbuvir (an NS5B polymerase inhibitor) and velpatasvir (an NS5A inhibitor) is indicated for all HCV genotypes and can be used in a wide spectrum of patients, including those with decompensated cirrhosis [13,14,16,17]. Sofosbuvir–velpatasvir is recommended as a first-line HCV treatment in European Association for the Study of the Liver (EASL) guidelines [13].

Voxilaprevir, a reversible inhibitor of the HCV NS3/4A protease, has been shown to have pangenotypic activity as well as activity against most HCV RAS [18-20]. The combination of sofosbuvir, velpatasvir, and voxilaprevir is a retreatment option for patients who have failed an HCV regimen with an NS5A inhibitor [21] and is the first-line retreatment regimen recommended by EASL and the American Association for the Study of Liver Diseases (AASLD) for persons who failed prior HCV treatment [13,14].

In Asian populations, no prospective trial data has been

available for sofosbuvir–velpatasvir or sofosbuvir–velpatasvir–voxilaprevir. Prior to regulatory approval of sofosbuvir–velpatasvir and sofosbuvir–velpatasvir–voxilaprevir in Korea, we initiated a Phase 3b, prospective, multicenter study to examine the safety and efficacy of sofosbuvir–velpatasvir and sofosbuvir–velpatasvir–voxilaprevir in Korean patients with chronic HCV.

METHODS

Study design

This was a Phase 3b, multicenter, open-label study. Participants were enrolled in 2 cohorts, each receiving fixed-dose tablets once daily with or without food for 12 weeks. Cohort 1 received sofosbuvir–velpatasvir (400/100 mg), and cohort 2 received sofosbuvir–velpatasvir–voxilaprevir (400/100/100 mg). After 12 weeks of treatment, follow-up visits occurred at post-treatment weeks 4 and 12.

The study protocol was approved by the review board or ethics committee of each institution prior to study initiation (approval number: AMC IRB 2019-1542). The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki.

Patients

Eligible participants were ≥19 years old, had a BMI ≥ 18 kg/m^2, and had chronic hepatitis C infection with quantifiable HCV RNA (≥ 15 IU/mL) at screening. Cohort 1 participants, who had genotype 1 or 2 HCV infection and were either treatment-naïve or treatment-experienced with interferon-based treatments, received sofosbuvir–velpatasvir. This cohort excluded persons who were previously exposed to any DAA agent targeting HCV NS5A or NS5B. Cohort 2 participants, who had genotype 1 infection and had failed prior treatment with an NS5A inhibitor taken for at least 4 weeks, received sofosbuvir–velpatasvir–voxilaprevir. Persons with or without compensated cirrhosis were eligible for study participation. Major exclusion criteria were decompensated liver disease or past or current hepatocellular carcinoma.

All participants provided written informed consent prior to undergoing any study procedures.

Assessments

Virology

HCV RNA levels were quantified by using the Roche COBAS Ampliprep/COBAS TaqMan HCV Test, v2.0 (Roche Molecular Systems, Inc., Branchburg, NJ, USA), which has a lower limit of quantification (LLOQ) of 15 IU/mL. At screening, HCV genotype (and subtype, if possible) were determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay. For confirming HCV subtype and characterizing virologic resistance, HCV baseline and postbaseline amplification and deep sequencing were performed by DDL Diagnostic Laboratory (Rijswijk, Netherlands). Genotype and subtype were confirmed or determined by basic local alignment search tool analyses of NS3, NS5A, and NS5B sequences from deep sequencing. Reported resistance-associated variants (RAVs) were present in more than 15% of the sequence reads for NS3, NS5A, or NS5B.

Plasma HCV RNA levels were evaluated at screening; on day 1 of treatment; at treatment weeks 2, 4, 8, and 12; and at follow-up weeks 4 and 12. Plasma samples for viral sequencing were collected at all visits during treatment and follow-up, following the same schedule as for HCV RNA evaluation.

Safety

Complete physical examinations were conducted at screening, on day 1 of treatment, and at the final treatment visit. At the screening and all treatment and follow-up visits, data regarding vital signs were collected. Reported adverse events, concomitant medication intake, and clinical laboratory samples were collected at all visits through follow-up week 4. The Medical Dictionary for Regulatory Activities, version 23.1, was used to code treatment-emergent clinical and laboratory adverse events.

Endpoints and analyses

The primary efficacy endpoint was achievement of SVR12, defined as having HCV RNA < LLOQ (15 IU/mL) 12 weeks following the completion of treatment. A 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method was calculated for percentages of participants achieving SVR12. The primary safety endpoint was any adverse event leading to discontinuation of study drug. All analyses were performed using SAS Software version 9.4 (SAS Institute Inc., Cary, NC, USA).

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Table 1. Patient demographics and baseline characteristics

Variable	SOF–VEL (n = 54)	SOF–VEL–VOX (n = 33)
Age, yr	60 (27–85)	62 (31–80)
Sex at birth		
Female	29 (53.7)	18 (54.5)
Male	25 (46.3)	15 (45.5)
Asian race	54 (100.0)	33 (100.0)
BMI, kg/m^2	25 (18–36)	25 (19–32)
Genotype		
1	27 (50.0)	32 (97.0)
1a	1 (1.9)	-
1b	26 (48.1)	32 (97.0)
2	27 (50.0)	1 (3.0)
HCV treatment history		
Treatment naïve	46 (85.2)	-
Treatment experienced	8 (14.8)	33 (100.0)
Prior HCV treatment		
PEG-IFN + RBV	5 (9.3)	-
Other IFN-containing	3 (5.6)	1 (3.0)[a]
NS5A ± DAA(s)	-	32 (97.0)
NS5A + NS5B	-	2 (6.1)
NS5A + NS3 ± NS5B	-	29 (87.9)
NS5A + other	-	1 (3.0)
HCV RNA, $\log_{10}$ IU/mL	5.9 (1.2–7.3)	6.5 (5.4–7.1)
HCV RNA ≥ 800,000 IU/mL	30 (55.6)	30 (90.9)
IL28B genotype		
CC	41 (75.9)	23 (69.7)
CT	13 (24.1)	9 (27.3)
TT	-	-
Missing	-	1 (3.0)
Compensated cirrhosis	11 (20.4)	9 (27.3)
ALT, U/L	52 (9–212)	67 (17–319)
eGFR[b], mL/min/1.73 m^2	89 (38–179)	86 (44–141)
<90	31 (57.4)	21 (63.6)
≥90	23 (42.6)	12 (36.4)

Values are presented as mean (range) or number (%).
ALT, alanine aminotransferase; BMI, body mass index; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; IFN, interferon; IL28B, interleukin-28B; PEG, pegylated; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.
[a]Participant had prior treatment with PEG-IFN followed by SOF plus ribavirin. This was an eligibility criteria deviation for the SOF–VEL–VOX-treated cohort.
[b]Estimated using the Cockcroft-Gault Equation.

RESULTS

Patient population

A total of 87 participants were enrolled at 22 study sites in the Republic of Korea. Study screening through follow-up occurred from January to November 2020. Demographics and baseline characteristics were generally balanced across both treatment cohorts (Table 1). All participants were Asian, and more than half (54%) were female. Mean age was 60 years for sofosbuvir–velpatasvir and 62 years for sofosbuvir–velpatasvir–voxilaprevir. Among participants receiving sofosbuvir–velpatasvir, 50.0% (27/54) had genotype 1 HCV infection and 50.0% (27/54) had genotype 2. Among participants receiving sofosbuvir–velpatasvir–voxilaprevir, 97.0% (32/33) had genotype 1 HCV infection, and 3.0% (n = 1, eligibility criteria deviation) had genotype 2. More than three quarters (26/33, 78.8%) of participants in the sofosbuvir–velpatasvir–voxilaprevir group had previously received treatment with asunaprevir and daclatasvir (Table 2, Supplementary Table 1).

All participants who received sofosbuvir–velpatasvir–voxilaprevir completed treatment (n = 33) (Fig. 1). Of the 54 individuals receiving sofosbuvir–velpatasvir, 53 completed treatment and one participant discontinued study treatment at week 4 after meeting prespecified stopping criteria regarding increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). One participant assigned sofosbuvir–velpatasvir was excluded from the efficacy analysis for having undetectable HCV at baseline. This individ-

Table 2. Prior regimens of 33 participants receiving sofosbuvir–velpatasvir–voxilaprevir

Regimen	No. of participants
Asunaprevir + daclatasvir	26
Peginterferon or interferon ± ribavirin	9[a]
Daclatasvir + sofosbuvir	2
Elbasvir/grazoprevir	2
Ledipasvir	1
Ombitasvir + dasabuvir + paritaprevir + ritonavir	1
Sofosbuvir + ribavirin	1

[a]Nine participants received peginterferon/interferon ± ribavirin as well as either asunaprevir + daclatasvir (n = 7); daclatasvir + sofosbuvir (n = 1); or sofosbuvir + ribavirin (n = 1) (Supplementary Table 1).

ual had HCV RNA 6.6 $\log_{10}$ IU/mL at screening, completed treatment with sofosbuvir–velpatasvir, and was included in the safety analysis set.

Virologic response

SVR12 was achieved in 98.1% (52/53) of participants who received sofosbuvir–velpatasvir and 100% (33/33) who received sofosbuvir–velpatasvir–voxilaprevir (Table 3). All participants who completed treatment achieved SVR12. One participant, assigned to sofosbuvir–velpatasvir, had virologic relapse after stopping treatment at week 4 due to meeting protocol-defined stopping criteria (more detail provided in Safety section).

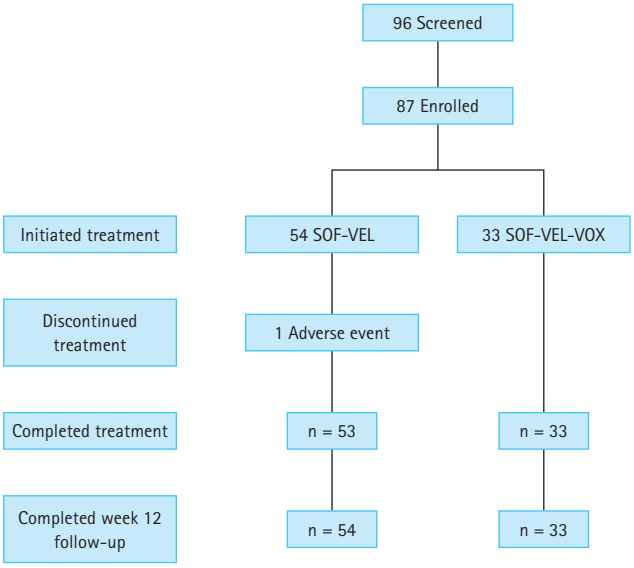

Figure 1. Patient disposition throughout the study. SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

Table 3. Treatment response to sofosbuvir–velpatasvir and sofosbuvir–velpatasvir–voxilaprevir

Response	SOF–VEL (n = 53)[a]	SOF–VEL–VOX (n = 33)
SVR4	52 (98.1)	33 (100.0)
SVR12	52 (98.1)	33 (100.0)
95% CI	90–100	89–100
Virologic failure		
On treatment	0	0
Relapse	1	0
Discontinued study treatment	1	0

Values are presented as number (%) or number only.
CI, confidence interval; SOF, sofosbuvir; SVR4 and SVR12, sustained virologic response 4 and12 weeks after treatment; VEL, velpatasvir; VOX, voxilaprevir.
[a]One patient had no detectable HCV RNA at baseline and was removed from the full analysis set. At screening, HCV RNA was 6.6 $\log_{10}$ IU/mL for this patient.

Resistance

In the sofosbuvir–velpatasvir cohort, pretreatment RAVs for NS5A and NS5B inhibitors were observed in 58% and 9% of participants, respectively. SVR12 was achieved by all participants with pretreatment NS5A and/or NS5B nucleoside inhibitor RAVs who received sofosbuvir–velpatasvir for 12 weeks. The participant who discontinued sofosbuvir–velpatasvir at week 4 had NS5A RAV L31M at baseline and at relapse (follow-up week 4) but no NS5B NI RAVs at these times.

In the sofosbuvir–velpatasvir–voxilaprevir cohort, all 33 participants had pretreatment RAVs to either NS3 (2/33, 6.1%), NS5A (14/33, 42.4%), or both (17/33, 51.5%). NS5B RAVs were observed in 9%. All 33 achieved SVR12.

Safety

Overall, sofosbuvir-velpatasvir and sofosbuvir–velpatasvir–voxilaprevir were well tolerated in Korean patients with chronic HCV (Table 4).

Sofosbuvir–velpatasvir

With sofosbuvir–velpatasvir, the most commonly reported adverse events were headache (7.4%, 4 participants) and nausea (3.7%, 2 participants). Three individuals (5.6%) had serious adverse events, none of which were considered by investigators to be treatment-related. One participant had a Grade 3 adverse event of liver function test increased, which was considered treatment-related. The event led to study drug discontinuation because the increases in ALT and AST met prespecified protocol stopping criteria (ALT and/or AST above upper limit of normal [ULN] and > 5× day 1 or nadir; confirmed by immediate repeat testing). The elevations in ALT and AST were first reported on day 15, and on day 20 concentrations were ALT 408 IU/L and AST 206 U/L. The elevations were not associated with any an increase in other lab parameters (e.g., total bilirubin) and did not meet Hy's Law. Study treatment was discontinued at week 4. On day 140 the event was deemed resolved based on local lab results (ALT = 29 U/L, AST = 28 U/L) that were within normal ranges. At follow-up week 4, the mean ± standard devia-

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Table 4. Adverse events and laboratory abnormalities

Adverse events	SOF–VEL (n = 54)	SOF–VEL–VOX (n = 33)
No. of participants with any		
Adverse events	23 (42.6)	15 (45.5)
Grade 3 or 4 adverse events[a]	3 (5.6)	1 (3.0)
Treatment-related adverse events	5 (9.3)	6 (18.2)
Grade 3 or 4 treatment-related adverse events	1 (1.9)[b]	0 (0.0)
Serious adverse events	3 (5.6)	1 (3.0)
Treatment-related serious adverse events	0 (0.0)	0 (0.0)
Adverse events leading to discontinuation	1 (1.9)	0 (0.0)
Adverse events leading to discontinuation		
Liver function test increased	1 (1.9)[b]	-
Adverse events in ≥ 5% of participants in either treatment group		
Headache	4 (7.4)	3 (9.1)
Nausea	2 (3.7)	3 (9.1)
Rash	0 (0.0)	3 (9.1)
Serious adverse events		
Cerebral infarction	1 (1.9)	-
Erythema nodosum	1 (1.9)	-
Facial bones fracture	-	1 (3.0)
Hematochezia	1 (1.9)	-
Pyrexia	1 (1.9)	-
Grade 3 laboratory abnormalities		
Platelets, 25,000 to < 50,000/mm^3	1 (1.9)	1 (3.0)
ALT, > 5 to 10× ULN	1 (1.9)	-
AST, > 5 to 10× ULN	1 (1.9)	-
Hemoglobin, 70 to < 90 g/L or decrease ≥ 45 g/L	1 (1.9)	-
Hyperglycemia, > 250 to 500 mg/dL	1 (1.9)	-

Values are presented as number (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.
[a]Grade 3 adverse events were erythema nodosum (n = 1), facial bones fracture (n = 1), hematochezia (n = 1), liver function test increased (n = 1), and pyrexia (n = 1). There were no grade 4 adverse events.
[b]Grade 3 liver function test increased. Study drug was discontinued because the increase in ALT and AST met prespecified stopping criteria. The biochemical elevations in ALT and AST were first reported on day 15, not associated with any an increase in other lab parameters (e.g., total bilirubin), and did not meet Hy's Law. On day 140 the event was deemed resolved based on local lab results (ALT = 29 U/L, AST = 28 U/L) that were within normal ranges.

tion (SD change in eGFR was -1.5 ± 11.40 mL/min. A single participant had a Grade 1 elevation of bilirubin (> 1.0 to 1.5 × ULN); no Grade 2–4 elevations in bilirubin occurred.

Sofosbuvir–velpatasvir–voxilaprevir

With sofosbuvir–velpatasvir–voxilaprevir, the most commonly reported adverse events were headache, nausea, and rash (9.1%, 3 participants each). One participant (3.0%) had a serious adverse event, which was considered not treatment-related. No participants receiving sofosbuvir–velpatasvir–voxilaprevir had adverse events leading to discontinuation of study drug. At follow-up week 4, the mean ± SD change in eGFR was -3.3 ± 11.32 mL/min. Grade 1 elevations (>1.0 to 1.5 × ULN) in bilirubin occurred in 4 partic-

ipants receiving sofosbuvir velpatasvir voxilaprevir (12.1%); no Grade 2–4 elevations in bilirubin occurred.

DISCUSSION

Streamlining strategies for treating HCV is recommended for public health initiatives aimed at eliminating hepatitis [3]. Such strategies include using treatments that encompass large patient populations and do not require genotyping or evaluation of fibrosis status prior to initiation [4]. Sofosbuvir–velpatasvir has the benefits of being pangenotypic and lacking a protease inhibitor, which allows for use in a wide spectrum of patients, including those with hepatic impairment [13,14,16,17]. In persons with decompensated cirrhosis, HCV protease inhibitors are contraindicated due to toxicity from increased drug concentrations in the liver [22]. Real-world study data indicate the potential for drug-drug interactions is minimal with sofosbuvir–velpatasvir and lower in comparison to regimens containing an HCV NS3/4A protease inhibitor [23,24]. In addition, dose adjustment of sofosbuvir–velpatasvir is not required in persons with any degree of renal impairment, including those undergoing dialysis [25-28]. In regions where prevalence of HCV is highest in older populations, such as Korea, regimens free of protease inhibitors have specific benefits for those with comorbidities and taking multiple prescribed medications [29].

In this study of Korean individuals with chronic HCV, both sofosbuvir–velpatasvir and sofosbuvir–velpatasvir–voxilaprevir were highly effective and well tolerated. All participants were infected with HCV genotype 1 or 2, which is representative of more than 98% of infections in Korea [10]. The SVR rate with sofosbuvir–velpatasvir, 98% among DAA-naïve participants, is comparable to the rate of 99% reported previously in registrational Phase 3 studies of non-genotype 3, treatment-naïve persons [30,31] as well rates of 96% to 99% for sofosbuvir–velpatasvir use in real-world cohort analyses [32,33]. For participants who previously failed treatment including an NS5A inhibitor, sofosbuvir–velpatasvir–voxilaprevir SVR was 100%, comparable to the 96% reported among study participants in the POLARIS-1 study who received sofosbuvir–velpatasvir–voxilaprevir and almost all (> 99%) previously received an NS5A inhibitor [21]. In real-world cohort analyses of > 750 DAA-experienced patients, SVR of 91% has been reported with sofosbuvir–velpatasvir–voxilaprevir retreatment [34,35]. Smaller analyses of sofosbuvir–velpatasvir–voxilaprevir retreatment have yielded SVR rates of 94% after glecaprevir–pibrentasvir failure [36] and 100% after sofosbuvir–velpatasvir failure [37].

In our study, all participants who completed treatment achieved SVR12. Indeed, the importance of treatment adherence has been underscored by analyses of The Taiwan HCV Registry of more than 13,000 patients, where incomplete adherence was the most important factor associated with treatment failure [38].

No participants in this study had treatment-related serious adverse events. One participant, who received sofosbuvir–velpatasvir, discontinued study treatment at week 4 after meeting prespecified stopping criteria for increases in ALT and AST, which later spontaneously resolved. This individual experienced virologic relapse and was the only participant who initiated treatment and did not reach SVR.

Triple therapy with sofosbuvir–velpatasvir–voxilaprevir is the first-line retreatment regimen recommended by EASL and the AASLD [13,14]. With the current availability of multiple, highly efficacious DAA regimens, failure to achieve SVR is rare but nonetheless does occur. In Asia, the combination regimen of daclatasvir with asunaprevir was at one time widely used but has since been shown to have lower efficacy than later-generation DAA regimens [39]. For Korean patients who had treatment failure with daclatasvir and asunaprevir, there has been a lack of suitable retreatment options. As shown by this study, sofosbuvir–velpatasvir–voxilaprevir represents a good option for patients who have been waiting for a rescue therapy.

This study has limitations. Cohort 1, treated with sofosbuvir–velpatasvir, only enrolled patients with either HCV genotype 1 or 2 infection. This was to facilitate comparison of results from this study with those from the ASTRAL 1 and 2 Phase 3 registrational trials for sofosbuvir–velpatasvir. Given that 98% of HCV patients in Korea have either HCV genotype 1 or 2 infection [10], our results are relevant to the Korean HCV population. For individuals with other HCV genotypes, genotype 3 has been identified as a challenging factor in achieving SVR [40], although data have been conflicting. In the largest real-world dataset to date, which included 1,514 patients with HCV genotype 3, genotype 3 was not associated with lower SVR with sofosbuvir–velpatasvir treatment [32]. Large-scale Korean real-world data in such population would be helpful in addressing this question. Among the participants in this study who had prior DAA failure, none had a history of treatment with gleca-

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previr–pibrentasvir (Table 2), a commonly used regimen in Korea. However, existing evidence from large registrational studies supports use of sofosbuvir–velpatasvir in all genotypes [30,31] and sofosbuvir–velpatasvir–voxilaprevir after prior failure with a DAA regimen containing an NS5A inhibitor [21].

In conclusion, sofosbuvir–velpatasvir and sofosbuvir–velpatasvir–voxilaprevir were highly effective and well tolerated in a Korean population with chronic HCV. Sofosbuvir–velpatasvir represents an important option as a pangenotypic, panfibrotic regimen with a favorable drug-drug interaction profile, and it is approved in Korea for use in patients with decompensated cirrhosis (in combination with ribavirin) or end-stage renal disease. Sofosbuvir–velpatasvir–voxilaprevir was effective and safe for Korean HCV patients with prior DAA failure.

KEY MESSAGE

1. In a Korean population chronically infected with hepatitis C virus (HCV), 98.8% (85/86) who received either sofosbuvir–velpatasvir or sofosbuvir–velpatasvir–voxilaprevir achieved sustained virologic response, or cure.
2. Sofosbuvir–velpatasvir represents an important option as a pangenotypic regimen covering a wide spectrum of patients, including those with decompensated cirrhosis or end-stage renal disease.
3. Sofosbuvir–velpatasvir–voxilaprevir is an important retreatment option for Korean HCV patients with prior DAA failure.

REFERENCES

1. World Health Organization. Global hepatitis report, 2017 [Internet]. Geneva: World Health Organization, c2017 [cited 2020 September 20]. Available from: https://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua = 1/.
2. Gamkrelidze I, Pawlotsky JM, Lazarus JV, et al. Progress towards hepatitis C virus elimination in high-income countries: an updated analysis. Liver Int 2021;41:456-463.
3. American Association for the Study of Liver Diseases. Call-to-action to advance progress towards viral hepatitis elimination: a focus on simplified approaches to HCV testing and cure [Internet]. Alexandria, VA: American Association for the Study of Liver Diseases, c2019 [cited 2023 April 1]. Available from: https://www.aasld.org/news/global-hepatology-societies-call-better-hcv-testing-and-access-treatment.
4. Mangia A, Albanese AP, Bourliére M, et al. Guidelines have a key role in driving HCV elimination by advocating for simple HCV care pathways. Adv Ther 2021;38:1397-1403.
5. Lim YS. Current status of liver disease in Korea: hepatitis C. Korean J Hepatol 2009;15 Suppl 6:S25-S28.
6. Moore KJ, Gauri A, Koru-Sengul T. Prevalence and sociodemographic disparities of Hepatitis C in Baby Boomers and the US adult population. J Infect Public Health 2019;12:32-36.
7. Zaltron S, Spinetti A, Biasi L, Baiguera C, Castelli F. Chronic HCV infection: epidemiological and clinical relevance. BMC Infect Dis 2012;12 Suppl 2(Suppl 2):S2.
8. Greenaway C, Thu Ma A, Kloda LA, et al. The seroprevalence of hepatitis C antibodies in immigrants and refugees from intermediate and high endemic countries: a systematic review and meta-analysis. PLoS One 2015;10:e0141715.
9. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008;48:418-431.
10. Nam JY, Jang ES, Kim YS, et al. Epidemiological and clinical characteristics of hepatitis C virus infection in South Korea from 2007 to 2017: a prospective multicenter cohort study. Gut Liver 2020;14:207-217.
11. Salive ME. Multimorbidity in older adults. Epidemiol Rev 2013;35:75-83.
12. Park H, Chen C, Wang W, Henry L, Cook RL, Nelson DR. Chronic hepatitis C virus (HCV) increases the risk of chronic kidney disease (CKD) while effective HCV treatment decreases the incidence of CKD. Hepatology 2018;67:492-504.
13. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update of the series. J Hepatol. 2020;73:1170-1218.
14. Ghany MG, Morgan TR; AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C guidance 2019 update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. Hepatology 2020;71:686-721.
15. Korean Association for the Study of the Liver. KASL clinical practice guidelines: management of hepatitis C. Clin Mol Hepatol 2016;22:76-139.

16. Curry MP, O'Leary JG, Bzowej N, et al.; ASTRAL-4 Investigators. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618-2628.
17. Liu CH, Chen CY, Su WW, et al. Sofosbuvir/velpatasvir plus ribavirin for Child-Pugh B and Child-Pugh C hepatitis C virus-related cirrhosis. Clin Mol Hepatol 2021;27:575-588.
18. Gane EJ, Schwabe C, Hyland RH, et al. Efficacy of the combination of sofosbuvir, velpatasvir, and the NS3/4A protease inhibitor GS-9857 in treatment-naïve or previously treated patients with hepatitis C virus genotype 1 or 3 infections. Gastroenterology 2016;151:448-456.e1.
19. Lawitz E, Reau N, Hinestrosa F, et al. Efficacy of sofosbuvir, velpatasvir, and GS-9857 in patients with genotype 1 hepatitis C virus infection in an open-label, phase 2 trial. Gastroenterology 2016;151:893-901.e1.
20. Gane EJ, Kowdley KV, Pound D, et al. Efficacy of sofosbuvir, velpatasvir, and GS-9857 in patients with hepatitis C virus genotype 2, 3, 4, or 6 infections in an open-label, phase 2 trial. Gastroenterology 2016;151:902-909.
21. Bourlière M, Gordon SC, Flamm SL, et al.; POLARIS-1 and POLARIS-4 Investigators. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med 2017;376:2134-2146.
22. Mak LY, Seto WK, Lai CL, Yuen MF. An update on the toxicological considerations for protease inhibitors used for hepatitis C infection. Expert Opin Drug Metab Toxicol 2018;14:483-491.
23. Mangia A, Scaglione F, Toniutto P, et al. Drug-drug interactions in italian patients with chronic hepatitis C treated with pangenotypic direct acting agents: insights from a real-world study. Int J Environ Res Public Health 2021;18:7144.
24. Liu CH, Yu ML, Peng CY, et al. Comorbidities, concomitant medications and potential drug-drug interactions with interferon-free direct-acting antiviral agents in hepatitis C patients in Taiwan. Aliment Pharmacol Ther 2018;48:1290-1300.
25. Desnoyer A, Pospai D, Lê MP, et al. Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C. J Hepatol 2016;65:40-47.
26. Borgia SM, Dearden J, Yoshida EM, et al. Sofosbuvir/velpatasvir for 12 weeks in hepatitis C virus-infected patients with end-stage renal disease undergoing dialysis. J Hepatol 2019;71:660-665.
27. Liu CH, Chen CY, Su WW, et al. Sofosbuvir/velpatasvir with or without low-dose ribavirin for patients with chronic hepatitis C virus infection and severe renal impairment. Gut 2022;71:176-184.
28. De A, Roy A, Verma N, et al. Sofosbuvir plus velpatasvir combination for the treatment of chronic hepatitis C in patients with end stage renal disease on renal replacement therapy: a systematic review and meta-analysis. Nephrology (Carlton) 2022;27:82-89.
29. Chung JW, Choi HY, Ki M, Jang ES, Jeong SH. Comorbidities and prescribed medications in Korean patients with chronic hepatitis C: a nationwide, population-based study. Gut Liver 2021;15:295-306.
30. Feld JJ, Jacobson IM, Hézode C, et al.; ASTRAL-1 Investigators. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med 2015;373:2599-2607.
31. Foster GR, Afdhal N, Roberts SK, et al.; ASTRAL-2 Investigators; ASTRAL-3 Investigators. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med 2015;373:2608-2617.
32. 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.
33. 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.
34. Degasperi E, Spinetti A, Lombardi A, et al.; NAVIGATORE-Lombardia and Veneto Study Groups. Real-life effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in hepatitis C patients with previous DAA failure. J Hepatol 2019;71:1106-1115.
35. Belperio PS, Shahoumian TA, Loomis TP, Backus LI. Real-world effectiveness of sofosbuvir/velpatasvir/voxilaprevir in 573 direct-acting antiviral experienced hepatitis C patients. J Viral Hepat 2019;26:980-990.
36. Pearlman B, Perrys M, Hinds A. Sofosbuvir/velpatasvir/voxilaprevir for previous treatment failures with glecaprevir/pibrentasvir in chronic hepatitis C infection. Am J Gastroenterol 2019;114:1550-1552.
37. Ruane P, Strasser SI, Gane EJ, et al. Sofosbuvir/velpatasvir/voxilaprevir for patients with HCV who previously received a Sofosbuvir/Velpatasvir-containing regimen: results from a re-treatment study. J Viral Hepat 2019;26:770-773.
38. Chen CY, Huang CF, Cheng PN, et al. Factors associated with treatment failure of direct-acting antivirals for chronic hepatitis C: a real-world nationwide hepatitis C virus registry programme in Taiwan. Liver Int 2021;41:1265-1277.

https://doi.org/10.3904/kjim.2022.252

39. Kwon JH, Yoo SH, Nam SW, et al. Clinical outcomes after the introduction of direct antiviral agents for patients infected with genotype 1b hepatitis C virus depending on the regimens: a multicenter study in Korea. J Med Virol 2019;91:1104-1111.
40. Cheng PN, Mo LR, Chen CT, et al.; TACR investigators. Sofosbuvir/velpatasvir for hepatitis C Virus infection: real-world effectiveness and safety from a nationwide registry in Taiwan. Infect Dis Ther 2022;11:485-500.

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Data sharing
Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

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Supplementary Table 1. Treatment histories of participants receiving sofosbuvir–velpatasvir–voxilaprevir

Participant ID	Prior HCV Treatment	Response
05608-58202	Peginterferon + ribavirin	Met stopping rule
	Asunaprevir + daclatasvir	Relapse/breakthrough
05608-58205	Asunaprevir + daclatasvir	Relapse/breakthrough
05608-58230	Daclatasvir + sofosbuvir	Relapse/breakthrough
05609-58206	Ledipasvir	Relapse/breakthrough
05609-58207	Asunaprevir + daclatasvir	Relapse/breakthrough
06334-58211	Asunaprevir + daclatasvir	Relapse/breakthrough
06334-58232	Asunaprevir + daclatasvir	Relapse/breakthrough
06337-58212	Ombitasvir + dasabuvir + paritaprevir + ritonavir	Relapse/breakthrough
06341-58216	Asunaprevir + daclatasvir	Null responder
06342-58204	Asunaprevir + daclatasvir	Relapse/breakthrough
06342-58213	Peginterferon + ribavirin	Disc. due to adverse event
	Asunaprevir + daclatasvir	Relapse/breakthrough
06342-58226	Asunaprevir + daclatasvir	Relapse/breakthrough
06758-58214	Elbasvir/grazoprevir	Relapse/breakthrough
06758-58215	Asunaprevir + daclatasvir	Relapse/breakthrough
06758-58233	Asunaprevir + daclatasvir	Relapse/breakthrough
06874-58203	Elbasvir/grazoprevir	Relapse/breakthrough
06874-58208	Peginterferon + ribavirin	Relapse/breakthrough
	Asunaprevir + daclatasvir	Relapse/breakthrough
08276-58201	Peginterferon + ribavirin	Relapse/breakthrough
	Daclatasvir + sofosbuvir	Relapse/breakthrough
08276-58228	Asunaprevir + daclatasvir	Non-responder
08519-58224	Interferon + ribavirin	Relapse/breakthrough
	Asunaprevir + daclatasvir	Relapse/breakthrough
08519-58225	Asunaprevir + daclatasvir	Relapse/breakthrough
08705-58209	Asunaprevir + daclatasvir	Relapse/breakthrough
08705-58229	Asunaprevir + daclatasvir	Null responder
09819-58217	Peginterferon + ribavirin	Partial responder
	Asunaprevir + daclatasvir	Partial responder
13696-58227	Peginterferon + ribavirin	Null responder
	Asunaprevir + daclatasvir	Null responder
14525-58218	Asunaprevir + daclatasvir	Relapse/breakthrough
14781-58231	Asunaprevir + daclatasvir	Relapse/breakthrough
15499-58210	Asunaprevir + daclatasvir	Partial responder
15499-58223	Asunaprevir + daclatasvir	Relapse/breakthrough
15524-58221	Asunaprevir + daclatasvir	Relapse/breakthrough
16681-58222	Peginterferon	Relapse/breakthrough
	Sofosbuvir + ribavirin	Relapse/breakthrough
16683-58219	Asunaprevir + daclatasvir	Relapse/breakthrough
16683-58220	Asunaprevir + daclatasvir	Relapse/breakthrough
	Peginterferon + ribavirin	Relapse/breakthrough