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ORIGINAL ARTICLE

Sofosbuvir-velpatasvir-voxilaprevir in adolescents 12 to 17 years old with HCV infection

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Abstract

Background and Aims: Sofosbuvir-velpatasvir-voxilaprevir is a pangenotypic regimen for chronic HCV infection. In the USA and Europe, sofosbuvir-velpatasvir-voxilaprevir once daily for 12 weeks is indicated for adults who previously received an HCV NS5A inhibitor. In Europe, sofosbuvir-velpatasvir-voxilaprevir is also indicated in the absence of prior HCV direct-acting antiviral (DAA) therapy as an 8-week or 12-week regimen. In an open-label study, we evaluated the safety, efficacy, and pharmacokinetics of sofosbuvir-velpatasvir-voxilaprevir in adolescents 12 to 17 years with chronic HCV of any genotype.

Methods: In this Phase 2, multicenter study, sofosbuvir-velpatasvir-voxilaprevir 400/100/100 mg daily was administered to adolescents for 8 weeks if DAA-naïve or for 12 weeks for cirrhosis or prior DAA failure. The key efficacy endpoint was sustained virologic response 12 weeks after therapy (SVR12). Intensive pharmacokinetic sampling was done in 14 patients at week 2 or 4, and samples for population pharmacokinetics were collected in all patients.

Results: All patients (n = 21) were naïve to HCV DAAs, and none had cirrhosis. HCV genotype 3a infection was most common, occurring in 43% of patients. Overall, 100% of patients (21 of 21) reached SVR12. The most common adverse events were abdominal pain and headache (24% each) and nausea (19%); no adverse events led to discontinuation. The only serious adverse event, hypotension, was considered related to study drug and resolved the same day without interruption of treatment. Sofosbuvir-velpatasvir-voxilaprevir exposures were similar to those observed in adults.

Abbreviations: ALT, alanine aminotransferase; AUC, area under the curve; BMI, body mass index; CTX, C-type collagen sequence; DAA, direct-acting antiviral; LLOQ, lower limit of quantification; PK, pharmacokinetic; P1NP, procollagen type 1 N-terminal propeptide; RAS, resistance-associated substitution; SVR, sustained virological response; ULN, upper limit of normal.

Conclusions: The pangenotypic regimen of sofosbuvir-velpatasvir-voxilaprevir is highly efficacious and well-tolerated in treating chronic HCV infection in adolescents.

INTRODUCTION

Approximately 3.25 million children worldwide have chronic infection with HCV.[1] The prevalence of pediatric HCV varies throughout the globe, with estimates of 0.05%–0.36% in the USA and Europe and 5.8% in regions of Africa.[2] A minority of children spontaneously clear infection, usually by age 7 years.[3–5] Most children with chronic HCV are asymptomatic or have mild nonspecific symptoms.[6,7] However, approximately 20% of infected children have clinical signs or symptoms of HCV, with hepatomegaly being the most common.[6] Even when signs or symptoms are present, infection can remain unsuspected, given the subtle clinical presentation. Twenty-five percent of HCV-infected children have persistent alanine aminotransferase (ALT) elevations,[6] and HCV infection in childhood can lead to serious liver damage in adulthood. Fortunately, successful treatment before development of advanced liver disease improves outcomes.[8]

Indeed, successful treatment for chronic HCV has the benefits of decreasing liver inflammation, halting or reversing fibrosis progression, and lowering risk of HCC.[9–11] In 2017, the first all-oral, interferon-free antiviral regimens were approved for treating children with chronic HCV, with an indication for adolescents aged 12 to 17.[12] Currently, four interferon-free direct-acting antiviral (DAA) regimens have been approved for adolescents.[13]

The pangenotypic regimen sofosbuvir-velpatasvir-voxilaprevir includes targeted inhibitors of HCV's NS5B polymerase, NS5A phosphoprotein, and NS3/4A protease. In clinical studies, sofosbuvir-velpatasvir-voxilaprevir has sustained virologic response (SVR) rates of ≥95% in adults treated with 8 or 12 weeks depending on HCV treatment history.[14–16] We evaluated the safety, efficacy, and pharmacokinetics of 8 or 12 weeks of sofosbuvir-velpatasvir-voxilaprevir in adolescents aged 12–17 years old.

METHODS

Patients

Eligible patients were 12 to <18 years old. Participants had chronic infection (≥6 months) with HCV of any genotype and plasma HCV-RNA levels ≥1000 IU/ml. Patients were either DAA-naïve or experienced. There were no restrictions for type of prior DAA. Patients with or without compensated cirrhosis were eligible. Cirrhosis status was determined based on availability of prior biopsy results or based on investigator assessment of available noninvasive fibrosis tests (including FibroTest, Fibrosis-4 Index, aspartate aminotransferase [AST]–to–platelet ratio index, and transient elastography) and/or clinical signs and symptoms. Patients were excluded from participating in the study if they had any of the following conditions: history of decompensated liver disease; chronic liver disease of a non-HCV etiology; international normalized ratio of prothrombin time >1.2 × upper limit of normal (ULN); platelets <50,000/mm^3; albumin <3.5 g/dl; ALT >10 × ULN; AST >10 × ULN; direct bilirubin >1.5 × ULN; estimated glomerular filtration rate <90 ml/min/1.73m^2 as calculated by the Schwartz Formula; evidence of HCC; infection with hepatitis A, hepatitis B, or HIV; significant cardiovascular disease; evidence of a gastrointestinal malabsorption syndrome that could interfere with absorption of orally administered medications; history of solid organ or bone marrow transplantation; clinically relevant alcohol or drug abuse within 12 months of screening; or psychiatric hospitalization, suicide attempt, or disability resulting from psychiatric illness within the prior 5 years. Parents or legal guardians provided written informed consent before patients undertook any study-related procedures. Patients provided written assent if possible.

Study design

In this Phase 2, multicenter, open-label study, sofosbuvir-velpatasvir-voxilaprevir (400/100/100 mg) fixed-dose combination tablets were administered once daily with food for 8 weeks to DAA-naïve patients without cirrhosis. Patients who were DAA-naïve with compensated cirrhosis or who had a prior history of DAA treatment were to receive 12 weeks of treatment, although no patients met these criteria. The first 14 patients enrolled underwent an intensive pharmacokinetic (PK) evaluation at week 2 or 4 and continued treatment without interruption. After this group of participants completed the intensive PK day, the PK samples were analyzed to assess exposures relative to adults to confirm the dose was appropriate; additional participants were then enrolled. After treatment, follow-up visits occurred at posttreatment weeks 4, 12, and 24.

The study protocol was approved by the review board or ethics committee of each institution before study

initiation. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki.

Assessments

Virology

At the screening visit, serum HCV-RNA levels were quantified 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. Viral genotype and subtype were determined at screening by the Siemens VERSANT HCV Genotype INNO-LiPA 2.0 Assay (Siemens Medical Solutions, Malvern, PA, USA). HCV genotype and subtype were further confirmed by basic local alignment search tool sequencing. Plasma HCV-RNA levels were evaluated on day 1 of treatment, at treatment weeks 1, 2, 4, and 8, and at follow-up weeks 4, 12, and 24.

Plasma samples for viral sequencing were collected at all visits during treatment and follow-up, following the same schedule as for HCV-RNA evaluation. The HCV NS3, NS5A, and NS5B coding regions were amplified by DDL Diagnostic Laboratory (Rijswijk, Netherlands) using standard reverse-transcription PCR technology. Following amplification, PCR products were deep sequenced with an assay cutoff of 1%. Baseline NS3, NS5A, and NS5B deep-sequencing analysis was performed for all patients. For patients with virologic failure, deep sequencing of HCV NS3, NS5A, and NS5B was performed at the first virologic failure time point with HCV RNA >1000 IU/ml. Amino acid substitutions in NS5A and NS5B in the samples collected at virologic failure were compared with the respective baseline sequence for each patient. Reported resistance-associated substitutions (RASs) were present in more than 15% of the sequence reads.

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 visits, data regarding vital signs, reported adverse events, concomitant medication intake, and clinical laboratory tests were collected. At all follow-up visits, symptom-directed physical exams were done, and vital signs and reported adverse events were collected. At the week-4 follow-up visit, concomitant medications were reported and clinical laboratory tests were done. The Medical Dictionary for Regulatory Activities, version 22.1, was used to code treatment emergent clinical and laboratory adverse events.

Growth and development were assessed using height, weight, and body mass index (BMI) percentiles and Tanner pubertal stages. Tanner pubertal stage assessments were done on day 1 and week 8 of treatment and weeks 12 and 24 following treatment. Height and weight measurements were done at all screening, treatment, and follow-up visits. Weight, height, and BMI age-adjusted percentile scores were calculated using the 2000 U.S. Centers for Disease Control and Prevention Growth Charts. Radiographic bone age assessment was done at day 1 of treatment and at the final treatment visit. Blood was collected for assessing the bone resorption biomarker C-type collagen sequence (CTX) and the bone formation biomarker procollagen type 1 N-terminal propeptide (P1NP) on day 1 of treatment and posttreatment week 24.

Acceptability and palatability

Acceptability and palatability of sofosbuvir-velpatasvir-voxilaprevir 400/100/100 mg tablets were assessed via a questionnaire using a 5-point facial hedonic scale on day 1 and at the end of treatment by the patients and at the end of treatment by their caregivers/parents.

Pharmacokinetics

To determine PK for sofosbuvir, its primary metabolite GS-331007, velpatasvir, and voxilaprevir, a single sparse PK blood sample was collected from all patients any time during week-1 and week-8 visits. Additionally, two sparse PK samples were collected at weeks 2 and 4 before dose and between 15 min to 4 h after dose, unless the patient was in the intensive PK substudy. For patients in the intensive PK substudy, PK blood samples were collected at week 2 or 4 starting within 30 min before dosing and 0.5, 1, 2, 3, 4, 6, 8, and 12 h after dose.

Endpoints

The key efficacy endpoint was achievement of SVR12, defined as having HCV RNA <LLOQ (15 IU/ml) 12 weeks after discontinuing study drugs. The primary safety endpoint was assessment of adverse events, with a focus on those that led to discontinuation of study drug. The primary PK endpoint was AUC_{tau} of sofosbuvir, its primary metabolite GS-331007, velpatasvir, and voxilaprevir.

Statistical analyses

Efficacy

A two-sided 95% CI based on the Clopper-Pearson method was calculated for the percentage of patients achieving SVR12. Missing SVR values were imputed as a success if bracketed by values that were termed successes.

Pharmacokinetics

Population PK modeling was applied to the combined data from PK samples collected in the intensive PK substudy as well as all other sparse PK samples to characterize the PK of sofosbuvir, GS-331007, velpatasvir, and voxilaprevir using mixed-effect modeling techniques. Exposures of sofosbuvir, GS-331007, velpatasvir, and voxilaprevir (AUC_{tau}, C_{max}, and C_{tau}, if applicable) in pediatric patients were summarized using descriptive statistics (*n*, arithmetic mean, geometric mean and its 90% CI, percent coefficient of variation [%CV], SD, median, Q1, Q3, minimum, and maximum) and were compared with exposure data from the adult Phase 2/3 sofosbuvir-velpatasvir-voxilaprevir population. The primary PK endpoint of this analysis was evaluated by carrying out an analysis of variance for log-transformed sofosbuvir, GS-331007, velpatasvir, and voxilaprevir AUC_{tau}. The secondary PK endpoints of this analysis were the C_{max} and C_{tau} (if applicable) of sofosbuvir, GS-331007, velpatasvir, and voxilaprevir. The 90% CIs were constructed for the ratio of geometric means of each PK parameter. The equivalence boundary was set as 50% to 200% based on exposure–response (efficacy and safety) relationships observed in the integrated adult data.

RESULTS

Patient population

From January to December of 2019, 21 patients were treated at 10 study sites in Italy, Poland, and the UK. The median age for the study population was 14 years (range 12–16 years), and 76% (16 of 21) were infected through perinatal transmission (Table 1). No patients had previously received treatment with an HCV DAA; 24% (5 of 21) had failed prior treatment with pegylated-interferon or interferon plus ribavirin, including 1 patient who had failed two prior courses of pegylated-interferon plus ribavirin. Sixty-two percent (13 of 21) of patients were female, and 76% (16 of 21) were White. Nine patients (43%) were infected with HCV genotype 3a. No patients had cirrhosis based on prior biopsy or

TABLE 1 Patient demographics and baseline characteristics

	Sofosbuvir-velpatasvir-voxilaprevir 8 weeks, 12–17 years old (*n* = 21)
Age, years (median, range)	14 (12, 16)
Female, *n* (%)	13 (62)
Race, *n* (%)	
White	16 (76)
Asian	2 (10)
Other	2 (10)
Black	1 (5)
Weight, kg (median, range)	54 (38, 86)
Genotype, *n* (%)	
1a	2 (10)
1b	4 (19)
2c	4 (19)
3a	9 (43)
4d	1 (5)
4d + 4r	1 (5)
Resistance-associated substitutions, *n* (%)	
NS5A	10 (48)
NS3	1 (5)
NS5A and NS3	0
NS5B	3 (14)
HCV RNA, log_{10} IU/ml (median, range)	6.0 (4.3, 7.1)
HCV RNA ≥800,000 IU/ml, *n* (%)	11 (52)
HCV treatment history, *n* (%)	
Treatment naive	16 (76)
Direct-acting antiviral–naive	21 (100)
Without cirrhosis, *n* (%)	21 (100)
Transient elastography, kPa (median, range)	5.6 (4.6, 7.9)
FibroTest score (median, range)	0.2 (0.1, 0.5)
FibroTest stage, *n* (%)	
F0	15 (71)
F0–F1	2 (10)
F1	3 (14)
F1–F2	1 (5)
APRI (median, range)	0.2 (0.2, 0.8)
FIB−4 (median, range)	0.3 (0.2, 0.5)
ALT, U/l (median, range)	29 (15, 108)
Mode of HCV infection, *n* (%)	
Perinatal transmission	16 (76)
Unknown	3 (14)
Contact with infected individual	1 (5)
Blood product transfusion	1 (5)

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase–to–platelet ratio index; FIB-4, Fibrosis-4 Index.

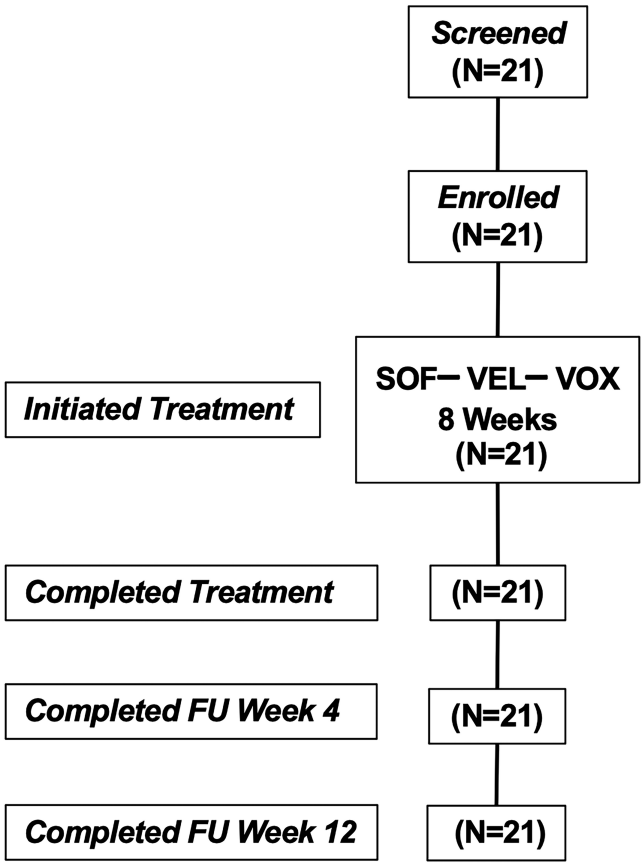

FIGURE 1 Patient disposition throughout the study

TABLE 2 Treatment response to sofosbuvir-velpatasvir-voxilaprevir

	Sofosbuvir-Velpatasvir-Voxilaprevir 8 Weeks, 12–17 Years Old (*n* = 21)
SVR12, *n* (%)	21 (100)
95% CI	84%–100%
Virologic failure, *n*	0
HCV RNA <LLOQ, *n* (%)	
Week 1	11 (52)
Week 2	17 (81)
Week 4	19 (91)
Week 8 (end of treatment)	21 (100)

Abbreviations: LLOQ, lower limit of quantification (15 IU/ml); SVR12, sustained virologic response 12 weeks after treatment.

investigator assessment; noninvasive liver fibrosis test results are summarized in Table 1. All 21 patients who initiated treatment completed it (Figure 1).

Virologic response

Overall, 100% of patients reached SVR12 (21 of 21; 95% CI, 84%–100%) (Table 2). No patients had virologic failure. Most patients (81%, 17 of 21) had HCV RNA <LLOQ by the week-2 treatment visit. Two additional patients reached viral negativity by week 4, and the remaining 2 became HCV RNA–negative during the second month of treatment.

TABLE 3 Baseline resistance-associated substitutions

HCV subtype	Baseline RAS[a] (*n* = number of patients)
NS5A[b]	
1a	K24R (*n* = 1)
1a	Y93Y/N (*n* = 1)
1b	L31I (*n* = 1)
2c	T24S (*n* = 3)
2c	T24S + F28C (*n* = 1)
3a	M28 M/V + Y93Y/H (*n* = 1)
4d	L30R (*n* = 1)
4d+4r	L28L/M + L30R (*n* = 1)
NS3/4A[c]	
1b	Y56F + Q80K (*n* = 1)
NS5B[d]	
3a	E237G (*n* = 1)
3a	N142T (*n* = 1)
4d+4r	V321I (*n* = 1)

[a]Resistance-associated substitutions (RASs) were defined as those that were reported at a 15% deep sequencing assay cutoff.

[b]NS5A RASs: genotype 1a: K24A/E/G/N/R, M28A/G/T/V, Q30ANY, L31F/I/M/V, P32L, S38F, H58D/L/N, A92K/P/T, and Y93ANY; genotype 1b: Q24K/R, L28V, R30H/Q/S, L31F/I/M/V, P32L, P58D/R/T, A92K, and Y93ANY; genotype 2a: T24A/P/S, F28A/C/S/V, L31F/I/M/V, P58D/S/T, C92A/K/N/R/S/T, and Y93ANY; genotype 2b: S24T, L28F/V, L31I/M/V, P58A/D, C92A/S/T, and Y93ANY; genotype 3: M28A/G/T/V, A30E/G/H/K/S/V, L31F/I/M/V, P58D/G, and Y93ANY; and genotype 4: K24G/R, L28A/M/S/T/V, L30E/G/H/K/R/S/T, M31F/I/V, P58D/L/S, A92K/T, and Y93ANY.

[c]NS3 RASs: genotype 1a: V36A/G/I/L/M/T, Q41H/K/R, F43L/S/V, T54A/C/G/S, V55A/I, Y56H, Q80K/L/R, S122D/N/R, R155ANY, A156ANY, D168ANY, and I170A/T/V; genotype 1b: V36A/G/I/L/M/T, Q41R, F43L/S/V, T54A/C/G/S, V55A/I, Y56F/H, Q80K/L/R, S122D/N/R, R155ANY, 156ANY, D168ANY, and V170A/T; genotype 2a: L36A/G/I/L/M/T, Q41R, F43L/S/V, T54A/C/G/S, V55A/I, Y56H, G80K/L/R, R155ANY, A156ANY, and D168ANY; genotype 2b: L36A/G/I/L/M/T, Q41R, F43L/S/V, 54A/C/G/S, V55A/I, Y56H, G80K/L/R, R155ANY, A156ANY, and D168ANY; genotype 3: L36A/G/I/L/M/T, Q41K/R, F43L/S/V, T54A/C/G/S, V55A/I, Y56H, N77S, Q80K/L, R155ANY, A156ANY, Q168ANY, and Q178R; and genotype 4: L36A/G/I/L/M/T, Q41R, F43L/S/V, T54A/C/G/S, V55A/I, Y56H, Q80K/L, R155ANY, A156ANY, and D168ANY.

[d]NS5B RASs: S96T, N142T, L159F, E237G, S282ANY, C289I/L, L320F/I/V, and V321A/I.

Resistance

The numbers of patients with pretreatment RASs were as follows: 10 patients (48%) with an NS5A RAS, 3 patients (14%) with an NS5B nucleoside inhibitor RAS, and 1 patient (5%) with an NS3/4A RAS (Table 3). The presence of pretreatment NS3/4A, NS5A, and/or NS5B RASs did not affect treatment outcome, as all patients with a pretreatment RAS achieved SVR12 and SVR24. No on-treatment breakthrough or relapse

TABLE 4 Adverse events and laboratory abnormalities

	Sofosbuvir-velpatasvir-voxilaprevir 8 weeks, 12–17 years old (*n* = 21)
Patients with any adverse event, *n* (%)	15 (71)
Grade 3 or 4 adverse events, *n*	0
Patients with a serious adverse event, *n* (%)	1 (5)
Patients with adverse events leading to discontinuation, *n* (%)	0
Adverse events in >1 patient, *n* (%)	
Abdominal pain	5 (24)
Headache	5 (24)
Nausea	4 (19)
Diarrhea	3 (14)
Fatigue	3 (14)
Rhinitis	3 (14)
Asthenia	2 (10)
Cough	2 (10)
Dizziness	2 (10)
Serious adverse events, *n* (%)	
Hypotension	1 (5)
Grade 3 or 4 laboratory abnormalities, *n* (%)	
Hyperkalemia, grade 4 (>7 mmol/l)	1 (5)

was observed in patients through posttreatment weeks 12 or 24.

Safety

Overall, treatment with sofosbuvir-velpatasvir-voxilaprevir for 8 weeks was safe and well-tolerated by adolescents 12 to 17 years old. The most commonly reported adverse events were abdominal pain and headache (each 24% of patients) and nausea (19% of patients) (Table 4). Most patients (71%, 15 of 21) reported experiencing at least one adverse event, and 43% (9/21) had a treatment-related adverse event. In addition to abdominal pain, gastrointestinal adverse events of diarrhea and vomiting were reported by 14% (3 of 21) and 5% (1 of 21) of patients. All adverse events were mild (Grade 1) or moderate (Grade 2) in severity. No patients had study drug interruption or premature discontinuation because of an adverse event.

One serious adverse event—hypotension—occurred in a 14-year-old otherwise healthy girl at day 10 of treatment. The participant had a moderate adverse event of diarrhea on day 10 and presented with confusion, fatigue, and blood pressure 88/47 mmHg (pulse 54 beats/min) and was admitted for observation. After oral replacement fluid was administered, symptomatic hypotension resolved. The hypotension was considered related to study drug by the investigator. She also had a treatment-related, mild adverse event of bradycardia that began on Day 8 and resolved 24 weeks after completing the study treatment. In addition, she had treatment-related intermittent adverse events of nausea and diarrhea; all were mild in severity and resolved on the day of onset except one adverse event diarrhea, which resolved the following day. None of her adverse events led to treatment interruption of discontinuation.

The only Grade 3 or 4 laboratory abnormality that occurred was an increase in potassium (>7 mmol/L) that was asymptomatic and not observed on repeat testing. At baseline, 24% of patients (5 of 21) had ALT >ULN. Normalization of ALT was observed in all 5 patients at week 4 and in 4 of 4 patients (one missing value) through the posttreatment week 4 visit, coincident with suppression of viral replication.

No notable effects of study drug on growth were observed as assessed by changes from baseline through posttreatment week 24 in height, weight, and BMI age-adjusted percentiles; radiographic bone age assessments; or bone biomarker assessments (CTX and P1NP) (Table 5).

At baseline, Tanner scores were stage 4 or 5 for pubic hair and genitalia development in 75% (6 of 8) of males and 69% (9 of 13) of females. At end of treatment and at posttreatment weeks 12 and 24, no males or females assessed had a decrease from baseline in Tanner staging.

Acceptability and palatability

All patients were able to swallow the standard adult-size tablets; 71% (15 of 21) and 75% reported that it was very easy or easy to swallow the study drug on day 1 and at week 8, respectively. Most patients reported they either did not taste the study drug or that the taste

TABLE 5 Median (Q1, Q3) growth measurement changes from baseline

	Baseline	Change at end of treatment (8 weeks)	Change at 24 weeks after treatment
Height-for-age percentile	47.9 (32.4, 63.2)	0 (−3.0, 1.3)	−0.2 (−3.1, 4.3)
Weight-for-age percentile	54.0 (30.9, 75.9)	−2.5 (−3.5, −1.2)	−1.6 (−5.2, 4.3)
BMI-for-age percentile	57.4 (30.2, 73.6)	−3.9 (−5.7, −0.5)	−2.8 (−7.1, 2.5)
Radiographic bone age, years	14.5 (13.7, 16.0)	0 (0, 0.5)	—
Bone biomarkers, ng/ml			
CTX	1.35 (1.05, 2.35)	—	−0.22 (−0.55, −0.04)
P1NP	383.25 (175.00, 944.20)	—	−101.50 (−359.00, −24.98)

Abbreviations: BMI, body mass index; CTX, C-type collagen sequence; P1NP, procollagen type 1 N-terminal propeptide.

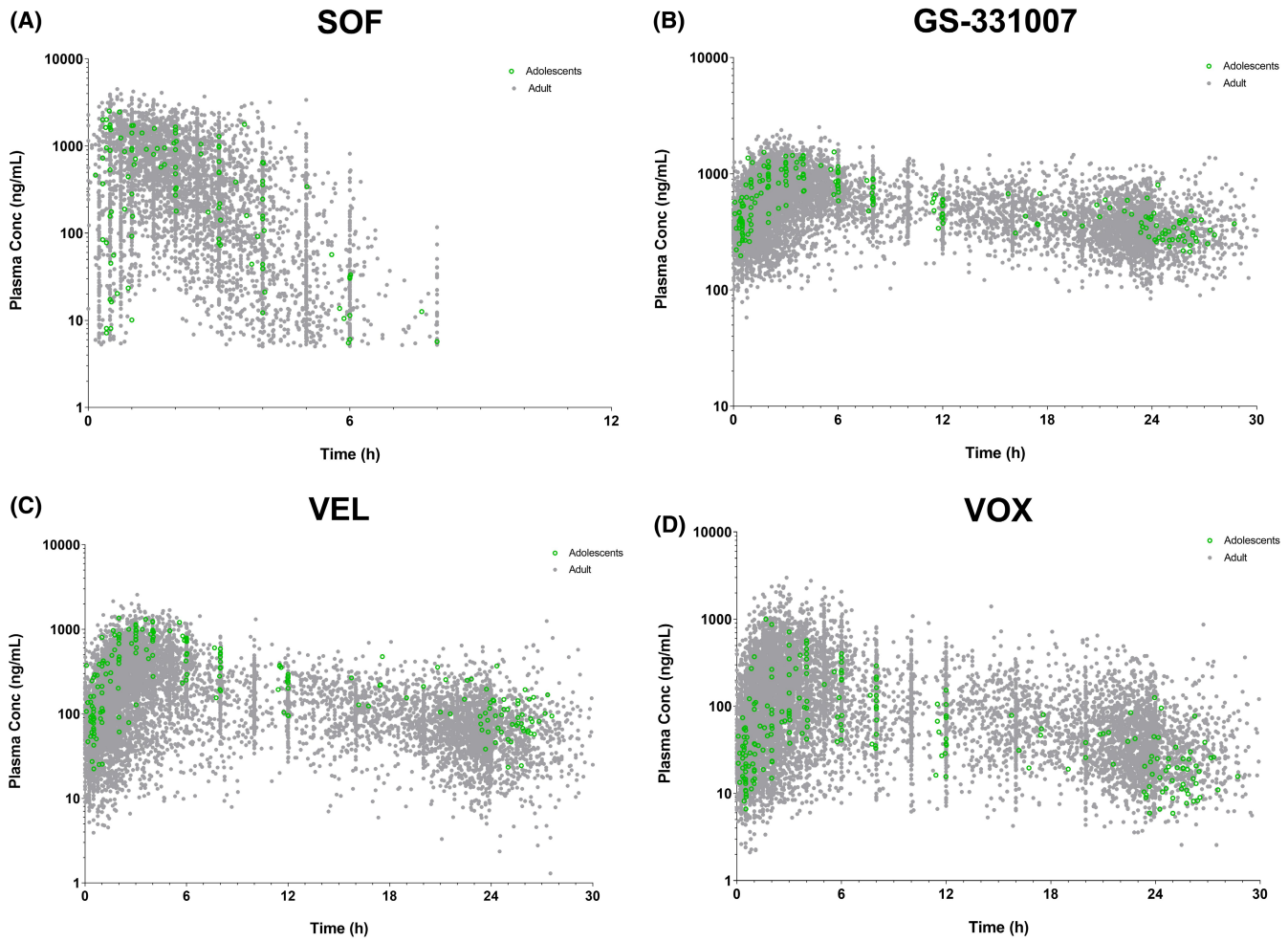

FIGURE 2 Plasma concentrations of sofosbuvir (A), GS-331007 (B), velpatasvir (C), and voxilaprevir (D) in lead-in phase pharmacokinetic samples per pediatric age group, plotted against time since last dose of sofosbuvir-velpatasvir-voxilaprevir. Gray dots represent all concentrations observed in the adult studies with sofosbuvir-velpatasvir-voxilaprevir

was good or neutral (maybe bad or maybe good) on day 1 (81%) and at week 8 (75%). The ease of taking the study drug over the treatment period was reported to be very easy or easy by 75% (15 of 20) and as neutral by the remaining 25% of patients at week 8. Parent and caregiver responses at the end of treatment visit were consistent with the patient reports.

Pharmacokinetics

In adolescents, sofosbuvir-velpatasvir-voxilaprevir 400/100/100 mg exposures were similar to those previously observed in adults (Figure 2). The AUC_{tau} and C_{max} of sofosbuvir and GS-331007 were within the predefined equivalence boundary of 50% to 200% when

TABLE 6 Summary of sofosbuvir, GS-331007, velpatasvir, and voxilaprevir steady-state exposures in adolescents and adults

	Mean (%CV)		%GMR (90% CI)
	Adolescents SOF-VEL-VOX (400/100/100 mg) (*n* = 21)	Adults[a] SOF-VEL-VOX (400/100/100 mg) (*n* = 1595)	Adolescent vs. adult[a] population
Sofosbuvir			
AUC_{tau} (ng•h/ml)	2475 (50)	1665 (30)	138 (124, 153)
C_{max} (ng/ml)	1305 (70)	678 (35)	163 (139, 191)
GS−331007			
AUC_{tau} (ng•h/ml)	14,890 (21)	12,834 (29)	118 (107, 131)
C_{max} (ng/ml)	1278 (16)	744 (28)	177 (159, 196)
Velpatasvir			
AUC_{tau} (ng•h/ml)	6773 (35)	4041 (49)	177 (147, 212)
C_{max} (ng/ml)	622 (38)	311 (56)	216 (175, 266)
C_{tau} (ng/ml)	92 (50)	51 (65)	189 (154, 230)
Voxilaprevir			
AUC_{tau} (ng•h/ml)	2206 (64)	2577 (74)	89 (69, 114)
C_{max} (ng/ml)	231 (84)	192 (86)	120 (90, 159)
C_{tau} (ng/ml)	24 (72)	47 (82)	52 (41,66)

Abbreviations: and VOX, voxilaprevir; CV, coefficient of variation; GMR, geometric mean ratio; SOF, sofosbuvir; VEL, velpatasvir.
[a]Adult data from Phase 2/3 clinical studies. SOF, *n* = 1038; GS-331007, *n* = 1593; VOX, *n* = 1591.

compared with adults from Phase 2/3 studies (Table 6). Although the upper bound of the 90% CI for velpatasvir AUC_{tau}, C_{max}, and C_{tau} in adolescent patients modestly exceeded the upper equivalence bound, the exposures were within the range observed in the adult Phase 2/3 population, in which no exposure–response relationships for velpatasvir exposures and safety assessments were identified. The AUC_{tau} and C_{max} of voxilaprevir were within the predefined equivalence boundary, but the lower bound of the 90% CI for voxilaprevir C_{tau} was modestly below the lower equivalence bound. The adult Phase 2/3 population used for the comparison consisted of both patients without cirrhosis (58%) and with cirrhosis (42%). In adult patients, voxilaprevir exposure parameters were higher in those with versus without compensated cirrhosis. Because all of the adolescent patients in this study had no cirrhosis, a sensitivity analysis was performed comparing voxilaprevir exposures in adolescent patients with adults with no cirrhosis in the Phase 2/3 population. In this sensitivity analysis, voxilaprevir C_{tau} was within the predefined equivalence boundary.

DISCUSSION

Among children, adolescents have the highest prevalence of HCV.[1] The European Society for Pediatric Gastroenterology, Hepatology and Nutrition advises early treatment of adolescents with HCV, before the risk of horizontal infection increases through sexual transmission or injecting drug use.[17] Intravenous drug abuse is a significant and increasingly common route of HCV infection in adolescents and young adults in the West. In the Appalachian region of the USA, among persons 12 to 29 years, HCV infection increased more than 3-fold from 2006 to 2012.[18] Given the increased transmission among young persons, in early 2020, the U.S. Preventive Services Task Force expanded HCV screening recommendations, suggesting that screening be considered in persons younger than 18 years who have a risk factor for infection, such as history of injection drug use.[19,20] Screening and treatment efforts among adolescents are important measures for meeting the World Health Organization's goal of eliminating all forms of viral hepatitis as a public health threat by 2030.[21]

Our study supports sofosbuvir-velpatasvir-voxilaprevir treatment in adolescents. Of the 21 DAA-naïve adolescents—43% of whom had HCV genotype 3 infection—all (100%) reached SVR12 with 8 weeks of sofosbuvir-velpatasvir-voxilaprevir. This rate was consistent with the SVR12 rates of 95%–96% observed with sofosbuvir-velpatasvir-voxilaprevir in Phase 3 trials in DAA-naïve adults.[13] Our results support using the current adult dose of sofosbuvir-velpatasvir-voxilaprevir (400/100/100 mg) for adolescents.

In our study, weight was not a criterion for entry, and all participants weighed ≥38 kg. Sofosbuvir-velpatasvir-voxilaprevir has not been studied in persons weighing <30 kg; thus, a recommended dose has not been determined for this group. For the combination regimen of sofosbuvir-velpatasvir, dosing is lower relative to adults in children and adolescents weighing <30 kg,

but no adjustment in dosing is recommended if a child's weight decreases during the treatment period based on PK and safety data (Figure S1). Indeed, the pediatric population PK models for the individual drugs indicate that exposures for all DAAs in the sofosbuvir-velpatasvir-voxilaprevir combination increase with decreasing body weight. Velpatasvir, sofosbuvir, and its metabolite GS-331007 potentially exceed the adult exposures for weights closer to 30 kg. Based on the available safety data, this is not considered a concern. Currently, sofosbuvir-velpatasvir-voxilaprevir is not approved for pediatric populations in the USA. In the European Union, the Committee for Medicinal Products for Human Use adopted a positive scientific opinion recommending an extension to the indication for sofosbuvir-velpatasvir-voxilaprevir for the treatment of chronic HCV infection in adolescents aged 12 years and older and weighing at least 30 kg, pending the European Commission approval, which occurred in September 2021.

Sofosbuvir-velpatasvir-voxilaprevir's high SVR12 rate in adolescents is comparable with other DAA treatments in children and adolescents.[22] Although most of the currently available DAA treatments for children and adolescents with or without compensated cirrhosis have a duration of 12 weeks, the results of our study confirm that sofosbuvir/velpatasvir/voxilaprevir can be effectively used for the shortened treatment duration of 8 weeks. Sofosbuvir-velpatasvir-voxilaprevir's pangenotypic activity means that it can be administered without viral genotyping, which could be especially useful in regions that lack genotype testing facilities, such as low-income and middle-income countries with relatively high HCV prevalence in children.[1]

Sofosbuvir-velpatasvir-voxilaprevir was well tolerated, and all patients were able to swallow the standard adult-size tablets. The most common adverse events were mild to moderate abdominal pain, headache, and nausea. Interferon-based regimens have known effects on growth and development in children,[23] but we found no effects on short-term growth and development with sofosbuvir-velpatasvir-voxilaprevir. Population PK-based simulations indicated comparable exposures of sofosbuvir, GS-331007, velpatasvir, and voxilaprevir in adolescents relative to adults when given the same 400/100/100 mg dose. A single serious adverse event, hypotension, resolved on the same day it was reported without interruption of treatment.

Virological failure after DAA treatment is frequently due to RASs, amino acid substitutions that diminish DAA effectiveness in vitro and/or in vivo. Several RASs in the NS3, NS5A, and NS5B coding regions of HCV have been associated with reduced susceptibility to DAAs.[24] In adults, the triple combination of sofosbuvir-velpatasvir-voxilaprevir has high efficacy in retreating adults who failed to achieve SVR after a DAA treatment course.[16] Our study protocol was inclusive of DAA-naïve patients with compensated cirrhosis as well as patients who previously received an HCV DAA inhibitor, and such patients were to receive 12 weeks of treatment. However, all enrolled patients were DAA-naïve without cirrhosis; thus, we were not able to evaluate sofosbuvir-velpatasvir-voxilaprevir in adolescents with cirrhosis or prior DAA failure. The Phase 3 studies of sofosbuvir-velpatasvir-voxilaprevir in DAA-experienced adults included 46% with compensated cirrhosis, and SVR12 rates were 96%–98%.[16] Given the comparable PK profiles of sofosbuvir-velpatasvir-voxilaprevir in adolescents and adults, 12 weeks of treatment is projected to result in high SVR rates in adolescents who are DAA-experienced with or without compensated cirrhosis or DAA-naïve with compensated cirrhosis, although further studies would be needed for confirmation.

This Phase 2 study included a total of 21 participants. Larger Phase 3 and 4 studies, especially in real-world settings, would have greater potential for enrolling adolescents with cirrhosis or prior failure with various DAA regimens, including those used in lower-income or middle-income countries. For example, although the combination of sofosbuvir and daclatasvir (an NS5A inhibitor) has been used to treat children and adolescents with chronic HCV in Egypt[25–28] and is the DAA regimen of choice in many low-income and middle-income countries for curative treatment of HCV infection in adults, there are limited data on daclatasvir PK, safety, efficacy, and resistance development in pediatric populations.[29,30] In addition, in the present study, nearly half of the participants had a relatively low viral load at baseline. Although baseline viral load has not been found to be associated with SVR rates or development or persistence of resistance variants in studies of sofosbuvir-velpatasvir-voxilaprevir in adults, larger studies would have greater potential to address this question in adolescents.

Given the high success rates with HCV-DAA treatments in adolescents,(13,22) the population of adolescent patients with HCV who fail a DAA-inclusive regimen is anticipated to be small. Nevertheless, sofosbuvir-velpatasvir-voxilaprevir provides an important retreatment option for adolescents with a prior treatment failure with a sofosbuvir-containing regimen, without concern for HCV genotype or presence of compensated cirrhosis. Given the current availability of other highly effective all-DAA regimens for adolescents, we believe sofosbuvir-velpatasvir-voxilaprevir's primary use will be for retreatment.

In summary, the pangenotypic regimen of sofosbuvir-velpatasvir-voxilaprevir is highly efficacious and well-tolerated in treating chronic HCV infection in adolescents aged 12 to 17 years. The regimen provides an 8-week treatment option for DAA-naïve adolescents without cirrhosis as well as a retreatment option for those who have failed prior DAA-based therapies.

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CONFLICTS OF INTEREST

Dr. Parhy owns stock in and is employed by Gilead. Dr. Hsueh owns stock in and was previously employed by Gilead. Dr. Kelly consults for, advises, is on the speakers' bureau for, and received grants from Gilead and Abbvie. Dr. Indolfi advises Kedrion Pharma. Dr. Shao owns stock in and is employed by Gilead. Dr. Kersey owns stock in and is employed by Gilead. Dr. Pawkowska received grants from Gilead. Dr. Yue owns stock in Gilead. He is employed by Certara.

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DATA SHARING STATEMENT

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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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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