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ORIGINAL ARTICLE

Hepatology

Sofosbuvir–velpatasvir in children 3–17 years old with hepatitis C virus infection

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Abstract

Background: The safety and efficacy of sofosbuvir–velpatasvir in children aged 3–17 years with chronic hepatitis C virus (HCV) infection of any genotype were evaluated.

Abbreviations: AUC, area under the curve; CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantification; PK, pharmacokinetic; RAS, resistance-associated substitution; RT-PCR, reverse transcription polymerase chain reaction; SVR, sustained virological response; ULN, upper limit of normal; USPSTF, United States Preventive Services Task Force.

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Methods: In this Phase 2, multicenter, open-label study, patients received once daily for 12 weeks either sofosbuvir–velpatasvir 400/100 mg tablet (12–17 years), 200/50 mg low dose tablet or oral granules (3–11 years and ≥17 kg), or 150/37.5 mg oral granules (3–5 years and <17 kg). The efficacy endpoint was sustained virologic response 12 weeks after therapy (SVR12). Dose appropriateness was confirmed by intensive pharmacokinetics in each age group.

Findings: Among 216 patients treated, 76% had HCV genotype 1% and 12% had genotype 3. Rates of SVR12 were 83% (34/41) among 3–5-year-olds, 93% (68/73) among 6–11-year-olds, and 95% (97/102) among 12–17-year-olds. Only two patients experienced virologic failure. The most common adverse events were headache, fatigue, and nausea in 12–17-year-olds; vomiting, cough, and headache in 6–11-year-olds; and vomiting in 3–5-year-olds. Three patients discontinued treatment because of adverse events. Four patients had serious adverse events; all except auditory hallucination ($n = 1$) were considered unrelated to study drug. Exposures of sofosbuvir, its metabolite GS-331007, and velpatasvir were comparable to those in adults in prior Phase 2/3 studies. Population pharmacokinetic simulations supported weight-based dosing for children in this age range.

Interpretation: The pangenotypic regimen of sofosbuvir–velpatasvir is highly effective and safe in treating children 3–17 years with chronic HCV infection.

KEYWORDS
direct-acting antiviral, pediatrics, pharmacokinetics, polymerase inhibitor

1 | INTRODUCTION

Globally, an estimated 3.25 million children <18 years old have active infection with hepatitis C virus (HCV).[1] In children, perinatal transmission is a primary route of HCV acquisition.[2] Of children infected perinatally, an estimated 8%–25% spontaneously clear HCV infection, usually by age 7.[3–5] The remainder develop chronic HCV infection, with liver disease generally progressing more slowly than in adults. However, HCV-infected children can experience progression of liver disease, and bridging fibrosis has been seen in patients younger than 5 years.[6] Cirrhosis,[7–9] hepatocellular carcinoma,[10,11] and end-stage liver disease requiring liver transplantation[4,12] have been reported in the pediatric HCV population.

In Western Europe and the United States, HCV seroprevalence in children is generally low, with estimates of up to 0.09%.[13] However, in the United States, the incidence of HCV infection in children increased during an opioid epidemic. During 2011–2014, the percentage of infants born to HCV-infected women increased by 68%,[14] and children 2–3 years old had a three-fold higher incidence of HCV infection than 12–13 year-olds.[15]

Multiple all-oral, direct-acting antiviral treatment regimens have been approved for use in children.[16] Virological cure, defined as achieving posttreatment sustained virologic response (SVR), decreases liver inflammation, fibrosis progression, and risk of hepatocellular carcinoma.[17–19] SVR can also lead to reversal of fibrosis or cirrhosis[17] and reduces viral transmission.

What is Known

- For treating chronic hepatitis C virus (HCV) infection, the combination antiviral regimen sofosbuvir–velpatasvir is highly effective in treating adults with any HCV genotype.
- In children, the safety, efficacy, and pharmacokinetics of sofosbuvir–velpatasvir had not been evaluated.

What is New

- In 216 children aged 3–17 years with chronic HCV infection, sofosbuvir–velpatasvir given once daily for 12 weeks had a cure rate of 92%.
- Rates of cure were 95% among 12–17-year-olds (97/102), 93% in 6–11-year-olds (68/73), and 83% in 3–5-year-olds (34/41).
- Overall, sofosbuvir–velpatasvir was well tolerated in both tablet and granule formulations; 1.4% (3/216) of participants discontinued because of an adverse event. Pharmacokinetic simulations supported weight-based dosing for children.

The HCV NS5B polymerase inhibitor sofosbuvir is a potent antiviral with low susceptibility to viral resistance, forming the backbone of multiple antiviral

regimens.[20] The pangenotypic combination regimen of sofosbuvir–velpatasvir is highly effective in adults[21,22] but had not been investigated in children.

We evaluated the efficacy and safety of sofosbuvir–velpatasvir in children ages 3–17 years with chronic HCV of any genotype. Three different doses were administered; dosing was based on age in 12–17 year-olds and weight in 3–11 year-olds. To assess appropriateness of the doses, a subset of patients underwent pharmacokinetic (PK) evaluation. We also monitored for resistance-associated substitutions (RASs) in HCV, which can reduce effectiveness of direct-acting antivirals.[23]

2 | METHODS

2.1 | Patients

Eligible patients were 3–17 years old and had chronic infection with HCV of any genotype, with plasma HCV RNA levels at least 1000 IU/mL. Patients were either HCV treatment naïve or treatment experienced with an interferon-based regimen ± ribavirin ± a protease inhibitor. Patients with cirrhosis as determined by the investigator were eligible; a liver biopsy was not required for study entry. Key exclusion criteria were decompensated liver disease; chronic liver disease of a non-HCV cause; platelets <50,000/mm^3; albumin <3.5 g/dL; alanine aminotransferase >10 × ULN; aspartate aminotransferase >10 × ULN; hepatocellular carcinoma; coinfection with hepatitis A or B or HIV; clinically relevant alcohol or drug abuse within 12 months; or psychiatric hospitalization, suicide attempt, or disability resulting from psychiatric illness within 5 years. Parents or legal guardians provided written informed consent before patients undertook any study-related procedures. Patients provided written assent in accordance with local review board requirements and the investigators' discretion.

2.2 | Study design

This was a Phase 2, multicenter, open-label study. Patients were enrolled in sequential age groups of 12–17, 6–11, and 3–5 years after PK data confirmed the preceding group's dose was appropriate. Sofosbuvir–velpatasvir fixed-dose combination tablets or oral granules were administered once daily for 12 weeks. Patients 12–17 years received sofosbuvir–velpatasvir 400/100 mg daily either as one standard tablet or two 200/50 mg tablets. Patients 6–11 years received sofosbuvir–velpatasvir 200/50 mg daily in one tablet or in four packets of oral granules each containing 50/12.5 mg sofosbuvir–velpatasvir. Patients 3–5 years weighing ≥17 kg received sofosbuvir–velpatasvir 200/50 mg daily (four packets of oral granules containing 50/12.5 mg sofosbuvir–velpatasvir), and those weighing <17 kg received sofosbuvir–velpatasvir 150/37.5 mg (three packets of oral granules). The oral granules could be swallowed directly, followed by water or milk, or mixed with a spoonful of soft, nonacidic food. At least 17 patients in each age group underwent intensive PK evaluation during the first 7 days of dosing. Following the PK lead-in phase, patients continued treatment with no interruption of study drug administration, and additional patients were enrolled following dose confirmation. Follow-up visits occurred at posttreatment Weeks 4, 12, and 24.

The study protocol (ClinicalTrials.gov Identifier: NCT03022981) 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.

2.3 | Assessments

2.3.1 | Virology

Plasma HCV RNA levels at screening, Day 1, and each on-treatment and posttreatment visit were quantified by the Roche COBAS Ampliprep/COBAS TaqMan HCV Test, v2.0 (Roche Molecular Systems, Inc.), which has a lower limit of quantification (LLOQ) of 15 IU/mL.

HCV genotype and subtype were determined by basic local alignment search tool (BLAST) sequencing. 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 NS5A and NS5B coding regions were amplified by DDL Diagnostic Laboratory (Rijswijk) using standard reverse transcription polymerase chain reaction (RT-PCR) technology. Following amplification, PCR products were deep sequenced with an assay cutoff of 1%. Reported RASs were present in more than 15% of the sequence reads for NS5A or NS5B.

2.3.2 | Safety

At the screening and all treatment visits, data regarding vital signs, reported adverse events, concomitant medication intake, and clinical laboratory tests were collected. The Medical Dictionary for Regulatory Activities, version 22.1, was used to code treatment-emergent adverse events. Severity of adverse events was assessed as grade 1, 2, 3, or 4 using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities.

Effects on growth were assessed via changes in height, weight, and BMI percentiles using the 2000 US Center for Disease Control reference charts

(https://www.cdc.gov/growthcharts/cdc_charts.htm) as well as radiographic bone age at Day 1 and end of treatment. Effects on development were assessed via Tanner Pubertal Stages at Day 1, end of treatment, and follow-up visits 12- and 24-weeks posttreatment.

2.3.3 | PKs

At the Day 7 visit, serial blood samples were collected from 56 patients to determine PK for sofosbuvir, its primary metabolite GS-331007, and velpatasvir. For all patients, starting at Week 1, sparse blood samples were collected for PK analyses at on-treatment visits.

2.3.4 | Acceptability/palatability of the formulations

Adolescent patients 12–17 years old self-reported whether they could swallow sofosbuvir–velpatasvir placebo tablets 400/100 or 200/50 mg. Patients aged 6–11 years old made the same assessment for sofosbuvir–velpatasvir placebo tablets 200/50 mg. Swallowability was not assessed for the oral granule formulation.

Questionnaires were administered to patients and to parents/caregivers to assess acceptability (ease of taking, ease of preparation for oral granules) and palatability (taste) of the formulation received on Day 1, Week 12, and early termination (as applicable). Acceptability and palatability were assessed using a numeric response marked on a modified 100 mm visual analog scale that incorporated a five-point facial hedonic scale; a higher score indicated better acceptability and/or palatability. Responses ≥40 on the scale were considered taste being palatable or ease of taking study drug as being acceptable.

2.4 | Endpoints

The primary safety endpoint was assessment of adverse events, with a focus on those that led to discontinuation of study drug. The key efficacy endpoint was achievement of SVR12, defined as having HCV RNA < LLOQ (15 IU/mL) 12 weeks after discontinuing study drugs. For the PK lead-in phase, the primary endpoint was steady-state exposure of sofosbuvir, its primary metabolite GS-331007, and velpatasvir.

2.5 | Statistical analyses

2.5.1 | Efficacy

A 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method was calculated for percentages of patients achieving SVR12. Missing SVR values were imputed as a success if bracketed by values that were termed successes.

2.5.2 | PKs

The primary PK endpoint of the PK lead-in phase was AUC_{tau} of sofosbuvir, GS-331007, and velpatasvir. To evaluate if the exposures achieved in pediatric patients of this study were similar to the exposures observed in adult patients, sofosbuvir, GS-331007, and velpatasvir exposure data from this study were compared to the integrated adult data. The primary endpoint of this analysis was evaluated by carrying out an analysis of variance (ANOVA) for log-transformed sofosbuvir, GS-331007, and velpatasvir AUC_{tau}. Secondary endpoints were the C_{max} of sofosbuvir, GS-331007, and velpatasvir and C_{tau} of velpatasvir. The 90% CIs were constructed for the ratio of geometric means of each PK parameter. The equivalence boundary was set as 70%–200%. Population PK modeling was applied on the combined data from serial and sparse PK samples to characterize the PK of sofosbuvir, GS-331007, and velpatasvir using mixed-effect modeling techniques; 90% CIs were constructed for the ratio of the geometric means of each PK parameter and analyte.

3 | RESULTS

3.1 | Patient population

The first patient was enrolled on January 26, 2017. A total of 216 patients were enrolled at 28 study sites in the United States ($n = 22$), Italy ($n = 3$), United Kingdom ($n = 2$), and Belgium ($n = 1$). Participant ages ranged from 3 to 17 years, and 93% (200/216) were infected through perinatal transmission (Table 1). Eighty-eight percent (190/216) of patients were treatment naïve. Seventy-six percent (165/216) had HCV genotype 1, and 12% (25/216) had genotype 3. Based on clinical history and/or prior biopsy, no patient had cirrhosis; baseline APRI and FibroTest® scores were consistent with this finding.

Of the 216 patients who initiated treatment, 204 (94%) completed treatment (Figure 1). Three patients discontinued study drug because of adverse events (described in the Safety section), and three were withdrawn at investigator discretion. The youngest cohort (3–5 years) accounted for more than half of treatment discontinuations (58%, 7/12); five of the seven discontinuations were children who had vomiting or spitting up of study drug. Data collection for the study's primary endpoint occurred through November

TABLE 1 Patient demographics and baseline characteristics.

	Sofosbuvir–velpatasvir 12 weeks		
	3–5 years (*n* = 41)	6–11 years (*n* = 73)	12–17 years (*n* = 102)
Median (range) age (year)	4 (3, 5)	8 (6, 11)	15 (12, 17)
Female, *n* (%)	24 (59)	38 (52)	52 (51)
Race, *n* (%)			
White	32 (78)	66 (90)	74 (73)
Black or African American	3 (7)	4 (6)	9 (9)
Other/not disclosed/not permitted	6 (15)	2 (3)	6 (6)
Asian	-	1 (1)	11 (11)
American Indian or Alaska Native	-	-	2 (2)
Region, *n* (%)			
United States	38 (93)	57 (78)	77 (76)
Non-United States	3 (7)	16 (22)	25 (25)
Median (range) weight (kg)	19 (13, 35)	27 (18, 78)	57 (22, 147)
Genotype[a] *n* (%)			
1a	29 (71)	47 (64)	57 (56)
1b	2 (5)	9 (12)	20 (20)
1c	1 (2)	-	-
2	6 (15)	2 (3)	5 (5)
3a	2 (5)	11 (15)	12 (12)
4/4a	1 (2)	4 (6)	2 (2)
6		-	6 (6)
Resistance-associated substitutions, *n*/*n* (%)			
NS5A	6/33 (18)	7/68 (10)	16/98 (16)
NS5B	1/30 (3)	0/68 (0)	5/97 (5)
Median (range) HCV RNA, $\log_{10}$ IU/mL	5.9 (1.1, 7.3)	5.9 (3.7, 7.2)	6.1 (4.9, 7.1)
HCV RNA ≥ 800,000 IU/mL, *n* (%)	20 (49)	35 (48)	59 (58)
HCV treatment history, *n* (%)			
Treatment naive	41 (100)	69 (95)	80 (78)
Treatment experienced	-	4 (5)	22 (22)
Cirrhosis, *n* (%)			
No	10 (24)	31 (43)	40 (39)
Unknown	31 (76)	42 (58)	62 (61)
Median (range) APRI	0.33 (0.12, 0.69)	0.34 (0.14, 2.04)	0.33 (0.10, 4.18)
Median (range) Fibrotest	0.09 (0.03, 0.70)	0.16 (0.03, 0.43)	0.17 (0.05, 0.79)
Median (range) ALT, U/L	47 (12, 245)	45 (17, 297)	33 (13, 304)
Median (range) eGFR,[b] mL/min/1.73 m^2	153 (96, 212)	156 (119, 217)	157 (116, 248)
Mode of HCV infection, *n* (%)			
Perinatal transmission	40 (98)	69 (95)	91 (89)
Unknown/other	1 (2)	1 (1)	9 (9)

(Continues)

TABLE 1 (Continued)

	Sofosbuvir–velpatasvir 12 weeks		
	3–5 years ($n = 41$)	6–11 years ($n = 73$)	12–17 years ($n = 102$)
Contact with infected individual	-	3 (4)	1 (1)
Blood product transfusion	-	-	1 (1)

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus.

[a]For 3–5 year-olds, four had genotype 2b, one had genotype 2a, and one had genotype two unconfirmed subtype.

For 6–11 year-olds, two had genotype 2b, two had 4a, one had 4d, and one had 4p.

For 12–18 year-olds, one had genotype 2a, three had 2b, and one had 2c; two had 4a; and three had 6a, one had 6e, and two had 6n.

[b]Estimated using the Schwartz Formula.

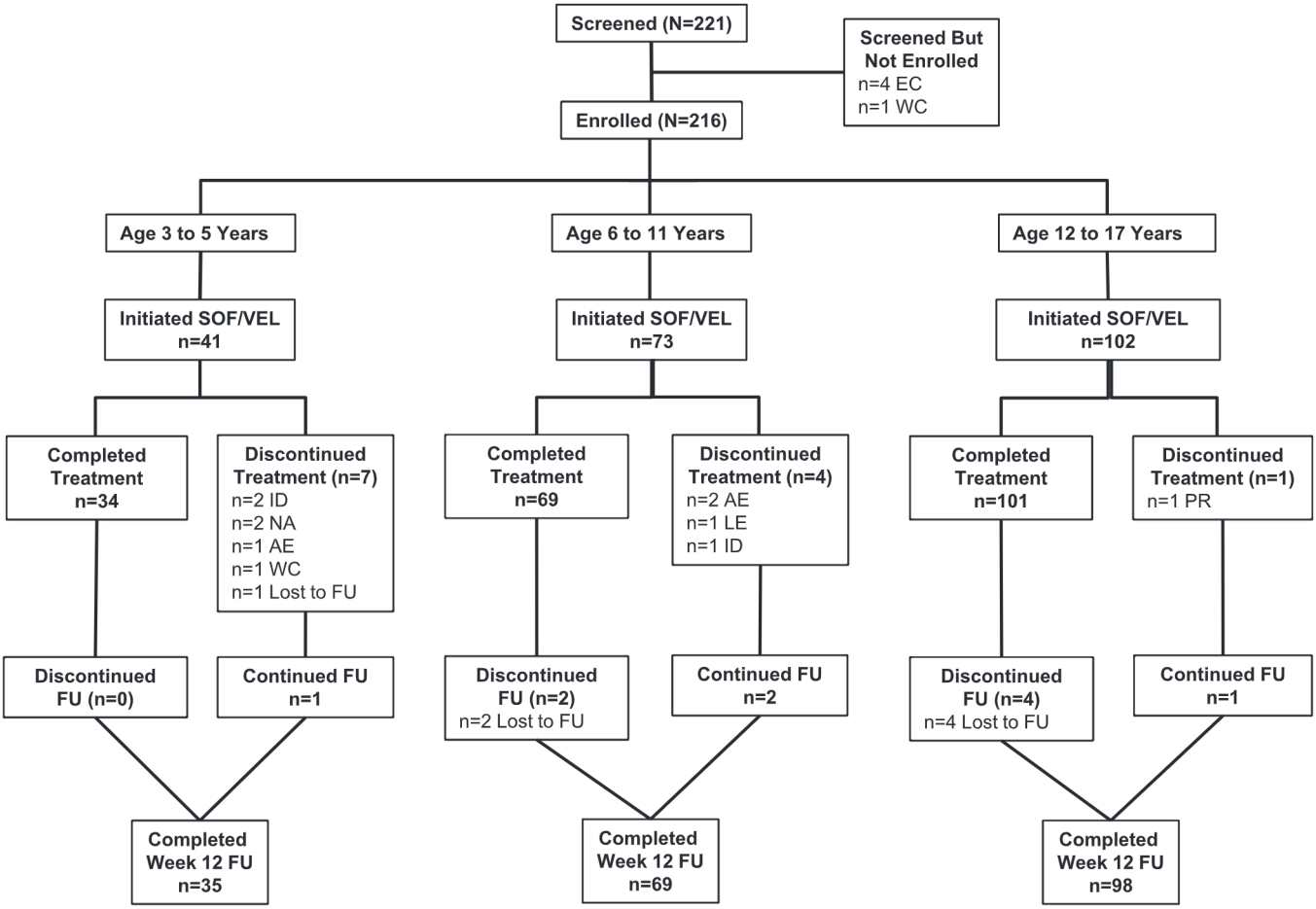

FIGURE 1 Patient disposition throughout the study. AE, adverse event; EC, did not meet eligibility criteria; FU, follow-up; ID, investigator discretion; LE, lack of efficacy; NA, non-adherence; PR, pregnancy; SOF, sofosbuvir; VEL, velpatasvir; WC, withdrew consent.

19, 2019. Safety data were collected until February 26, 2020.

3.2 | Virologic response

Overall, 92% of patients reached SVR12 (199/216) (Table 2).

3.2.1 | 12–17 years old

SVR12 was achieved by 95% of 12–17-year-olds (97/102). Of the five not achieving SVR12, four completed treatment but did not have posttreatment Week 12 assessments. The fifth patient, who was treatment naïve and had HCV genotype 1a, was categorized as having virologic relapse. After reaching HCV RNA < LLOQ at the

TABLE 2 Treatment response to sofosbuvir–velpatasvir.

	Sofosbuvir–velpatasvir 12 weeks		
	3–5 years ($n = 41$)	6–11 years ($n = 73$)	12–17 years ($n = 102$)
SVR12, *n* (%)	34 (83)	68 (93)	97 (95)
95% confidence interval	68–93	85–98	89–98
Virologic failure, *n*			
On treatment	0	1	0
Relapse			
Completed study treatment	0	0	0
Discontinued study treatment	0	0	1[a]
Other outcome, *n*			
Lost to follow-up	1	2[b]	4[b]
Discontinued due to investigator discretion	2	1	0
Discontinued due to nonadherence	2	0	0
Adverse event	0	1[c]	0
Parent/guardian withdrew consent	1	0	0
Discontinued treatment early, not due to virologic failure	1[d]	0	0

Abbreviation: SVR12, sustained virologic response 12 weeks after treatment.

[a]Patient experienced virologic relapse after discontinuing study drug due to pregnancy.

[b]Completed treatment and did not have posttreatment Week 12 assessments.

[c]Spitting up study drug.

[d]Decreased appetite, irritability, psychomotor hyperactivity, spitting up study drug

Week 4 visit, this patient had pregnancy confirmed on Day 29 and discontinued study drug starting on Day 30. Four weeks after stopping treatment, the patient had HCV RNA 245,000 IU/mL.

3.2.2 | 6–11 years old

SVR12 was achieved by 93% of 6–11-year-olds (68/73). Of the five not reaching SVR12, two completed treatment but did not have posttreatment Week 12 assessments. The third patient had virologic failure on treatment (nonresponse). This patient was treatment-naïve and had genotype 1a HCV infection with no baseline NS5A or NS5B nucleoside inhibitor RASs. HCV RNA levels were 7.00 $\log_{10}$ IU/mL at baseline, 3.94 $\log_{10}$ IU/mL at Week 1, 6.69 $\log_{10}$ IU/mL at Week 4, and 2.54 $\log_{10}$ IU/mL at Week 8; consequently, treatment was discontinued. Study drug adherence as measured by tablet counts was 100%, although sofosbuvir, GS-331007, and velpatasvir concentrations were below the level of quantification at Weeks 2 and 4 and low at Week 8, suggesting potential nonadherence with dosing. An NS5A RAS, L31V, emerged at treatment Week 8. No NS5B nucleoside inhibitor RASs emerged postbaseline. The fourth participant discontinued treatment on Day 7 due to spitting up study drug, which was considered an adverse event. The fifth participant was discontinued from study treatment based investigator decision on Day 15 after difficulty taking study treatment in tablet and oral granule form.

3.2.3 | 3–5 years old

SVR12 was achieved by 83% of 3–5-year-olds (34/41). Of the seven who did not reach SVR12, six discontinued treatment within the first week (two were discontinued by the investigator on Day 1; one had parent consent withdrawn after the first dose; two were discontinued on Day 2 or Day 7 due to nonadherence; and one was lost to follow-up after Day 5), and one discontinued treatment at Day 20 due to decreased appetite, irritability, psychomotor hyperactivity, and spitting up study drug. Of the two participants who were discontinued by the investigator on Day 1, one spit out study drug due to behavioral issues and the other had adverse events of projectile vomiting and negative taste experience with study drug.

3.3 | Resistance

3.3.1 | 12–17 years old

In the 12–17-year-old group, pretreatment NS5A RASs were observed in 16 of 98 patients (16%) with available

deep sequencing data. Five of 97 patients (5%) with available sequencing data had NS5B nucleoside inhibitor RASs ($n = 3$ L159F and $n = 2$ M289L). The presence of pretreatment NS5A and/or NS5B RAVs did not impact treatment outcome, as all patients 12–17 years old with pretreatment RASs achieved SVR12 (Supplementary Table S1).

3.3.2 | 6–11 years old

Among 6–11-year-olds, 10% (7 of 68 with available sequence data) had pretreatment NS5A RASs, and none had pretreatment NS5B nucleoside inhibitor RASs. All patients 6–11 years with pretreatment NS5A RASs achieved SVR12. One patient with on-treatment virologic failure, described above, had NS5A RAS L31V emerge at Week 8 of treatment. This patient, with genotype 1a HCV infection, had no pretreatment NS5A or NS5B nucleoside inhibitor RASs. The patient had no NS5B RASs at any time point.

3.3.3 | 3–5 years old

Pretreatment NS5A RASs were present in 6 of 33 (18%) 3–5 year-olds who had available pretreatment deep sequencing data. All six patients with baseline NS5A RASs achieved SVR12. One patient, with HCV genotype 2b, had a pretreatment NS5B RAS of M289I, and this patient achieved SVR12.

3.4 | Safety

Overall, sofosbuvir–velpatasvir was well tolerated. Two patients aged 6–11 years and five patients aged 3–5 years had adverse events of spitting up study drug ($n = 6$) or abnormal taste ($n = 1$).

3.4.1 | 12–17 years old

The most common adverse events were headache (30%), fatigue (22%), and nausea (17%) (Table 3). Two patients had serious adverse events; both continued study drug for the full duration of therapy. The first was a girl with an ongoing history of attention deficit hyperactivity disorder who experienced a grade 3 serious adverse event of suicidal ideation, which was assessed as not related to study drug and resolved 2 days after onset. A second patient, who had a complex medical history that included ongoing bipolar disorder II, frequent suicidal thoughts, and suicide attempt, had an ongoing grade 3 serious adverse event of exacerbated bipolar disorder II on Day 1, a grade 3 serious adverse event of suicidal ideation on Day 69, a grade 4 serious adverse event of suicide attempt on Day 75 that resolved on the same day, and resolution of suicidal ideation on Day 80. On posttreatment Day 59, the patient also had a grade 4 serious adverse event of suicide attempt that resolved on the same day. All serious adverse events in this patient were assessed as not related to study drug.

A grade 3 (10.0–<20.0 × ULN) elevation of creatine kinase occurred in a 17-year-old participant on Day 8. The elevation was isolated and asymptomatic and was associated with weekly physical therapy.

3.4.2 | 6–11 years old

The most common adverse events were vomiting (16%), headache (15%), and cough (15%). One patient had a grade 2 serious adverse event of constipation that was assessed as not related to study drug. Two patients discontinued treatment because of adverse events. One patient, in the 6–11-year-old group, had a grade 3 serious adverse event of auditory hallucinations on Day 37 of treatment that was assessed as related to study drug. Study drug was discontinued on Day 39, and the event resolved on posttreatment Day 10. The patient achieved SVR12. A second patient in the 6–11-year-old group had a grade 1 adverse event of spitting up study drug on Day 1, and, following an interruption in dosing, treatment was discontinued treatment on Day 7.

3.4.3 | 3–5 years old

The most common adverse events were vomiting (27%), cough (15%), and pyrexia (15%). One participant had decreased appetite (grade 1), irritability (grade 2), psychomotor hyperactivity (grade 1), and spitting up study drug (grade 1), which led to treatment discontinuation on Day 20.

3.5 | Growth and development

No clinically significant effects of study treatment on development or growth as assessed by changes from baseline through posttreatment Week 24 in Tanner pubertal stages; height, weight, or BMI percentiles; and radiographic bone age were observed in any of the three age groups.

3.6 | PKs

Sofosbuvir–velpatasvir 400/100 mg (ages 12–17 years), 200/50 mg (ages 6–11 years and 3–5 ≥ 17 kg), and 150/37.5 (≤5 years and <17 kg) resulted in exposures of sofosbuvir, GS-331007, and velpatasvir comparable to

TABLE 3 Adverse events and laboratory abnormalities.

	Sofosbuvir–velpatasvir 12 weeks		
	3–5 years (*n* = 41)	6–11 years (*n* = 73)	12–17 years (*n* = 102)
No. (%) of patients with any adverse event	32 (78)	59 (81)	77 (76)
No. of grade 3 or 4 adverse events	0	1 (1)	2 (2)
No. (%) of patients with a serious adverse event	0	2 (3)	2 (2)
No. (%) of patients with adverse events leading to discontinuation	1 (2)	2 (3)	0
Adverse events leading to discontinuation, *n* (%)			
Spitting up study drug	1 (2)	1 (1)	-
Decreased appetite	1 (2)	-	-
Hallucination, auditory	-	1 (1)	-
Irritability	1 (2)	-	-
Psychomotor hyperactivity	1 (2)	-	-
Adverse events in ≥10% patients in ≥1 age group, *n* (%)			
Headache	2 (5)	11 (15)	30 (29)
Fatigue	5 (12)	9 (12)	22 (22)
Vomiting	11 (27)	12 (16)	9 (9)
Cough	6 (15)	11 (15)	10 (10)
Pyrexia	6 (15)	8 (11)	10 (10)
Nausea	-	5 (7)	17 (17)
Diarrhea	5 (12)	6 (8)	7 (7)
Abdominal pain	2 (5)	9 (12)	6 (6)
Nasal congestion	5 (12)	4 (6)	6 (6)
Nasopharyngitis	1 (2)	7 (10)	6 (6)
Abdominal pain upper	2 (5)	3 (4)	10 (10)
Rhinorrhea	6 (15)	4 (6)	4 (4)
Rash	1 (2)	7 (10)	-
Upper respiratory tract infection	2 (5)	7 (10)	3 (3)
Spitting up study drug	4 (10)	2 (3)	-
Serious adverse events, *n* (%)			
Suicidal ideation	-	-	2 (2)
Suicide attempt	-	-	1 (1)
Bipolar disorder	-	-	1 (1)
Constipation	-	1 (1)	-
Hallucination, auditory	-	1 (1)	-
Laboratory abnormalities, *n* (%)			
Neutrophils, grade 3 (500–<750/mm^3)	-	-	2 (2)
Alkaline phosphatase, grade 3 (>5.00–10.00 × ULN)	1 (3)	-	-
Creatine kinase, grade 3 (10.0–<20.0 × ULN)	-	-	1 (1)
Hemoglobin, grade 3 (7.0–<9.0 g/dL)	-	-	1 (1)
Hyperglycemia, grade 3 (>250–500 mg/dL)	-	-	1 (1)

Abbreviation: ULN, upper limit of normal.

historical data collected in the adult Phase 2/3 sofosbuvir–velpatasvir clinical studies. Using intensive PK data from a subset of participants (data not shown), the 90% CIs of geometric mean ratios of each parameter were comparable for each age-based cohort. The subsequent population PK analysis using combined intensive and sparse population samples from all participants also demonstrated comparable exposure (Table 4). Comparability of concentrations in the three pediatric age groups relative to adults is shown in Figure 2.

3.6.1 | 12–17 years old

The 90% CIs for the geometric mean ratios of sofosbuvir, GS-331007, and velpatasvir were within the predefined equivalence boundary of 70%–200% for each parameter. Although sofosbuvir AUC_{tau} and C_{max} and velpatasvir C_{max} were higher than observed in the adult population, these differences were not considered clinically significant.

3.6.2 | 6–11 years old

The 90% CIs for the geometric mean ratios of sofosbuvir, GS-331007, and velpatasvir were within the predefined equivalence boundary of 70%–200% for each parameter.

3.6.3 | 3–5 years old

The 90% CIs for the geometric mean ratios of velpatasvir AUC_{tau} and GS-331007 AUC_{tau} and C_{max} were within the predefined equivalence boundary of 70%–200%. The upper boundaries of velpatasvir C_{max} and sofosbuvir AUC_{tau} and C_{max} were higher than observed in the adult population, although these were not considered clinically significant.

3.7 | Acceptability and palatability

3.7.1 | 12–17 years old

Among the 12–17-year-old patients, 90% (92/102) were able to swallow the 400/100-mg placebo tablet, and 100% (10/10) were able to swallow the 200/50 mg tablet. On Day 1, 95% (97/102) of participants who responded either did not taste the study drug or reported the taste as palatable (score marked ≥40), and 97% (97/100) reported the ease of taking study drug as acceptable (score marked ≥40). At Week 12 or

TABLE 4 Sofosbuvir, GS-331007, and velpatasvir exposures in HCV-infected pediatric subjects 3 years of age and older and geometric mean ratios compared to adults.

Age group	Dose	Population PK parameter[a]	Mean (% CV)			% Geometric mean ratio (90% CI)		
			Sofosbuvir	GS-331007	Velpatasvir	Sofosbuvir	GS-331007	Velpatasvir
Adults ($n = 1428$)[b]	400/100 mg	C_{max}	566 (31)	868 (28)	259 (54)	—	—	—
		AUC_{tau}	1260 (37)	14,000 (28)	2970 (50)	—	—	—
		C_{trough}	NA	NA	41.5 (65)	—	—	—
12–<18 ($n = 102$)[c]	400/100 mg	C_{max}	1360 (92)	1190 (25)	351 (40)	176 (164;190)	138 (132;144)	142 (130;156)
		AUC_{tau}	2640 (83)	13,600 (27)	3950 (44)	172 (161;185)	98 (93;102)	135 (124;147)
		C_{trough}	NA	NA	38.2 (61)	NA	NA	94 (85;104)
6–<12 ($n = 70$)[d]	200/50 mg	C_{max}	1160 (81)	987 (30)	312 (37)	163 (151;175)	114 (108;120)	128 (115;143)
		AUC_{tau}	2130 (67)	10,400 (28)	3270 (38)	148 (137;160)	75 (71;79)	114 (104;126)
		C_{trough}	NA	NA	30.0 (46)	NA	NA	75 (67;84)
3–<6 ($n = 36$)[e]	200/50 or 150/37.5 mg	C_{max}	1410 (69)	1130 (29)	494 (46)	200 (181;220)	131 (122;142)	192 (165;224)
		AUC_{tau}	2540 (57)	12,500 (49)	4480 (49)	183 (165;203)	87 (81;94)	150 (131;172)
		C_{trough}	NA	NA	54.6 (76)	NA	NA	117 (100;137)

Abbreviations: CI, confidence interval; CV, coefficient of variation; PK, pharmacokinetic.

[a]Concentrations in ng/mL; AUCs in ng·h/mL. Parameters rounded to three significant figures. Population PK modeling used combined data from serial and sparse PK samples and using mixed-effect techniques.

[b]Sofosbuvir $n = 982$; velpatasvir $n = 1425$.

[c]Sofosbuvir $n = 91$.

[d]Sofosbuvir $n = 69$; One patient, although included in the population PK analysis, was excluded from the summary of PK exposures due to administration of oral granules.

[e]Sofosbuvir $n = 34$.

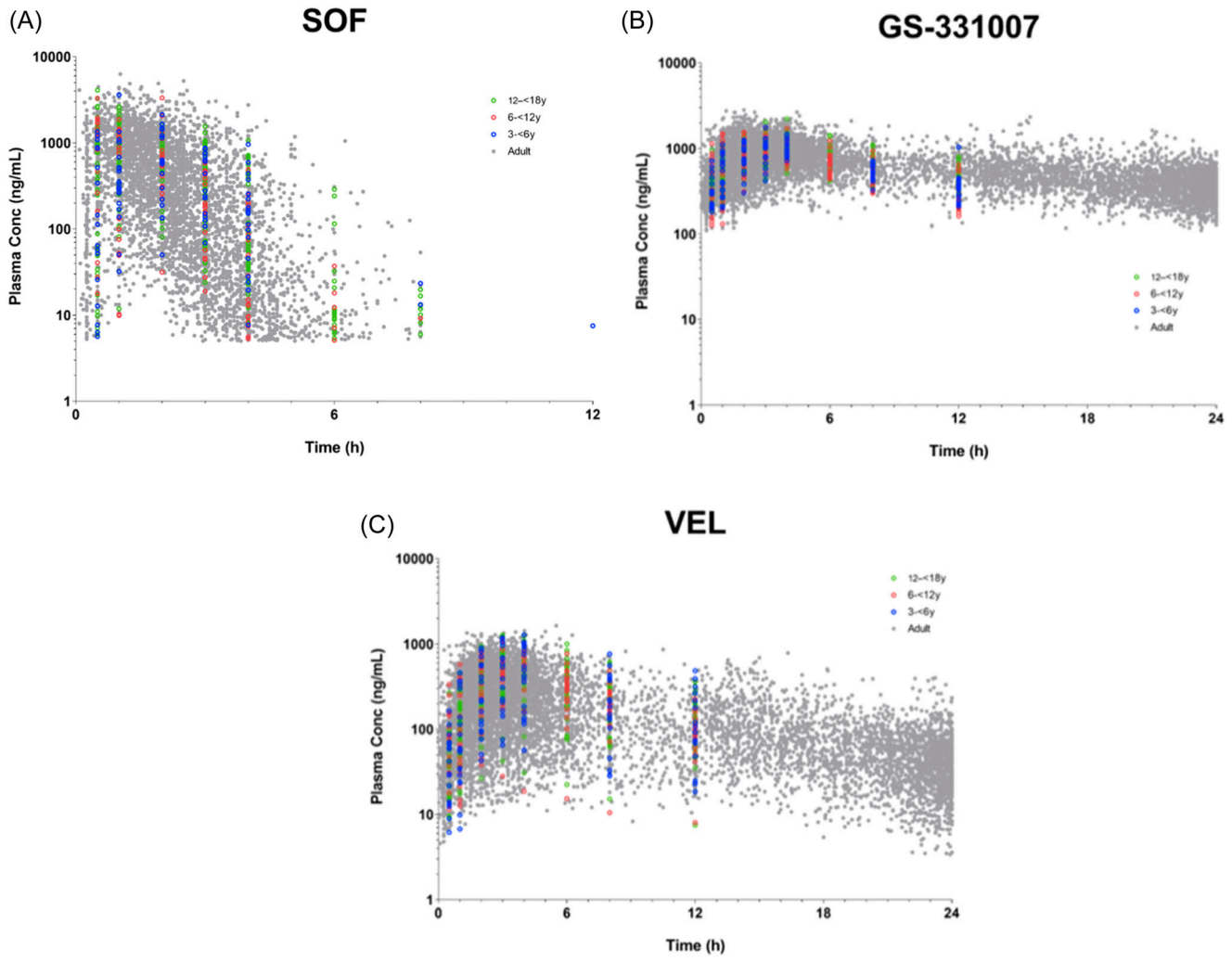

FIGURE 2 Plasma concentrations of (A) sofosbuvir (SOF), (B) GS-331007, and (C) velpatasvir (VEL) in hepatitis C virus (HCV)-infected pediatric subjects 3 years of age and older compared to adults. Plasma concentrations of SOF, GS-331007, and VEL in lead-in phase PK samples per pediatric age group, plotted against time since last dose of SOF/VEL. Gray dots represent all concentrations observed in the adult studies with SOF/VEL.

early termination, 90% (91/101) of participants either did not taste the study drug or reported the taste as palatable, and 95% (95/100) reported the ease of taking study drug as acceptable.

3.7.2 | 6–11 years old

Of participants aged 6–11 years, 99% (72/73) were able to swallow the 200/50-mg placebo tablet. On Day 1, 83% (59/71) participants either did not taste the study drug or reported the taste as palatable (score marked ≥40), and 89% (63/71) reported the ease of taking study drug as acceptable (score marked ≥40). At Week 12 or early termination, 84% (59/70) of participants either did not taste the study drug or reported the taste as palatable, and 100% (70/70) reported the ease of taking study drug and as acceptable.

3.7.3 | 3–5 years old

A total of 39 patients aged 3–5 years who were administered 200/50 mg or 150/37.5 mg oral granules completed the acceptability questionnaire on Day 1; 69% (27/39) reported they either did not taste the study drug or rated the taste as palatable (score marked ≥40), and 59% (23/39) rated the ease of taking study drug as acceptable. At Week 12, 71% (22/31) either did not taste the study drug or found the taste to be palatable, and 90% (28/31) rated the ease of taking study drug as acceptable. At Week 12, among parents/caregivers who completed questionnaires, 66% (23/35)

reported the participant found the study drug palatable, and 91% (31/34) reported the participant found it acceptable.

4 | DISCUSSION

In this study of sofosbuvir–velpatasvir, 92% of children and adolescents aged 3–17 years achieved SVR12, with only two patients experiencing virologic failure. The efficacy rates observed in this pediatric trial are comparable to the 95%–99% SVR12 rates seen in the adult Phase 3 trials of sofosbuvir–velpatasvir.[21,22] Treatment was safe and well tolerated, with only four serious adverse events.

For children aged 6 years and above, a smaller and lower dose tablet was developed. An oral granule formulation was developed for participants aged 3–5 years as well as older children unable to swallow a tablet. Overall, sofosbuvir–velpatasvir was well tolerated in both tablet and granule formulations. However, five of seven discontinuations among patients aged 3–5 years were in children who had difficulty ingesting study drug and/or refused to take study drug. This age group had the lowest rate of SVR, 83%, likely because of the disproportionate number of treatment discontinuations ($n = 7$), which was more than the treatment discontinuations in other age groups combined ($n = 5$).

One participant experienced virologic relapse. This participant had achieved viral suppression on treatment but discontinued at Week 4 because of pregnancy, and subsequently viral load increased. The relapse was not surprising, given that the shortest indicated duration of sofosbuvir–velpatasvir is 8 weeks, and nonadherence to therapy can result in a lack of virologic suppression or relapse.

Two girls in the 12–17-year-old cohort with complex medical and social histories had serious adverse events of suicidal ideation, and one also had a suicide attempt. As judged by the investigators, these events were considered not related to study treatment. Suicidal ideation is prevalent in adolescents, with 20%–24% reporting having had suicidal ideation,[24] and HCV infection is associated with increased risks of anxiety, insomnia, and depression in children (hazard ratio, 3.70 [95% CI, 3.40, 4.03]).[25]

Limitations of this study include a lack of patients with known cirrhosis, although this is consistent with a milder course of disease in HCV-infected children versus adults. Some HCV genotypes had low representation within age subgroups, and no patients had HCV genotype five infection.

Sofosbuvir–velpatasvir 400/100 mg (ages 12–17 years), 200/50 mg (ages 6–11 years and 3–5 ≥ 17 kg), and 150/37.5 (≤5 years and <17 kg) resulted in exposures of sofosbuvir, GS-331007, and velpatasvir comparable to those from historical data collected in the adult Phase 2/3 sofosbuvir–velpatasvir clinical studies. Although sofosbuvir mean C_{max} and AUC_{tau} were numerically higher in the pediatric populations relative to adults, the 90% CIs were within 70–200 except for sofosbuvir in children 3–5 years. Based on the totality of the data, including the observed safety profile in this study as well as in other studies evaluating sofosbuvir, ledipasvir–sofosbuvir, and sofosbuvir–velpatasvir–voxilaprevir, these differences are not considered clinically significant. Sofosbuvir–velpatasvir is approved in the United States and Europe for use in children from 3 years of age. The approved dose regimens are based on weight, using the same doses administered in this study, such that those weighing <17 kg receive 150/37.5 mg, 17–<30 kg receive 200/50 mg, and ≥30 kg receive the adult dose of 400/100 mg/day.

In summary, sofosbuvir–velpatasvir represents an important treatment option for pediatric patients with chronic HCV infection, regardless of HCV genotype or liver disease severity.

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CONFLICT OF INTEREST STATEMENT

Maureen M. Jonas has received research grants from Gilead, AbbVie, and Merck; has served as a consultant (DSMB) for Gilead; and has served as a consultant for Mirum and Vertex. Rene Romero has received research grants from Gilead. Philip Rosenthal has received research grants from Gilead, AbbVie, Merck, Albireo, Mirum, Arrowhead, and Travere; has served as a consultant for Gilead, AbbVie, Albireo, Mirum, Travere, Encoded, Biomarin, Vertex, Dicerna, and Audentes. Chuan-Hao Lin has received research grants from Gilead and Mirum. Gabriella Verucchi has received research grants from Gilead and AbbVie; has served as a consultant for Gilead, AbbVie, and Merck. Jessica Wen has received research grants from Gilead, AbbVie, and Alexion; and has served as a consultant for Gilead. William F. Balistreri has received research grants from Gilead, AbbVie, and Merck; has served as a consultant for Alexion, Albireo, Digestive Care, and Otsuka. Daniel H. Leung has received research grants from AbbVie, Gilead, and Mirum; has served as a consultant for Merck and Gilead. Michael R. Narkewicz has served as a consultant for Vertex; has received research funding from Gilead and AbbVie. Regino P. Gonzalez-Peralta has received research grants from Gilead, Merck, AbbVie, and Mirum; has served on advisory boards for Alexion and Murium; has served on drug monitoring boards for Orphalan and Albireo; and has served on speakers bureau for Mirum and Albireo.

Alessandra Mangia has received research grants from Gilead and Merck has served as a consultant for Gilead, Merck, and Intercept. Wikrom Karnsakul has received research grants from Gilead and Albireo. Jiang Shao, Jan de Jong, Bandita Parhy, Anu Osinusi, and Kathryn Kersey are employees of and own stock in Gilead Sciences. Karen F. Murray has received research grants from Gilead; has served as a consultant for Albireo and Gilead. Etienne M. Sokal is the chairman of Promethera Biosciences; has served as a consultant for Novartis. Kathleen B. Schwarz has received research grants from Gilead, has served as a consultant for Mirum, UptoDate, and Gilead. The remaining authors declare no conflict of interest.

DATA AVAILABILITY 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 nonconflict 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 can be found online in the Supporting Information section at the end of this article.

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