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Authors

Rosenthal, Philip
Schwarz, Kathleen B
Gonzalez-Peralta, Regino P
[et al.](#)

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Sofosbuvir and Ribavirin Therapy for Children Aged 3 to <12 Years With Hepatitis C Virus Genotype 2 or 3 Infection

Philip Rosenthal,¹ Kathleen B. Schwarz,² Regino P. Gonzalez-Peralta,³ Chuan-Hao Lin,⁴ Deidre A. Kelly,⁵ Scott Nightingale,⁶ William F. Balistreri,⁷ Sanjay Bansal,⁸ Maureen M. Jonas,⁹ Benedetta Massetto,¹⁰ Diana M. Brainard,¹⁰ Chia-Hsiang Hsueh,¹⁰ Jiang Shao,¹⁰ Bandita Parhy,¹⁰ Suzanne Davison,¹¹ Cornelia Feiterna-Sperling,¹² Lynette A. Gillis,¹³ Giuseppe Indolfi,¹⁴ Etienne M. Sokal ,¹⁵ Karen F. Murray,¹⁶ and Stefan Wirth¹⁷

Currently, the only approved hepatitis C virus (HCV) treatment for children aged <12 years is pegylated interferon plus ribavirin. In an open-label study, we evaluated the safety and efficacy of sofosbuvir plus ribavirin for 12 weeks in children aged 3 to <12 years chronically infected with genotype 2 or for 24 weeks in patients with genotype 3. Patients aged 3 to <6 years weighing <17 kg received sofosbuvir 150 mg, and patients aged 3 to <6 years weighing \geq 17 kg and all patients aged 6 to <12 years received sofosbuvir 200 mg once daily. Intensive pharmacokinetic sampling conducted in each age group confirmed the appropriateness of sofosbuvir doses. For all patients, ribavirin dosing was determined by baseline weight (up to 1,400 mg/day, two divided doses). The primary efficacy endpoint was sustained virologic response 12 weeks after therapy (SVR12). Fifty-four patients were enrolled (41 aged 6 to <12 years and 13 aged 3 to <6 years). Most were treatment naïve (98%) and infected perinatally (94%). All but one patient achieved SVR12 (53/54, 98%; 95% confidence interval, 90%-100%). The patient who did not achieve SVR12 was a 4-year-old who discontinued treatment after 3 days because of “abnormal drug taste.” The most commonly reported adverse events in patients aged 6 to <12 years were vomiting (32%) and headache (29%), and those in patients aged 3 to <6 years were vomiting (46%) and diarrhea (39%). One 3-year-old patient had a serious adverse event of accidental ribavirin overdose requiring hospitalization for monitoring; this patient completed treatment and achieved SVR12. **Conclusion:** Sofosbuvir plus ribavirin was well tolerated and highly effective in children aged 3 to <12 years with chronic HCV genotype 2 or 3 infection. (HEPATOLOGY 2020;71:31-43).

Worldwide, it is estimated that 2.1 to 5 million children under 15 years of age have chronic hepatitis C virus (HCV) infection.^(1,2) In children, chronic HCV infection is often asymptomatic or with mild, nonspecific symptoms. However, progression to significant fibrosis can occur,⁽³⁾ and cases of cirrhosis,⁽⁴⁻⁶⁾ hepatocellular carcinoma,^(7,8) and end-stage liver disease requiring liver

Abbreviations: AUC, area under the curve; BMI, body mass index; CI, confidence interval; GT, genotype; HCV, hepatitis C virus; INR, international normalized ratio of prothrombin time; NI, nucleotide inhibitor; NS5B, nonstructural protein 5B; PK, pharmacokinetic; RAS, resistance-associated substitution; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response.

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Dr. Regino P. Gonzalez-Peralta is currently affiliated with Advent Health for Children, Orlando, Florida, USA.

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transplantation^(9,10) have been reported. In addition, quality of life and cognitive function may be compromised in children with HCV.⁽¹⁰⁻¹²⁾

In children, the primary route of HCV infection is through perinatal transmission, with an approximate transmission rate from an HCV-infected mother of 5%.⁽¹³⁾ In the presence of inadequately controlled human immunodeficiency virus (HIV) coinfection or high HCV RNA viral loads (>6 log IU/mL) in the mother, transmission rates are as high as 14%.⁽¹⁴⁾ The increasing intravenous opioid use by women of child-bearing age in some countries such as the United States raises concern about a possible increase in the number of newborns infected with HCV.⁽¹⁵⁾ Furthermore, the prevalence rate may be underestimated as a result of the lack of universal screening in pregnant women or in newborns.⁽¹⁶⁾

In 2017, sofosbuvir and ledipasvir-sofosbuvir were approved to treat HCV in adolescents aged 12 to <18 years and, in certain countries, in younger pediatric

patients weighing at least 35 kg.⁽¹⁷⁻²⁰⁾ However, for children younger than 12 years of age (or in certain countries <35 kg), the only approved treatment remains pegylated interferon plus ribavirin administered for 24 weeks for genotype (GT)2 and GT3 or 48 weeks for GT1. Treatment with pegylated interferon plus ribavirin is undesirable because of safety concerns, poor tolerability, and its parenteral route of administration.⁽²¹⁾ Concern for the effects of pegylated interferon and ribavirin on growth and development in this age group also limits their use.⁽²²⁾ As such, current international guidelines recommend that in patients younger than 12 years of age, treatment should be deferred until direct-acting antivirals are available.^(2,23-25)

We evaluated the safety and efficacy of sofosbuvir, a potent oral HCV nonstructural protein 5B (NS5B) polymerase inhibitor, in combination with weight-based ribavirin, in children aged 3 to <6 years and 6 to <12 years with HCV GT2 or GT3 chronic infection.

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ARTICLE INFORMATION:

From the ¹University of California San Francisco, San Francisco, CA; ²Johns Hopkins University School of Medicine, Baltimore, MD; ³University of Florida College of Medicine and Shands Children's Hospital, Gainesville, FL; ⁴Children's Hospital Los Angeles, Los Angeles, CA; ⁵Birmingham Children's Hospital, Birmingham, United Kingdom; ⁶University of Newcastle and John Hunter Children's Hospital, Australia; ⁷Cincinnati Children's Hospital Medical Center, Cincinnati, OH; ⁸Kings College Hospital, London, United Kingdom; ⁹Boston Children's Hospital, Boston, MA; ¹⁰Gilead Sciences, Inc., Foster City, CA; ¹¹Leeds Children's Hospital, Leeds, United Kingdom; ¹²Charité - Universitaetsmedizin Berlin, Berlin, Germany; ¹³Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN; ¹⁴Meyer Children's University Hospital, Florence, Italy; ¹⁵Cliniques Universitaires St. Luc, Université Catholique de Louvain, Brussels, Belgium; ¹⁶University of Washington School of Medicine and Seattle Children's Hospital, Seattle, WA; ¹⁷Helios Medical Center, Witten/Herdecke University, Wuppertal, Germany.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Philip Rosenthal, M.D.
University of California, San Francisco
550 16th Street Mailcode 0136

San Francisco, CA, 94143
E-mail: prosenrh@ucsf.edu
Tel.: +1-415-476-7114

Patients and Methods

PATIENTS

Eligible patients were 3 to <12 years of age and had chronic infection with HCV G2 or G3, with plasma HCV RNA levels $\geq 1,000$ IU/mL at screening. Patients could be either HCV treatment naïve or experienced. Patients with or without cirrhosis were eligible; liver biopsy was not required for study entry. Patients were required to have an absolute neutrophil count $\geq 1,500/\text{mm}^3$ and a hemoglobin level of ≥ 11 g/dL for females and ≥ 12 g/dL for males. Patients were excluded from participating in the study if they had any of the following conditions: decompensated liver disease; chronic liver disease of a non-HCV etiology; alfa-fetoprotein level >50 ng/mL; serum creatinine >1.5 mg/dL; estimated glomerular filtration rate <90 mL/minute/ 1.73 m² as calculated by the Schwartz Formula; evidence of hepatocellular carcinoma or other malignancy; infection with hepatitis A, hepatitis B, or HIV; significant cardiovascular, pulmonary, or neurological disease; evidence of a gastrointestinal malabsorption syndrome that could interfere with absorption of orally administered medications; history of solid organ or bone marrow transplantation; chronic daily nonsteroidal anti-inflammatory drug therapy; systemic corticosteroid use for ≥ 5 days (pulmonary/nasal administration was permitted); psychiatric hospitalization, suicide attempt, or disability resulting from psychiatric illness. Parents or legal guardians provided written informed consent before patients undertook any study-related procedures. Patients who could read and write provided written assent.

STUDY DESIGN

This was a phase 2, multicenter, open-label study. Based on the approved indication for sofosbuvir in adult patients, treatment was administered for 12 weeks in patients with HCV GT2 and 24 weeks in those with HCV GT3. Sofosbuvir was administered once daily. Patients aged 6 to <12 years received 200 mg sofosbuvir as either two 100-mg tablets or four 50-mg capsules containing granules, as determined by a swallowability assessment completed at screening or treatment day 1. Patients aged 3 to <6

years weighing ≥ 17 kg received sofosbuvir 200 mg in four 50-mg capsules containing granules, and those weighing <17 kg received sofosbuvir 150 mg in three 50-mg capsules containing granules. Tablets were administered with or without food. Granules were to be removed from the capsules and were administered orally with or without food. If taken with food, the granules were to be sprinkled on a spoonful of nonacidic soft food at room temperature or cooler, such as pudding or ice cream, and then swallowed without chewing. If taken without food, the granules were to be taken first and then washed down with liquid, and not mixed into the liquid. These requirements were meant to preserve the taste-mask coating over the bitter taste of sofosbuvir during administration. Ribavirin dosing was twice daily, based on weight (Table 1), and was to be taken with food.

At least 10 patients 6 to <12 years of age underwent an intensive pharmacokinetic (PK) evaluation (PK lead-in phase) on day 7 of dosing in order to confirm the appropriateness of the sofosbuvir dose selected (200 mg). Based on the intensive PK data in the patients aged 6 to <12 years, the sofosbuvir doses tested in the younger patients aged 3 to <6 years were selected (200 mg ≥ 17 kg and 150 mg for <17 kg). Similarly, at least 10 patients aged 3 to <6 years were to be enrolled into a PK lead-in phase, with intensive PK evaluation on day 7. Patients of both age groups enrolled in the PK lead-in phase had to be naïve to HCV treatment and have no documented cirrhosis. In

TABLE 1. Ribavirin Dosing and Administration

Body Weight (kg)	Ribavirin Daily Dose	No. of Capsules*
<47	15 mg/kg/day	Oral solution. Divided dose in morning and evening
47-49	600 mg/day	1 \times 200-mg capsules AM 2 \times 200-mg capsules PM
50-65	800 mg/day	2 \times 200-mg capsules AM 2 \times 200-mg capsules PM
66-80	1,000 mg/day	2 \times 200-mg capsules AM 3 \times 200-mg capsules PM
81-105	1,200 mg/day	3 \times 200-mg capsules AM 3 \times 200-mg capsules PM
>105	1,400 mg/day	3 \times 200-mg capsules AM 4 \times 200-mg capsules PM

*For patients of any weight who were unable or unwilling to take ribavirin capsules, oral solution could be used at 15 mg/kg/day divided morning and evening.

addition, patients in the 6 to <12-year-old group were to weigh ≥ 17 kg and <45 kg, whereas there was no weight limit for patients in the 3 to <6-year-old group. Patients enrolled in the PK lead-in phases continued treatment without interruption, while additional patients of each age group were enrolled on confirmation that the selected doses were appropriate. There were no weight limits for the additional patients of either age group enrolled in the study.

Study visits occurred at screening, treatment day 1, and weeks 1, 2, 4, 8, 12, (and as applicable) 16, 20, and 24. All patients were to complete follow-up visits at posttreatment weeks 4, 12, and 24. Instead of the week 1 study visit, patients in the pharmacokinetic lead-in phase attended two study visits of day 3 and day 7.

The study protocol was approved by the review board or ethics committee of each institution before study initiation. The study (ClinicalTrials.gov Identifier: NCT02175758; EudraCT Number: 2014-002283-32) was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki.

ASSESSMENTS

Efficacy

Screening assessments included measurement of the serum HCV RNA level, and the HCV genotype and subtype. HCV RNA levels were quantified by using the Ampliprep/COBAS TaqMan HCV Test, v2.0 (Roche Molecular Systems, Inc., Branchburg, NJ), which has a lower limit of quantification (LLOQ) of 15 IU/mL. HCV genotype and subtype were determined using the Siemens VERSANT HCV Genotype INNO-LiPA2.0 Assay. Plasma HCV RNA levels were evaluated on treatment day 1; at treatment weeks 1, 2, 4, 8, and 12 for all patients and at weeks 16, 20, and 24 for patients receiving 24 weeks of treatment; and at posttreatment weeks 4, 12, and 24.

Resistance

Plasma samples for viral sequencing were collected at all visits during treatment and follow-up, following the same schedule as for HCV RNA evaluation. Sequencing of the HCV NS5B regions

was attempted for all enrolled patients at baseline and with virologic failure, if applicable. The HCV NS5B coding region was amplified by DDL Diagnostic Laboratory (Rijswijk, the Netherlands) using standard reverse-transcription polymerase chain reaction technology. Following amplification, polymerase chain reaction products were deep sequenced, and resistance-associated substitutions (RASs) that were present in more than 15% of the sequence reads were reported. NS5B nucleoside inhibitor RASs were defined as follows: S96T, N142T, L159F, E237G, S282any, M/F289L/I, L320F/I/V, and V321A/I.

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. Concomitant medications were reported at the follow-up week 4 visit, and clinical laboratory tests were done at the follow-up weeks 4 and 12 visits.

Swallowability and Palatability

For patients aged 6 to <12 years, swallowability of the tablet formulation was assessed at screening or day 1 using a placebo-to-match tablet. Any patient unable to swallow the tablet received the granule formulation. For any patients aged 6 to <12 years dosed with granules and all patients aged 3 to <6 years receiving the granule formulation, palatability was assessed on day 1 after the first dose of study drug. Patients reported whether they were able to taste the formulation (yes or no).

Growth and Development

All patients underwent a Tanner pubertal stage assessment at baseline and follow-up week 12 visits.^(26,27) Z scores were calculated for height, weight, and body mass index (BMI) assessed at baseline and at follow-up week 12.

Pharmacokinetics

For the first patients (at least 10) in each age group, an intensive PK lead-in evaluation was performed to confirm the appropriateness of the sofosbuvir doses selected for each age group. At the day 7 visit, serial blood samples were collected to determine the pharmacokinetics of sofosbuvir and its primary metabolite, GS-331007. Blood samples were collected at time 0 (≤ 30 minutes before dosing), after which patients were provided a standardized meal. Within 5 minutes after consuming the meal, patients were dosed with study drug. For patients aged 6 to <12 years, blood samples were collected at 0.5, 1, 2, 3, 4, 8, and 12 hours after dosing; food intake for this age group was restricted until after the collection of the 4-hour postdose sample. For patients aged 3 to <6 years, blood samples were collected at 2, 4, 8, and 12 hours after dosing with no food intake restrictions. For the PK analysis, the predose (0 minute) concentration results also served as 24-hour postdose concentrations.

ENDPOINTS

The primary efficacy endpoint was the percentage of patients who achieved sustained virologic response 12 weeks after discontinuing study drugs (SVR12), defined as having HCV RNA $< \text{LLOQ}$ (15 IU/mL). The primary safety endpoint was any adverse event leading to permanent discontinuation of study drug(s).

STATISTICAL ANALYSES

Efficacy, safety, and pharmacokinetics were assessed in all patients who received at least one dose of study drug. The SVR12 rate was calculated with a 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method. Missing SVR values were imputed as a success if bracketed by values that were termed successes. Clinical and laboratory adverse events were summarized using the Medical Dictionary for Regulatory Activities, version 20.1. Z scores were calculated for height and weight changes over time. An age- and sex-specific z score was derived for each weight, height, and BMI measurement according to the downloadable SAS program available on the Centers for Disease Control and Prevention (CDC) web site using the year 2000 growth charts. CDC methods and the SAS program were applied to calculate the z score.^(28,29)

The pharmacokinetic parameters of study drug were estimated by noncompartmental analysis using WinNonlin V7 (Certara USA, Inc., Princeton, NJ). Results were summarized descriptively. Appropriateness of the dose was confirmed by comparing GS-331007 area under the curve (AUC_{tau}) from each age group with the integrated adult data from phase 2 and 3 clinical studies. The 90% CIs were constructed for the ratio of geometric means of pharmacokinetic parameters mentioned above. The equivalence boundary was set as 50% to 200% of the adult data. Exploratory analyses using the same approach were conducted for GS-331007 C_{max} , sofosbuvir AUC_{tau} , and sofosbuvir C_{max} .

Results

PATIENT POPULATION

From July 17, 2015, to September 13, 2018, 63 patients were screened, and 54 patients (41 aged 6 to <12 years and 13 aged 3 to <6 years) were enrolled and treated at 28 sites in Australia, Belgium, Germany, Italy, New Zealand, the United Kingdom, and the United States. The 9 patients not enrolled did not meet eligibility criteria.

Among 41 patients aged 6 to <12 years, 13 had GT2 HCV infection and 28 had GT3 HCV infection (Table 2). The median age was 9 (range, 6-11) years, 98% (40/41) were infected through perinatal transmission, and all but one were treatment naïve. The single patient who was treatment experienced was an 8-year-old who had prior partial response to pegylated interferon plus ribavirin. Seventy-three percent of patients were female, and 71% were white. None of the patients had documented cirrhosis. Of the 41 patients who initiated treatment, all completed treatment (Fig. 1).

Among 13 patients aged 3 to <6 years, 5 had GT2 HCV infection and 8 had GT3 HCV infection (Table 2). The median age was 4 (range, 3-5) years, 85% (11/13) were infected through perinatal transmission, and all were treatment naïve. Seventy-seven percent of patients were female, and 69% were white. Eight patients (62%) weighed less than 17 kg at baseline. None of the patients had documented cirrhosis. Of the 13 patients who initiated treatment, 12 completed treatment (Fig. 1). One patient discontinued treatment after 3 days because of "abnormal drug taste."

TABLE 2. Patient Demographics and Baseline Characteristics

Characteristics	3 to <6 Years (n = 13)	6 to <12 Years (n = 41)
Age (years)	4 (3-5)	9 (6-11)
Female sex	10 (77)	30 (73)
Race		
White	9 (69)	29 (71)
Asian	1 (8)	8 (20)
Black	1 (8)	0
Other	2 (15)	4 (10)
Weight (kg)	17 (13, 19)	30 (15, 80)
Weight <17 kg, n (%)	8 (62)	1 (2)
Median weight for age percentile (IQR)	51.9 (35.8)	51.7 (63.8)
Height (cm)	102 (97-113)	131 (109-160)
BMI (kg/m ²)	15 (13-17)	17 (13-32)
Median BMI for age percentile (IQR)	52.1 (28.9)	60.2 (50.1)
HCV genotype		
2	5 (39)	13 (32)
2a/2c	0	4 (10)
2b	4 (31)	7 (17)
No confirmed subtype	1 (8)	2 (5)
3	8 (62)	28 (68)
3a	8 (62)	28 (68)
HCV RNA (log ₁₀ IU/mL)	5.4 (4.4-7.2)	5.8 (2.2-7.8)
HCV RNA ≥800,000 IU/mL	3 (23)	19 (46)
HCV treatment history		
Treatment naïve	13 (100)	40 (98)
Nonresponse to PEG + RBV	0	1 (2)
Cirrhosis		
No	2 (15)	5 (12)
Unknown	11 (85)	36 (88)
ALT (U/L)	25 (11-76)	34 (14-583)
eGFR (mL/min/1.73 m ²)*	151 (99-232)	158 (79-241)
Mode of HCV infection		
Perinatal transmission	11 (85)	40 (98)
Unknown	2 (15)	1 (2)

Note: Data are presented as n (%) or median (range) unless otherwise indicated.

*Estimated using the Schwartz Formula.

Abbreviations: ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; PEG, peginterferon.

VIROLOGIC RESPONSE

Among patients aged 6 to <12 years, all (100%; 95% CI, 91%-100%) achieved SVR12 (13/13 [95% CI, 75%-100%] with GT2 and 28/28 [95% CI,

88%-100%] with GT3; Table 3). Among patients aged 3 to <6 years, 12/13 (92%; 95% CI, 64%-100%) achieved SVR12 (4/5 [80%; 95% CI, 28%-100%] with GT2 and 8/8 [95% CI, 63%-100%] with GT3). No patients had virologic nonresponse or relapse after treatment. The GT2 patient who did not achieve SVR12 was a 4-year-old who discontinued treatment after 3 days because of an adverse event of “abnormal drug taste.”

SAFETY

Overall, treatment was generally safe and well tolerated. In both age groups, all adverse events were mild or moderate in intensity. Among patients aged 6 to <12 years, the most commonly reported adverse events were vomiting (32%) and headache (29%; Table 4). Among the patients aged 3 to <6 years, the most common adverse events were vomiting (46%) and diarrhea (39%). All adverse events of diarrhea lasted ≤5 days and resolved while treatment was ongoing, with the exception of one case that lasted for 2 months, beginning during treatment and resolving during the posttreatment period. All adverse events of vomiting lasted for 1 or 2 days, and the majority resolved without changes to drug dosing, with the exception of 1 patient in the 6 to <12-year-old group and 2 patients in the 3 to <6-year-old group for whom treatment was interrupted for 1 day. Two of these three patients were able to complete treatment. One 4-year-old patient with a medical history of fetal alcohol syndrome had an adverse event of vomiting of both the sofosbuvir granules and ribavirin oral solution on day 1, and study drug was interrupted for 1 day; dosing was again attempted on day 3 when the patient experienced an adverse event of product use issue (reported term, “spitting up dose”) for both sofosbuvir granules and ribavirin oral solution and an adverse event of “product taste abnormal” (reported term, “bad taste”) for sofosbuvir granules that resulted in permanent study drug discontinuation. This is the only patient across the two age groups that did not complete treatment because of an adverse event. According to the investigator, the sofosbuvir granules were administered with applesauce and yogurt on day 1, both of which are acidic and may have broken down the taste-mask coating of the granules.

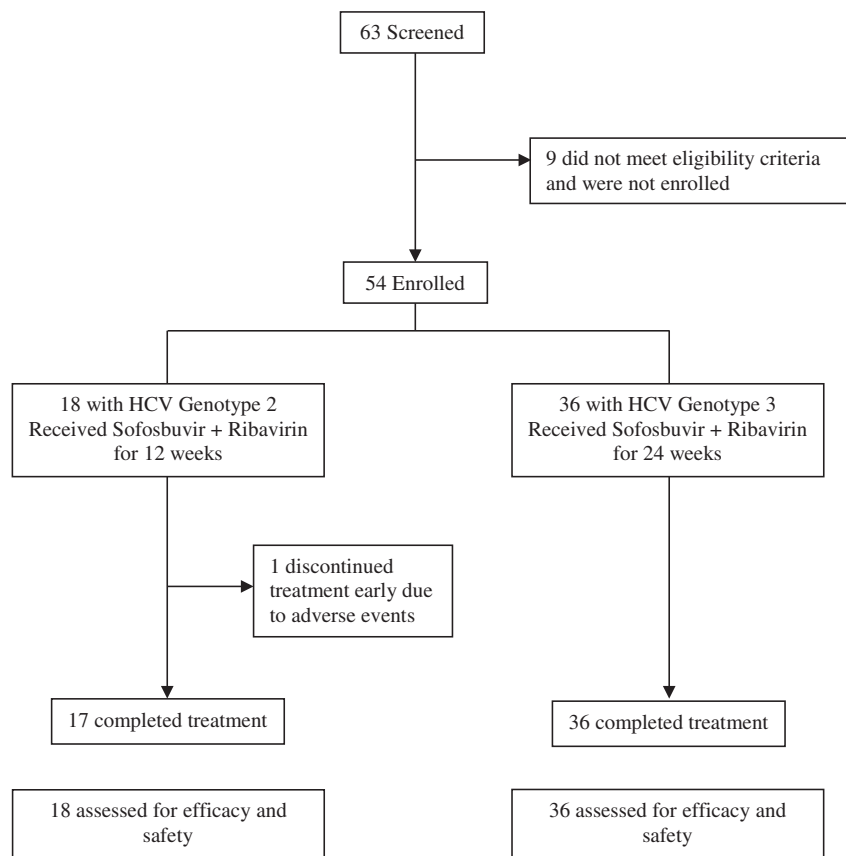


FIG. 1. Patient disposition.

Across both age groups, only 1 patient experienced a serious adverse event. One 3-year-old patient had a serious adverse event of accidental overdose of ribavirin by ingestion on day 83, which required hospitalization for monitoring, and which led to interruption of sofosbuvir and ribavirin from day 83 to day 92. The patient remained asymptomatic. Sofosbuvir was restarted on day 92; ribavirin was initially restarted at a lower dose on day 92, and the full dose was reintroduced on day 102 when the event was considered resolved.

Only 1 patient had a grade 3 laboratory abnormality of increased international normalized ratio of prothrombin time (INR). This occurred in a 10-year-old patient with a baseline level of INR 1.1 who experienced grade 3 increases of INR level at week 2 (3.2), week 4 (3.6), and week 20 (3.0), followed by normalization at the last visit on treatment. The same blood samples were also tested at a local laboratory and the abnormal INR results were not confirmed. According

to the investigator, this patient had normal liver tests and these abnormal INR results were potentially due to testing error. This laboratory abnormality was not reported as an adverse event and was not associated with any adverse events. One 6-year-old female patient had a postbaseline hemoglobin level of 9.9 g/dL at week 4, which increased to 11.4 g/dL by week 8 and remained at a normal level for the remainder of the study, without requiring ribavirin dose interruption or modification. No grade 3 or 4 laboratory abnormalities were observed in the 3 to <6-year-old group.

Ribavirin treatment was interrupted for 1 patient in the 6 to <12-year-old group for 1 day because of vomiting. For 2 patients in the 3 to <6-year-old group, ribavirin was interrupted for one because of vomiting during attempted dosing and for the other because of an accidental overdose of ribavirin as described above. One 3-year-old patient discontinued ribavirin along with sofosbuvir on treatment day

TABLE 3. Treatment Response to Sofosbuvir and Ribavirin

	3 to <6 Years			6 to <12 Years		
	SOF 200 mg or 150 mg + RBV 12 Weeks	SOF 200 mg or 150 mg + RBV 24 Weeks	Total (n = 13)	SOF 200 mg + RBV 12 Weeks	SOF 200 mg + RBV 24 Weeks	Total (n = 41)
	HCV GT2 (n = 5)	HCV GT3 (n = 8)		HCV GT2 (n = 13)	HCV GT3 (n = 28)	
HCV RNA < 15 IU/mL, n/n (%)						
On treatment						
Week 1	2/4 (50)	3/8 (38)	5/12 (42)	6/13 (46)	11/28 (39)	17/41 (41)
Week 2	3/4 (75)	7/8 (88)	10/12 (83)	10/13 (77)	22/28 (79)	32/41 (78)
Week 4	3/4 (75)	8/8 (100)	11/12 (92)	13/13 (100)	27/28 (96)	40/41 (98)
Week 8	4/4 (100)	8/8 (100)	12/12 (100)	13/13 (100)	27/28 (96)	40/41 (98)
Week 12	4/4 (100)	8/8 (100)	12/12 (100)	13/13 (100)	28/28 (100)	41/41 (100)
After treatment						
Week 4	4/5 (80)	8/8 (100)	12/13 (92)	13/13 (100)	28/28 (100)	41/41 (100)
Week 12 (SVR12)	4/5 (80)	8/8 (100)	12/13 (92)	13/13 (100)	28/28 (100)	41/41 (100)
95% CI	28%-100%	63%-100%	64%-100%	75%-100%	88%-100%	91%-100%
Virologic failure, n (%)						
On treatment	0	0	0	0	0	0
Relapse	0	0	0	0	0	0
Early treatment discontinuation, n (%)	1 (20)	0	1 (8)	0	0	0

Abbreviation: NA, not applicable.

3 as described above because of the adverse event of spitting up and “abnormal drug taste.” With the exception of 1 patient with an isolated postbaseline hemoglobin level of 9.9 g/dL described above, no patient experienced clinically significant hemoglobin reductions or changes in lymphocyte, reticulocyte, platelet, or neutrophil counts typically observed in patients treated with ribavirin.

PALATABILITY AND SWALLOWABILITY

Among the 41 patients aged 6 to <12 years, 40 were assessed for swallowability of the 100-mg tablet formulation, whereas 1 patient inadvertently performed the swallowability assessment with a sofosbuvir 400-mg placebo tablet instead of the 100-mg tablet. This patient was able to swallow the 400-mg placebo tablet and was administered sofosbuvir 100-mg tablets. Of the 40 patients assessed with the 100-mg placebo tablet, 34 (85%) were able to swallow it successfully. The remaining 6 patients (15%) were administered sofosbuvir as granules. In addition, 1 patient who was able

to swallow the placebo tablet was instead administered the granule formulation because of an adverse event of “abnormal product taste” reported after administration of the tablet formulation on day 1. Of the 7 patients who were administered oral granules, 3 (43%) were able to taste the granules; all 3 completed treatment.

In patients aged 3 to <6 years, 12 of 13 patients were administered oral granules, and 9 (75%) reported being able to taste the study medication. Among these 9 patients, 8 (89%) completed treatment. One patient performed the swallowability test for the sofosbuvir 100-mg tablet and was administered this formulation in spite of being <6 years of age.

GROWTH AND DEVELOPMENT

As assessed by Tanner pubertal staging, study treatment did not affect pubertal development through 12 weeks of posttreatment follow-up. At baseline, 34 of 41 patients aged 6 to <12 years were at Tanner stage 1 for pubic hair and genitalia or breast development. At posttreatment week 12, all

TABLE 4. Adverse Events and Laboratory Abnormalities

	3 to <6 Years			6 to <12 Years		
	SOF 200 mg or 150 mg + RBV 12 Weeks	SOF 200 mg or 150 mg + RBV 24 Weeks	Total (n = 13)	SOF 200 mg + RBV 12 Weeks	SOF 200 mg + RBV 24 Weeks	Total (n = 41)
	HCV GT2 (n = 5)	HCV GT3 (n = 8)		HCV GT2 (n = 13)	HCV GT3 (n = 28)	
No. (%) of patients with any adverse event	5 (100)	8 (100)	13 (100)	9 (69)	26 (93)	35 (85)
No. of grade 3 or 4 adverse events	0	0	0	0	0	0
No. (%) of patients with a serious adverse event	0	1 (13)	1 (8)	0	0	0
No. (%) of patients with adverse events leading to discontinuation	1 (20)	0	1 (8)	0	0	0
Adverse events leading to discontinuation, n						
Product use issue	1 (20)	0	1 (8)	0	0	0
Product taste abnormal	1 (20)	0	1 (8)	0	0	0
Adverse events in ≥10% of patients of either age group, n (%)						
Vomiting	3 (60)	3 (38)	6 (46)	2 (15)	11 (39)	13 (32)
Headache	0	0	0	4 (31)	8 (29)	12 (29)
Fatigue	1 (20)	1 (13)	2 (15)	3 (23)	5 (18)	8 (20)
Diarrhea	2 (40)	3 (38)	5 (38)	1 (8)	3 (11)	4 (10)
Cough	1 (20)	0	1 (8)	1 (8)	7 (25)	8 (20)
Decreased appetite	0	3 (38)	3 (23)	2 (15)	2 (7)	4 (10)
Nasopharyngitis	0	0	0	1 (8)	4 (14)	5 (12)
Nausea	0	1 (13)	1 (8)	0	4 (14)	4 (10)
Oropharyngeal pain	0	1 (13)	1 (8)	0	4 (14)	4 (10)
Rhinorrhea	0	1 (13)	1 (8)	1 (8)	3 (11)	4 (10)
Pyrexia	1 (20)	0	1 (8)	0	4 (14)	4 (10)
Serious adverse events						
Accidental overdose	0	1 (13)	1 (8)	0	0	0
Laboratory abnormalities						
INR, Grade 3 (>2.0 to 3.0 × ULN)	0	0	0	0	1 (4)	1 (2)
Deaths	0	0	0	0	0	0

Abbreviation: ULN, upper limit of normal.

40 patients with available data had no change or an increase from baseline Tanner staging. For patients aged 3 to <6 years, 11 of 11 with available Tanner staging were at Tanner stage 1 for pubic hair and genitalia or breast development at both baseline and at posttreatment week 12.

Median changes in z scores for height, weight, and BMI were calculated in each age group by treatment from baseline to end of treatment (12 weeks for GT2 and 24 weeks for GT3), and from end of treatment

to posttreatment week 12 (Table 5). For patients aged 6 to <12 years, the median changes from baseline to end of treatment among all measures ranged between -0.07 and -0.02, and from end of treatment to posttreatment week 12 between -0.01 and 0.05. For patients aged 3 to <6 years, the median changes from baseline to end of treatment ranged between -0.41 and -0.01 among all measures, and median changes from end of treatment to posttreatment week 12 ranged between -0.16 and 0.32.

TABLE 5. Median z Score Changes in Height, Weight, and BMI

	3 to <6 Years		6 to <12 Years	
	SOF 200 mg or 150 mg + RBV 12 Weeks	SOF 200 mg or 150 mg + RBV 24 Weeks	SOF 200 mg + RBV 12 Weeks	SOF 200 mg + RBV 24 Weeks
	HCV GT2 (n = 5)	HCV GT3 (n = 8)	HCV GT2 (n = 13)	HCV GT3 (n = 28)
z score change in height				
Baseline to EOT	-0.02 (-0.17 to 0.02)	-0.01 (-0.48 to 0.13)	-0.06 (-0.41 to 0.06)	-0.10 (-0.36 to 0.24)
EOT to PTw12	-0.16 (-0.33 to 0.31)	0.01 (-0.34 to 0.11)	0.02 (-0.21 to 0.33)	0.05 (-0.19 to 0.38)
z score change in weight				
Baseline to EOT	-0.05 (-0.25 to 0.00)	-0.41 (-0.69 to 0.35)	-0.04 (-0.36 to 1.39)	-0.18 (-0.53 to 0.36)
EOT to PTw12	-0.03 (-0.11 to 0.29)	0.09 (-0.21 to 0.22)	0.05 (-0.35 to 0.29)	0.04 (-0.30 to 0.40)
z score change in BMI				
Baseline to EOT	-0.12 (-0.25 to 0.24)	-0.38 (-1.19 to 0.47)	-0.02 (-0.46 to 2.70)	-0.19 (-0.57 to 0.65)
EOT to PTw12	0.32 (-0.40 to 0.49)	0.13 (-0.35 to 0.71)	0.02 (-0.39 to 0.45)	-0.01 (-0.48 to 0.34)

Note: Data are presented as median (range).

Abbreviations: EOT, end of treatment; PTw12, post-treatment week 12.

PHARMACOKINETICS

The 12 patients aged 6 to <12 years and the 11 patients aged 3 to <6 years who underwent intensive PK sampling had similar demographics to the overall study populations. During dosing, 2 patients aged 6 to <12 years were overdosed and 1 aged 3 to <6 years was dosed with a tablet instead of granules; these patients were excluded from the intensive PK analysis. The plasma exposures of sofosbuvir and GS-331007 in the 20 patients from both age groups receiving the age/weight-based doses of 150 mg or 200 mg of sofosbuvir were comparable to those observed in adults receiving 400 mg of sofosbuvir in clinical trials. The 90% CIs for GS-331007 AUC_{tau} in patients from both age groups were within the predefined PK equivalence boundaries of 50% to 200% when compared with adults from the phase 2 and 3 studies (Table 6). These data supported the appropriateness of doses evaluated in the study.

RESISTANCE ANALYSES

Baseline deep sequencing of the NS5B nucleotide inhibitor (NI) region was performed on all 41 patients aged 6 to <12 years and was obtained for 40 of 41 patients. Full-length NS5B amplification was unsuccessful for 1 patient with GT3; a short fragment was obtained for this patient. At baseline, the NS5B NI RAS M289I was detected in 2 of 41 patients, both of whom had GT2b. Both achieved SVR12.

Deep sequencing was performed on all 12 patients aged 3 to <6 years who completed treatment, and sequences were obtained for 11 of 12 patients. NS5B amplification was unsuccessful for 1 patient with GT3a infection because of assay failure. No baseline NS5B NI RASs were detected in any patients.

Discussion

Sofosbuvir plus ribavirin is approved for treatment of chronic HCV infection in adolescents 12 years and older and, in certain countries, in younger patients weighing at least 35 kg; however, pegylated interferon plus ribavirin continues to be the only approved treatment for younger children.⁽¹⁷⁻²⁰⁾ Therefore, the availability of an all-oral, interferon-free, direct-acting antiviral regimen for younger children remains an unmet medical need. To our knowledge, this is largest study of sofosbuvir plus ribavirin in children younger than 12 years of age, and as young as 3 years old. Previously, 24 treatment-naïve patients aged 5 to 12 years who received sofosbuvir plus ribavirin for 24 weeks achieved SVR in a study by Hashmi et al. (data not reported).⁽³⁰⁾

In our study, sofosbuvir plus ribavirin for 12 or 24 weeks was highly effective in treating children 3 to <12 years of age with chronic hepatitis C infection genotypes 2 or 3, with 100% of patients aged 6 to

TABLE 6. Mean (% CV) Sofosbuvir and GS-331007 Exposures

	Adults (n = 1,695)	3 to <6 Years (n = 10)	3 to <6 Years vs. Adults % GMR (90% CI)	6 to <12 Years (n = 10)	6 to <12 years vs. Adults % GMR (90% CI)
Sofosbuvir*					
AUC _{tau} (ng•hour/mL)	1,030 (36.5)	1,690 [†]	NA	960 (45.1)	89.8 (75.0-108)
C _{max} (ng/mL)	511 (32.5)	681 [†]	NA	609 (43.4)	114 (92.4-140)
GS-331007					
AUC _{tau} (ng•hour/mL)	7,120 (30.7)	10,300 (18.1)	150 (127-176)	7,650 (22.5)	110 (93.3-129)
C _{max} (ng/mL)	582 (36.3)	1,320 (20.0)	239 (195-292)	905 (25.6)	161 (132-198)

Note: Data are presented to 3 significant digits.

*n = 838 for sofosbuvir in adults.

[†]n = 1 for sofosbuvir in patients aged 3 to <6 years as 9 patients could not be evaluated by noncompartmental analysis.

Abbreviations: CV, coefficient of variation; GMR, geometric mean ratio; NA, not applicable.

<12 years and 92% of patients aged 3 to <6 years achieving SVR12. No patient experienced virologic failure. The only patient who did not reach SVR12 was 4 years old and discontinued treatment after 3 days because of the adverse event of spitting up and “abnormal drug taste” related to study drug. These results are similar to prior observations in adolescents 12 to <18 years of age in which sofosbuvir plus ribavirin was highly efficacious and well tolerated in this younger population.⁽³¹⁾ Despite the well-described hematologic toxicity of ribavirin, only 1 patient in this study (1/54, 2%) experienced a transient reduction in hemoglobin to below 10 g/dL. This reduction resolved while still on treatment without changing or interrupting ribavirin dosing. In addition, no patient interrupted or modified ribavirin dosing because of an adverse event of low hemoglobin. In the study by Murray et al., 2 pediatric patients aged 6 to 11 years with GT3 infection who received ledipasvir-sofosbuvir plus ribavirin similarly did not experience hematologic laboratory abnormalities despite treatment with ribavirin.⁽³²⁾

Most patients aged 6 to <12 years were able to swallow the 100-mg tablet, and all completed treatment. Additionally, although 3 of 7 patients receiving the oral granule formulation reported being able to taste the medication, all but 1 completed treatment. According to the investigator, this patient was administered the oral granules with acidic foods, which should be avoided in order to preserve the taste-mask coating. This highlights the importance of administering granules with appropriate nonacidic and soft foods in order to ensure successful dosing in young children.

The SVR12 rates in this study for both age groups (patients 6 to <12 years of age, 100% in both GT2 and GT3, and in patients 3 to <6 years of age, 80% in GT2 and 100% in GT3⁽³¹⁾) were comparable to the SVR12 rates observed with sofosbuvir plus ribavirin in adolescents 12 to <18 years of age (100% [13/13] in GT2 and 97% [38/39] in GT3) as well as response rates in treatment-naïve adults (97% for GT2^(33,34) and 94% in GT3⁽³⁴⁾).

In summary, the safety and efficacy of treatment with sofosbuvir plus ribavirin observed in this study supports its use in children. Treating HCV infection in pediatric patients could limit both horizontal and perinatal transmission of the virus, which could be important in reaching the World Health Organization’s goal of eliminating chronic HCV infection as a major public health threat by 2030.⁽³⁵⁾

Limitations of this study include a relatively small sample size, and only patients with GT2 or GT3 were enrolled. The decision to enroll only GT2 or GT3 pediatric patients follows the approved indications for adults, as only patients with GT2 or GT3 are approved for sofosbuvir plus ribavirin treatment. For adult patients with GT1 or GT4, sofosbuvir treatment is administered with ribavirin and peginterferon alfa. Because of the undesirable safety effects of peginterferon, we elected not to evaluate sofosbuvir plus ribavirin and peginterferon in GT1 or GT4 pediatric patients. Additionally, only 1 patient had prior treatment experience and no patients had known cirrhosis; therefore, we were unable to evaluate whether these factors affect response to sofosbuvir and ribavirin in children 3 to <12 years of age. Although the ideal treatment for pediatric patients would not include

ribavirin, sofosbuvir plus ribavirin was well tolerated in this study, with no patient discontinuing ribavirin because of low hemoglobin levels. In addition, although the follow-up period was short, we did not observe an impact on development and growth, which are issues that have previously been reported with the use of pegylated interferon plus ribavirin.⁽²²⁾ Clinical trials with ribavirin-free, pangenotypic regimens such as sofosbuvir-velpatasvir (ClinicalTrials.gov identifier: NCT03022981) and glecaprevir-pibrentasvir (NCT03067129) in the age groups studied here are ongoing.

In conclusion, sofosbuvir and ribavirin was well tolerated and highly effective in treating children aged 3 to <12 years with chronic HCV GT2 or GT3 infection. As such, sofosbuvir in combination with ribavirin would provide an important strategy for treating chronic HCV infection in the pediatric population as well as improving public health.

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