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

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Abbreviations: ALT, alanine aminotransferase; AUC, area under the curve; BMI, body mass index; CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; GMR, geometric mean ratio; HCV, hepatitis C virus; INR, international normalized ratio of prothrombin time; LLOQ, lower limit of quantification; RAS, resistance-associated substitution; RBV, ribavirin; RT-PCR, reverse transcription polymerase chain reaction; SOF, sofosbuvir; SVR, sustained virological response; ULN, upper limit of normal.

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Conflicts of Interest:

Philip Rosenthal has received research support from Gilead, AbbVie, Merck, BMS, Roche, Retrophin, and Albireo, and consults for Gilead, AbbVie, Roche, Dicerna, Intercept, Alexion, Retrophin, Albireo, Audentes, and Mirum. **Kathleen Schwarz** has received grants from Gilead, BMS, and Roche/Genentech, and consults for Gilead and Roche/Genentech. **Regino Peralta-Gonzalez** has served on advisory boards for Genentech-Roche, Shire, Kadmon, and Alexion, and has received grant support from Gilead, AbbVie, and Merck. **Chuan-Hao Lin** has received research grants from Gilead. **William F. Balistreri** has received grants from Gilead, AbbVie, and Merck, and has served on advisory boards for Alexionm Kadmon, Otsuka, and DigestiveCare. **Sanjay Bansal** has served as an investigator in sponsored studies by Gilead and AbbVie. **Maureen M. Jonas** has received grants from Roche, AbbVie, and Gilead, and has served as a consultant for Gilead. The following authors are employees of Gilead Sciences and may hold stock interest in the company: **Benedetta Massetto, Diana M. Brainard, Chia-Hsiang Hsueh, Jiang Shao, and Bandita Parhy**. **Suzanne Davison** has served as a speaker for Gilead and Vertex. **Cornelia Feiterna-Sperling** has served as an investigator in sponsored studies by AbbVie and Gilead. **Etienne M. Sokal** serves as CMO/CSO of Prometheus, and as an investigator for AbbVie, Roche, Gilead, Intercept, Alexion, Takeda, and BMS. **Karen F. Murray** has received grants from Shire, Mirum, Merck, and Gilead, consults for Gilead, and owns stock in Merck. **Stefan Wirth** consults for Roche, Gilead, Abbvie, Novartis and BMS. **Deidre Kelly, Scott Nightingale, Lynette A. Gillis, and Giuseppe Indolfi** declare no conflicts of interest.

ABSTRACT

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 ≥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 1400 mg/day, two divided doses). The primary efficacy endpoint was sustained virologic response 12 weeks after therapy (SVR12). 54 patients were enrolled (41 aged 6 to <12 years and 13 aged 3 to <6 years). Most were treatment-naive (98%) and infected perinatally (94%). All but one patient achieved SVR12 (53/54, 98%, 95% CI 90-100%). The patient who did not achieve SVR12 was a 4 year-old who discontinued treatment after three days due to 'abnormal drug taste'. The most commonly reported adverse events in patients aged 6 to <12 years were vomiting (32%) and headache (29%) and in patients aged 3 to <6 years, 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.

Keywords: direct-acting antiviral, pediatrics, polymerase inhibitor, pharmacokinetics

INTRODUCTION

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, non-specific 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 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 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 due to 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 GT-3 or 48 weeks for GT-1. Treatment with pegylated interferon plus ribavirin is undesirable due to 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 DAAs are available. [2,23-25]

We evaluated the safety and efficacy of sofosbuvir, a potent oral HCV NS5B polymerase inhibitor, in combination with weight-based ribavirin, in children aged 3 to <6 years old and 6 to <12 years old with HCV genotype 2 or 3 chronic infection.

METHODS

Patients

Eligible patients were 3 to <12 years old and had chronic infection with HCV genotype 2 or 3, with plasma HCV RNA levels ≥1000 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 ≥1,500/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 (eGFR) <90 mL/min/1.73m^2 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 non-steroidal 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, multi-center, open-label study. Based on the approved indication for sofosbuvir in adult patients, treatment was administered for 12 weeks in patients with HCV genotype 2 and 24 weeks in those with HCV genotype 3. Sofosbuvir was administered once daily. Patients aged 6 to <12 years old 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 old 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 old underwent an intensive pharmacokinetic 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 6 to <12 year old patients, the sofosbuvir doses to be tested in the younger patients aged 3 to <6 years old were selected (200 mg ≥ 17 kg and 150 mg for <17 kg). Similarly, at least 10 patients aged 3 to <6 years old 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 addition, patients in the 6 to <12 year old

group were to weigh ≥17 kg and <45 kg, while there was no weight limits 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 upon 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, Weeks 1, 2, 4, 8, 12, (and as applicable) 16, 20, and 24. All patients were to complete follow-up visits at Post-Treatment 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 prior to 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 Post-Treatment 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, Netherlands) using standard reverse transcription polymerase chain reaction (RT-PCR) technology. Following amplification, PCR 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 old, 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 old dosed with granules and all patients aged 3 to <6 years old 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 prior to 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 old, blood samples were collected at 0.5, 1, 2, 3, 4, 8, and 12 hours post-dose; food intake for this age group was restricted until after the collection of the 4-hour post-dose sample. For patients aged 3 to <6 years old, blood samples were collected at 2, 4, 8, and 12 hours post-dose 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 <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 (CDC) website 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 AUC_{tau} from each age group with the integrated adult data from Phase 2 and 3 clinical studies. The 90% confidence intervals 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 of 2015 to September 13 of 2018, 63 patients were screened, and 54 patients (41 aged 6 to <12 years old and 13 aged 3 to <6 years old) were enrolled and treated at 28 sites in the 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 old, 13 had genotype 2 HCV infection and 28 had genotype 3 HCV infection. The median age was 9 (range 6 to 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.

Among 13 patients aged 3 to <6 years old, 5 had genotype 2 HCV infection and 8 had genotype 3 HCV infection (**Table 2**). The median age was 4 (range 3 to 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 (Figure 1). One patient discontinued treatment after 3 days due to 'abnormal drug taste'.

Virologic Response

Among patients aged 6 to <12 years old, all (100%, 95% CI, 91-100%) achieved SVR12 (13/13 [95% CI, 75-100%] with genotype 2 and 28/28 [95%, CI 88-100%] with genotype 3) (**Table 3**). Among patients aged 3 to <6 years old, 12/13 (92%; 95% CI 64-100%) achieved SVR12, (4/5 [80%, 95% CI, 28-100%] with genotype 2 and 8/8 [95% CI, 63-100%] with genotype 3). No patients had virologic nonresponse or relapse after treatment. The genotype 2 patient who did not achieve SVR12 was a 4 year-old who discontinued treatment after 3 days due to 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 old, the most commonly reported adverse events were vomiting (32%) and headache (29%) (**Table 4**). Among the patients aged 3 to <6 years old, the most common adverse events were vomiting (46%) and diarrhea (39%). All adverse events of diarrhea lasted ≤5 days and resolved while treatment was on going, with the exception of one case that lasted for two months beginning during treatment and resolving during the post treatment period. All adverse events of vomiting lasted for one or two days, and the majority resolved without changes to drug dosing, with the exception of one patient in the 6 to <12 year old group and two patients in the 3 to <6 year old group for whom treatment was interrupted for one 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 one 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.

Across both age groups, only one 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 one patient had a Grade 3 lab 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 lab 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 post baseline 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 one patient in the 6 to <12 year old group for one day due to vomiting. For two patients in the 3 to <6 year old group, ribavirin was interrupted for one due to vomiting during attempted dosing, and for one due to an accidental overdose of ribavirin as described above. One 3 year old patient discontinued ribavirin along with sofosbuvir on treatment day 3 as described above due to the adverse event of spitting up and ‘abnormal drug taste’. With the exception of one patient with an isolated post baseline 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 old, 40 were assessed for swallowability of the 100 mg tablet formulation, while one 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, one 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 old, 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 old.

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 old were at Tanner stage 1 for pubic hair and genitalia or breast development. At posttreatment week 12, all 40 patients with available data had no change or an increase from baseline Tanner staging. For patients aged 3 to <6 years old, 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 genotype 2, and 24 weeks for genotype 3), and from end of treatment to post-treatment week 12 (**Table 5**). For patients aged 6 to <12 years old, 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 post-treatment week 12 between -0.01 and 0.05. For patients aged 3 to <6 years old, 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 post-treatment week 12 ranged between -0.16 and 0.32.

Pharmacokinetics

The 12 patients aged 6 to <12 years old and the 11 patients aged 3 to <6 years old who underwent intensive pharmacokinetic sampling had similar demographics to the overall study populations. During dosing, two patients aged 6 to < 12 years old were overdosed and one aged 3 to <6 years old was dosed with a tablet instead of granules; these patients were excluded from the intensive pharmacokinetic analysis. The plasma exposures of sofosbuvir and GS-331007 in the 20 patients from both age groups receiving the 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 pharmacokinetic equivalence boundaries of 50% to 200% when compared to 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 old and was obtained for 40 of 41 patients. Full length NS5B amplification was unsuccessful for one patient with genotype 3; 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 genotype 2b. Both achieved SVR12.

Deep sequencing was performed on all 12 patients aged 3 to <6 years old who completed treatment, and sequences were obtained for 11 of 12 patients. NS5B amplification was unsuccessful for one patient with genotype 3a infection due to 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, for 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 old with chronic hepatitis C infection genotypes 2 or 3, with 100% (n/N) of patients aged 6 to <12 years old, and 92% (n/N) of patients aged 3 to <6 years old 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 old where sofosbuvir plus ribavirin was highly efficacious and well tolerated in this younger population.[31] Despite the well-described hematologic toxicity of ribavirin, only one 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 due to an adverse event of low hemoglobin. In Murray et al, two pediatric patients aged 6 to 11 years with genotype 3 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 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 one 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 non-acidic 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 old, 100% in both genotype 2 and 3, and in patients 3 to <6 years old, 80% in genotype 2 and 100% in genotype 3[31]) were comparable to the SVR12 rates observed with sofosbuvir plus ribavirin in adolescents 12 to <18 years old (100% [13/13] in genotype 2 and 97% [38/39] in genotype 3) as well as response rates in treatment-naïve adults (97% for genotype 2[33,34] and 94% in genotype 3[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 genotype 2 or 3 were enrolled. The decision to enroll only genotype 2 or 3 pediatric patients follows the approved indications for adults, as only patients with genotype 2 or 3 are approved for sofosbuvir plus ribavirin treatment. For adult patients with genotype 1 or 4 sofosbuvir treatment is administered with ribavirin and peginterferon alfa. Due to the undesirable safety effects of peginterferon, we elected not to evaluate sofosbuvir plus ribavirin and peginterferon in genotype 1 or 4 pediatric patients. Additionally, only one patient had prior treatment experience and no patient had known cirrhosis, and therefore we were unable to evaluate whether these factors affect response to sofosbuvir and ribavirin in children 3 to <12 years old. 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 due to 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 summary, sofosbuvir and ribavirin was well tolerated and highly effective in treating children aged 3 to <12 years with chronic HCV genotype 2 or 3 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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Table 1. Ribavirin Dosing and Administration

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

[a]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.

Table 2. Patient Demographics and Baseline Characteristics

	3 to <6 Years (n=13)	6 to <12 Years (n=41)
Median (range) age, years	4 (3, 5)	9 (6, 11)
Female, n (%)	10 (77)	30 (73)
Race, n (%)		
White	9 (69)	29 (71)
Asian	1 (8)	8 (20)
Black or African American	1 (8)	0
Other	2 (15)	4 (10)
Median (range) 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)
Median (range) height, cm	102 (97, 113)	131 (109, 160)
Median (range) 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, n (%)		
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)
Median (range) HCV RNA, $\log_{10}$ IU/mL	5.4 (4.4, 7.2)	5.8 (2.2, 7.8)
HCV RNA ≥800,000 IU/mL, n (%)	3 (23)	19 (46)
HCV treatment history, n (%)		
Treatment naive	13 (100)	40 (98)
Nonresponse to PEG + RBV	0	1 (2)
Cirrhosis, n (%)		
No	2 (15)	5 (12)
Unknown	11 (85)	36 (88)
Median (range) ALT, U/L	25 (11, 76)	34 (14, 583)
Median (range) eGFR,[a] (mL/min/1.73 m^2)	151 (99, 232)	158 (79, 241)
Mode of HCV infection, n (%)		
Perinatal transmission	11 (85)	40 (98)
Unknown	2 (15)	1 (2)

[a]Estimated using the Schwartz Formula.
ALT, alanine aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; PEG, peginterferon; RBV, ribavirin.

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		SOF 200 mg +RBV 12 Weeks	SOF 200 mg +RBV 24 Weeks	
	HCV GT2 (n=5)	HCV GT3 (n=8)	Total (n=13)	HCV GT2 (n=13)	HCV GT3 (n=28)	Total (n=41)
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% to 100%	63% to 100%	64% to 100%	75% to 100%	88% to 100%	91% to 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

GT, genotype; HCV, hepatitis C virus; NA, not applicable; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after treatment.

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		SOF 200 mg +RBV 12 Weeks	SOF 200 mg +RBV 24 Weeks	
	HCV GT2 (n=5)	HCV GT3 (n=8)	Total (n=13)	HCV GT2 (n=13)	HCV GT3 (n=28)	Total (n=41)
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 x ULN)	0	0	0	0	1 (4)	1 (2)
Deaths	0	0	0	0	0	0

GT, genotype; HCV, hepatitis C virus; INR, international normalized ratio of prothrombin time; RBV, ribavirin; SOF, sofosbuvir; ULN, upper limit of normal.

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)
Median (range) z-score change in height				
Baseline to EOT	-0.02 (-0.17, 0.02)	-0.01 (-0.48, 0.13)	-0.06 (-0.41, 0.06)	-0.10 (-0.36, 0.24)
EOT to PTw12	-0.16 (-0.33, 0.31)	0.01 (-0.34, 0.11)	0.02 (-0.21, 0.33)	0.05 (-0.19, 0.38)
Median (range) z-score change in weight				
Baseline to EOT	-0.05 (-0.25, 0.00)	-0.41 (-0.69, 0.35)	-0.04 (-0.36, 1.39)	-0.18 (-0.53, 0.36)
EOT to PTw12	-0.03 (-0.11, 0.29)	0.09 (-0.21, 0.22)	0.05 (-0.35, 0.29)	0.04 (-0.30, 0.40)
Median (range) z-score change in BMI				
Baseline to EOT	-0.12 (-0.25, 0.24)	-0.38 (-1.19, 0.47)	-0.02 (–0.46, 2.70)	-0.19 (-0.57, 0.65)
EOT to PTw12	0.32 (-0.40, 0.49)	0.13 (-0.35, 0.71)	0.02 (-0.39, 0.45)	-0.01 (-0.48, 0.34)

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

	Adults (n=1695)	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[a]					
AUC_{tau} (ng•h/mL)	1,030 (36.5)	1690[b]	NA	960 (45.1)	89.8 (75.0, 108)
C_{max} (ng/mL)	511 (32.5)	681[b]	NA	609 (43.4)	114 (92.4, 140)
GS-331007					
AUC_{tau} (ng•h/mL)	7,120 (30.7)	10,300 (18.1)	150 (127, 176)	7650 (22.5)	110 (93.3, 129)
C_{max} (ng/mL)	582 (36.3)	1320 (20.0)	239 (195, 292)	905 (25.6)	161 (132, 198)

Data are presented to 3 significant digits.
[a]n=838 for sofosbuvir in adults.
[b]n=1 for sofosbuvir in patients aged 3 to <6 years as 9 patients could not be evaluated by non-compartmental analysis (NCA)
AUC, area under the curve; CV, coefficient of variation; GMR, geometric mean ratio; NA, not applicable

Figure Legend

Figure 1. Patient disposition

Figure 1. Patient Disposition Throughout the Study. FU, follow-up; HCV, hepatitis C virus; RBV, ribavirin; SOF, sofosbuvir.