Safety and Efficacy of Ledipasvir-Sofosbuvir With or Without Ribavirin for Chronic Hepatitis C in Children Ages 6-11

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Abbreviations: ALT, alanine aminotransferase; AUC, area under the curve; BMI, body mass index; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; GMR, geometric mean ratio; HCV, hepatitis C virus; INR, international normalized ratio of prothrombin time; LDV, ledipasvir; 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:

Karen F. Murray has received research support from Gilead, Shire, and Merck, has served as a consultant (DMC) for Gilead, and owns stock in Merck. **William F. Balistreri** has received research support and has served as a consultant (DMC) for Gilead. **Sanjay Bansal** has received research support from Gilead and Merck. **Regino P. Gonzalez-Peralta** has received research support from AbbVie, Gilead, and Merck, and has served on advisory boards for Genentech-Roche, Shire, and Kadmon. **Jessica Wen** has received research support from AbbVie, Bristol Myers-Squibb, Gilead, and Genentech-Roche, and has served as a consultant (DSMB) for Gilead. The following authors are employees of Gilead Sciences and may hold stock interest in the company: **Benedetta Massetto, Kathryn Kersey, Jiang Shao, Kimberly L. Garrison, Bandita Parhy,** and **Diana M. Brainard**. **Maureen M. Jonas** has received research support from Gilead, Roche, AbbVie, Merck, Bristol-

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ABSTRACT

Currently, there are no interferon-free treatments available for HCV-infected patients younger than 12 years of age. We evaluated the safety and effectiveness of the all-oral regimen ledipasvir–sofosbuvir ± ribavirin, in HCV-infected children aged 6 to <12 years. In an open-label study, patients aged 6 to <12 years received ledipasvir 45 mg- sofosbuvir 200 mg as two fixed-dose combination tablets 22.5/100 mg once daily, with or without ribavirin, for 12 or 24 weeks, depending on HCV genotype and cirrhosis status. The primary efficacy endpoint was sustained virologic response 12 weeks after therapy (SVR12). Twelve patients underwent intensive pharmacokinetic sampling to confirm the appropriateness of the ledipasvir and sofosbuvir dosages. 92 patients were enrolled (88 genotype 1, 2 genotype 3, and 2 genotype 4), with a median age of 9 years (range, 6-11). Most were perinatally infected (97%) and treatment-naive (78%). Two were confirmed to have cirrhosis, while the degree of fibrosis was unknown in 55 patients. The overall SVR12 rate was 99% (91/92, 95% CI 94-100%). The single patient not reaching SVR relapsed 4 weeks after completing 12 weeks of treatment. The most common adverse events were headache and pyrexia. One patient had 3 serious adverse events: tooth abscess, abdominal pain, and gastroenteritis, which were considered to be not related to study treatment. The area under the concentration-time curve and maximum concentration values for

sofosbuvir, its primary metabolite GS-331007, and ledipasvir, were within predefined pharmacokinetic equivalence boundaries (50%-200%) compared to values in adults in phase 2/3 of the ledipasvir and sofosbuvir studies.

Conclusions: Ledipasvir–sofosbuvir was well tolerated and highly effective in children 6 to <12 years old with chronic HCV.

Keywords: direct-acting antiviral, pediatrics, polymerase inhibitor, NS5A inhibitor, pharmacokinetics

INTRODUCTION

Globally, the seroprevalence of hepatitis C virus (HCV) infection in the pediatric populations varies, with estimates of 0.05% to 0.36% in the United States and Europe to up to 5.8% in regions of Africa (1,2). It is estimated that 11 million people under the age of 15 years are HCV antibody positive, of whom 5 million are viremic (3). The increasing incidence of HCV infection among young adults, including women of childbearing age that has been reported since 2011 suggests a potential increase in the number of HCV-infected newborns at risk of developing chronic infection (4). Most children with chronic HCV are asymptomatic or have mild, nonspecific symptoms; however, despite a lack of symptoms, some children progress to having significant fibrosis or cirrhosis (5-7), and a small minority develop hepatocellular carcinoma (8,9) or end-stage liver disease requiring liver transplantation (10,11). In addition, childhood HCV infection has been reported to impact cognitive development and overall health (12,13).

Currently, treatment with direct-acting antivirals (DAAs) is recommended for all HCV-infected pediatric patients, independent of disease severity, for whom DAAs are approved (14). In 2017, ledipasvir-sofosbuvir fixed-dose combination and sofosbuvir in combination with ribavirin were approved for use in treatment-naïve and interferon-experienced adolescents aged 12 to < 18 years old with chronic HCV infection. In addition, in the US and some other countries, both DAAs have been approved for patients weighing at least 35 kg (15-18). For patients younger than 12 years, the only currently approved treatment option is pegylated-interferon plus weight-based ribavirin for

24 or 48 weeks, depending on HCV genotype. However, interferon-based therapy is inadequate with regards to both efficacy and safety, with children experiencing poor tolerability and potential impacts on growth and development (19, 20).

We evaluated the safety and effectiveness of ledipasvir 45 mg–sofosbuvir 200 mg for 12 or 24 weeks, with or without ribavirin, in children 6 to <12 years old with HCV genotype 1, 3, or 4 infection.

A subset of patients underwent intensive pharmacokinetic evaluation after 10 days of treatment to determine if exposure to sofosbuvir, its primary metabolite GS-331007, and ledipasvir was similar to that observed in adults.

METHODS

Patients

Eligible patients were 6 to <12 years old and had chronic infection with HCV genotype 1, 3, or 4, 5, 6 with plasma HCV RNA levels $\geq 10^4$ IU/mL. Patients were required to have an absolute neutrophil count $\geq 1{,}500/mm^3$ and a hemoglobin level ≥11 g/dL for females and ≥12 g/dL for males. Patients could be either treatment-naïve or interferon-experienced. Liver biopsy to confirm the presence of cirrhosis was not required.

Patients were excluded from participation if they had any of the following: decompensated liver disease; acute infection with hepatitis A, chronic infection with hepatitis B, or HIV; alpha-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; significant cardiovascular, pulmonary, or neurological disease; daily use of non-steroidal anti-inflammatory drugs; systemic corticosteroid use for more than 2 weeks (pulmonary/nasal administration was permitted); or psychiatric hospitalization, suicide attempt, or disability resulting

from psychiatric illness in the previous 5 years.

Parents or legal guardians provided written informed consent before patients undertook any study-related procedures. Patients who could read and write provided written assent. Assent was obtained in accordance with requirements of local institutional review boards.

Study Design

This was a Phase 2, multi-center, open-label study (ClinicalTrials.gov Identifier: NCT02249182). All patients received the ledipasvir-sofosbuvir fixed dose combination tablet of 22.5mg/100mg and took two tablets, once daily without regard to food, for 12 or 24 weeks, with or without ribavirin depending on the HCV genotype and cirrhosis status. Ribavirin was administered twice daily with dose dependent upon weight (Table 1). The doses of ledipasvir (45 mg) and sofosbuvir (200 mg) were half of those used in adults, and were selected based on the pharmacokinetics of sofosbuvir, its major circulating metabolite GS-331007, and ledipasvir in adolescents (21).

All patients were assigned to ledipasvir–sofosbuvir for 12 weeks, except for interferon-experienced cirrhotic patients with HCV genotype 1, who received ledipasvir-sofosbuvir for 24 weeks. HCV genotype 3 interferon-experienced patients with or without cirrhosis were assigned to ledipasvir-sofosbuvir plus ribavirin for 24 weeks.

The first 12 patients enrolled underwent intensive pharmacokinetic evaluation on the 10^{th} day of treatment to confirm the appropriateness of the ledipasvir-sofosbuvir dose used before additional patients were enrolled.

The study protocol was approved by the review board or ethics committee of each institution prior to study initiation. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki.

Efficacy Evaluation

Blood samples for determining serum HCV RNA levels were drawn at screening, on day 1 of treatment, at treatment weeks 1, 2, 4, 8, and 12 for all patients and treatment weeks 16, 20, and 24 for those receiving 24 weeks of treatment, and at follow-up weeks 4, 12, and 24. Plasma HCV RNA levels were analyzed by using the Roche 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.

The primary efficacy endpoint was the percentage of patients who achieved SVR12, defined as HCV RNA < LLOQ (15 IU/mL) 12 weeks after stopping the study drugs. The SVR12 rate was calculated with a 2-sided 95% exact confidence interval based on the Clopper-Pearson method. Missing SVR values were imputed as a success if bracketed by values that were termed successes.

Safety Evaluations

During treatment, vital signs, reported adverse events, concomitant medication intake, and clinical laboratory tests were collected at every visit. Complete physical examinations were conducted on Day 1 and at the final treatment visit. During every follow-up visit, vital signs and reported adverse events were collected and symptom-directed physical examinations were done. Concomitant medications were reported at the follow-up week 4 visit, and clinical laboratory tests were done at the week 4 and 12 follow-up visits. Treatment-emergent clinical and laboratory adverse events were summarized using the Medical Dictionary for Regulatory Activities, version 20.1.

At baseline all patients underwent a Tanner pubertal stage assessment (22,23). For patients who had achieved Tanner stage 5 at baseline, no further Tanner staging was done. Those who scored below Tanner stage 5 underwent Tanner assessments again at the end of treatment and at follow-up weeks 12 and 24.

At screening up to baseline, tablet swallowability was to be evaluated with placebo to match the 22.5mg/100mg tablet.

Pharmacokinetic Analyses

For all patients, single plasma samples for pharmacokinetic analysis of sofosbuvir, its metabolite GS-331007, and ledipasvir were collected at the week 1 on-treatment study visit. Additionally, the first 12 patients underwent an intensive pharmacokinetic evaluation and had serial pharmacokinetic blood samples collected on day 10 of treatment to evaluate the pharmacokinetics of sofosbuvir, GS-331007, and ledipasvir in order to confirm the appropriateness of the ledipasvir–sofosbuvir dose used before additional patients were enrolled. Patients participating in the intensive pharmacokinetic evaluation had to be HCV-treatment naïve, have no evidence of cirrhosis and weigh 17 to < 45 kg. Patients were administered ledipasvir-sofosbuvir along with a standardized meal containing approximately 400 kilocalories and 13 grams of fat. Following the pharmacokinetic evaluation on day 10, patients continued on the study with no interruption of study drug administration.

Exposure data for sofosbuvir, GS-331007, and ledipasvir from the initial cohort were compared to the integrated adult data from Phase 2 and 3 clinical studies using an analysis of variance for log-transformed sofosbuvir, GS-331007, and ledipasvir. The 90% confidence intervals were constructed for the ratio of geometric means of the pharmacokinetic parameters area under the curve (AUC_{tau}), maximum drug concentration (C_{max}), and concentration at the end of dosing (C_{tau}), as appropriate. The equivalence boundaries were set as 50% to 200%.

Resistance Analyses

During treatment and follow-up, plasma samples for viral sequencing were collected at the same time points as for HCV RNA levels. The HCV NS5A and NS5B coding regions were amplified by DDL Diagnostic Laboratory (Rijswijk, Netherlands) using standard reverse transcription polymerase chain

reaction (RT-PCR) technology at baseline for all patients, and at time of virologic failure. The PCR products from baseline samples were deep sequenced by DDL. Reported resistance-associated substitutions (RASs) were present in more than 15% of the sequence reads.

RESULTS

Patient Population

From 4 August 2015 to 14 February 2018, 92 patients were enrolled and followed at 31 study sites in Australia, New Zealand, the United Kingdom, and the United States. The median age was 9 years (range 6 to 11), 59% of patients were male, 79% were white, and most were perinatally infected (97%) and treatment-naïve (78%) (Table 2). Two patients had cirrhosis as confirmed by liver biopsy; the patients were 8 and 11 years old, and both were white females with genotype 1a infection reported to have been acquired through vertical transmission. Of the remaining 90 patients, 35 were reported as not having cirrhosis and in 55 patients the degree of fibrosis was unknown. Overall, 96% had genotype 1 (77 genotype 1a, 10 genotype 1b, and 1 genotype 1l), 2% (n=2) had genotype 4, and 2% (n=2) had genotype 3.

Virologic Response

Overall, 99% (91/92, 95% CI 94-100%) of patients achieved SVR12 (Table 3). SVR12 rates were 99% (88/89, 95% CI 94-100%) for ledipasvir–sofosbuvir 12 weeks (86/87, 99% in genotype 1 and 2/2, 100% in genotype 4), 100% (1/1 genotype 1; 95% CI 2.5-100.0%) for ledipasvir–sofosbuvir 24 weeks, and 100% (2/2 genotype 3; 95% CI 15.8-100.0%) for ledipasvir–sofosbuvir plus ribavirin for 24 weeks. The single patient who did not achieve SVR12 was an 8 year old treatment-naïve female with genotype 1a infection and cirrhosis who received ledipasvir-sofosbuvir for 12 weeks and experienced virologic relapse 4 weeks after treatment .

Safety

The 3 most commonly reported adverse events were headache (18% of patients), pyrexia (17%), and abdominal pain (15%) (Table 4). No patient discontinued treatment because of an adverse event. All adverse events were mild or moderate in intensity. One patient had 3 serious adverse events of moderate intensity, all of which were considered by the investigator as unrelated to study treatment: abdominal pain, gastroenteritis, and tooth abscess. Most laboratory abnormalities were mild in severity; 4 patients (4%) had grade 3-4 lab abnormalities, 2 of whom had asymptomatic Grade 3 amylase elevation with Grade 2 or 3 elevations already present at screening. One patient who received ledipasvir-sofosbuvir for 12 weeks had Grade 3 hemoglobin level, corresponding to a decrease ≥ 4.5 g/dL from baseline (18.3 g/dL), with hemoglobin levels ranging from 13.0 g/dL to 14.4 g/dL on treatment, and one patient had asymptomatic, transient and isolated Grade 4 neutropenia.

Study treatment did not affect pubertal development through 12 weeks of post-treatment follow up as assessed by Tanner pubertal staging performed by the investigators. Of the 54 males enrolled, all had pubic hair and genitalia staging assessment: 94% (51/54) had no change, 4% (2/54) had an increase, and 2% (1/54) were reported to have a reduction in pubic hair staging; 93% (50/54) did not have a change, 7% (4/54) had an increase in genitalia staging. Among the 38 females enrolled, 34 had pubic hair assessment and underwent breast staging: 91% (31/34) had no change and 9% (3/34) had an increase in pubic hair staging; 74% (25/34) had no change, 24% (8/34) had an increase, and 3% (1/34) had a reduction in breast staging, at post treatment week 12.

Acceptability of the small placebo tablet ledipasvir- sofosbuvir 22.5/50mg (9x4mm) was evaluated by swallowability assessment of the corresponding placebo tablet in 82 patients, and the adult placebo tablet (19x10mm) in 9 patients. All patients were able to swallow the tablets.

Pharmacokinetics

A total of 12 patients were enrolled in the PK lead-in cohort. The median age was 9 years (range 6 to 11), and most were white (58%) and male (67%). The median weight of patients in this group was 33 kg (range 20 to 41) with a corresponding median weight for age percentile of 64.4% (range 1.0-98.6%). The median body mass index was 17 kg/m^2 (range 14 to 23) with a corresponding median body mass index for age percentile of 57.7% (range 1.5-98.5%). Two patients inadvertently received an adult dose, ledipasvir 90 mg-sofosbuvir 400 mg once daily for 3 days and 17 days, before receiving ledipasvir 45mg and sofosbuvir 200 mg once daily; pharmacokinetic exposures for the patient who received the adult dose for 17 days were dose-normalized to generate expected exposures for the pediatric dose. Administration of ledipasvir 45 mg and sofosbuvir 200 mg in HCV-infected children provided comparable similar plasma exposures of ledispavir, sofosbuvir, and GS-331007 to those observed with the adult dose ledispavir 90 mg-sofosbuvir 400 mg. The AUC_{tau} and C_{max} for ledispavir, sofosbuvir, and GS-331007 in children aged 6 to <12 years were within the predefined pharmacokinetic equivalence boundaries of 50% to 200% when compared with adults from Phase 2 and 3 studies (Table 5).

Resistance Analyses

Deep sequencing for baseline resistance analysis was performed for all 92 patients. With a 15% cutoff, NS5A RASs were detected in 13 patients with genotypes 1 and 4 (14%) and included K24R, L31M, M28T, Q30H Y93C/H for genotype 1 and L28M for genotype 4. The NS5B nucleotide inhibitor RAS L159F was detected in 3 genotype 1b patients (3%). All patients with baseline NS5A or NS5B nucleotide inhibitor RASs achieved SVR12. The genotype 1a patient who relapsed did not have baseline RASs and, but developed NS5A RAS Y93H at relapse.

DISCUSSION

Sofosbuvir plus ribavirin and ledipasvir-sofosbuvir fixed-dose combination has recently been approved for use in treatment naïve or interferon-experienced patients with chronic HCV who are 12 to < 18 years old and, in some countries including the US, weighing at least 35kg (15-18). However, for all infected children < 12 years of age, the standard of care is still pegylated-interferon and weight-based ribavirin. Therefore, there remains a significant unmet medical need for all-oral, interferon-free, direct-acting antiviral regimens for younger children. A recent study conducted in the United States found that only 16% of children born to HCV-infected mothers underwent testing (24); this suggests that the estimate of 5 million patients younger than 15 years having chronic viremic infection (3) is likely an underestimation of the true disease burden.

In our study, treatment with the ledipasvir-sofosbuvir with or without ribavirin for 12 or 24 weeks was highly effective in children 6 to <12 years old with genotype 1, 3, and 4 HCV infection, with an overall SVR rate of 99%. There was no apparent difference in the prevalence of baseline NS5A RASs in children 6 to <12 compared with adolescents or adults, although the number of younger patients was relatively small (25, 26).

These high rates of SVR were comparable to those observed in adolescents (98%) (19) and adults (93-99%) (27-30). In addition, both patients with genotype 3 treated with ledipasvir-sofosbuvir plus ribavirin for 24 weeks achieved SVR12. One cirrhotic patient did not achieve SVR12; currently there are no re-treatment options for pediatric patients with DAA experience.

Consistent with observations in adolescents and adults, treatment with ledipasvir-sofosbuvir was well tolerated in children 6 to <12 years old. The most commonly reported adverse events in this study were headache, pyrexia, abdominal pain. Based on Tanner pubertal staging, treatment with 12 weeks of ledipasvir-sofosbuvir did not affect short-term sexual development.

While this study included mostly HCV genotype 1 patients and only 2 patients with confirmed cirrhosis, the high treatment response and the comparable exposure between children and adults observed in this study suggest the possibility for extrapolation of these results to other HCV

genotypes and patients with cirrhosis, who would especially benefit from alternative treatments given the significant toxicities associated with pegylated interferon in this patient population.

In summary, ledipasvir 45 mg-sofosbuvir 200 mg once daily with or without ribavirin was highly effective and safe for children 6 to <12 years old with chronic HCV genotype 1, 3 and 4 infection. Given the poor tolerability and the well-documented side effects of pegylated interferon, expanding treatment options for children 6 to <12 with chronic HCV infection to include an all oral, DAA regimen would represent an important advancement in care in this patient population.

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NOTE

The current affiliation for Dr. Regino P Gonzalez-Peralta is Florida Hospital for Children and Florida Hospital Transplant Institute, Orlando, Florida

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FIGURE LEGEND

Figure 1. Patient Disposition Throughout the Study. FU, follow-up; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

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.[a]
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

[a]If necessary, oral solution could be used at 15 mg/kg/day divided morning and evening in patients weighing ≥47 kg.

Table 2. Patient Demographics and Baseline Characteristics

	LDV/SOF 12 Weeks (n=89)	**LDV/SOF 24 Weeks (n=1)**	**LDV/SOF+RBV 24 Weeks (n=2)**	**Total (N=92)**
Median (range) age, yr.	9 (6-11)	11 (11)	9 (7-11)	9 (6-11)
Male, n (%)	53 (60)	0	1 (50)	54 (59)
Race, n (%)				
White	70 (79)	1 (100)	2 (100)	73 (79)
Black or African American	7 (8)	0	0	7 (8)
Asian	5 (6)	0	0	5 (5)
Hawaiian or Pacific Islander	2 (2)	0	0	2 (2)
Other	5 (6)	0	0	5 (5)
Median (range) BMI, kg/m^2	17 (13-31)	20	21 (19-24)	17 (13-31)
Median BMI for age percentile (range)	64.4 (.8-99.6)	71.9	93.3 (91.3-95.4)	66.0 (.8-99.6)
Median (range) weight, kg	30 (17-76)	38	43 (30-55)	30 (17-76)
Median weight for age percentile (range)	54.1 (.5-99.6)	33.8	93.1 (90.4-95.7)	54.8 (.5-99.6)
Genotype, n (%)				
1a	76 (85)	1 (100)	0	77 (83)

1b	10 (11)	0	0	10 (11)
1l	1 (1)	0	0	1 (1)
3a	0	0	2 (100)	2 (2)
4a/4c/4d	2 (2)	0	0	2 (2)
Median (range) HCV RNA, $\log_{10}$ IU/mL	6.1 (4.6-7.3)	6.2	5.7 (5.5-5.9)	6.1 (4.6-7.3)
HCV RNA ≥800,000 IU/mL, n (%)	52 (58)	1 (100)	1 (50)	54 (59)
Response to prior HCV treatment, n (%)				
Nonresponder	14 (16)	1 (100)	1 (50)	16 (17)
Relapse/breakthrough	2 (2)	0	1 (50)	3 (3)
Interferon intolerant	1 (1)	0	0	1 (1)
IL-28B, n (%)				
CC	23 (26)	0	0	23 (25)
CT	53 (60)	0	2 (100)	55 (60)
TT	12 (13)	1 (100)	0	13 (14)
Missing	1 (1)	0	0	1 (1)
Cirrhosis, n (%)				
No	33 (37)	0	2 (100)	35 (38)
Yes	1 (1)	1 (100)	0	2 (2)
Unknown	55 (62)	0	0	55 (60)
Median (range) ALT, U/L	55 (14-255)	94	70 (58-82)	57 (14-255)

Median (range) eGFR,[a] (mL/min/1.73 m^2)	152.8 (116.3-249.5)	181.0	153.3 (138.6-168.0)	152.9 (116.3-249.5)
Mode of HCV infection, n (%)				
Perinatal transmission	86 (97)	1 (100)	2 (100)	89 (97)
Blood product transfusion	1 (1)	0	0	1 (1)
Unknown	2 (2)	0	0	2 (2)

[a]Estimated using Schwartz Formula

ALT, alanine aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; LDV, ledipasvir; IV, intravenous; RBV, ribavirin; SOF, sofosbuvir.

Table 3. Treatment Response

	LDV/SOF 12 Weeks (n=89)	LDV/SOF 24 Weeks (n=1)	LDV/SOF+RBV 24 Weeks (n=2)	Total (N=92)
HCV RNA <15 IU/mL, n/n (%)				
After treatment				
Week 4	88/89 (99)	1/1 (100)	2/2 (100)	91/92 (99)
Week 12 (SVR)	88/89 (99)	1/1 (100)	2/2 (100)	91/92 (99)
95% CI	94 - 100	3 - 100	16 - 100	94 - 100
Virologic failure, n				
On treatment	0	0	0	0
Relapse	1	0	0	1

CI, confidence interval; HCV: hepatitis C virus; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response.

Table 4. Adverse Events and Laboratory Abnormalities

	LDV/SOF 12 Weeks (n=89)	LDV/SOF 24 Weeks (n=1)	LDV/SOF+RBV 24 Weeks (n=2)
No. (%) of patients with any adverse event	62 (70)	1 (100)	2 (100)
No. of Grade 3 or 4 adverse events	0	0	0
No. of patients with a serious adverse event	1 (1)	0	0
Adverse events leading to discontinuation, n	0	0	0
Deaths, n	0	0	0
Adverse events in ≥ 5% of all patients, n (%)			
Headache	16 (18)	0	1 (50)
Pyrexia	15 (17)	0	1 (50)
Abdominal pain	14 (16)	0	0
Fatigue	13 (15)	0	1 (50)
Vomiting	13 (15)	0	1 (50)
Cough	12 (14)	1 (100)	1 (50)
Diarrhea	12 (14)	0	0
Oropharyngeal pain	10 (11)	0	0
Nausea	9 (10)	0	1 (50)
Rash	8 (9)	0	0
Upper respiratory infection	7 (8)	0	0
Nasal congestion	5 (6)	1 (100)	0
Dizziness	5 (6)	0	0
Serious adverse events, n (%)			
Abdominal pain	1 (1)	0	0
Gastroenteritis	1 (1)	0	0

Tooth abscess	1 (1)	0	0
Laboratory abnormalities			
Total amylase, >2 to 5.0 x ULN (Grade 3)	2 (2)	0	0
Hemoglobin, 7.0 to < 9.0 or decrease ≥ 4.5 g/dL from baseline (Grade 3)	1 (1)	0	0
Neutrophils, <500/mm^3 (Grade 4)	1 (1)	0	0

INR, International Normalized Ratio of prothrombin time; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; ULN, upper limit of normal.

Table 5. Mean (%CV) Sofosbuvir, GS-331007, and Ledipasvir Exposures

	Children (n=12)	**Adults (n=2113†)**	**Children vs. Adults % GMR (90% CI)**
Sofosbuvir			
AUC_{tau} (ng•h/mL)	1600 (29.7)	1380 (34.0)	116 (101, 133)
C_{max} (ng/mL)	906 (36.0)	659 (34.0)	139 (116, 167)
GS-331007			
AUC_{tau} (ng•h/mL)	8140 (31.6)	12500 (29.2)	65.2 (56.9, 74.7)
C_{max} (ng/mL)	772 (24.4)	736 (28.2)	106 (92.8, 122)
Ledipasvir			
AUC_{tau} (ng•h/mL)	7520 (58.0)	8530 (60.8)	86.9 (66.5, 114)
C_{max} (ng/mL)	432 (51.3)	364 (51.4)	116 (92.1, 147)
C_{tau} (ng/mL)	248 (67.5)	247 (59.2)	91.1 (69.5, 120)
CLcr (mL/min^2)	159 (19.2)	108 (29.4)	150 (132, 172)

AUC, area under the curve; CL_{cr} = creatinine clearance, derived in children by Schwartz formula and for adults by Cockcroft-Gault equation; CV, coefficient of variation; GMR, geometric mean ratio. Parameters presented to 3 significant digits.

†n=1542 for sofosbuvir