The Safety and Effectiveness of Ledipasvir–Sofosbuvir in Adolescents 12 to 17 Years Old With Hepatitis C Virus Genotype 1 Infection

William F. Balistreri[1], Karen F. Murray[2], Philip Rosenthal[3], Sanjay Bansal[4], Chuan-Hao Lin[5], Kathryn Kersey,[6] Benedetta Massetto,[6] Yanni Zhu[6], Bittoo Kanwar[6], Polina German[6], Evguenia Svarovskaia,[6] Diana M. Brainard[6], Jessica Wen[7], Regino P. Gonzalez-Peralta[8], Maureen M. Jonas[9], and Kathleen Schwarz[10]

From the [1]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [2]Seattle Children's Hospital, Seattle, Washington, USA; [3]University of California San Francisco, San Francisco, California, USA; [4]Kings College Hospital, London, United Kingdom; [5]Children's Hospital Los Angeles, Los Angeles, California, USA; [6]Gilead Sciences, Inc., Foster City, California, USA; [7]The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; [8]University of Florida College of Medicine and Shands Children's Hospital, Gainesville, Florida, USA; [9]Boston Children's Hospital, Boston, Massachusetts, USA; [10]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

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Address correspondence to:
William F. Balistreri, MD
Medical Director, Emeritus, Pediatric Liver Care Center

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Division of Pediatric Gastroenterology, Hepatology and Nutrition
Cincinnati Children's Hospital
240 Albert Sabin Way
MLC 2010
Cincinnati, OH 45229
Phone: 513.636.4594
Email: william.balistreri@cchmc.org

Abbreviations: ALT, alanine aminotransferase; APRI, Aspartate Aminotransferase (AST)-to-Platelet Ratio Index; 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; PK, pharmacokinetic; RAS, resistance-associated substitution; RT-PCR, reverse transcription polymerase chain reaction; SOF, sofosbuvir; SVR, sustained virological response; ULN, upper limit of normal.

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ABSTRACT

No all-oral, direct-acting antiviral regimens have been approved for children with chronic hepatitis C virus (HCV) infection. We conducted a Phase 2, multi-center, open-label study to evaluate the efficacy and safety of ledipasvir–sofosbuvir in adolescents with chronic HCV genotype 1 infection. One hundred patients ages 12 to 17 years received a combination tablet of 90 mg ledipasvir and 400 mg sofosbuvir once daily for 12 weeks. On the 10th day following initiation of dosing, 10 patients underwent an intensive pharmacokinetic evaluation of the concentrations of sofosbuvir, ledipasvir, and the sofosbuvir metabolite GS-331007. The primary efficacy endpoint was the percentage of patients with a sustained virologic response 12 weeks posttreatment (SVR12). Median age of patients was 15 years (range, 12-17 years). A majority (80%) were HCV treatment naïve, and 84% were infected through perinatal transmission. One patient had cirrhosis and 42 did not; in 57 patients the degree of fibrosis was unknown. Overall, 98% (98/100; 95% CI, 93% to 100%) of patients reached SVR12. No patient had virologic failure. The 2 patients who did not achieve SVR12 were lost to follow-up either during or after treatment. The 3 most commonly reported adverse events were headache (27% of patients),

diarrhea (14%), and fatigue (13%). No serious adverse events were reported. AUC_{tau} and C_{max} values for sofosbuvir, ledipasvir, and GS-331007 were within the predefined pharmacokinetic equivalence boundaries of 50% to 200% when compared with adults from Phase 2 and 3 studies of ledipasvir and sofosbuvir.

Conclusion: Ledipasvir–sofosbuvir was highly effective in treating adolescents with chronic HCV genotype 1 infection. The dose of ledipasvir–sofosbuvir currently used in adults was well tolerated in adolescents and had an appropriate pharmacokinetic profile.

INTRODUCTION

Treatment options available for children with chronic hepatitis C virus (HCV) infection do not reflect the recent advances in care (1). Although adults with HCV of all genotypes now have the option of receiving a number of highly effective, all-oral treatment regimens, the sole treatment regimen that is currently approved for children is combination therapy with interferon or peginterferon and ribavirin for 24 or 48 weeks, depending on the HCV genotype (2). Chronic HCV infection in children is largely asymptomatic or associated with mild, nonspecific symptoms; however, significant fibrosis or cirrhosis can occur (3–5). Some children with chronic HCV may progress to develop hepatocellular carcinoma (6,7) or end-stage liver disease requiring liver transplantation (8,9). In addition, because of side effects, poor tolerability, and the relatively low likelihood of success associated with peginterferon and ribavirin treatment (10–12), it has been suggested that most children with chronic HCV infection should defer treatment until interferon-free regimens are available (2).

The prevalence of HCV in children varies globally, with estimates of 0.05% to 0.36% in the United States and Europe (13) and up to 5.8% in regions of Africa (14). However, in the United States, HCV infection rates have recently increased among adolescents and young adults, especially in Eastern rural regions, in association with the rise of injected opioid use (15,16). Given the increase in HCV infection rates among persons entering or within their childbearing years, the risk for perinatal transmission to infants has also risen in many areas (17).

We evaluated the safety and effectiveness of an all-oral, direct-acting antiviral regimen in adolescents 12 to 17 years old with HCV genotype 1 infection. Participants received 12 weeks of treatment with ledipasvir, an NS5A inhibitor, and sofosbuvir, a potent NS5B polymerase inhibitor. The combination of sofosbuvir and ledipasvir has shown high rates of sustained

virologic response (SVR) in adults with HCV genotype 1, including those with compensated cirrhosis (18–20). In our study, a subset of patients underwent a period of intensive pharmacokinetic evaluation to determine if children who receive this combination treatment have similar exposure to ledipasvir, sofosbuvir, and GS-331007, a metabolite of sofosbuvir, to that demonstrated in adults.

METHODS

Patients

Eligible patients were 12 to <18 years old and had chronic infection with HCV genotype 1, 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. Patients with or without cirrhosis were included; the presence of cirrhosis was determined based on existing biopsy results, but biopsy was not required for study entry. Patients were excluded from participating in the study if they had any of the following: decompensated liver disease; infection with hepatitis A, hepatitis B, or HIV; 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; daily use of nonsteroidal anti-inflammatory drugs; systemic corticosteroid use for more than 2 weeks (pulmonary/nasal administration was permitted); clinically relevant alcohol or drug abuse within 12 months of screening; or psychiatric hospitalization, suicide attempt, or disability resulting from psychiatric illness within the prior 5 years. Up to 40% of patients could be treatment experienced. 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

In this Phase 2, multi-center, open-label study, patients received the ledipasvir–sofosbuvir fixed-dose combination tablet (90 mg ledipasvir, 400 mg sofosbuvir) once daily, without regard to food, for 12 weeks. On the 10th day following initiation of dosing, 10 patients participated in a PK lead-in cohort and underwent an intensive pharmacokinetic evaluation, following administration of LDV/SOF with a standardized meal (~400 kcal containing 13g of fat). To be eligible for the PK lead-in cohort, patients had to weigh ≥45 kg, be naïve to HCV treatment, and have no documented cirrhosis. Patients who completed the pharmacokinetic lead-in were immediately enrolled into the treatment phase with no interruption of study drug administration. After 12 weeks of treatment, follow-up visits were conducted at post-treatment weeks 4, 12, and 24.

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; 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. With approximately 100 patients, a 2-sided 95.0% confidence interval of the SVR12 rate would extend, at most, 5.9% in both directions from the observed SVR12 rate, assuming the expected SVR12 rate is 90%. 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. 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 (MedDRA®), version 18.1. At baseline all patients underwent a Tanner pubertal stage assessment. For patients who had received Tanner stage 5 at baseline, no further Tanner staging was done. Those who scored below Tanner 5 underwent Tanner assessments again at the end of treatment and at follow-up weeks 12 and 24.

Pharmacokinetic Analyses

Serial PK blood samples were collected at the day 10 visit from the first 10 patients enrolled to determine the pharmacokinetics of sofosbuvir, its metabolite GS-331007, and ledipasvir to confirm the appropriateness of the adult ledipasvir–sofosbuvir dose in adolescents before additional patients were enrolled. Single plasma PK samples were collected at all scheduled on-

treatment study visits for patients in the treatment phase.

The GS-331007, sofosbuvir, and ledipasvir exposure data from this study were compared to the integrated adult data from Phase 2 and 3 clinical studies using an analysis of variance for log-transformed GS-331007, sofosbuvir, and ledipasvir. The 90% confidence intervals were constructed for the ratio of geometric means of pharmacokinetic parameters AUC_{tau}, C_{max}, and C_{tau} (as appropriate). The equivalence boundary was 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. The PCR products from baseline samples were deep sequenced with an assay cut off at 1% by DDL. Resistance-associated substitutions (RASs) which were present in more than 15% of the sequence reads were reported.

RESULTS

Patient Population

From November of 2014 to October of 2015, 100 patients were enrolled at 24 study sites across the United States, United Kingdom, and Australia. The median age of patients was 15 years (Table 1), and the majority were HCV treatment naïve (80%); 84% were infected through perinatal transmission. Sixty-three percent of patients were female, and 90% were white. Seventy-six percent had a non-CC *IL-28B* genotype. HCV genotype 1a was present in 81% of patients, and 1b in 19%. One patient was known to have cirrhosis, and 42 patients did not have

cirrhosis; in the remaining 57 patients the stage of fibrosis/cirrhosis was unknown.

Of the 100 patients who initiated treatment, 99 completed treatment, and 1 discontinued treatment and was lost to follow-up (Figure 1). Of the 99 who completed treatment, 2 patients did not attend the week 4 and 12 follow-up visits, but 1 of these patients completed a follow-up visit 24 weeks after completing treatment.

Virologic Response

Overall, 98% (98/100; 95% CI, 93% to 100%) of patients reached SVR12 (Table 2). Among treatment-naïve patients, 98% (78/80, 95% CI, 91% to 100%) achieved SVR12. The only person with confirmed cirrhosis, who was treatment naïve, achieved SVR12. Of the 20 treatment-experienced patients in the study, 100% (95% CI, 83% to 99%) achieved SVR12.

No patients had virologic nonresponse. Both patients who did not achieve SVR12 were lost to follow-up before completing the posttreatment week 12 visit. The high overall SVR12 rate, with no cases of virologic nonresponse, preclude meaningful interpretation of subgroup analyses.

Safety

The 3 most commonly reported adverse events were headache (27% of patients), diarrhea (14%), and fatigue (13%) (Table 3). No patient experienced serious adverse events or discontinued treatment because of an adverse event. All adverse events were mild or moderate in intensity; no patient experienced Grade 3 or 4 adverse events. Most laboratory abnormalities were mild in severity; 9 patients (9%) experienced Grade 3-4 laboratory abnormalities. Only 1 Grade 3 lab abnormality—serum amylase elevation—was experienced by more than 1 patient. The Grade 3 serum amylase elevations, which were transient and asymptomatic, were experienced by 3 patients; no pancreatitis was reported. One patient had a Grade 4 AST elevation (573 U/L) at the week 4 follow-up visit. The AST elevation was isolated and associated with the start of

isotretinoin treatment for acne. Concurrently, the patient had a Grade 2 ALT elevation (155 U/L) but no change in the serum bilirubin level. With continued isotretinoin administration, the patient's AST levels subsequently normalized.

Study treatment did not affect development through 12 weeks of follow up after treatment as assessed by Tanner pubertal staging. For males who underwent Tanner staging at posttreatment week 12, 91% (32/35) had no change and 9% (3/35) had an increase in pubic hair staging, and 94% (33/35) had no change and 6% (2/35) had an increase in genitalia staging. For females who underwent Tanner staging at posttreatment week 12, 75% (45/60) had no change and 25% (15/60) had an increase in pubic hair staging, and 82% (49/60) had no change and 18% (11/60) had an increase for breast development.

Pharmacokinetics

The 10 patients enrolled in the PK lead in cohort had a median age of 16 (range 13-17), and most were white (80%) and female (70%). The median weight and BMI of patients in this group were 68 kg (range 47-87) and 27 kg/m^2 (range 19-35), respectively.

Administration of ledipasvir–sofosbuvir 90/400 mg in HCV-infected adolescents provided comparable plasma exposures of sofosbuvir, GS-331007, and ledipasvir to those observed in adults. The AUC_{tau} and C_{max} for sofosbuvir, GS-331007, and ledipasvir in adolescents were within the predefined PK equivalence boundaries of 50% to 200% when compared with adults from Phase 2 and 3 studies (Table 4). The upper bound of the 90% CI for ledipasvir C_{max} was modestly higher than 200% in adolescents (GMR [90% CI]: 162 [125, 209]); this difference is not considered clinically relevant based on the established exposure-safety analysis for ledipasvir.

Resistance Analyses

Deep sequencing for baseline resistance analysis was successful for 97 of the 100 adolescent patients in the trial. With a 15% cutoff, NS5A RASs were detected in 5 of the 97 patients (5%) and included K24G (n=1), Q30H (n=1), L31M (n=1), and Y93H/C (n=2) (Table 5). Similarly, at the 15% cutoff, NS5B polymerase inhibitor RASs were detected in 5 of the 97 patients (5%). NS5B polymerase inhibitor RASs detected at baseline included L159F (n=1 genotype 1a and n=2 genotype 1b), E237G (n=1 genotype 1a), and N142T (n=1 genotype 1a). All patients with baseline NS5A or NS5B polymerase inhibitor RASs were treatment naïve, and all achieved SVR12.

DISCUSSION

The availability of all-oral, direct-acting antiviral regimens for children with chronic HCV infection is an unmet need. Although the estimated prevalence of HCV infection in children is low (up to 0.4%) in Europe and the United States (13), there are regions where a substantial number of children are infected. In Egypt, for example, the HCV seroprevalence rate is 6% in children, largely related to unsafe injection practices during a campaign of parenteral anti-schistosomiasis treatment in the 1960s-1980s (21). Approximately 4% to 6% of children with chronic HCV infection have evidence of advanced fibrosis or cirrhosis, and some children eventually require liver transplantation for end-stage liver disease as a consequence of HCV infection (22). Despite well-established guidelines for treating HCV in adults, there is no universal consensus on when or if to treat chronic HCV infection in children. Treatment of pediatric patients has been controversial as the current standard of care, peginterferon and weight-based ribavirin, is associated with significant side effects, including growth impairment, and poor tolerability (10–12).

In adults, all-oral, direct-acting HCV regimens offer the benefits of greater tolerability, improved response rates, fewer adverse events, easier administration, and shorter duration relative to peginterferon and ribavirin (23). Multiple direct-acting HCV regimens are available for adults with HCV genotype 1 infection. In the meantime, many children with chronic HCV have deferred treatment until these newer options receive approval for pediatric use (24), putting them at risk for disease progression.

In our study, treatment with the direct-acting antivirals ledipasvir and sofosbuvir for 12 weeks was highly effective in treating adolescents with chronic HCV genotype 1 infection, with an overall SVR rate of 98%. The 2 patients who did not achieve SVR12 were lost to follow-up. The presence of RASs at baseline did not affect treatment response; all 10 patients with a baseline NS5A or NS5B RAS achieved SVR12. Overall, there was no apparent difference in the prevalence of baseline NS5A RASs in adolescents as compared with adults, although the number of adolescent patients was relatively small.

In general, the adverse events noted in this study were consistent with those reported in prior studies of ledipasvir–sofosbuvir in adults. Similar to what has been observed in adults, treatment with ledipasvir–sofosbuvir was well tolerated in adolescents (18,19). The most commonly reported events in this study, headache, diarrhea, and fatigue, have been reported in adult populations (18,19). Notably, based on Tanner pubertal staging, 12 weeks of ledipasvir–sofosbuvir did not affect short-term development.

Although our study included only HCV genotype 1 patients, given the similarity of chronic HCV infection in children and adults, the efficacy data in this study and the comparable exposure suggest the possibility for extrapolation to other genotypes. However, it is unknown whether pediatric patients treated outside the context of a clinical trial would have similarly high

success rates with ledipasvir–sofosbuvir. In this study, only one patient had cirrhosis, and therefore the combination of ledipasvir–sofosbuvir in adolescents with cirrhosis warrants further study.

Successful treatment of children with HCV could have several public health benefits, including reductions in the rates of disease progression and transmission. Data from adults indicates successful treatment with ledipasvir–sofosbuvir leads to improvements in quality of life (25).

In summary, ledipasvir–sofosbuvir was highly effective in treating adolescents with chronic HCV genotype 1 infection. The dosing of ledipasvir–sofosbuvir currently used in adults was well tolerated and had comparable PK exposure. The availability of an all-oral, direct-acting antiviral regimen for adolescents with chronic HCV infection would improve care for patients who currently have limited treatment options.

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References

1. American Association for the Study of Liver Diseases and Infectious Diseases Society of America. Recommendations for Testing, Managing, and Treating Hepatitis C. Available at: http://www.hcvguidelines.org/. Accessed August 22, 2016.

2. Lee CK, Jonas MM. Treating HCV infection in children. Clinical Liver Disease. 2015;5:14–16.

3. Bortolotti F, Vajro P, Cadrobbi P, Lepore L, Zancan L, Barbera C, et al. Cryptogenic chronic liver disease and hepatitis C virus infection in children. J. Hepatol. 1992;15:73–76.

4. Badizadegan K, Jonas MM, Ott MJ, Nelson SP, Perez-Atayde AR. Histopathology of the liver in children with chronic hepatitis C viral infection. Hepatology. 1998;28:1416–1423.

5. Goodman ZD, Makhlouf HR, Liu L, Balistreri W, Gonzalez-Peralta RP, Haber B, et al. Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial. Hepatology. 2008;47:836–843.

6. Strickland DK, Jenkins JJ, Hudson MM. Hepatitis C infection and hepatocellular carcinoma after treatment of childhood cancer. J. Pediatr. Hematol. Oncol. 2001;23:527–529.

7. González-Peralta RP, Langham MR, Andres JM, Mohan P, Colombani PM, Alford MK, et al. Hepatocellular carcinoma in 2 young adolescents with chronic hepatitis C. J. Pediatr. Gastroenterol. Nutr. 2009;48:630–635.

8. Barshes NR, Udell IW, Lee TC, O'Mahony CA, Karpen SJ, Carter BA, et al. The natural history of hepatitis C virus in pediatric liver transplant recipients. Liver Transpl. 2006;12:1119–1123.

9. Bortolotti F, Verucchi G, Cammà C, Cabibbo G, Zancan L, Indolfi G, et al. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. Gastroenterology. 2008;134:1900–1907.

10. Schwarz KB, Gonzalez-Peralta RP, Murray KF, Molleston JP, Haber BA, Jonas MM, et al. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. Gastroenterology. 2011;140:450–458.e1.

11. Jonas MM, Balistreri W, Gonzalez-Peralta RP, Haber B, Lobritto S, Mohan P, et al. Pegylated interferon for chronic hepatitis C in children affects growth and body composition: results from the pediatric study of hepatitis C (PEDS-C) trial. Hepatology. 2012;56:523–531.

12. Schwarz KB, Molleston JP, Jonas MM, Wen J, Murray KF, Rosenthal P, et al. Durability of Response in Children Treated With Pegylated Interferon alfa [corrected] 2a ± Ribavirin for Chronic Hepatitis C. J. Pediatr. Gastroenterol. Nutr. 2016;62:93–96.

13. El-Shabrawi MH, Kamal NM. Burden of pediatric hepatitis C. World J. Gastroenterol. 2013;19:7880–7888.

14. Barakat SH, El-Bashir N. Hepatitis C virus infection among healthy Egyptian children: prevalence and risk factors. J. Viral Hepat. 2011;18:779–784.

15. Suryaprasad AG, White JZ, Xu F, Eichler B-A, Hamilton J, Patel A, et al. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006-2012. Clin. Infect. Dis. 2014;59:1411–1419.

16. Zibbell JE, Iqbal K, Patel RC, Suryaprasad A, Sanders KJ, Moore-Moravian L, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. MMWR Morb. Mortal. Wkly. Rep. 2015;64:453–458.

17. Koneru A, Nelson N, Hariri S, Canary L, Sanders KJ, Maxwell JF, et al. Increased Hepatitis C Virus (HCV) Detection in Women of Childbearing Age and Potential Risk for Vertical Transmission - United States and Kentucky, 2011-2014. MMWR Morb. Mortal. Wkly. Rep. 2016;65:705–710.

18. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N. Engl. J. Med. 2014;370:1889–1898.

19. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N. Engl. J. Med. 2014;370:1483–1493.

20. Bourlière M, Bronowicki J-P, de Ledinghen V, Hézode C, Zoulim F, Mathurin P, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). Lancet Infect Dis. 2015;15:397–404.

21. Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet. 2000;355:887–891.

22. Hu J, Doucette K, Hartling L, Tjosvold L, Robinson J. Treatment of hepatitis C in children: a systematic review. PLoS ONE. 2010;5:e11542.

23. Suwanthawornkul T, Anothaisintawee T, Sobhonslidsuk A, Thakkinstian A, Teerawattananon Y. Efficacy of Second Generation Direct-Acting Antiviral Agents for Treatment Naïve Hepatitis C Genotype 1: A Systematic Review and Network Meta-Analysis. PLoS ONE. 2015;10:e0145953.

24. Granot E, Sokal EM. Hepatitis C Virus in Children: Deferring Treatment in Expectation of Direct-Acting Antiviral Agents. Isr. Med. Assoc. J. 2015;17:707–711.

25. Younossi ZM, Stepanova M, Marcellin P, Afdhal N, Kowdley KV, Zeuzem S, et al. Treatment with ledipasvir and sofosbuvir improves patient-reported outcomes: Results from the ION-1, -2, and -3 clinical trials. Hepatology. 2015;61:1798–1808.

26. Kirby B, German P, Kanwar B, Ni L, Lakatos I, Ling J, et al. Pharmacokinetics of once daily sofosbuvir or ledipasvir/sofosbuvir in HCV-infected adolescents. Hepatology. 2015;62:1040A.

Table 1. Patient Demographics and Baseline Characteristics

	Treatment Naïve (n=80)	Treatment Experienced (n=20)	Total (N=100)
Median (range) age, yr.	15 (12, 17)	15 (12, 17)	15 (12, 17)
Female, n (%)	50 (63)	13 (65)	63 (63)
Race, n (%)			
White	71 (89)	19 (95)	90 (90)
Black or African American	7 (8)	0	7 (7)
Asian	2 (3)	0	2 (2)
Not disclosed	0	1 (5)	1 (1)
Median (range) BMI, kg/m^2	21 (13, 37)	22 (18, 32)	21 (13, 37)
Genotype, n (%)			
1a	66 (83)	15 (75)	81 (81)
1b	14 (18)	5 (25)	19 (19)
Mean (SD) HCV RNA, log_{10} IU/mL	1.85	2.29	1.94
HCV RNA ≥800,000 IU/mL, n (%)	44 (55)	11 (55)	55 (55)
Response to prior HCV treatment, n (%)			
Nonresponder	0	13 (65)	13 (13)
Relapse/breakthrough	0	6 (30)	6 (6)
Interferon intolerant	0	1 (5)	1 (1)
IL-28B, n (%)			
CC	20 (25)	4 (20)	24 (24)
CT	42 (53)	11 (55)	53 (53)
TT	18 (23)	5 (25)	23 (23)
Cirrhosis, n (%)			
No	31 (39)	11 (55)	42 (42)
Yes	1 (1)	0	1 (1)
Unknown	48 (60)	9 (45)	57 (57)
Mean (SD) ALT, U/L	54 (56.2)	50 (36.2)	53 (52.7)
Mean (SD) eGFR,[a] ($mL/min/1.73\ m^2$)	153.6 (36.9)	144.9 (33.0)	151.9 (36.1)
Mode of HCV infection, n (%)			
Contaminated needle or IV drug use	5 (6)	0	5 (5)
Blood product transfusion	1 (1)	1 (5)	2 (2)
Contact with infected individual	2 (3)	0	2 (2)
Perinatal transmission	65 (81)	19 (95)	84 (84)
Unknown	7 (9)	0	7 (7)

[a]Estimated using Schwartz Formula

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

Table 2. Treatment Response to Ledipasvir–Sofosbuvir 12 Weeks

	Treatment Naïve (n=80)	Treatment Experienced (n=20)	Total (N=100)
HCV RNA <15 IU/mL, n/n (%)			
On treatment			
Week 2	60/80 (75)	15/20 (75)	75/100 (75)
Week 4	77/80 (96)	20/20 (100)	97/100 (97)
Week 8	79/79 (100)	20/20 (100)	99/99 (100)
Week 12	79/79 (100)	20/20 (100)	99/99 (100)
After treatment			
Week 4	78/80 (98)	20/20 (100)	98/100 (98)
Week 12 (SVR)	78/80 (98)	20/20 (100)	98/100 (98)
95% CI	91% to 100%	83% to 100%	93% to 100%
Virologic failure, n (%)			
On treatment	0	0	0
Relapse	0	0	0
Did not complete study, n (%)	2 (3)	0	2 (2)

HCV: hepatitis C virus.

Table 3. Adverse Events and Laboratory Abnormalities

	Patients (N=100)
No. (%) of patients with any adverse event	71 (71)
No. of Grade 3 or 4 adverse events	0
No. of patients with a serious adverse event	0
Adverse events leading to discontinuation, n	0
Deaths, n	0
Adverse events in ≥ 5% of patients, n (%)	
Headache	27 (27)
Diarrhea	14 (14)
Fatigue	13 (13)
Nausea	11 (11)
Vomiting	11 (11)
Cough	10 (10)
Oropharyngeal pain	10 (10)
Abdominal pain	7 (7)
Abdominal pain upper	7 (7)
Nasopharyngitis	7 (7)
Nasal congestion	6 (6)
Upper respiratory infection	6 (6)
Dysmenorrhea	5 (5)
Laboratory abnormalities	
Serum amylase >2 x ULN	3 (3)
Aspartate aminotransferase >10.0 x ULN	1 (1)
Bilirubin >2.5 x ULN	1 (1)
Creatine kinase ≥10 x ULN	1 (1)
Hemoglobin <10 g/dL	1 (1)
INR >2.0 x ULN	1 (1)
Lymphocytes <500/mm^3	1 (1)
Potassium >6.5 mmol/L	1 (1)

INR, International Normalized Ratio of prothrombin time;
LDV, ledipasvir; SOF, sofosbuvir.

Table 4. Mean (%CV) Sofosbuvir, GS-331007, and Ledipasvir Exposures

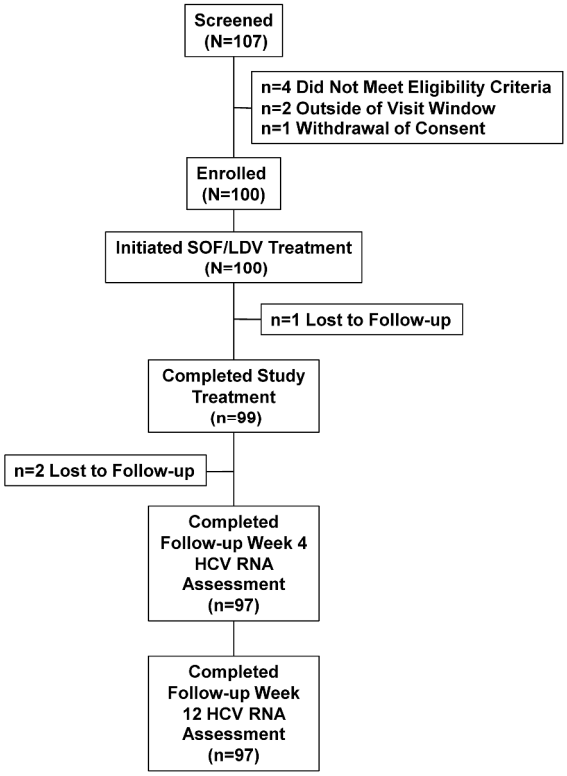
	Adolescents (n=10)	Adults (n=2113)[a]	Adolescents vs. Adults % GMR (90% CI)
Sofosbuvir[b]			
AUC_{tau} (ng•h/mL)	2180 (26.6)	1380 (34.0)	160 (138, 185)
C_{max} (ng/mL)	1140 (57.2)	659 (34.0)	156 (127, 190)
GS-331007			
AUC_{tau} (ng•h/mL)	12,700 (13.7)	12,500 (29.2)	105 (91, 122)
C_{max} (ng/mL)	1010 (21.5)	736 (28.2)	139 (120, 161)
Ledipasvir			
AUC_{tau} (ng•h/mL)	10,200 (50.9)	8530 (60.8)	127 (95, 170)
C_{max} (ng/mL)	564 (41.2)	364 (51.4)	162 (125, 209)
C_{tau} (ng/mL)	319 (71.5)	247 (59.2)	128 (95, 172)

[a]Reference (26).
[b]n=1542 for sofosbuvir parameters in adults.
AUC, area under the curve; CV, coefficient of variation; GMR, geometric mean ratio.

Table 5. Baseline Resistance-Associated Substitutions (RASs)

Patient ID	HCV Subtype	Treatment Experience	Cirrhosis	RAS	Treatment Outcome
				NS5A	
01754-52102	1a	Naive	No	Y93C (48.5%)	SVR12
01733-52103	1a	Naive	No	K24G (>99%)	SVR12
04489-52116	1b	Naive	No	Y93H (28.1%)	SVR12
01756-52118	1a	Naive	No	Q30H (60.5%)	SVR12
08719-52167	1b	Naive	No	L31M (96.1%)	SVR12
				NS5B Polymerase Inhibitor	
09159-52002	1a	Naive	No	L159F (98.5%)	SVR12
09159-52007	1a	Naive	No	E237G (>99%)	SVR12
01733-52103	1a	Naive	No	N142T (90.6%)	SVR12
01736-52132	1b	Naive	No	L159F (>99%)	SVR12
01731-52158	1b	Naive	No	L159F (>99%)	SVR12

Figure 1. Patient Disposition Throughout the Study. HCV, hepatitis C virus; LDV, ledipasvir; SOF, sofosbuvir. *One patient who did not complete the follow-up week 4 and 12 visits returned for a follow-up visit 24 weeks after treatment.



Patient Disposition Throughout the Study. HCV, hepatitis C virus; LDV, ledipasvir; SOF, sofosbuvir. *One patient who did not complete the follow-up week 4 and 12 visits returned for a follow-up visit 24 weeks after treatment.

Figure 1

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