Long-Term Safety and Efficacy of Sofosbuvir-Based Direct-Acting Antivirals in Pediatric Patients With Hepatitis C Virus

1881-A

Daniel H Leung[1], Suzanne Whitworth[2], Jessica Wen[3], Giuseppe Indolfi[4], Karen F Murray[5], Philip Rosenthal[6], Chuan-Hao Lin[7], Wikrom Karnsakul[8], Sanjay Bansal[9], Jonathan R Honegger[10], William Balistreri[11], Kathleen Schwarz[12], Vithika Suri[13], Xu Zhang[13], Kathryn Kersey[13], Winita Hardikar[14], Regino P Gonzales-Peralta[15]

[1]Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA; [2]Cook Children's Health Care System, Fort Worth, TX, USA; [3]University of Pennsylvania and The Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Pediatric and Liver Unit, Meyer Children's University Hospital IRCCS, Firenze, Italy; [5]The Pediatric Institute, Cleveland Clinic and Cleveland Clinic Children's, Cleveland, OH, USA; [6]University of California, San Francisco, CA, USA; [7]Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA, USA; [8]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [9]King's College Hospital, London, UK; [10]Nationwide Children's Hospital, The Ohio State University Wexner Medical Center, Columbus, OH, USA; [11]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [12]Pediatric Liver Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [13]Gilead Sciences, Inc., Foster City, CA, USA; [14]The Royal Children's Hospital, Melbourne, VIC, Australia; [15]AdventHealth for Children, AdventHealth Transplant Institute, Orlando, FL, USA

Key Findings

- Treatment with SOF-based regimens in children and adolescents with chronic HCV infection resulted in durable SVR, which was maintained through a median of 4 years of follow-up
- DAA treatment had no impact on growth or development of secondary sexual characteristics

Conclusions

These results demonstrate the long-term safety and efficacy of SOF-based DAAs and support the use of DAAs for children and adolescents with chronic HCV infection

Introduction

- An estimated 3.2 million children and adolescents are living with chronic hepatitis C virus (HCV) infection worldwide[1]
- Due in part to the ongoing opioid epidemic, rates of HCV infection among pregnant individuals have increased. Vertical transmission from mother to child is the primary route of HCV transmission to children, and in the US, an estimated 1700 infants are born with HCV infection annually[2,3]
- Direct-acting antivirals (DAAs) have revolutionized treatment for children with chronic HCV infection compared with pegylated interferon + ribavirin (RBV), which has suboptimal efficacy, extensive side effects, and negative impacts on growth[4,5]
- Treatment with sofosbuvir (SOF)-based DAAs for 8 to 24 weeks results in high sustained virologic response (SVR) rates and favorable safety profiles in children aged ≥3 years.[6-12] This study was conducted to assess the long-term outcomes of SOF-based DAA regimens in children and adolescents

References: 1. World Health Organization. Hepatitis C fact sheet. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c. Published June 2023. Accessed August 4, 2023. **2.** Chappell CA, et al. *J Infect Dis*. 2020;222(Suppl 9):S789-93. **3.** Ko JH, et al. *MMWR Morb Mortal Wkly Rep*. 2019;68(39):833-8. **4.** Jonas M, et al. *Hepatology*. 2012;56(2):523-31. **5.** Karnsakul W, et al. *J Viral Hepat*. 2019;26(9):1034-9. **6.** Rosenthal P, et al. *Hepatology*. 2020;71(1):31-43. **7.** Wirth S, et al. *Hepatology*. 2017;55(4):1102-10. **8.** Schwarz KB, et al. *Hepatology*. 2020;71(2):422-30. **9.** Balistreri WF, et al. *Hepatology*. 2017;66(2):371-8. **10.** Murray KF, et al. *Hepatology*. 2018;68(6):2158-66. **11.** Jonas M, et al. *J Pediatr Gastroenterol Nutri*. In press. **12.** Indolfi G, et al. *Hepatology*. 2022;76(2):445-55. **13.** Centers for Disease Control and Prevention. CDC Growth Charts. https://www.cdc.gov/growthcharts/cdc_charts.htm. Published May 2020. Accessed August 4, 2023.

Acknowledgments: This study was funded by Gilead Sciences, Inc. Medical writing support was provided by Charlotte Bavley, PhD, of AlphaScientia, a Red Nucleus company, and was funded by Gilead Sciences, Inc.

Disclosures: DHL reports clinical trial support from AbbVie and Gilead Sciences, Inc. **JW** is a member of a data safety monitoring board for Gilead Sciences, Inc., and reports research support from AbbVie, Albireo, Alexion, and Mirum and consulting fees from AbbVie. **GI** reports personal consulting fees from Albireo, Kedrion Pharma, and Mirum. **KFM** is an advisor for Albireo and Gilead Sciences, Inc. **PR** is a member of safety monitoring boards for Audentes, Encoded, and Taysha, and reports research support from AbbVie, Albireo, Arrowhead, Merck, Mirum, Takeda, and Travere Therapeutics; consulting fees from BioMarin, Dicerna, MedinCell, and RNAV8; and speaker bureau fees from Mirum. **CHL** reports research support from Gilead Sciences, Inc., and Mirum. **WK** reports research support from Travere Therapeutics and consulting fees from Albireo and Mirum. **JRH** reports research support from Gilead Sciences, Inc. **WB** is a member of a data safety monitoring board or advisory board for Mirum and reports research support from AbbVie and Gilead Sciences, Inc.; consulting fees from Alexion; and speaker fees from Mirum. **KS** reports research support from Albireo and Gilead Sciences, Inc., and consulting fees from Gilead Sciences, Inc.; Mirum; Sarepta; and Up to Date. **VS**, **XZ**, and **KK** are employees of Gilead Sciences, Inc., and own stock in Gilead Sciences, Inc. **RPGP** reports research support from AbbVie; Gilead Sciences, Inc.; and Merck. **SW**, **SB**, **WH** report no conflicts of interest.

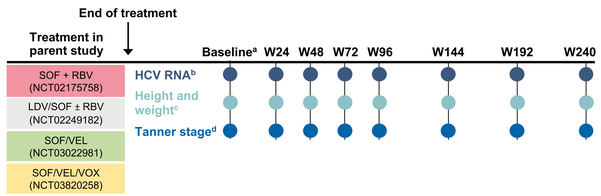
Objective

- To report the final follow-up data from the pediatric registry study (NCT02510300) describing virologic outcomes and effects on growth and development in children and adolescents treated with SOF-based regimens for chronic HCV infection

Methods

- Children and adolescents aged ≥3 years who received SOF + RBV (NCT02175758),[6,7] ledipasvir (LDV)/SOF ± RBV (NCT02249182),[8,9,10] SOF/velpatasvir (VEL; NCT03022981),[11] or SOF/VEL/voxilaprevir (VOX; NCT03820258)[12] in prior (parent) clinical trials for chronic HCV infection were eligible to enroll in this follow-up registry study
- Participants in 9 countries were enrolled between October 2015 and June 2021, and assessments were conducted through January 2023
- Study baseline was the date of each participant's last visit in the parent study, and participants were monitored for up to 5 years
- Assessments occurred every 6 to 12 months and included the following:
  - HCV RNA levels
  - Percentiles and z-scores for weight, height, and body mass index (BMI)
  - Tanner pubertal stage
- Participants with ≥1 postbaseline assessment were included in the analysis

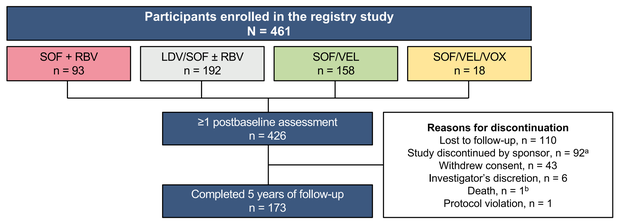
Study Design



[a]Date of last visit in parent study. [b]HCV RNA analyzed by COBAS AmpliPrep, COBAS TaqMan HCV Quantitative Test, v2.0 (Roche Molecular Diagnostics, Pleasanton, CA, USA). [c]Percentiles and z-scores were calculated using the Centers for Disease Control and Prevention reference charts (2000).[13] [d]Tanner stage was assessed and shifts from baseline at each study visit were determined.
HCV, hepatitis C virus; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir; W, week.

Results

Participant Disposition



[a]The study ended early after all participants had discontinued or reached at least week 144 of follow-up.
[b]Death not related to treatment (progressive cerebellar glioblastoma).
LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

Duration of Follow-Up

	SOF + RBV n = 88	LDV/SOF ± RBV n = 178	SOF/VEL n = 142	SOF/VEL/VOX n = 18	Total N = 426
Duration, weeks, median (range)	239 (25–312)	239 (21–325)	169 (9–256)	143 (80–149)	193 (9–325)

LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

- Median (range) follow-up from the last visit in the parent study was 3.7 (0.2–6.3) years among all participants

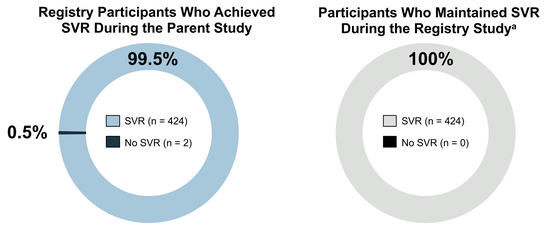
Baseline Characteristics

	SOF + RBV n = 88	LDV/SOF ± RBV n = 178	SOF/VEL n = 142	SOF/VEL/VOX n = 18	Total N = 426
Age, years, mean (range)	12 (3–18)	11 (3–18)	11 (3–18)	14 (12–18)	12 (3–18)
Male, n (%)	36 (41)	78 (44)	58 (41)	7 (39)	179 (42)
Race, n (%)					
White	69 (78)	152 (85)	108 (76)	13 (72)	342 (80)
Black	4 (5)	12 (7)	11 (8)	1 (6)	28 (7)
Asian	8 (9)	7 (4)	9 (6)	2 (11)	26 (6)
Other[a] or not reported	7 (8)	7 (4)	14 (10)	2 (11)	30 (7)
HCV genotype, n (%)					
GT1	0	173 (97)	104 (73)	4 (22)	281 (66)
GT2	26 (30)	0	9 (6)	4 (22)	39 (9)
GT3	62 (70)	2 (1)	16 (11)	8 (44)	88 (21)
GT4	0	3 (2)	6 (4)	2 (11)	11 (3)
GT5	0	0	0	0	0
GT6	0	0	6 (4)	0	6 (1)
Unknown	0	0	1 (1)	0	1 (<1)
Weight z-score, median (Q1, Q3)	0.3 (−0.5, 1.0)	0.3 (−0.5, 1.1)	0.2 (−0.5, 1.0)	0.1 (−0.7, 0.5)	0.3 (−0.5, 1.0)
Height z-score, median (Q1, Q3)	0.0 (−0.9, 0.7)	−0.2 (−1.0, 0.5)	−0.2 (−0.8, 0.5)	0.0 (−0.5, 0.4)	−0.2 (−0.9, 0.5)
BMI z-score, median (Q1, Q3)	0.2 (−0.4, 1.1)	−0.4 (−0.2, 1.3)	0.5 (−0.3, 1.2)	0.1 (−0.7, 0.5)	0.4 (−0.3, 1.2)

[a]Other races include American Indian/Alaska Native and Native Hawaiian/Pacific Islander.
BMI, body mass index; GT, genotype; HCV, hepatitis C virus; LDV, ledipasvir; Q, quartile; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

- The mean (SD) age was 12 (4.1) years, and 42% of participants were male

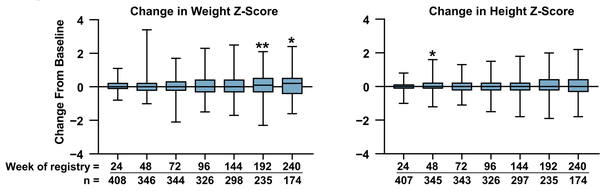
Durability of SVR



[a]Among participants who achieved SVR during the parent study.
SVR, sustained virologic response.

- Among those who achieved SVR, median (range) duration of SVR was 4.0 (0.6–6.5) years
- Participants who did not achieve SVR in the parent study had NS5A resistance–associated variants (RAVs)
  - One participant treated with LDV/SOF had the NS5A RAV Y93H, which developed at week 4 posttreatment and was maintained through week 144
  - One participant treated with SOF/VEL had the NS5A RAV L31V, which developed at week 8 on treatment; the L31V RAV was not detected at weeks 24 and 48, was detected as a mixture (L31L/V) at week 72, and was not detected at weeks 96, 144, or 192
  - No NS5B RAVs were detected during the parent or registry studies

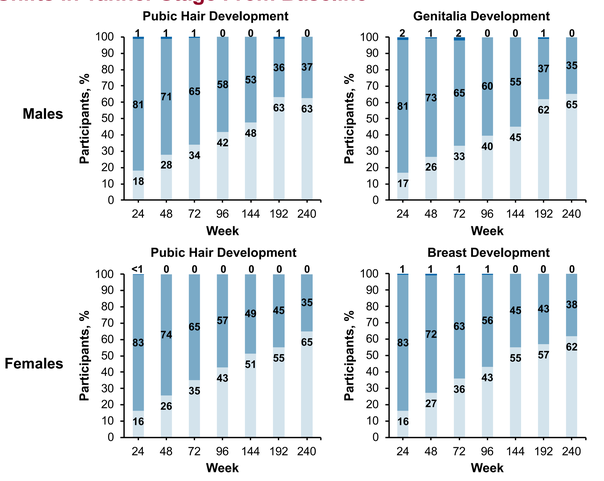
Long-Term Impact on Growth[a]



[a]Pooled analysis of participants who received SOF + RBV, LDV/SOF ± RBV, SOF/VEL, and SOF/VEL/VOX in parent clinical trials.
*P <.05; **P <.01 based on Wilcoxon signed-rank test if median change from baseline is different from 0.
BMI, body mass index; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

- Median changes in z-scores for weight were 0.1 and 0.2 at weeks 192 and 240, respectively, and the median change in BMI z-score was 0.1 at week 240. Median change in z-score at all other time points was 0.0 for weight, height, and BMI
- Comparable results were also observed when data were stratified by treatment regimen, age group, and sex

Shifts in Tanner Stage From Baseline[a]



[a]Pooled analysis of participants who received SOF + RBV, LDV/SOF ± RBV, SOF/VEL, and SOF/VEL/VOX in parent clinical trials. [b]Decreases in Tanner stage were not sustained or consistent across Tanner stage assessments and reflect known qualitative variability of these measurements.
LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

- Treatment with SOF-based DAAs did not impact development of secondary sexual characteristics as assessed by Tanner stage