FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination +/- Ribavirin in Adolescents and Children with Chronic HCV-Infection
Name of Test Drug:	Ledipasvir (LDV)/sofosbuvir (SOF) fixed-dose combination (FDC)
Dose and Formulation:	LDV/SOF FDC (90/400 mg) (1 × 90/400-mg tablet, 4 × 22.5/100-mg tablets, or 8 × 11.25/50-mg packets with granules) LDV/SOF FDC (45/200 mg) (2 × 22.5/100-mg tablets or 4 × 11.25/50-mg packets with granules) LDV/SOF FDC (33.75/150 mg) (3 × 11.25/50-mg packets with granules)
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-337-1116
Phase of Development:	Phase 2
IND No.:	115268
EudraCT No.:	2014-003578-17
ClinicalTrials.gov Identifier:	NCT02249182
Study Start Date:	05 November 2014 (First Subject Screened)
Study End Date:	15 June 2018 (Last Subject Last Observation for the Primary Endpoint)
Principal or Coordinating Investigator:	Name: William Balistreri, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Benedetta Massetto, MD, PhD Telephone: PPD Fax: PPD
Report Date:	27 November 2018
Previous Report Date(s):	16 June 2016 (Interim Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-337-1116

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination +/- Ribavirin in Adolescents and Children with Chronic HCV-Infection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 33 study sites in the United States (US), United Kingdom (UK), Australia, and New Zealand.

Publications:

Schwarz KB, Rosenthal P, Murray KF, Honegger JR, Hardikar W, Hague R, et al. Ledipasvir/Sofosbuvir for 12 Weeks Is Safe and Effective in Children 3 to <6 Years Old with Chronic Hepatitis C Virus Infection. Hepatology 2018;68 (S1): 116A-117A.

Begley R, Meng A, Massetto B, Shao J, Ling J, and Mathias A. Pharmacokinetics of Once Daily Sofosbuvir or Ledipasvir/Sofosbuvir in HCV-Infected Pediatrics Aged 3 to <6 Years Old. Hepatology 2018;68 (S1): 582A.

Murray KF, Balistreri WF, Bansal S, Whitworth S, Evans HM, Gonzalez-Peralta RP, et al. Safety and Efficacy of Ledipasvir-Sofosbuvir With or Without Ribavirin for Chronic Hepatitis C in Children Ages 6-11. Hepatology 2018 (epub ahead of print)

Younossi ZM, Stepanova M, Balistreri W, Schwarz K, Murray KF, Rosenthal P, et al. Health-related Quality of Life in Adolescent Patients With Hepatitis C Genotype 1 Treated With Sofosbuvir and Ledipasvir. J Pediatr Gastroenterol Nutr 2018;66 (1): 112-6.

Balistreri WF, Murray KF, Rosenthal P, Bansal S, Lin CH, Kersey K, et al. The Safety and Effectiveness of Ledipasvir-Sofosbuvir in Adolescents 12-17 Years Old With Hepatitis C Virus Genotype 1 Infection. Hepatology 2017;66 (2):371-8.

Garrison KL, Mathias A, Kersey K, Kanwar B, Ni L, Jain A, et al. Pharmacokinetics of Once-Daily Sofosbuvir and Ledipasvir/Sofosbuvir in HCV-Infected Pediatrics Aged 6 to < 12 Years Old. Hepatology 2016;64 (S1): 436A.

Kirby B, German P, Kanwar B, Ni L, Lakatos I, Ling J, Mathias A. Pharmacokinetics of Once-Daily Sofosbuvir and Ledipasvir/Sofosbuvir in HCV-Infected Adolescents. Hepatology 2015;62 (S1): 1040A-1041A.

Study Period:

05 November 2014 (First Subject Screened)

15 June 2018 (Last Subject Last Observation for the Primary Endpoint)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- **Pharmacokinetic (PK) lead-in phase:** To evaluate the steady-state PK and confirm the dose of ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) in chronic hepatitis C virus (HCV)-infected pediatric subjects
- **Treatment phase:** To evaluate the safety and tolerability of LDV/SOF FDC ± ribavirin (RBV) for 12 or 24 weeks in chronic HCV-infected pediatric subjects

The secondary objectives of this study were as follows:

- **PK lead-in phase:**
  - To evaluate the safety, tolerability, and antiviral activity of 10 days of dosing of LDV/SOF FDC in chronic HCV-infected pediatric subjects
- **Treatment phase:**
  - To determine the antiviral efficacy of 12 or 24 weeks of LDV/SOF FDC ± RBV treatment in chronic HCV-infected subjects (including the impact of HCV genotype, IL28B genotype, and prior treatment experience), as assessed by the proportion of subjects with sustained viral response (SVR) 12 weeks after completion of treatment (SVR12)
  - To determine the antiviral efficacy of 12 or 24 weeks of LDV/SOF FDC ± RBV treatment in chronic HCV-infected subjects, as assessed by the proportion of subjects with SVR 4 and 24 weeks after completion of treatment (SVR4 and SVR24)
  - To evaluate the kinetics of circulating HCV RNA during treatment and after completion of treatment
  - To evaluate the emergence of viral resistance to LDV and SOF during treatment and after completion of treatment
  - To evaluate acceptability assessed by swallowability of tablets and palatability of granules
  - To evaluate the effect on growth and development of pediatric subjects during and after treatment

The exploratory objective of this study was as follows:

- To identify or validate genetic markers that may be predictive of the natural history of disease, response to therapy, and/or tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics), in subjects who provide their separate and specific consent

Methodology: This Phase 2, open-label, multicohort, 2-part study evaluated the PK, safety, and efficacy of LDV/SOF±RBV in pediatric subjects aged 3 to < 18 years with chronic genotype 1, 3, 4, 5, or 6 HCV infection. Per the study protocol, subjects with genotype 2 HCV infection were eligible for enrollment once data in adult patients were available; however, no subjects with genotype 2 HCV infection were enrolled because LDV/SOF was not approved for treatment of adults with genotype 2 HCV infection in any country in which this study was conducted, at the time of enrollment.

Approximately 220 subjects were planned to be enrolled: approximately 100 adolescent subjects 12 to < 18 years old and approximately 120 pediatric subjects 3 to < 12 years old. Subjects could be either treatment naive or treatment experienced, with up to 40 subjects allowed to be treatment experienced.

Subjects of 3 age groups were enrolled in a sequential fashion: 12 to < 18 years old, followed by 6 to < 12 years old, and 3 to < 6 years old.

Subjects received 1 of the following treatments based on country of enrollment, HCV genotype, prior treatment experience, and cirrhosis status:

	United States/Australia/New Zealand	**United Kingdom**
Treatment Naive with or without Cirrhosis		
Genotype 1	LDV/SOF 12 weeks	LDV/SOF 12 weeks
Genotypes 4, 5, or 6	LDV/SOF 12 weeks	LDV/SOF 12 weeks
Treatment Experienced without Cirrhosis		
Genotype 1	LDV/SOF 12 weeks	LDV/SOF 12 weeks
Genotypes 4, 5, or 6	LDV/SOF 12 weeks	LDV/SOF 12 weeks
Genotype 3	NA	LDV/SOF+RBV 24 weeks
Treatment Experienced with Cirrhosis		
Genotype 1	LDV/SOF 24 weeks	LDV/SOF 24 weeks
Genotypes 4, 5, or 6	LDV/SOF 12 weeks	LDV/SOF 24 weeks
Genotype 3	NA	LDV/SOF+RBV 24 weeks

NA = not applicable

This study consisted of a PK lead-in phase and a treatment phase.

PK Lead-In Phase

The PK lead-in phase evaluated and/or confirmed the age-appropriate LDV/SOF dose by analyzing PK and safety data of LDV/SOF through 10 days of dosing. Three cohorts, each with at least 10 treatment-naive subjects without history of cirrhosis, were sequentially enrolled:

- Cohort 1: 12 to < 18 years old weighing ≥ 45 kg
- Cohort 2: 6 to < 12 years old weighing ≥ 17 kg and < 45 kg
- Cohort 3: 3 to < 6 years old (at least 4 subjects weighing ≥ 17 kg and at least 4 subjects weighing < 17 kg)

Intensive PK and safety results through Day 10 of treatment for each cohort were reviewed to confirm the appropriateness of the evaluated LDV/SOF dose prior to initiating the treatment phase of that age group and determining the age-appropriate dose to be evaluated in the PK lead-in phase of the next age group.

Treatment Phase

Subjects who participated in the PK lead-in phase were immediately rolled over into the treatment phase with no interruption of study drug administration.

Additional treatment-naive or treatment-experienced subjects were enrolled into the treatment phase upon confirmation of the age-appropriate LDV/SOF dose from the PK lead-in phase. The treatment phase was initiated sequentially by age group as defined in Cohorts 1, 2, and 3 of the PK lead-in phase. No weight limits applied to the additional subjects enrolled in the treatment phase. Subjects were to complete the following visits: screening, Day 1, Weeks 1, 2, 4, 8, and 12 (and Weeks 16, 20, and 24 for the 24-week treatment group) during the treatment phase followed by posttreatment visits 4, 12, and 24 weeks after discontinuation of therapy. For subjects who participated in the PK lead-in phase, the first visit in the treatment phase was the Week 2 visit.

Subjects 3 to < 6 years old providing written consent were eligible for participation in an optional intensive PK substudy. Intensive serial PK blood samples were collected at Week 4 or 8 at the following time points: 0 (predose), 0.5, 1, 2, 3, 4, 5, 8, and 12 hours postdose (with predose also serving as t = 24).

Subjects providing separate and specific consent were eligible for participation in the pharmacogenomics substudy. A blood sample was drawn for this substudy at the Day 1 visit or at any time during the study.

Subjects who attained SVR24, or those who did not attain SVR24 and did not initiate experimental or approved anti-HCV therapy, could enroll in a long-term registry study (GS-US-334-1113) for assessment of growth, quality of life, and long-term viral suppression (if applicable).

Analysis of data for subjects 12 to < 18 years old who had completed the posttreatment Week 12 visit or had prematurely discontinued from the study was previously reported in the interim clinical study report (CSR) (16 June 2016). This final analysis was conducted when all subjects 3 to < 18 years old completed the posttreatment Week 24 visit or prematurely discontinued from the study.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 220 subjects

Analyzed:

- Full Analysis Set: 226 subjects
- Safety Analysis Set: 226 subjects
- PK Analysis Set: 226 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females 3 to < 18 years of age, with chronic HCV genotype 1, 3, 4, 5, or 6 infection, HCV RNA ≥ 1000 IU/mL, and were HCV treatment naive or treatment experienced. In the PK lead-in phase only, enrolled subjects were treatment naive. Weight limits were defined for subjects enrolled in the PK lead-in phase only: subjects in Cohort 1 (12 to < 18 years old) were required to weigh ≥ 45 kg, subjects in Cohort 2 (6 to < 12 years old) were required to weigh ≥ 17 kg and < 45 kg, and Cohort 3 was to include at least 4 subjects weighing ≥ 17 kg and at least 4 subjects weighing < 17 kg. Weight limits did not apply to additional subjects of each age group enrolled in the treatment phase.

Duration of Treatment: Treatment duration was 12 or 24 weeks, with up to 24 weeks of posttreatment follow-up.

Test Product, Dose, Mode of Administration, and Batch No.:

Test product:

- LDV/SOF FDC (90/400-mg tablet) (adult-strength tablet)
- LDV/SOF FDC (22.5/100-mg tablet) (low-dose tablet)
- LDV/SOF FDC (11.25/50-mg packets containing granules)
- Placebo-to-match LDV/SOF FDC (90/400-mg tablet)
- Placebo-to-match LDV/SOF FDC (22.5/100-mg tablet)
- RBV 40-mg/mL oral solution

The study protocol included a RBV 200-mg capsule formulation; however, the 2 subjects who received RBV in this study were administered the RBV 40-mg/mL oral solution. Information regarding the capsule formulation is not presented here but is provided in the protocol.

Dosages and formulations by age group:

LDV/SOF doses evaluated in the PK lead-in phase for each age group were confirmed to be the appropriate doses based on intensive PK and safety results through Day 10 of treatment for each cohort. As such, the same doses were used in the treatment phase for each corresponding age group.

- 12 to < 18 years old (dose = LDV/SOF FDC [90/400 mg]): LDV/SOF was administered to subjects 12 to < 18 years old at a dose of 90/400 mg orally once daily (1 × 90/400-mg tablet, 4 × 22.5/100-mg tablets, or 8 × 11.25/50-mg packets containing granules). The selection of the formulation was based on the swallowability assessment using matching placebo tablet at screening or baseline.
- 6 to < 12 years old (dose = LDV/SOF FDC [45/200 mg]): LDV/SOF was administered to subjects 6 to < 12 years old at a dose of 45/200 mg orally once daily (2 × 22.5/100-mg tablets or 4 × 11.25/50-mg packets containing granules). The selection of the formulation was based on the swallowability assessment using matching placebo tablet at screening or baseline.
- 3 to < 6 years old weighing ≥ 17 kg (dose = LDV/SOF FDC [45/200 mg]): LDV/SOF FDC (4 × 11.25/50-mg packets containing granules) was administered orally once daily.

- 3 to < 6 years old weighing < 17 kg (dose = LDV/SOF FDC [33.75/150 mg]): LDV/SOF FDC (3 × 11.25/50-mg packets containing granules) were administered orally once daily.
- Ribavirin was administered orally with LDV/SOF in subjects with genotype 3 HCV infection only, at a total daily dose according to weight at baseline as shown below.

Body Weight kg (lb)	RBV Daily Dose
< 47 (< 103)	15 mg/kg/day
47−49 (103−108)	600 mg/day
50−65 (110–143)	800 mg/day
66−80 (145–176)	1000 mg/day
81−105 (178−231)	1200 mg/day
> 105 (> 231)	1400 mg/day

The batch numbers of study drugs administered in this study were as follows:

- LDV/SOF FDC (90/400-mg tablet): DK1313B3, DK1309B1
- LDV/SOF FDC (22.5/100-mg tablet): DK1407B1
- LDV/SOF FDC (11.25/50-mg packets containing granules): EL1602D1
- Placebo-to-match LDV/SOF FDC (90/400 mg): DK1207B1
- Placebo-to-match LDV/SOF FDC (22.5/100 mg): DK1406B1
- RBV 40-mg/mL oral solution: H22001

Reference Therapy, Dose, Mode of Administration, and Batch No.: None

Criteria for Evaluation:

Efficacy: Blood samples to determine serum levels of HCV RNA were collected from subjects at screening; baseline/Day 1; Days 3 and 10 (PK lead-in phase only); Weeks 1 (excluding subjects who rolled over from the PK lead-in phase), 2, 4, 8, 12, or early termination as applicable (all subjects); Weeks 16, 20, and 24 (24-week treatment group); and posttreatment Weeks 4, 12, and 24 (all subjects). The COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Pharmacokinetics: For subjects in the PK lead-in phase, intensive serial PK blood samples were collected over 12 hours postdose at the Day 10 visit at the following time points: 0 (predose), 0.5, 1, 2, 3, 4, 5, 8, and 12 hours postdose for subjects 12 to < 18 years old and 6 to < 12 years old; and 0 (predose), 0.5, 2, 4, 8, and 12 hours postdose for subjects 3 to < 6 years old.

During the treatment phase, a single PK blood sample was collected from all subjects at Weeks 1 (excluding subjects who rolled over from the PK lead-in phase), 2, 4, 8, 12, or early termination, as applicable (all subjects) and Weeks 16, 20, and 24 (24-week treatment group).

For subjects 3 to < 6 years old who participated in the optional intensive PK substudy, intensive serial PK blood samples were collected at Week 4 or 8 at the following time points: 0 (predose), 0.5, 1, 2, 3, 4, 5, 8, and 12 hours postdose (with predose also serving as t = 24).

The PK of LDV, SOF, and SOF metabolite GS-331007 were assessed.

Safety: Safety assessments included monitoring of adverse event (AEs) and concomitant medications, clinical laboratory analyses, Tanner pubertal stage assessments, height and weight measurements, bone age assessments, vital signs measurements, and physical examinations.

Quality of Life: Health-related quality of life was assessed using the PedsQL™ Pediatric Quality of Life Inventory V4.0 Short Form (SF15). The quality of life assessments were completed at Day 1, end of treatment (Week 12, Week 24, or at early termination, if applicable), and posttreatment Weeks 12 and 24. Subjects ≥ 5 years old and their parents/guardians were administered a survey based on the age of the subject at the time of the assessment (5 to 7 years old, 8 to 12 years old, or 13 to 18 years old). For subjects 3 to 4 years old, only the parents/guardians were administered the survey.

Other: Swallowability assessments were to be performed for the tablet formulations at screening up to Day 1. Palatability assessments were to be performed for oral granules at Day 1.

Statistical Methods:

Efficacy: The key efficacy endpoint was SVR12, defined as HCV RNA < LLOQ 12 weeks after completion of the study drug, in the Full Analysis Set. The point estimate of SVR12 rate and 2-sided 95% exact CI based on the Clopper-Pearson method were provided by treatment group and total in each age group.

Secondary efficacy endpoints included SVR4, SVR24, proportion of subjects with HCV RNA < LLOQ by study visit while on treatment and during the posttreatment follow-up period, HCV RNA $\log_{10}$ IU/mL and changes from baseline through end of treatment, the proportion of subjects with virologic failure, and the proportion of subjects with alanine aminotransferase (ALT) normalization. The 2-sided 95% exact confidence interval (CI), based on the Clopper-Pearson method, was provided for the percentage of subjects with SVR4, SVR24, and for the percentages of subjects with HCV RNA < LLOQ at each postbaseline visit for the Full Analysis Set. Summary statistics were presented for absolute values and changes from baseline in HCV RNA ($\log_{10}$ IU/mL) by visit through end of treatment, virologic outcomes, and proportion of subjects with ALT normalization by visit.

Pharmacokinetics: Concentrations of SOF, GS-331007, and LDV from subjects in the PK lead-in phase of each age group were presented by subject and time point. Pharmacokinetic parameters from subjects in the PK lead-in phase were summarized (AUC_{tau}, AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, $t_{1/2}$, volume of distribution, and clearance, as appropriate). Population PK modeling was applied on the combined data from both intensive PK samples from subjects in the PK lead-in phase and sparse PK samples collected in the treatment phase for all subjects to characterize the PK of SOF, GS-331007, and LDV using mixed-effect modeling techniques. Estimated PK parameters using the population PK model will be presented in a separate Population PK report.

To confirm the appropriateness of the LDV/SOF dose for each age group, PK parameters for LDV, SOF, and GS-331007 from subjects in the PK lead-in phase of each age group were compared with those in the population PK-derived exposure data from adult Phase 2/3 studies. Geometric mean ratios and their 90% CIs were provided.

Safety: All enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety data included all data collected on or after the first dose of any study drug up to the date of the last dose of study drug plus 30 days. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1.

Quality of Life: The health-related quality of life questionnaires (SF15) were completed at Day 1, end of treatment (Week 12, Week 24, or at early termination, if applicable), and at posttreatment Weeks 12 and 24 by the subjects (except for toddlers 3 to 4 years old) and their parents/legal guardians. A Wilcoxon signed rank test was used to explore within-treatment group changes in status from baseline to end of treatment and from end of treatment to each of the posttreatment time points.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and maximum) by treatment group. All categorical endpoints were summarized by number and percentage of subjects who met the endpoint definitions.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

12 to < 18 Years Old

Of the 100 adolescent subjects enrolled, all received at least 1 dose of study drug and were included in the Safety Analysis Set and Full Analysis Set. All subjects were enrolled to receive LDV/SOF for 12 weeks. All but 1 subject completed study treatment. One subject prematurely discontinued study treatment due to being lost to follow-up.

Overall, the majority of subjects were female (63.0%), white (91.0%), and non-Hispanic/Latino (85.0%), with a mean age of 15 years. The mean (SD) baseline BMI value for subjects was 23.0 (5.32) kg/m^2.

Overall, the majority of subjects had been infected through vertical transmission (84.0%). All adolescent subjects had genotype 1 HCV infection, 81.0% with the genotype 1a subtype and 19.0% with the genotype 1b subtype. The majority of subjects had non-CC (CT or TT) IL28B alleles (76.0%), and HCV RNA ≥ 800,000 IU/mL (55.0%), with a mean (SD) baseline HCV RNA value of 6.0 (0.55) log_{10} IU/mL. One subject (1.0%) had known cirrhosis based on prior biopsy. The mean (SD) baseline ALT value was 53 (52.7) U/L, and 26.0% of subjects had baseline ALT values > 1.5 × ULN. The mean (SD) baseline eGFR using the Schwartz formula was 151.9 (36.13) mL/min/1.73 m^2. The majority of the subjects were treatment naive (80.0%).

The baseline and demographic characteristics have been updated in the final analysis from those reported in the interim CSR (16 June 2016) for small changes to the baseline characteristics for the subjects previously reported in the interim CSR (the majority of which consisted of a change of cirrhosis status from “unknown” to “no”, or “no” to “unknown”). None of the changes impacted the interpretation of study results.

6 to < 12 Years Old

All 92 subjects who were enrolled received at least 1 dose of study drug and were included in the Safety Analysis Set and Full Analysis Set. In this age group, 89 subjects were enrolled to receive LDV/SOF for 12 weeks, 1 subject was enrolled to receive LDV/SOF for 24 weeks, and 2 subjects with genotype 3 HCV infection were enrolled to receive LDV/SOF+RBV for 24 weeks. All subjects (100.0%) completed study treatment.

Overall, the majority of subjects were male (58.7%), white (79.3%), and non-Hispanic/Latino (84.8%), with a mean age of 9 years. The mean (SD) baseline BMI value for subjects was 18.2 (3.47) kg/m^2.

Overall, the majority of subjects had been infected through vertical transmission (96.7%). The majority of subjects had genotype 1 HCV infection (95.7%, 88 subjects [77 with the genotype 1a subtype, 10 with the genotype 1b subtype, and 1 with undetermined subtype]). Two subjects (2.2%) had genotype 3 HCV infection, and 2 subjects (2.2%) had genotype 4 HCV infection. The majority of subjects had non-CC (CT or TT) IL28B alleles (73.9%), and HCV RNA ≥ 800,000 IU/mL (58.7%), with a mean (SD) baseline HCV RNA value of 6.0 (0.59) log_{10} IU/mL. Two subjects (2.2%) had known cirrhosis based on prior biopsy. The mean (SD) baseline ALT value was 66 (41.1) U/L, and 55.4% of subjects had baseline ALT values > 1.5 × ULN. The mean (SD) baseline eGFR using the Schwartz formula was 156.4 (24.38) mL/min/1.73 m^2. The majority of subjects were treatment naive (78.3%).

3 to < 6 Years Old

All 34 subjects who were enrolled received at least 1 dose of study drug and were included in the Safety Analysis Set and Full Analysis Set. All subjects were enrolled to receive LDV/SOF for 12 weeks. A total of 33 subjects (97.1%) completed study treatment. One subject prematurely discontinued study treatment due to an AE of product taste abnormal.

The majority of subjects were female (70.6%), white (79.4%), and non-Hispanic/Latino (82.4%), with a mean age of 4 years. The mean (SD) baseline BMI value for subjects was 16.7 (2.35) kg/m^2.

All subjects had been infected through vertical transmission (100.0%). The majority of subjects had genotype 1 HCV infection (97.1%, 33 subjects [28 with the genotype 1a subtype and 5 with the genotype 1b subtype]). One subject (2.9%) had genotype 4 HCV infection. The majority of subjects had non-CC (CT or TT) IL28B alleles (64.7%). The majority of subjects had HCV RNA ≥ 800,000 IU/mL (55.9%) and a mean (SD) baseline HCV RNA value of 6.0 (0.62) log_{10} IU/mL. No subjects had cirrhosis based on prior biopsy. The mean (SD) baseline ALT value was 62 (31.6) U/L, and 52.9% of subjects had baseline ALT values > 1.5 × ULN. The mean (SD) baseline eGFR using the Schwartz formula was 169.1 (28.04) mL/min/1.73 m^2. All subjects were treatment naive (100.0%).

Efficacy and Virologic Resistance Results:

12 to < 18 Years Old

The key efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after completion of treatment with study drug) in the Full Analysis Set. The SVR12 rates were as follows for adolescent subjects 12 to < 18 years old treated with LDV/SOF for 12 weeks:

- LDV/SOF for 12 weeks (overall): 98.0% (95% CI: 93.0% to 99.8%) of subjects (98 of 100) achieved SVR12; all subjects had genotype 1 HCV infection.
  - Treatment-naive subjects with or without cirrhosis: 97.5% (95% CI: 91.3% to 99.7%) of subjects (78 of 80) achieved SVR12. The only subject with known cirrhosis achieved SVR12.
  - Treatment-experienced subjects without cirrhosis: 100.0% (95% CI: 83.2% to 100.0%) of subjects (20 of 20) achieved SVR12.

No subjects experienced virologic failure. Two subjects who did not achieve SVR12 were categorized as "other". Both subjects completed the Week 12 visit (HCV RNA < LLOQ), but had not returned for any subsequent visits.

The overall concordance between SVR12 and SVR24 was 100.0%.

HCV RNA levels (log_{10} IU/mL) declined rapidly with similar decreases in HCV RNA observed for treatment-naive and treatment-experienced subjects. Consistent with the rapid and sustained decline in HCV RNA, 96.3% of treatment-naive subjects and 100.0% of treatment-experienced subjects had HCV RNA < LLOQ at Week 4. All subjects, both treatment-naive and treatment-experienced, had HCV RNA < LLOQ at Week 8.

Virologic Resistance: Pretreatment NS5A and NS5B NI RAVs were each observed in 5.1% of subjects with virologic outcome who were included in the Resistance Analysis Population. The presence of pretreatment NS5A and/or NS5B RAVs did not impact treatment outcome as all subjects with pretreatment RAVs achieved SVR12 and SVR24. There were no on-treatment virologic failures or relapses through posttreatment Week 24 and, therefore, no subject qualified for resistance testing posttreatment.

6 to < 12 Years Old

The key efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after completion of treatment with study drug) in the Full Analysis Set. The SVR12 rates for subjects 6 to < 12 years old were as follows:

- LDV/SOF for 12 weeks (overall): 98.9% (95% CI: 93.9% to 100.0%) of subjects (88 of 89) achieved SVR12, including 98.9% (86 of 87 subjects) with genotype 1 HCV infection and 100.0% (2 of 2 subjects) with genotype 4 HCV infection.
  - Treatment-naive subjects with or without cirrhosis: 98.6% (95% CI: 92.5% to 100.0%) of subjects (71 of 72) achieved SVR12, including 98.6% (69 of 70 subjects) with genotype 1 HCV infection and 100.0% (2 of 2 subjects) with genotype 4 HCV infection.
  - Treatment-experienced subjects without cirrhosis: 100.0% (95% CI: 80.5% to 100.0%) of subjects (17 of 17) achieved SVR12; all subjects had genotype 1 HCV infection.
- LDV/SOF for 24 weeks (genotype 1 HCV infection; treatment-experienced subjects with cirrhosis): 100.0% (95% CI: 2.5% to 100.0%) of subjects (1 of 1) achieved SVR12.
- LDV/SOF+RBV for 24 weeks (genotype 3 HCV infection; treatment-experienced subjects with or without cirrhosis): 100.0% (95% CI: 15.8% to 100.0%) of subjects (2 of 2) achieved SVR12.

Overall, 1 subject (1.1%, 1 of 92) experienced virologic failure. This subject, who was enrolled in the LDV/SOF 12 week group, was treatment naive with genotype 1a HCV infection and cirrhosis and relapsed at the posttreatment Week 4 visit. The subject was reported to have 97.6% study drug adherence.

Concordance between SVR12 and SVR24 was 100.0% in all 3 treatment groups.

HCV RNA levels (log_{10} IU/mL) declined rapidly with similar decreases in HCV RNA observed across treatment groups. Consistent with the rapid and sustained decline in HCV RNA, 96.6% of subjects in the LDV/SOF 12 week group had HCV RNA < LLOQ at Week 4, and all of them had HCV RNA < LLOQ at Week 8. The 3 subjects in the LDV/SOF±RBV 24 week groups had HCV RNA < LLOQ at Week 2.

Virologic Resistance: Pretreatment NS5A and NS5B NI RAVs were observed in 14.1% and 3.2% of subjects with virologic outcome who were included in the Resistance Analysis Population, respectively. The presence of pretreatment NS5A and/or NS5B RAVs did not impact treatment outcome, as all subjects with pretreatment RAVs achieved SVR12 and SVR24. One subject infected with genotype 1a HCV failed to achieve SVR12 and SVR24. This subject had no pretreatment NS5A or NS5B NI RAVs at baseline and had emergent NS5A RAV Y93H at relapse.

3 to < 6 Years Old

The key efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after completion of treatment with study drug) in the Full Analysis Set. The overall SVR12 rates for subjects 3 to < 6 years old were as follows:

- LDV/SOF for 12 weeks (genotype 1 or 4 HCV infection; treatment-naive subjects with or without cirrhosis): 97.1% (95% CI: 84.7% to 99.9%) of subjects (33 of 34) achieved SVR12, including 97.0% (32 of 33 subjects) with genotype 1 HCV infection and 100.0% (1 of 1 subject) with genotype 4 HCV infection.

No subjects experienced on-treatment virologic failure or relapse. One subject who did not achieve SVR12 was categorized as “other”. This subject prematurely discontinued study treatment due to an AE of product taste abnormal.

Overall concordance between SVR12 and SVR24 was 100.0%.

HCV RNA levels (log_{10} IU/mL) declined rapidly with similar decreases in HCV RNA observed. Consistent with the rapid and sustained decline in HCV RNA, 97.0% of subjects had HCV RNA < LLOQ at Week 4, and all subjects had HCV RNA < LLOQ at Week 8.

Virologic Resistance: Pretreatment NS5A and NS5B NI RAVs were observed in 12.1% and 6.1% of subjects with virologic outcome who were included in the Resistance Analysis Population, respectively. The presence of pretreatment NS5A and/or NS5B RAVs did not impact treatment outcome as all subjects with pretreatment RAVs achieved SVR12 and SVR24. There were no on-treatment virologic failures or relapses through posttreatment Week 24 and, therefore, no subject qualified for resistance testing posttreatment.

Pharmacokinetics Results: Plasma concentration data from all PK samples (intensive and sparse) were combined and used to generate PK parameters for all subjects using a Population PK modeling approach. Population PK derived parameters are presented for all subjects in a separate Population PK Report (m2.7.2).

Safety Results:

All AEs and laboratory abnormalities discussed in this CSR were treatment emergent and are referred to as AEs and laboratory abnormalities in this report, unless otherwise specified. Evaluations of safety data through 30 days after the last dose of study drugs in subjects 12 to < 18 years old were summarized in Section 11 of the interim CSR (16 June 2016).

12 to < 18 Years Old

Overall, treatment with LDV/SOF for 12 weeks was generally safe and well tolerated by adolescents 12 to < 18 years of age.

The majority of subjects (71.0%, 71 of 100) experienced at least 1 AE. The 3 most commonly reported AEs were headache (26.0%), and fatigue and diarrhea (each 13.0%). All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. No SAEs, AEs leading to discontinuation of study drug, or deaths were reported.

The majority of adolescent subjects 12 to < 18 years old had at least 1 laboratory abnormality (68.0%, 68 of 100), the majority of which were Grade 1 or 2 in severity. Nine subjects (9.0%) had Grade 3 (8 subjects) or Grade 4 (1 subject) laboratory abnormalities. The only Grade 3 or 4 laboratory abnormality that occurred in > 1 subject was Grade 3 increased serum amylase (3.0%, 3 of 100 subjects). Three subjects with Grade 1 or 2 increased amylase at screening and baseline had transient Grade 3 elevations in amylase. There were no cases of clinical pancreatitis. One subject had a Grade 4 laboratory abnormality of elevated AST that was also reported as a Grade 2 AE and was associated with the start of treatment with isotretinoin for acne. The subject had a concurrent Grade 2 elevation in ALT but no changes in bilirubin. The subject's AST levels subsequently normalized with continued isotretinoin administration.

No notable effects of study treatment on development or growth as assessed by changes from baseline through posttreatment Week 24 in Tanner pubertal stages, bone age, height, weight, and BMI percentiles were observed.

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during the study.

6 to < 12 Years Old

Overall, treatment with LDV/SOF±RBV for 12 or 24 weeks was generally safe and well tolerated by subjects 6 to < 12 years of age.

The majority of subjects (70.7%, 65 of 92 subjects) experienced at least 1 AE (69.7% [62 of 89] of subjects in the LDV/SOF 12 week group; all 3 subjects in the LDV/SOF±RBV 24 week groups experienced at least 1 AE). Among subjects in the LDV/SOF 12 week group, the 3 most commonly reported AEs were headache (18.0%), pyrexia (16.9%), and abdominal pain (15.7%). For the 3 subjects in the LDV/SOF±RBV 24 week groups, the only AE reported in > 1 subject was cough. All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. No AEs leading to

discontinuation of study drug or deaths were reported. One subject in the LDV/SOF 12 week group experienced 3 treatment-emergent SAEs (tooth abscess, abdominal pain, and gastroenteritis), none of which were assessed by the investigator as related to study drug or led to dose modification.

The majority of subjects had at least 1 laboratory abnormality reported (57.6%, 53 of 92). For all but 4 subjects, the maximum laboratory abnormality grade was Grade 1 or Grade 2. The only Grade 3 or 4 laboratory abnormality that occurred in > 1 subject was Grade 3 increased serum amylase (2.2%, 2 of 92 subjects). Both subjects had Grade 2 increased amylase at baseline. There were no cases of clinical pancreatitis. A Grade 4 laboratory abnormality was reported for decreased neutrophils, which was isolated and transient.

No notable effects of study treatment on development or growth as assessed by changes from baseline through posttreatment Week 24 in Tanner pubertal stages, bone age, height, weight, and BMI percentiles were observed in either treatment group.

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during the study.

3 to < 6 Years Old

Treatment with LDV/SOF for 12 weeks was generally safe and well tolerated by subjects 3 to < 6 years of age.

The majority of subjects (73.5%, 25 of 34) experienced at least 1 AE. The 3 most commonly reported AEs were vomiting (23.5%), and pyrexia and cough (each 20.6%). All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. One subject prematurely discontinued LDV/SOF due to a Grade 1 AE of product taste abnormal on Day 2.

The majority of subjects 3 to < 6 years old had at least 1 laboratory abnormality reported (70.6%, 24 of 34). All laboratory abnormalities were Grade 1 or Grade 2 in severity.

No notable effects of study treatment on development or growth as assessed by changes from baseline through posttreatment Week 24 in Tanner pubertal stages, bone age, height, weight, and BMI percentiles were observed in either treatment group.

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during the study.

Health-Related Quality of Life:

The SF15 questionnaire represented 4 domains: physical, emotional, social, and school functioning, with the emotional, social, and school functioning domains representing the psychosocial health summary.

Results should be interpreted with caution as multiple endpoints were being tested, and the study was not powered to test these exploratory endpoints.

12 to < 18 Years Old

Overall, there were no statistically significant ($p < 0.05$) mean changes in physical or psychosocial functioning scores during treatment (baseline to end of treatment) or during follow-up (end of treatment to posttreatment Week 24) per the subject reports. Based on the

parent reports, there were statistically significant mean increases (improvement) in physical and psychosocial functioning scores during treatment, followed by non-statistically significant mean decreases (worsening) during the follow-up period.

6 to < 12 Years Old

Overall, there were no statistically significant ($p < 0.05$) mean changes in physical or psychosocial functioning scores in any treatment group based on either the subject or parent reports during treatment (baseline to end of treatment) or during the follow-up (end of treatment to posttreatment), except for a statistically significant mean decrease (worsening) in physical functioning score during treatment (followed by a non-statistically significant decrease [worsening] during the follow-up period), and a statistically significant mean increase (improvement) in psychosocial health summary during treatment (followed by a non-statistically significant increase [improvement] during the follow-up period) in subjects in the LDV/SOF 12 week group, based on the subject reports.

3 to < 6 Years Old

Overall, there were no statistically significant ($p < 0.05$) mean changes in physical or psychosocial functioning scores based on either the subject or parent reports during treatment (baseline to end of treatment) or during the follow-up period (end of treatment to posttreatment Week 24). Of the 34 subjects 3 to < 6 years old who were enrolled, 17 subjects completed the questionnaire at baseline, 1 subject had missing assessments at baseline, and 16 subjects were not administered the questionnaire because they were between the ages of 3 to 4 years old.

CONCLUSIONS: The conclusions from Study GS-US-337-1116 are as follows:

- Treatment with LDV/SOF±RBV for 12 or 24 weeks in subjects with genotype 1, 3, or 4 HCV infection resulted in high SVR12 rates in all age groups as follows:
  - The SVR12 rates for adolescents 12 to < 18 years old with genotype 1 HCV infection were as follows:
    - LDV/SOF for 12 weeks (overall): 98.0% (98 of 100 subjects); all subjects had genotype 1 HCV infection
      - Treatment-naive subjects with or without cirrhosis: 97.5% (78 of 80 subjects)
      - Treatment-experienced subjects without cirrhosis: 100.0% (20 of 20 subjects)
  - The SVR12 rates for subjects 6 to < 12 years old with genotype 1, 3, or 4 HCV infection were as follows:
    - LDV/SOF for 12 weeks (overall): 98.9% (88 of 89 subjects), including 98.9% (86 of 87 subjects) with genotype 1 HCV infection and 100.0% (2 of 2 subjects) with genotype 4 HCV infection
      - Treatment-naive subjects with or without cirrhosis: 98.6% (71 of 72 subjects), including 98.6% (69 of 70 subjects) with genotype 1 HCV infection and 100.0%

(2 of 2 subjects) with genotype 4 HCV infection

- Treatment-experienced subjects without cirrhosis: 100.0% (17 of 17 subjects); all subjects had genotype 1 HCV infection

- LDV/SOF for 24 weeks (genotype 1 HCV infection; treatment-experienced subjects with cirrhosis): 100.0% (1 of 1 subject)

- LDV/SOF+RBV for 24 weeks (genotype 3 HCV infection; treatment-experienced subjects with or without cirrhosis): 100.0% (2 of 2 subjects)

— The SVR12 rates for subjects 3 to < 6 years old with genotype 1 or 4 HCV infection were as follows:

- LDV/SOF for 12 weeks (genotype 1 or 4 HCV infection; treatment-naive subjects with or without cirrhosis): 97.1% (33 of 34 subjects), including 97.0% (32 of 33 subjects) with genotype 1 HCV infection and 100.0% (1 of 1 subject) with genotype 4 HCV infection

- No subjects 12 to < 18 years old or 3 to < 6 years old experienced on-treatment virologic failure or relapse. One subject 6 to < 12 years old, who had genotype 1a HCV infection and cirrhosis and was treatment naive, relapsed at the posttreatment Week 4 visit.

- The presence of pretreatment NS5A and/or NS5B NI RAVs did not impact treatment outcome as all subjects with pretreatment RAVs achieved SVR12 and SVR24.

- Intensive PK analyses in the PK lead-in phase showed no clinically relevant differences in exposures of LDV, SOF, or GS-331007 in each age group compared with adults from the Phase 2/3 population, confirming the appropriateness of the doses utilized in the treatment phase.

- Treatment with LDV/SOF±RBV for 12 or 24 weeks was generally safe and well tolerated in all age groups. No Grade 3 or 4 AEs were reported, and few treatment-emergent SAEs or AEs leading to discontinuation of study drug were reported (1 subject each). No deaths were reported. No clinically relevant laboratory abnormalities were observed.

- No notable effects of treatment with LDV/SOF±RBV for 12 or 24 weeks on development or growth as assessed by changes from baseline to posttreatment Week 24 in Tanner pubertal stages, bone age, height, weight, and BMI percentiles were observed in any age group.