FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2, Open-label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed Dose Combination in the Treatment of Hepatitis C Virus (HCV) Infection in Pediatric Subjects Undergoing Cancer Chemotherapy
Name of Test Drug:	Ledipasvir (LDV)/Sofosbuvir (SOF) Fixed-Dose Combination (FDC)
Dose and Formulation:	LDV/SOF FDC (90/400 mg) tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-337-1904
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	Not Applicable 2018-003741-42
ClinicalTrials.gov Identifier:	NCT02868242
Study Start Date:	28 August 2016 (First Subject Screened)
Study End Date:	12 November 2018 (Last Subject Last Observation for the Primary Endpoint) 03 February 2019 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Manal Hamdy El-Sayed, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Kathryn Kersey, MSc Telephone: PPD Fax: PPD
Report Date:	18 June 2019

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS
STUDY GS-US-337-1904

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

Title of Study: A Phase 2, Open-label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed Dose Combination in the Treatment of Hepatitis C Virus (HCV) Infection in Pediatric Subjects Undergoing Cancer Chemotherapy

Investigators: Manal Hamdy El-Sayed, MD

Study Centers: Single center in Egypt.

Publications: El-Sayed MH, Ebeid FSE, Zekri AR, Massetto B, Kersey K, Osinusi A, et al. Ledipasvir/Sofosbuvir for 12 Weeks Is Safe and Effective in Adolescents With Chronic Hepatitis C Virus Infection and Hematologic Malignancies Undergoing Chemotherapy [Poster FRI-338]. European Association for the Study of the Liver (EASL); 2018 11-15 April; Paris, France.

Study Period:

28 August 2016 (First Subject Screened)
12 November 2018 (Last Subject Last Observation for the Primary Endpoint)
03 February 2019 (Last Subject Last Observation for this Report)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To evaluate the efficacy of ledipasvir/sofosbuvir (LDV/SOF) in treating HCV infection in pediatric subjects who were undergoing cancer chemotherapy, as measured by the proportion who achieved a sustained virologic response (SVR) 12 weeks after the end of HCV treatment (SVR12)
- To evaluate the safety and tolerability of treatment with LDV/SOF for 12 weeks

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attained SVR at 4 and 24 weeks after cessation of HCV treatment (SVR4 and SVR24)
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of HCV treatment

The exploratory objectives of this study were as follows:

- To evaluate the efficacy of LDV/SOF in preventing HCV flares defined as ≥ 3-fold increase in alanine aminotransferase (ALT) from Day 1 combined with ≥ 1 $\log_{10}$ increase in HCV RNA from Day 1, per subject during the study period, in pediatric subjects undergoing cancer chemotherapy
- To evaluate the effect of treatment with LDV/SOF on liver fibrosis progression in subjects receiving cancer chemotherapy as measured by mean change in FibroScan® score from screening to posttreatment
- To evaluate the incidence of cancer chemotherapy interruptions due to HCV flare (as defined above)
- To evaluate the emergence of viral resistance to LDV and SOF during treatment and after cessation of treatment, if possible

Methodology:

This Phase 2, single-center, open-label study investigated the efficacy and safety of LDV/SOF in pediatric subjects with chronic HCV infection who were receiving maintenance cancer chemotherapy.

Subjects were assigned to receive LDV/SOF FDC 90/400 mg (1 × 90/400-mg tablet or 4 × 22.5/100-mg tablets) once-daily based on a swallowability assessment performed at screening up to baseline/Day 1.

Screening assessments were completed within 28 days of the Day 1 visit. All subjects completed the following study visits: screening, baseline/Day 1, and on-treatment visits at the end of Weeks 1, 4, 8, and 12. All subjects completed the posttreatment Week 4, 12, and 24 visits.

Number of Subjects (Planned and Analyzed):
Planned: Approximately 40 pediatric subjects
Analyzed: 19 pediatric subjects

- All Enrolled Analysis Set: 19 pediatric subjects
- Full Analysis Set (FAS): 19 pediatric subjects
- Safety Analysis Set: 19 pediatric subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were male and female treatment-naive or treatment-experienced pediatric subjects, aged 12 to < 18 years, with chronic genotype 1 or 4 HCV infection, who were on a maintenance cancer chemotherapy regimen for hematological malignancy. Per the original protocol, eligible subjects were ≥ 45 kg; this was updated to ≥ 35 kg in the amended protocol.

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

Test Product, Dose, Mode of Administration, and Lot Numbers:

LDV/SOF was administered orally to subjects at a dose of 90/400 mg/day (1 tablet once-daily,

with or without food) for 12 weeks. The lot number of LDV/SOF (90/400 mg) tablets administered in this study was DK1309B1.

Placebo-to-match (PTM) LDV/SOF (90/400 mg) tablets were administered orally for the swallowability assessment. The lot number of the PTM LDV/SOF (90/400 mg) tablets was DK1207B1.

All pediatric subjects were able to swallow the PTM LDV/SOF (90/400 mg) tablets in the swallowability assessment; therefore, the lower dose LDV/SOF (22.5/100 mg) tablets were not administered to any subjects.

Reference Therapy, Dose, Mode of Administration, and Lot Numbers: None.

Criteria for Evaluation:

Efficacy: Blood samples to determine HCV RNA levels were collected from subjects at screening, Weeks 1, 4, 8, and 12, and posttreatment Weeks 12 and 24.

The artus® HCV RG RT-PCR Kit by QIAGEN was used to measure HCV RNA in this study. The lower limit of quantitation (LLOQ) of the assay was 50 IU/mL.

No viral sequencing was performed on any samples.

Pharmacokinetics: No pharmacokinetic (PK) assessments were performed during this study.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital signs measurements, and physical examinations.

Other: Other endpoints included the number of HCV flares (defined as an increase in ALT $\geq 3 \times$ baseline from Day 1 with $\geq 1 \times \log_{10}$ increase in HCV RNA relative to baseline) per subject, the time to HCV flares, and the number of chemotherapy interruptions per subject due to HCV flare. Other endpoints also included fibrosis endpoints, assessed based on changes in FibroScan score from pretreatment to posttreatment, and changes in Fibrotest® score.

Statistical Methods: All tables, figures, and listings produced for this study are provided in Section 15.1 and Appendix 16.2. Documentation of statistical methods is provided in Appendix 16.1.6.

The All Enrolled Analysis Set included all subjects who were enrolled into the study after screening. The FAS included all enrolled subjects who received at least 1 dose of study drug. The Safety Analysis Set included all subjects who received at least 1 dose of study drug. Summary of subject disposition included the number of subjects treated (Safety Analysis Set), in the FAS, who completed study treatment, who did not complete study treatment (and the reasons for doing so), who completed the study, and who did not complete the study (and the reasons for doing so).

Subject Demographics and Baseline Characteristics: Subject demographic and baseline characteristics were summarized using descriptive statistics (n, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, and maximum) for continuous variables, and using the numbers and percentages of subjects for categorical variables. Age was calculated in years at the date of initial study drug administration. If a subject did not receive study drug after enrollment, the subject's age was calculated from the date that the subject signed the informed consent form.

The summary of demographic data was provided for the Safety Analysis Set.

Efficacy: Efficacy was evaluated using scheduled assessments of HCV RNA. The primary efficacy endpoint was SVR12, defined as HCV RNA < LLOQ (ie, < 50 IU/mL) 12 weeks after discontinuation of all study drugs in the FAS.

The proportion of subjects achieving SVR12 was determined. A point estimate with a 2-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) {Clopper 1934} was constructed for the SVR12 rate. No hypothesis testing was performed.

The secondary efficacy endpoints included SVR4, SVR24, and HCV viral kinetics.

All secondary efficacy endpoints were summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum). All categorical endpoints were summarized by number and percentage of subjects who met the endpoint definition.

SVR12 was presented by age at baseline (≤ 15 years and > 15 years), sex at birth, weight (≤ and > median), HCV genotype, baseline HCV RNA (IU/mL), IL28B genotype, baseline ALT (≤ and > 1.5 × upper limit of normal [ULN]), prior cirrhosis, prior HCV treatment, study completion, and adherence to study regimen.

Summary tables of the number and percentage of subjects with HCV RNA < LLOQ and ≥ LLOQ were provided for each posttreatment follow-up visit (95% exact CIs were presented for the overall proportion of subjects with HCV RNA < LLOQ).

In addition, a concordance table between SVR12 and SVR24 was provided. Subjects with both observed SVR12 and observed SVR24 data were included in the analysis.

Pharmacokinetics: No PK analyses were performed during this study.

Safety: All enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Treatment-emergent safety data were analyzed and defined as data collected from the first dose of study drug through the last dose date of the study drug plus 30 days.

All AEs and laboratory abnormalities discussed in this clinical study report (CSR) were treatment-emergent and are referred to as AEs and laboratory abnormalities for the purposes of this report. Adverse events and laboratory abnormalities were graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 16.1.1, Appendix 3). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.1.

Adverse events were summarized by system organ class and/or preferred term and included all AEs, all AEs of Grade 3 or above, all AEs of Grade 2 or above, treatment-related AEs, treatment-related AEs of Grade 3 or above, treatment-related AEs of Grade 2 or above, all serious adverse events (SAEs), treatment-related SAEs, AEs leading to premature discontinuation of LDV/SOF, and deaths.

Laboratory results were assigned toxicity grades of 0 to 4. Laboratory abnormalities were defined as values that increased at least 1 toxicity grade from baseline at any postbaseline time point to the date of the last dose of any study drug plus 30 days (ie, treatment-emergent). The number and percentage of subjects who had any graded laboratory abnormality or any Grade 3 or 4 laboratory abnormality were summarized.

The primary safety endpoint was any AE leading to permanent discontinuation of the study drug.

Vital signs (systolic and diastolic blood pressure, pulse), body weight, height, and body mass index (BMI) at each visit, and change from baseline at each visit were summarized for the Safety Analysis Set using descriptive statistics. A data listing for cirrhosis determination at screening was provided for all subjects. In addition, a data listing of any subjects who become pregnant during the study was provided.

Other: Number of subjects with HCV flares and time to first HCV flare were summarized. In addition, for those subjects with HCV flares, number of HCV flares and time to HCV flares were summarized for each subject. Number of subjects with chemotherapy interruptions due to HCV flare was summarized, and for those subjects with chemotherapy interruptions due to HCV flare, number of chemotherapy interruptions was summarized for each subject.

Summary statistics and shift table are presented for changes in FibroScan results from screening to posttreatment Weeks 12 and 24. Changes and shift table in Fibrotest score (< 0.75, ≥ 0.75) from baseline to Week 12, posttreatment Week 12, and posttreatment Week 24 are provided.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 24 subjects were screened in this study, and 19 subjects were enrolled and received LDV/SOF for 12 weeks. All 19 subjects (100.0%) completed treatment and were included in both the FAS and the Safety Analysis Set (Table 15.8.1.3.1).

The majority of subjects were male (16 of 19, 84.2%) and all were white (19 of 19, 100.0%) with a mean age of 14 years (range: 12 to 17 years) (Table 15.8.3.1).

The mean (range) BMI at baseline was 22.0 (18.1 to 32.2) kg/m², and the majority of subjects (10 of 19) had a BMI ≥ 21.1 kg/m² (Table 15.8.3.2.1 and Listing 16.2.4.2.1). All subjects had genotype 4 HCV infection. No subject had known cirrhosis and all were treatment-naive. Most subjects (13 of 19; 68.4%) had non-CC (CT or TT) IL28B alleles, while 6 of 19 (31.6%) subjects had the IL28B CC allele. The mean (SD) baseline HCV RNA was 5.3 (1.65) $\log_{10}$ IU/mL, and most subjects (12 of 19; 63.2%) had a baseline HCV RNA < 800,000 IU/mL. Most subjects had baseline ALT > 1.5 × ULN (12 of 19; 63.2%). The mean (SD) baseline creatinine clearance calculated using the Schwarz formula was 186.4 (35.05) mL/min/1.73m².

All subjects were able to swallow the LDV/SOF FDC 90/400-mg tablet (Table 15.11.9).

Summaries related to subject disposition, demographics, concomitant medication, baseline characteristics, and exposure to study drug are presented in Tables 15.8.1.3.1, 15.8.3.1, 15.8.3.2.1, 15.11.8.1, and 15.11.8.2, and Listings 16.2.4 to 16.2.5.

Efficacy Results: Overall, 100.0% (95% CI: 82.4% to 100.0%) of subjects (19 of 19) achieved SVR12 (Tables 15.9.1 and 15.9.2.1), with no subjects experiencing virologic failure after 12 weeks of treatment with LDV/SOF.

All subjects (100.0%) achieved SVR4 and SVR12. All subjects who achieved SVR12 also achieved SVR24 (95% CI: 82.4% to 100.0%) (Table 15.9.2.2). Concordance between SVR12 and SVR24 was 100.0% (Table 15.9.3).

No virologic resistance testing was done.

All efficacy analyses are provided in Listings 16.2.6.1 to 16.2.6.4.

Pharmacokinetics Results: No PK assessments were performed for this report.

Safety Results:

Adverse Events and Serious Adverse Events

In the study, most subjects (15 of 19 subjects; 78.9%) experienced at least 1 AE (Table 15.11.2.1.1.1). A total of 5 of 19 subjects (26.3%) experienced an AE that was considered by the investigator to be related to the study drug.

The most commonly reported AEs were pyrexia (5 subjects; 26.3%), followed by diarrhea and headache (4 subjects each; 21.1%), followed by vomiting (3 subjects; 15.8%), followed by anemia, cough, neutrophil count decreased, and pneumonia (2 subjects each; 10.5%) (Table 15.11.2.1.3.1).

Most AEs reported in the study were Grade 1 or Grade 2 in severity. A total of 4 subjects experienced a Grade 1 treatment-related AE and 1 subject experienced a Grade 2 treatment-related AE (Table 15.11.2.1.1.1). No subject experienced a Grade 4 AE (Listing 16.2.7.1). A total of 4 subjects (21.1%) experienced a Grade 3 AE as follows: neutrophil count decreased (2 subjects; 10.5%), osteoarthritis and pneumonia (1 subject each; 5.3%). None of these Grade 3 AEs was considered treatment-related by the investigator (Tables 15.11.2.2.2.1 and 15.11.2.3.3.1, and Listings 16.2.7.2 and 16.2.7.1).

A total of 3 of 19 subjects (15.8%) experienced an SAE (Table 15.11.4.1.1). The only SAE occurring in > 1 subject was pneumonia (2 subjects; 10.5%); SAEs of diarrhea and osteoarthritis were experienced by 1 subject each (5.3%). None of the SAEs was assessed as related to study drug (Table 15.11.4.3.1).

None of the AEs or SAEs led to premature discontinuation of LDV/SOF (Table 15.11.5.1). None of the chemotherapy interruptions or discontinuations was due to a study drug-related AE (Listing 16.2.7.5.3). No subject died during this study (Table 15.11.3). No subject became pregnant during the study (Listing 16.2.8.3).

Narratives for all SAEs are provided in Section 15.2. All AE results are provided in Tables 15.11.2.1.1.1, 15.11.2.1.3.1, 15.11.2.2.2.1, 15.11.2.3.3.1, 15.11.2.3.4.1, and 15.11.4.3.1 and Listing 16.2.7.2.

Clinical Laboratory Results

In total, 7 subjects (36.8%) had a Grade 3 laboratory abnormality and 8 subjects (42.1%) had a Grade 4 laboratory abnormality. In this study, Grade 3 and Grade 4 decreases in hematology laboratory parameters were observed as follows: neutrophils (10 subjects), hemoglobin and white blood cell count (5 subjects each), lymphocytes (4 subjects), and platelets (1 subject). Grade 3 and Grade 4 increases in chemistry laboratory parameters were observed as follows: ALT and alkaline phosphatase (3 subjects each) and sodium (1 subject) (Table 15.11.6.4.2).

Between study Day 1 and posttreatment Week 4, decreases in median ALT and aspartate aminotransferase were observed (Tables 15.11.6.1.8 and 15.11.6.1.9), consistent with improvement in liver function.

All laboratory results are provided in Tables 15.11.6.1.1 to 15.11.6.1.17, 15.11.6.4.1, and

15.11.6.4.2, and Listings 16.2.8.1.3.1 to 16.2.8.1.9.

Vital Signs Measurements

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) were noted during this study.

All vital signs measurements are provided in Tables 15.11.7.1 to 15.11.7.3 and Listing 16.2.8.2.1.

Other Analyses

No notable changes in weight, height, and BMI were reported during this study from baseline through posttreatment Week 4 (Table 15.11.7.4).

Other Results: HCV flare was defined as ≥ 3-fold increase in ALT from Day 1 of the study, combined with ≥ 1 $\log_{10}$ increase in HCV RNA from Day 1 of the study. No subject experienced HCV flares (Table 15.10.1), and no subject experienced a chemotherapy interruption due to HCV flares (Table 15.10.2 and Listing 16.2.8.5).

The mean baseline FibroScan score was 8.0 kPa (range: 4.4 to 14.0 kPa). Only 1 subject had a value > 12.5 kPa at baseline and the score for that subject had shifted to ≤ 12.5 kPa (from 14.0 to 7.7 kPa) at posttreatment Week 12 (Listing 16.2.8.1.10). The mean Fibrotest score at baseline was 0.5 (range: 0.1 to 1.0) and the mean change at posttreatment Week 12 was −0.2. These results were the same at posttreatment Week 24 (Tables 15.11.6.5.1 and 15.11.6.5.2).

CONCLUSIONS:

- In pediatric subjects with genotype 4 HCV infection undergoing maintenance cancer chemotherapy, treatment with LDV/SOF resulted in an SVR12 rate of 100%. Treatment with LDV/SOF resulted in rapid and sustained viral suppression. No subjects experienced on-treatment virologic failure or relapsed.
- Treatment with LDV/SOF for 12 weeks was well tolerated in this study. The most commonly reported AEs were pyrexia (5 subjects; 26.3%), followed by diarrhea and headache (4 subjects each; 21.1%), followed by vomiting (3 subjects; 15.8%), followed by anemia, cough, neutrophil count decreased, and pneumonia (2subjects each; 10.5%). No subject discontinued study drug due to an AE. No subject experienced chemotherapy interruption because of an ALT flare, and no subject discontinued chemotherapy or HCV therapy because of an HCV flare.