FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination, with or without Ribavirin, in Egyptian Adults with Chronic Genotype 4 HCV Infection
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 USA
Study No.:	GS-US-337-1643
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	Not Applicable Not Applicable
ClinicalTrials.gov Identifier:	NCT No. 02487030
Study Start Date:	07 September 2015 (First Subject Screened)
Study End Date:	11 November 2016 (Last Subject Last Observation for the Primary Endpoint)
Principal or Coordinating Investigator:	Name: Gamal El Din Esmat Gamil, MD, MSc, MB, BCh Affiliation: PPD
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Report Date:	02 August 2017

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-337-1643
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination, with or without Ribavirin, in Egyptian Adults with Chronic Genotype 4 HCV Infection

Investigators: Gamal El Din Esmat Gamil, MD, MSc, MB, BCh; PPD

Study Centers: Subjects were enrolled across 4 sites in Egypt.

Publications: Shiha G, Waked I, Soliman R, Abdelrazek W, Hassany M, Fouad R, et al. Ledipasvir/sofosbuvir for 8 or 12 weeks with or without ribavirin in HCV genotype 4 patients in Egypt. [Abstract OP158]. Asian Pacific Association for the Study of the Liver (APASL); 2017 15-19 February; Shanghai, China

Study Period:

07 September 2015 (First Subject Screened)
11 November 2016 (Last Subject Last Observation for the Primary Endpoint)

Phase of Development: Phase 3

Objectives:

The primary objectives of this study were as follows:

- To determine the efficacy of ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) ± ribavirin (RBV) in subjects with chronic genotype 4 hepatitis C virus (HCV) infection as measured by the proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR12)
- To assess the safety and tolerability of LDV/SOF FDC ± RBV as assessed by review of the accumulated safety data

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attained SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)

- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation
- To evaluate the emergence of viral resistance to sofosbuvir (SOF) and/or ledipasvir (LDV), as relevant, during treatment and after treatment discontinuation

The exploratory objective of this study was as follows:

- To explore the utility of nongenetic biomarkers, such as IP10, in predicting the natural history of disease, virologic response to therapy, and/or the tolerability of medical therapies

Methodology: This Phase 3, randomized (Cohorts 1 and 3), open-label, multicenter study evaluated the antiviral efficacy, safety, and tolerability of LDV/SOF FDC ± RBV in treatment-naive and treatment-experienced adults in Egypt with chronic genotype 4 HCV infection. Subjects received study drugs for 8 or 12 weeks and completed a Week 4 posttreatment visit; subjects with HCV RNA < lower limit of quantitation (LLOQ) completed Weeks 12 and 24 posttreatment visits unless they had confirmed viral relapse, at which time they were terminated early from the study.

For Cohorts 1 and 3, randomization was stratified by the presence or absence of cirrhosis at screening. Approximately 25% of the subjects randomized may have had compensated cirrhosis at screening.

Cohort 1 (treatment naive [TN])

Approximately 160 subjects were randomized in a 1:1:1:1 ratio as follows:

- Group 1: LDV/SOF 8 Week TN group
- Group 2: LDV/SOF+RBV 8 Week TN group
- Group 3: LDV/SOF 12 Week TN group
- Group 4: LDV/SOF+RBV 12 Week TN group

Cohort 3 (treatment experienced [TE])

Approximately 80 subjects were randomized in a 1:1 ratio as follows:

- Group 1: LDV/SOF 12 Week TE group
- Group 2: LDV/SOF+RBV 12 Week TE group

Cohort 2 (SOF or LDV/SOF experienced)

- Approximately 40 subjects who completed treatment in Study GS-US-334-0138 with SOF+RBV for 12 or 24 weeks or subjects who participated in Cohort 1 of this study with LDV/SOF ± RBV treatment for 8 weeks and did not achieve SVR12 were enrolled into Cohort 2. Subjects received 12 weeks of LDV/SOF+RBV. This cohort is referred to as the SOF or LDV/SOF Experienced group.

Number of Subjects (Planned and Analyzed):

Planned for Cohort 1: 160 subjects

Planned for Cohort 3: 80 subjects

Planned for Cohort 2: 40 subjects

Analyzed for Cohort 1:

- Randomized/Enrolled Analysis Set: 170 subjects
- Full Analysis Set (FAS): 170 subjects
- Safety Analysis Set: 170 subjects

Analyzed for Cohort 3:

- Randomized/Enrolled Analysis Set: 74 subjects
- FAS: 74 subjects
- Safety Analysis Set: 74 subjects

Analyzed for Cohort 2:

- Enrolled Analysis Set: 11 subjects
- FAS: 11 subjects
- Safety Analysis Set: 11 subjects

All Cohorts:

- Randomized/Enrolled Analysis Set: 255 subjects
- FAS: 255 subjects
- Safety Analysis Set: 255 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were treatment-naive (Cohort 1), treatment-experienced (Cohort 3), or SOF- or LDV/SOF-experienced (Cohort 2) males and nonpregnant/nonlactating females ≥ 18 years of age, with chronic genotype 4 HCV infection with or without compensated cirrhosis. Eligibility also included HCV RNA ≥ 10^4 IU/mL at screening (Cohorts 1 and 3) and HCV RNA > LLOQ (Cohort 2).

Duration of Treatment: Treatment duration was 8 or 12 weeks

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

- LDV/SOF (90/400 mg) was administered orally to subjects (1 FDC tablet once daily) with or without food for 8 or 12 weeks
- RBV (1000 or 1200 mg) was administered orally in a divided daily dose with food for 8 or 12 weeks, depending upon the subject's weight

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

- LDV/SOF: DK1309B1
- RBV: AC4297Z

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

Criteria for Evaluation:

Efficacy: Blood samples to determine HCV RNA levels were collected from subjects at screening, baseline/Day 1 (predose), Weeks 1, 2, 4, 8, and 12 (for subjects who received 12 weeks of study drugs only) during treatment (or upon early termination) and posttreatment Week 4 and Weeks 12 and 24 (if applicable). The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study. The LLOQ of this assay is 15 IU/mL.

Pharmacokinetics/Pharmacodynamics: No pharmacokinetic or pharmacodynamic assessments were performed for this report.

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

Statistical Methods:

Efficacy: For efficacy analyses, data were analyzed by Cohort 1 (LDV/SOF 8 Week TN group, LDV/SOF+RBV 8 Week TN group, LDV/SOF 12 Week TN group, LDV/SOF+RBV 12 Week TN group), Cohort 3 (LDV/SOF 12 Week TE group, LDV/SOF+RBV 12 Week TE group), and Cohort 2 using the FAS. The primary efficacy endpoint was the proportion of subjects with HCV RNA < LLOQ 12 weeks after discontinuation of the study drug (SVR12) in the FAS. The 2-sided 95% exact CI based on the Clopper-Pearson method was provided for the SVR12 rate for each treatment group by cohort.

Secondary efficacy endpoints included the proportion of subjects with SVR4 and SVR24; HCV RNA < LLOQ by study visit; HCV RNA absolute values and changes from baseline through end of treatment (EOT); virologic failure; and characterization of HCV drug resistance substitutions at baseline and during and after therapy with LDV/SOF (if data were available).

Analysis results were presented using descriptive statistics. All continuous endpoints were summarized using descriptive statistics (sample size, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and maximum). All categorical variables were summarized by the number and percentage of subjects in each category.

Pharmacokinetics/Pharmacodynamics: No pharmacokinetic or pharmacodynamic assessments were performed for this report.

Safety: All subjects who were randomized or enrolled and received at least 1 dose of study drug were included in the Safety Analysis Set. Safety data were analyzed by treatment group as shown below and included all data collected on or after the date of the first dose of 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 19.1.

The safety analysis was performed according to the following treatment groups:

- LDV/SOF 8 Week group: Treatment-naive and treatment-experienced subjects who took LDV/SOF for 8 weeks
- LDV/SOF+RBV 8 Week group: Treatment-naive and treatment-experienced subjects who took LDV/SOF+RBV for 8 weeks
- LDV/SOF 12 Week group: Treatment-naive and treatment-experienced subjects who took LDV/SOF for 12 weeks
- LDV/SOF+RBV 12 Week group: Treatment-naive and treatment-experienced subjects who took LDV/SOF+RBV for 12 weeks

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

Overall Disposition: A total of 255 subjects were enrolled, received at least 1 dose of study drug and were included in the Safety Analysis Set and FAS for their respective cohort (Cohort 1, 3, or 2). A total of 253 (99.2%) subjects completed study treatment. Disposition is discussed by cohort as follows.

Cohort 1 (treatment naive): A total of 170 subjects were enrolled and randomized into Cohort 1: 43 subjects were in the LDV/SOF 8 Week TN group, 42 subjects were in the LDV/SOF+RBV 8 Week TN group, 43 subjects were in the LDV/SOF 12 Week TN group, and 42 subjects were in the LDV/SOF+RBV 12 Week TN group. Two subjects in Cohort 1 prematurely discontinued study treatment: 1 subject (LDV/SOF+RBV 8 Week TN group) due to lack of efficacy and 1 subject (LDV/SOF+RBV 12 Week TN group) due to a serious adverse event (SAE) of road traffic accident.

Cohort 3 (treatment experienced): Of the 74 subjects randomized into Cohort 3, 36 subjects were in the LDV/SOF 12 Week TE group and 38 subjects were in the LDV/SOF+RBV 12 Week TE group. All 74 subjects completed study treatment.

Cohort 2 (SOF or LDV/SOF experienced): A total of 11 subjects were enrolled into Cohort 2 and completed study treatment. Six subjects had been previously treated with SOF+RBV for 12 or 24 weeks (Study GS-US-334-0138), while 5 subjects had been previously treated with LDV/SOF (n = 2) or LDV/SOF+RBV (n = 3) for 8 weeks (Cohort 1, Study GS-US-337-1643).

Demographics and Baseline Characteristics: Demographics and baseline characteristics are discussed by cohort as follows.

Cohort 1 (treatment naive): Across treatment groups, 53.5% of the subjects were male, with a mean (range) age of 49 years (21–74 years). The mean (range) baseline body mass index (BMI) was 30.4 (21.0–50.0) kg/m^2 and 50.0% of subjects had BMI ≥ 30 kg/m^2. The majority of subjects (81.8%) were noncirrhotic, had a non-CC IL28B genotype (78.2%) (CT = 61.8%, TT = 16.5%), and had HCV RNA < 800,000 IU/mL (56.5%, 96 of 170). Across treatment groups, the mean (SD) baseline HCV RNA value was 5.8 (0.66) $\log_{10}$ IU/mL.

Cohort 3 (treatment experienced): For Cohort 3, 77.0% of the subjects were male, with a mean (range) age of 50 years (24–74 years). The mean (range) baseline BMI was 28.6 (19.1–42.6) kg/m^2 and 39.2% of subjects had BMI ≥ 30 kg/m^2. The majority of subjects (73.0%) were noncirrhotic and most (82.4%) subjects had a non-CC IL28B genotype (CT = 60.8%, TT = 21.6%). Across treatment groups, the mean (SD) baseline HCV RNA value was 5.8 (1.06) $\log_{10}$ IU/mL and 55.4% of subjects had HCV RNA ≥ 800,000 IU/mL. The majority of subjects (89.2%; 66 of 74 subjects) had failed prior treatment with pegylated interferon (Peg-IFN) + RBV.

Cohort 2 (SOF or LDV/SOF experienced): For Cohort 2, 72.7% of the subjects were male, with a mean (range) age of 48 years (23–72 years). The mean (range) baseline BMI was 33.9 (23.6–50.8) kg/m^2 and 63.6% of subjects had BMI ≥ 30 kg/m^2. The majority of subjects (72.7%) were noncirrhotic and all 11 subjects had a non-CC IL28B genotype (CT = 72.7%, TT = 27.3%). Subjects had a mean (SD) baseline HCV RNA value of 6.2 (0.59) $\log_{10}$ IU/mL and 54.5% of subjects had HCV RNA ≥ 800,000 IU/mL. Six of 11 subjects had failed prior treatment with SOF+RBV, 3 subjects had failed prior treatment with LDV/SOF+RBV, and 2 subjects had failed prior treatment with LDV/SOF.

Efficacy Results: The SVR12 rates for Cohorts 1, 3, and 2 were high, ranging from 90.5% (Cohort 1, LDV/SOF+RBV 8 Week TN group) to 100.0% (Cohort 3, LDV/SOF+RBV 12 Week TE group, and Cohort 2). Overall, 10 subjects did not achieve SVR12, 8 due to virologic failure (1 subject had on-treatment failure and 7 subjects relapsed after completing study drug) and 2 subjects were categorized as "Other". Of the 7 subjects who relapsed after completing study drug, 2 subjects received LDV/SOF for 8 weeks, 3 subjects received LDV/SOF+RBV for 8 weeks, and 2 subjects received LDV/SOF for 12 weeks. For all 3 cohorts, the overall concordance between SVR12 and SVR24 was 100.0%.

The SVR12 rates and changes from baseline in HCV RNA levels throughout treatment are provided by cohort and treatment group below.

Cohort 1 (treatment naive)

The SVR12 rates were as follows:

- **LDV/SOF 8 Week TN group:** 95.3% (95% CI: 84.2% to 99.4%) of subjects (41 of 43) achieved SVR12
- **LDV/SOF+RBV 8 Week TN group:** 90.5% (95% CI: 77.4% to 97.3%) of subjects (38 of 42) achieved SVR12
- **LDV/SOF 12 Week TN group:** 97.7% (95% CI: 87.7% to 99.9%) of subjects (42 of 43) achieved SVR12

- **LDV/SOF+RBV 12 Week TN group:** 97.6% (95% CI: 87.4% to 99.9%) of subjects (41 of 42) achieved SVR12

A total of 8 subjects in Cohort 1 did not achieve SVR12: 7 subjects were virologic failure (2, 4, and 1 subject[s] in the LDV/SOF 8 Week TN group, LDV/SOF+RBV 8 Week TN group, and LDV/SOF 12 Week TN group, respectively). One subject in the LDV/SOF+RBV 12 Week TN group was categorized as "Other."

Four subjects (2 subjects in the LDV/SOF 8 Week TN group and 1 subject each in the LDV/SOF+RBV 8 Week TN and LDV/SOF 12 Week TN groups) did not achieve SVR4. Two subjects in the LDV/SOF+RBV 8 Week TN group achieved SVR4, but relapsed between the posttreatment Week 4 and 12 visits, and 1 subject in the LDV/SOF+RBV 8 Week TN group had on-treatment failure and discontinued study drugs early. The subject categorized as "Other" discontinued study drugs prematurely because of an SAE (road traffic accident).

Cohort 3 (treatment experienced)

The SVR12 rates were as follows:

- **LDV/SOF 12 Week TE group:** 94.4% (95% CI: 81.3% to 99.3%) of subjects (34 of 36) achieved SVR12
- **LDV/SOF+RBV 12 Week TE group:** 100.0% (95% CI: 90.7% to 100.0%) of subjects (38 of 38) achieved SVR12

A total of 2 subjects in Cohort 3 did not achieve SVR12−both subjects were in the LDV/SOF 12 Week TE group. Both subjects achieved SVR4, but 1 subject relapsed between the posttreatment Week 4 and 12 visits, and the other subject, categorized as "Other," died on posttreatment Day 84 without posttreatment Week 12 data.

Cohort 2 (SOF or LDV/SOF experienced)

The SVR12 rate was 100.0% (95% CI: 71.5% to 100.0%).

For all 3 cohorts, HCV RNA levels (log_{10} IU/mL) declined rapidly with similar decreases in HCV RNA observed throughout treatment. Time to virologic suppression was not associated with treatment outcome overall or treatment regimen.

Pharmacokinetics/Pharmacodynamics Results: No pharmacokinetic or pharmacodynamic assessments were performed for this report.

Safety Results: Overall, treatment with LDV/SOF ± RBV for 8 or 12 weeks was generally safe and well tolerated.

The proportion of subjects experiencing at least 1 AE was lower in the 2 non-RBV-containing treatment groups (37.2% and 40.5% of subjects in the LDV/SOF 8 Week and LDV/SOF 12 Week groups, respectively), compared with the 2 RBV-containing treatment groups (52.4% and 62.6% of subjects in the LDV/SOF+RBV 8 Week and LDV/SOF+RBV 12 Week groups, respectively). The proportion of subjects experiencing at least 1 AE was similar in the 2 LDV/SOF treatment groups despite the difference in duration of treatment (8 vs 12 weeks), whereas more subjects in the LDV/SOF+RBV 12-week regimen had AEs (62.6%) compared with the LDV/SOF+RBV 8-week regimen (52.4% of subjects). Additionally, a lower proportion

of subjects in the 2 non-RBV-containing treatment groups had AEs that were assessed as related to study drug (7.0% and 13.9% in the LDV/SOF 8 Week and LDV/SOF 12 Week groups, respectively), compared with the 2 RBV-containing treatment groups (23.8% and 35.2% in the LDV/SOF+RBV 8 Week and LDV/SOF+RBV 12 Week groups, respectively).

The most commonly reported AEs were headache, fatigue, dyspepsia, bronchitis, anemia, abdominal pain upper, pyrexia, and constipation. Fatigue, dyspepsia, bronchitis, and pyrexia were reported in similar proportions across treatment groups, whereas headache occurred in a higher proportion of subjects in the RBV-containing treatment groups. Only subjects in the 2 RBV-containing treatment groups experienced anemia, abdominal pain upper, and constipation. Anemia was associated with the longer duration of treatment, occurring in 4.8% and 7.7% of subjects in the 8- and 12-week RBV-containing regimens, respectively.

Across the 4 treatment groups, most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. Grade 3 (severe) and 4 (life-threatening) AEs were rare, occurring in 2 (2.2%) subjects, both in the LDV/SOF+RBV 12 Week group. These 2 subjects had a Grade 3 or 4 road traffic accident, and 1 of these subjects permanently discontinued all study drugs. None of the Grade 3 or 4 AEs were assessed as related to study drug.

Serious AEs were rare, occurring in 3 subjects, all in the LDV/SOF+RBV 12 Week group, and all were assessed as unrelated to study drug. One nontreatment-emergent death was reported during the study (sudden death unexplained) and was assessed as unrelated to study drug. Two pregnancies were reported during the study, with no adverse outcome reported for either pregnancy.

No subject in any treatment group had an AE that led to interruption of LDV/SOF treatment. In the RBV-containing treatment groups, 1 (2.4%) and 8 (8.8%) subjects in the LDV/SOF+RBV 8 Week and LDV/SOF+RBV 12 Week groups, respectively, had an AE that led to modification of RBV. Anemia was the only AE that led to dose reduction in > 1 subject, resulting in dose modification of RBV in 7 subjects.

Most subjects had at least 1 laboratory abnormality, and the maximum abnormality grade for most of these subjects was Grade 1 or 2. The incidence of Grade 3 and 4 laboratory abnormalities was higher in the LDV/SOF+RBV 12 Week group (16.5%) compared with the 3 other groups, which ranged from 7.0% to 7.6%. This difference was accounted for primarily by the expected decreases in hemoglobin consistent with the known toxicity profile of RBV. No Grade 4 hematology laboratory abnormality was reported in any group.

No subject in the non-RBV-containing treatment groups had ≥ Grade 2 decreased hemoglobin and 37 subjects in the RBV-containing treatment groups had ≥ Grade 2 decreased hemoglobin. A higher proportion of subjects in the LDV/SOF+RBV 12 Week group (9 subjects [9.9%]) had transient Grade 3 decreased hemoglobin compared with the LDV/SOF+RBV 8 Week group (2 subjects [4.8%]). Two (2.5%) subjects in the LDV/SOF 12 Week group had isolated Grade 3 decreased neutrophil levels.

The most common Grade 3 chemistry laboratory abnormality across treatment groups was increased serum glucose (hyperglycemia), all in subjects with a medical history of diabetes. A

single instance of Grade 3 or 4 lipase was reported for 1 subject each in the LDV/SOF 8 Week and LDV/SOF+RBV 12 Week groups and 2 (2.5%) subjects in the LDV/SOF 12 Week group. All Grade 3 and 4 elevated lipase levels were asymptomatic, with no cases of clinical pancreatitis. Grade 4 hyperbilirubinemia, a laboratory abnormality consistent with the expected toxicity profile of RBV, was reported in 1 subject in the LDV/SOF+RBV 12 Week group.

Consistent with known RBV-associated hemolytic anemia, decreases in hemoglobin and elevations in reticulocytes and platelets were observed during treatment among subjects in the RBV-containing groups; levels returned to baseline values at posttreatment follow-up Week 4.

No clinically meaningful changes were observed in lymphocytes, neutrophils, or white blood cells in any treatment group. No notable changes in total bilirubin values were observed in the 2 groups receiving LDV/SOF for 8 or 12 weeks. Consistent with RBV administration, transient increases from baseline in median total bilirubin values were observed in subjects during treatment with LDV/SOF+RBV for 8 or 12 weeks.

Across treatment groups, there were no notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse).

CONCLUSIONS: The conclusions from this study are as follows:

- LDV/SOF for 8 or 12 weeks in treatment-naive subjects with genotype 4 HCV infection was highly effective.
  - SVR12 rate was 95.3% in subjects treated with LDV/SOF for 8 weeks
  - SVR12 rate was 97.7% in subjects treated with LDV/SOF for 12 weeks
- LDV/SOF for 12 weeks in treatment-experienced subjects, including subjects previously treated with SOF or LDV/SOF, with genotype 4 HCV infection was highly effective.
  - SVR12 rate was 94.4% in subjects treated for 12 weeks with LDV/SOF
  - SVR12 rate was 100.0% in subjects previously treated with SOF+RBV or LDV/SOF ± RBV who received LDV/SOF+RBV for 12 weeks
- The addition of RBV did not significantly impact efficacy in treatment-naive or treatment-experienced subjects with chronic genotype 4 HCV infection.
- For all 3 cohorts, the overall concordance between SVR12 and SVR24 was 100.0%.
- LDV/SOF for 8 or 12 weeks was generally well tolerated. The addition of RBV to the regimen increased the incidence of AEs and laboratory abnormalities, but did not affect the overall high rates of treatment completion. No treatment-emergent deaths, treatment-related Grade 3 or 4 AEs, or treatment-related SAEs were observed.