FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavirin for 12 Weeks in Subjects with Chronic HCV Infection and Child-Pugh-Turcotte Class C Cirrhosis
Name of Test Drug:	Sofosbuvir (SOF)/velpatasvir (VEL) fixed-dose combination (FDC)
Dose and Formulation	SOF/VEL FDC (400/100 mg) tablet
Indication:	Hepatitis C Virus Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-342-4022
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	118605 2016-003066-10
ClinicalTrials.gov Identifier:	NCT02994056
Study Start Date:	23 January 2017 (First Subject Screened)
Study End Date:	25 September 2018 (Last Subject Last Observation for the Primary Endpoint) 12 December 2018 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Steven Flamm, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Anuj Gaggar, MD, PhD Telephone: PPD Fax: PPD
Report Date:	18 April 2019

STUDY SYNOPSIS

Study GS-US-342-4022
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavirin for 12 Weeks in Subjects with Chronic HCV Infection and Child-Pugh-Turcotte Class C Cirrhosis

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 13 centers in the United States and France.

Publications:

Flamm S, Lawitz E, Borg B, Charlton M, Landis C, Reddy R, et al. High Efficacy and Improvement in CPT Class With Sofosbuvir/Velpatasvir Plus Ribavirin for 12 Weeks in Patients With CPT C Decompensated Cirrhosis [Poster THU-138]. EASL: The International Liver Congress; 2019 10-14 April; Vienna, Austria.

Study Period:

23 January 2017 (First Subject Screened)
25 September 2018 (Last Subject Last Observation for the Primary Endpoint)
12 December 2018 (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 treatment with sofosbuvir (SOF)/velpatasvir (VEL) fixed-dose combination (FDC) with ribavirin (RBV) for 12 weeks in subjects with chronic hepatitis C virus (HCV) infection and Child-Pugh-Turcotte (CPT) class C cirrhosis as measured by the proportion of subjects with sustained viral response (SVR) 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of the treatment regimen

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 the study treatment regimen (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate therapeutic efficacy as measured by the change of CPT score and Model for End-Stage Liver Disease (MELD) score

- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment

The exploratory objectives of this study were 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 provided their separate and specific consent
- To assess the effect of treatment on health-related quality of life

Methodology:

This Phase 2, open-label, multicenter study evaluated the efficacy and safety of SOF/VEL+RBV for 12 weeks in subjects with chronic HCV infection and CPT class C cirrhosis.

Approximately 50 subjects were planned to be enrolled. All subjects were to complete the posttreatment Week 4 and Week 12 visits. Subjects who had HCV RNA less than the lower limit of quantitation (< LLOQ) at the posttreatment Week 12 visit were also to complete the posttreatment Week 24 visit unless a confirmed viral relapse occurred.

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

After completing all required study visits, subjects could enroll into the Cirrhosis SVR Registry Study if SVR was achieved or into the Sequence Registry Study if SVR was not achieved.

Number of Subjects (Planned and Analyzed)

Planned: Approximately 50 subjects

Analyzed:

- All Enrolled Analysis Set: 32 subjects
- Full Analysis Set (FAS): 32 subjects
- Safety Analysis Set: 32 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females aged 18 years or older with chronic HCV infection and CPT class C cirrhosis at screening.

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

Test Product, Dose, Mode of Administration, and Batch Number:

- SOF/VEL FDC tablets were administered orally to all subjects at a dose of 400/100 mg (1 FDC tablet once daily).

- RBV was administered orally to all subjects at a starting total daily dose of 600 mg (3 × 200 mg tablets divided twice daily). If the starting dose was well-tolerated, RBV could be titrated up to a maximum total daily dose of 1000 to 1200 mg (1000 mg for subjects weighing < 75 kg and 1200 mg for subjects weighting ≥ 75 kg) divided twice daily.

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

- SOF/VEL: DU1508B1
- RBV: AF1806Z and AC9247W

Reference Therapy, Dose, Mode of Administration, and Batch Number: None

Criteria for Evaluation:

Efficacy: Blood samples to determine HCV RNA levels were collected from all subjects at screening; baseline/Day 1 (predose); Weeks 2, 4, 8, and 12 during treatment; early termination (if applicable); and posttreatment Weeks 4, 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 the assay is 15 IU/mL.

Assessments to determine MELD and CPT scores were performed at screening and at all study visits.

Pharmacokinetics: A single pharmacokinetic (PK) blood sample was collected at each on-treatment visit for all subjects. No PK analyses 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.

Quality of Life: Health-related quality of life was assessed with the Short Form Health Survey (SF-36), Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, and the Work Productivity and Activity Impairment: Hepatitis C (WPAI: Hep C) questionnaire.

Statistical Methods:

Efficacy: The primary efficacy endpoint was the proportion of subjects with SVR12, defined as HCV RNA < LLOQ 12 weeks after cessation of study treatment in the FAS. Point estimates and 95% confidence intervals (using the Clopper-Pearson method) were provided for the SVR12 rate.

Secondary efficacy endpoints included the proportion of subjects with SVR4, SVR24, HCV RNA < LLOQ while on treatment by study visit, and virologic failure; HCV RNA absolute values and changes from baseline through end of treatment (EOT); changes from baseline in CPT and MELD scores in subjects who achieved SVR12 and SVR24; and characterization of HCV drug-resistant substitutions at baseline and after study treatment.

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

Pharmacokinetics: No PK analyses were performed for this report.

Safety: All subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs measurements, and physical examinations. 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 21.0.

Quality of Life: The health-related quality of life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C) were completed at baseline/Day 1, Week 12 during treatment, and posttreatment Week 12. A Wilcoxon signed-rank test explored within-group changes from baseline to each of the time points, and from EOT to posttreatment Week 12.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 32 subjects were enrolled in the study. All 32 subjects received at least 1 dose of study drug and were included in both the Safety Analysis Set and the FAS.

The majority of subjects completed study treatment (90.6%, 29 of 32 subjects). Three subjects (9.4%) prematurely discontinued study treatment: 2 due to AEs and 1 due to the investigator's discretion.

Demographics and baseline characteristics were generally consistent with a population with advanced liver disease. Overall, the majority of subjects were male (81.3%). The mean age was 55 years (range: 39-77), and 6.3% of subjects were ≥ 65 years of age. The mean baseline body mass index (BMI) value for subjects was 28.9 kg/m^2 (range: 19.8-44.3), and 65.6% of subjects had a BMI < 30 kg/m^2.

The majority of subjects (71.9%, 23 of 32) were CPT class C (score 10-15) at baseline based on CPT score calculations with prothrombin activation percentage for the coagulation parameter. The other 9 subjects were CPT class B (score 7-9). The majority of subjects had a baseline MELD score of 16 to 20 (53.1%, 17 subjects).

Overall, 18 subjects (56.3%) had genotype 1 HCV infection (16 subjects had genotype 1a, and 2 subjects had genotype 1b), 5 subjects (15.6%) had genotype 2 HCV infection, and 7 subjects (21.9%) had genotype 3 HCV infection. There were 2 subjects whose HCV genotype could not be determined due to low viral load.

Most subjects had interleukin 28B (IL28B) non-CC genotype (53.1%) and were treatment naive (87.5%).

Overall, the median (range) baseline estimated globular filtration rate using the Cockcroft-Gault equation was 105.6 (44.9-227.6) mL/min.

Efficacy Results: The primary efficacy endpoint of SVR12 rate was 78.1% (25 of 32 subjects, 95% CI: 60.0% to 90.7%). No subjects relapsed at posttreatment Week 12.

Seven of 32 subjects (21.9%) did not achieve SVR12 due to death (6 subjects) and withdrawal of consent (1 subject). One additional subject who achieved SVR12 later relapsed and did not achieve SVR24.

HCV RNA levels (log10 IU/mL) declined rapidly. Consistent with the rapid and sustained decline in HCV RNA, 96.6% of subjects with available HCV RNA data had HCV RNA < LLOQ at Week 4, and all subjects with available HCV RNA data had HCV RNA < LLOQ at Week 12.

Hepatic function improved from baseline to posttreatment Week 24, as observed by CPT class and MELD score changes. Eight of 19 subjects (42.1%) experienced an improvement in CPT class, and no subject experienced a worsening. Ten of 19 subjects (52.6%) an improvement in MELD score, 4 of 19 subjects (21.1%) had no change in MELD score, and 5 of 19 subjects (26.3%) had a worsening in MELD score.

Virologic Resistance Results: For subjects with virologic outcome and with available deep sequencing data at baseline, nonstructural protein 5A (NS5A) and nonstructural protein 5B (NS5B) resistance-associated variants (RAVs) were observed in 17.4% (4 of 23) and 4.3% (1 of 23) of subjects, respectively, using a 15% assay cutoff. The presence of pretreatment NS5A and/or NS5B nucleoside inhibitor (NI) RAVs did not impact treatment outcome as all subjects with pretreatment RAVs achieved SVR12 and SVR24. The 1 subject with genotype 3a HCV infection who experienced virologic relapse at posttreatment Week 24 had NS5A RAV Y93H emerge posttreatment.

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

Safety Results: Overall, treatment with SOF/VEL+RBV for 12 weeks was generally safe and well-tolerated. Adverse events were consistent with the expected clinical sequelae of decompensated cirrhosis and the known toxicities of RBV.

All but 1 subject (96.6%) experienced at least 1 AE. The most common AEs were anemia (25.0%), nausea (25.0%), and asthenia (18.8%). Most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. Grade 3 (severe) AEs were reported in 7 subjects (21.9%). Grade 4 AEs were reported in 4 subjects (12.5%) and included hepatocellular carcinoma (HCC) (2 subjects), sepsis, and respiratory distress. No Grade 3 or above AEs were considered related to study drug.

A total of 17 subjects (53.1%) experienced a serious adverse event (SAE). Hepatic hydrothorax, HCC, and sepsis (2 subjects each) were the only SAEs reported for > 1 subject. None of the SAEs was considered related to study drug, and all were generally consistent with advanced liver disease.

Six subjects experienced SAEs that led to premature interruption of SOF/VEL (hepatic encephalopathy, dehydration, Escherichia sepsis, hepatic hydrothorax, gastrointestinal hemorrhage, and benign prostatic hyperplasia). Two subjects experienced SAEs that led to discontinuation of SOF/VEL (sepsis and respiratory distress).

Of the 8 deaths, 2 were during the treatment period (ie, deaths were treatment emergent), and 6 were > 30 days after the EOT. None of the deaths was assessed by the investigator as related to study drugs, and the majority of deaths were associated with the progression of end stage liver disease (ie, liver failure, sepsis, multi-organ failure, gastrointestinal bleeding).

After completing treatment with SOF/VEL, 3 subjects underwent liver transplantation. All 3 subjects subsequently achieved SVR12 and SVR24.

The observed laboratory abnormalities were consistent with those expected in a population with decompensated liver disease and the known toxicities of RBV. The most common Grade 3 or 4 hematology laboratory abnormalities were decreased lymphocytes and platelets. Postbaseline hemoglobin values <10 g/dL were reported in 10 subjects (33.3%), and 1 subject had postbaseline hemoglobin values < 8.5 g/dL.

The most common Grade 3 or 4 chemistry laboratory abnormalities were increased total bilirubin and hyperuricemia.

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

Quality of Life Results: Overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C quality of life questionnaires indicated that no statistically significant worsening in health-related quality of life was observed between baseline and EOT for any of the assessments. The mean scores for most scales improved from EOT to posttreatment Week 12. These results should be interpreted with caution, as multiple endpoints were tested, and the study was not powered to test these exploratory endpoints.

CONCLUSIONS: The conclusions from Study GS-US-342-4022 in subjects with chronic HCV infection and decompensated CPT class C cirrhosis are as follows:

- The SVR12 rate was 78.1%.
- The SVR4 and SVR24 rates were 87.5% and 75.0%, respectively.
- One subject relapsed and did not achieve SVR24; the remaining 7 subjects not achieving SVR24 withdrew consent (1 subject) or died (6 subjects).
- Of the 19 subjects who achieved SVR24, 8 subjects (42.1%) had an improvement in CPT class from baseline to posttreatment Week 24, and none had a worsening.
- Of the 19 subjects who achieved SVR24, 10 subjects (52.6%) had an improvement (decrease) in MELD score, 4 subjects (21.1%) had no change in MELD score, and 5 subjects (26.3%) had a worsening (increase) in MELD score.
- Treatment with SOF/VEL+RBV for 12 weeks was generally safe and well-tolerated.