FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavirin for 12 or 24 Weeks in Subjects with Chronic Genotype 1 or 2 HCV Infection Who Have Previously Failed a Direct-Acting Antiviral-Containing Regimen
Name of Test Drug:	Sofosbuvir/velpatasvir (SOF/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-342-3921
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	Not Applicable Not Applicable
ClinicalTrials.gov Identifier:	NCT02822794
Study Start Date:	25 July 2016 (First Subject Screened)
Study End Date:	25 August 2017 (Last Subject Last Observation)
Principal or Coordinating Investigator:	Name: Namiki Izumi, MD, PhD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Brian McNabb, MD Telephone: PPD Fax: PPD
Report Date:	11 December 2017

STUDY SYNOPSIS

Study GS-US-342-3921
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavirin for 12 or 24 Weeks in Subjects with Chronic Genotype 1 or 2 HCV Infection Who Have Previously Failed a Direct-Acting Antiviral-Containing Regimen

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 18 sites in Japan.

Publications: Izumi N, Takehara T, Chayama K, Yatsuhashi H, Takaguchi K, Ide T, et al. Efficacy and safety of sofosbuvir/velpatasvir plus ribavirin for 12 or 24 weeks in genotype 1 or 2 HCV-infected Japanese patients with prior treatment failure to DAA-based regimens. Abstract 194. AASLD 2017. Hepatology 66:111A-112A, 2017.

Study Period:

25 July 2016 (First Subject Screened)
02 June 2017 (Last Subject Last Observation for the Primary Endpoint)
25 August 2017 (Last Subject Last Observation for this Report)

Phase of Development: Phase 3

Objectives:

The primary objectives of this study were as follows:

- To evaluate the antiviral efficacy of therapy with sofosbuvir/velpatasvir (SOF/VEL) fixed-dose combination (FDC) and ribavirin (RBV) for 12 or 24 weeks as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of each regimen 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 cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating hepatitis C virus (HCV) RNA during treatment and after cessation of each treatment regimen
- 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, virologic response to therapy, and/or the tolerability of medical therapies through genetic discovery research (eg, genomics) in subjects who provided a separate and specific consent
- To assess the effect of treatment with SOF/VEL+RBV on health-related quality of life

Methodology: This Phase 3, randomized, open-label, multicenter study in Japan assessed the antiviral efficacy, safety, and tolerability of SOF/VEL+RBV administered for 12 or 24 weeks in subjects with chronic genotype 1 or 2 HCV infection who had previously failed a direct-acting antiviral (DAA)-containing regimen. Subjects with genotype 1 HCV infection had failed prior treatment with a nonstructural protein (NS) 5A inhibitor, and subjects with genotype 2 HCV infection had failed prior treatment with any DAA-containing regimen.

Approximately 110 subjects were planned to be randomized (1:1) to 1 of the following 2 treatment groups:

- **SOF/VEL+RBV 12 Week group:** SOF/VEL FDC tablet (400/100 mg) once daily + weight-based RBV capsules for 12 weeks
- **SOF/VEL+RBV 24 Week group:** SOF/VEL FDC tablet (400/100 mg) once daily + weight-based RBV capsules for 24 weeks

Randomization was stratified by cirrhosis status (presence or absence) at screening and HCV genotype (genotype 1 or 2). Approximately 20 subjects may have had Child-Pugh-A compensated cirrhosis. Approximately 90 subjects with genotype 1 HCV infection and approximately 20 subjects with genotype 2 HCV infection were planned to be enrolled.

All subjects were to complete the posttreatment Week 4, 12, and 24 visits regardless of their treatment duration.

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

Number of Subjects (Planned and Analyzed):

Planned: Approximately 110 subjects

Analyzed:

- All Randomized Analysis Set: 117 subjects
- Full Analysis Set (FAS): 117 subjects
- Safety Analysis Set: 117 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females ≥ 20 years of age, with chronic genotype 1 or 2 HCV infection, who had previously failed a DAA-containing regimen, and had documentation of the presence or absence of cirrhosis.

Duration of Treatment: Treatment duration was 12 or 24 weeks.

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

- **SOF/VEL** was administered orally to subjects at a dose of 400/100 mg (1 FDC tablet once daily).
- **RBV** (Rebetol®) was administered orally to subjects using weight-based dosing at a total daily dose of 600, 800, or 1000 mg/day (3, 4, or 5 × 200-mg capsules divided twice daily).

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

- **SOF/VEL:** DU1506B1
- **RBV:** B001B

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; Day 1 (predose); Weeks 1, 2, 3, 4, 5, 6, 8, 10, and 12 (all subjects) and Weeks 16, 20, and 24 (subjects randomized to receive 24 weeks of treatment only) during treatment; early termination (if applicable); and posttreatment Weeks 4, 12, and 24. 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: A single pharmacokinetic (PK) blood sample was collected from all subjects at each on-treatment visit. A subset of subjects who provided separate consent (target of approximately 20 subjects) participated in an optional intensive PK substudy at the Week 2, 3, or 4 on-treatment visit. Serial PK samples were collected over 24 hours postdose to determine the plasma concentrations of SOF, its metabolites GS-566500 and GS-331007, VEL, and RBV (if appropriate).

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 questionnaires included 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 treatment, in the FAS. Point estimates and 2-sided 95% exact confidence intervals (CIs) for SVR12 based on the Clopper-Pearson method were provided for each treatment group. In the primary efficacy analysis, the SVR12 rate for subjects with genotype 1 HCV infection in each of the 2 treatment groups was compared to the historical control rate of 50% using a 2-sided exact 1-sample binomial test at the 0.025 significance level. No statistical hypothesis testing was performed in subjects with genotype 2 HCV infection.

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

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.

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 were analyzed by treatment group and 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 20.0.

Quality of Life: Health-related quality of life was assessed with the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C questionnaires. A Wilcoxon signed rank test explored within-treatment group changes from baseline to each of the postbaseline time points, and from EOT to each posttreatment time point. A Wilcoxon rank sum test explored between-treatment group differences in change from baseline to each of the postbaseline time points.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: All 117 randomized subjects received at least 1 dose of study drug and were included in both the Safety Analysis Set and FAS (57 subjects in the SOF/VEL+RBV 12 Week group and 60 subjects in the SOF/VEL+RBV 24 Week group). The majority of subjects completed study treatment (97.4%, 114 of 117 subjects). Three subjects (2.6%) prematurely discontinued study treatment (1 subject in the SOF/VEL+RBV 12 Week group and 2 subjects in the SOF/VEL+RBV 24 Week group). All 3 subjects prematurely discontinued study treatment due to AEs.

Demographics and baseline characteristics were generally balanced across both treatment groups. Overall, the majority of subjects were female (57.3%). The mean age was 63 years (range: 21−81), and 46.2% of subjects were ≥ 65 years of age. The mean baseline body mass index (BMI) value for subjects was 23.8 kg/m^2 (range: 18.0−35.9), and 35.0% of subjects had a BMI ≥ 25 kg/m^2.

The majority of subjects had genotype 1 HCV infection (81.2% [1a = 2.6%; 1b = 78.6%]); and 18.8% of subjects had genotype 2 HCV infection (2a/2c = 6.0%; 2b = 5.1%; no confirmed subtype = 7.7%). Most subjects had non-CC (CT or TT) IL28B genotypes (57.3%). A total of 39 subjects (33.3%) had cirrhosis at screening. Overall, the mean (SD) baseline HCV RNA value was 6.2 (0.54) log_{10} IU/mL, and most subjects had baseline HCV RNA ≥ 5 log_{10} IU/mL (95.7%) and HCV RNA ≥ 800,000 IU/mL (78.6%).

All subjects with genotype 1 HCV infection were NS5A inhibitor-experienced, most of whom failed treatment with DAAs from multiple classes, including NS5A inhibitors and NS3 inhibitors

(82.1%); NS5A inhibitors and NS5B inhibitors (8.4%); or NS5A inhibitors, NS5B inhibitors, and NS3 inhibitors (7.4%). Regarding specific DAA combinations, 86.3% of genotype 1 subjects were previously treated with daclatasvir (DCV) + asunaprevir (ASV) and 14.7% were previously treated with ledipasvir/sofosbuvir (LDV/SOF). Most subjects with genotype 2 HCV infection had been previously treated with an NS5B inhibitor (90.9%). Regarding specific DAAs, 90.9% of genotype 2 subjects were previously treated with SOF.

Efficacy Results: The study met the primary efficacy endpoint of an SVR12 rate that was statistically superior to the historical control rate of 50% ($p < 0.001$) for subjects with genotype 1 HCV infection in both treatment groups.

For both genotypes 1 and 2, and in total, extending the SOF/VEL+RBV treatment duration from 12 to 24 weeks increased the SVR12 rate. The SVR12 rates for selected populations were as follows:

Genotype 1 Subjects

- SOF/VEL+RBV 12 Week group: 85.1% (40 of 47 subjects; 95% CI: 71.7% to 93.8%)
- SOF/VEL+RBV 24 Week group: 97.9% (47 of 48 subjects; 95% CI: 88.9% to 99.9%)

Genotype 2 Subjects

- SOF/VEL+RBV 12 Week group: 70.0% (7 of 10 subjects; 95% CI: 34.8% to 93.3%)
- SOF/VEL+RBV 24 Week group: 91.7% (11 of 12 subjects; 95% CI: 61.5% to 99.8%)

Total

- SOF/VEL+RBV 12 Week group: 82.5% (47 of 57 subjects; 95% CI: 70.1% to 91.3%)
- SOF/VEL+RBV 24 Week group: 96.7% (58 of 60 subjects; 95% CI: 88.5% to 99.6%)

In the SOF/VEL+RBV 12 Week group, 10 of 57 subjects (17.5%) did not achieve SVR12. Of these, no subject had on-treatment virologic failure, 9 subjects relapsed, and 1 subject was categorized as "other." Of the 9 subjects who relapsed, 6 subjects had genotype 1 HCV infection and 3 subjects had genotype 2 HCV infection. The subject categorized as "other" had genotype 1 HCV infection and prematurely discontinued study drug on Day 8 due to an AE of rash.

In the SOF/VEL+RBV 24 Week group, 2 of 60 subjects (3.3%) did not achieve SVR12. No subject had on-treatment virologic failure, and 2 subjects relapsed. Of the 2 subjects who relapsed, 1 subject had genotype 1 HCV infection and 1 subject had genotype 2 HCV infection.

Most relapses occurred by the posttreatment Week 4 visit. In the SOF/VEL+RBV 12 Week group, 7 of 9 relapses occurred by posttreatment Week 4; 2 of 9 relapses occurred between posttreatment Weeks 4 and 12; and no relapses occurred between posttreatment Weeks 12 and 24. In the SOF/VEL+RBV 24 Week group, 1 of 2 relapses occurred by posttreatment Week 4; 1 of 2 relapses occurred between posttreatment Weeks 4 and 12; and no relapses occurred between posttreatment Weeks 12 and 24.

In the SOF/VEL+RBV 12 and 24 Week groups, 56 and 60 subjects, respectively, had HCV RNA assessed at both posttreatment Weeks 12 and 24, with 100.0% concordance between SVR12 and SVR24 in both treatment groups.

HCV RNA levels (log_{10} IU/mL) declined rapidly, with similar decreases in HCV RNA observed in both treatment groups. Consistent with the rapid and sustained decline in HCV RNA, 98.2% of subjects in the SOF/VEL+RBV 12 Week group and 98.3% of subjects in the SOF/VEL+RBV 24 Week group had HCV RNA < LLOQ at Week 4. At Week 8 through EOT, 100.0% of subjects in both treatment groups had HCV RNA < LLOQ.

Virologic Resistance Results: Overall, 94.8% (110 of 116 subjects) had NS5A resistance-associated variants (RAVs) at baseline. The SVR12 rate was 85.2% (46 of 54 subjects) for subjects with baseline NS5A RAVs in the SOF/VEL+RBV 12 Week group, and 96.4% (54 of 56 subjects) for subjects with baseline NS5A RAVs in the SOF/VEL+RBV 24 Week group. The presence of multiple RAVs and/or specific RAVs associated with high level resistance to NS5A inhibitors at baseline did not impact SVR12 rates in the 24 Week group. None of the 11 subjects who relapsed across both treatment groups had treatment-emergent NS5A or NS5B nucleoside inhibitor (NI) RAVs.

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

Safety Results: Overall, treatment with SOF/VEL+RBV for 12 or 24 weeks was generally safe and well tolerated. Adverse events were experienced by 80.7% of subjects (46 of 57) in the SOF/VEL+RBV 12 Week group and 75.0% of subjects (45 of 60) in the SOF/VEL+RBV 24 Week group.

The most common AEs reported for subjects in the SOF/VEL+RBV 12 Week group were viral upper respiratory tract infection (35.1%), anemia (24.6%), and headache (19.3%). The most common AEs reported for subjects in the SOF/VEL+RBV 24 Week group were viral upper respiratory tract infection and anemia (each 21.7%), and pruritus, dry skin, and gastroenteritis (each 6.7%).

Most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. Grade 3 (severe) AEs were reported for no subject in the SOF/VEL+RBV 12 Week group and 6.7% (4 subjects) in the SOF/VEL+RBV 24 Week group. No Grade 4 (life-threatening) AEs were reported in either treatment group. Hepatocellular carcinoma (2 subjects) was the only Grade 3 AE reported for > 1 subject. All Grade 3 AEs were considered not related to study drug.

Serious adverse events (SAEs) were reported for no subject in the SOF/VEL+RBV 12 Week group and 4 subjects (6.7%) in the SOF/VEL+RBV 24 Week group. Hepatocellular carcinoma (2 subjects) was the only SAE reported for > 1 subject. All SAEs were considered not related to study drug. No deaths were reported during this study.

A total of 3 subjects (1 subject in the SOF/VEL+RBV 12 Week group and 2 subjects in the SOF/VEL+RBV 24 Week group) prematurely discontinued all study drugs due to an AE (rash, hepatic angiosarcoma, and depression).

Most subjects had a least 1 laboratory abnormality reported, with the majority being Grade 1 or Grade 2. Grade 3 laboratory abnormalities were reported for 10.5% of subjects (6 of 57) in the SOF/VEL+RBV 12 Week group and 26.7% of subjects (16 of 60) in the SOF/VEL+RBV 24 Week group. No subject in either treatment group had a Grade 4 laboratory abnormality.

Consistent with the expected safety profile of RBV, decreases in hemoglobin and lymphocytes and elevations in reticulocytes and platelets were observed in both groups. The most common Grade 3 hematology laboratory abnormalities were decreased lymphocytes and decreased

hemoglobin. Grade 3 decreased lymphocytes were reported for 1 subject (1.8%) in the SOF/VEL+RBV 12 Week group and 7 subjects (11.7%) in the SOF/VEL+RBV 24 Week group. Grade 3 decreased hemoglobin was reported for 2 subjects (3.5%) in the SOF/VEL+RBV 12 Week group and 4 subjects (6.7%) in the SOF/VEL+RBV 24 Week group. Postbaseline hemoglobin values < 10 g/dL were reported for 7 subjects (12.3%) in the SOF/VEL+RBV 12 Week group and 5 subjects (8.3%) in the SOF/VEL+RBV 24 Week group. One subject in the SOF/VEL+RBV 24 Week group had postbaseline hemoglobin values < 8.5 g/dL. No subjects were reported to have received a blood transfusion or used an erythropoietin-containing agent in this study.

The most common Grade 3 serum chemistry laboratory abnormality was increased serum glucose, which was reported for 3 subjects (5.3%) in the SOF/VEL+RBV 12 Week group and 5 subjects (8.3%) in the SOF/VEL+RBV 24 Week group. All subjects with Grade 3 increased serum glucose had a medical history of diabetes.

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and 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 most assessments. A statistically significant ($p < 0.05$) worsening in health-related quality of life was observed between baseline and EOT for 2 assessments (the SF-36 domain of role physical in the SOF/VEL+RBV 12 Week group and the WPAI: Hep C percent activity impairment due to HCV in the SOF/VEL+RBV 24 Week group). 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 this study in Japanese subjects who had previously failed a DAA-containing regimen are as follows:

- The study met its predefined primary efficacy endpoint: subjects with chronic genotype 1 HCV infection who had failed prior treatment with an NS5A inhibitor-containing regimen achieved SVR12 rates of 85.1% and 97.9% in the SOF/VEL+RBV 12 and 24 Week groups, respectively, which were statistically superior to the historical control rate of 50% ($p < 0.001$).
- Extending the SOF/VEL+RBV treatment duration from 12 to 24 weeks increased the SVR12 rates. With 24 weeks of SOF/VEL+RBV:
  - The SVR12 rates were 97.9% for subjects with chronic genotype 1 HCV infection and 91.7% for subjects with chronic genotype 2 HCV infection.
  - Baseline NS5A RAVs did not impact treatment outcome, and no subject who relapsed developed treatment-emergent RAVs.
- Treatment with SOF/VEL+RBV for 12 or 24 weeks was generally safe and well tolerated in this study, with few Grade 3 AEs, SAEs, discontinuations due to AEs, and Grade 3 laboratory abnormalities. Most Grade 3 laboratory abnormalities were consistent with the known effects of RBV. No deaths, Grade 4 AEs, or Grade 4 laboratory abnormalities were observed.