FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination (FDC) and Sofosbuvir/Velpatasvir FDC and Ribavirin in Subjects with Chronic Genotype 3 HCV Infection and Cirrhosis
Name of Test Drug:	Sofosbuvir (SOF)/velpatasvir (VEL)
Dose and Formulation:	SOF/VEL 400/100 mg fixed-dose combination
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-342-2097
Phase of Development:	Phase 2
EudraCT No.:	2016-000417-73
ClinicalTrials.gov Identifier:	NCT02781558
Study Start Date:	29 July 2016 (First Subject Screened)
Study End Date:	06 October 2017 (Last Subject Last Observation for the Primary Endpoint)
Principal or Coordinating Investigator:	Name: Rafael Esteban, MD Affiliation: PPD
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Report Date:	22 February 2018

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-342-2097
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

A Phase 2, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination (FDC) and Sofosbuvir/Velpatasvir FDC and Ribavirin in Subjects with Chronic Genotype 3 HCV Infection and Cirrhosis

Investigators: This was a multicenter study.

Study Centers: This study was conducted at 29 sites in Spain.

Publications: At the time of this report, no data from the study had been published.

Study Period:

29 July 2016 (First Subject Screened)
06 October 2017 (Last Subject Last Observation for the Primary Endpoint)

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) (SOF/VEL) or SOF/VEL + ribavirin (RBV) for 12 weeks as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after cessation of each treatment regimen (SVR12)
- To evaluate the safety and tolerability of each treatment regimen

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attain SVR 4 weeks after cessation of each treatment regimen (SVR4)
- 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 each treatment regimen

The exploratory objective of this study was:

- 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) for subjects who provide their separate and specific consent

Methodology: This Phase 2, randomized, open-label, multicenter study evaluated the safety, tolerability, and antiviral efficacy of SOF/VEL ± RBV for 12 weeks in subjects with chronic genotype 3 HCV infection and compensated cirrhosis, with or without human immunodeficiency virus (HIV) coinfection.

Approximately 200 eligible subjects were to be randomized 1:1 to the following 2 treatment groups:

- SOF/VEL (n = 100): SOF/VEL (400/100 mg) 1 tablet once daily by mouth for 12 weeks
- SOF/VEL+RBV (n = 100): SOF/VEL (400/100 mg) 1 tablet once daily plus RBV (1000 or 1200 mg) 5 or 6 × 200 mg tablets divided into 2 daily doses by mouth for 12 weeks

The weight-based RBV dose was 1000 mg for subjects who weighed < 75 kg and 1200 mg for subjects who weighed ≥ 75 kg.

Randomization was stratified by prior HCV treatment experience (treatment naive or treatment experienced).

Number of Subjects (Planned and Analyzed):

Planned: Approximately 200 subjects

Analyzed: 204 subjects (101 in the SOF/VEL group and 103 in the SOF/VEL+RBV group)

- All Randomized Analysis Set:
  - 204 subjects (101 in the SOF/VEL group and 103 in the SOF/VEL+RBV group)
- Safety Analysis Set:
  - 204 subjects (101 in the SOF/VEL group and 103 in the SOF/VEL+RBV group)
- Full Analysis Set (FAS):
  - 204 subjects (101 in the SOF/VEL group and 103 in the SOF/VEL+RBV group)
- PK Analysis Set: 204 subjects
  - 204 subjects (101 in the SOF/VEL group and 103 in the SOF/VEL+RBV group)

Diagnosis and Main Criteria for Inclusion: Subjects were males and nonpregnant, nonlactating females ≥ 18 years with genotype 3 HCV infection and compensated cirrhosis.

Duration of Treatment: 12 weeks of treatment with SOF/VEL or SOF/VEL+RBV

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

SOF/VEL/ (1 × 400/100 mg tablet) was administered once daily by mouth for 12 weeks

RBV (5 or 6 × 200 mg tablet) was divided into 2 daily doses and administered by mouth for 12 weeks

The batch number of SOF/VEL administered in this study was DU1501B1.

The batch numbers of RBV administered in this study were AF1806Z and AC9247W.

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 2, 4, 8, and 12 during treatment (or upon early termination) and posttreatment Weeks 4 and 12 (if applicable). 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 is 15 IU/mL.

Virologic Resistance: Baseline deep sequencing analysis of HCV nonstructural protein (NS)5A and NS5B coding regions was performed for all subjects. For all subjects with virologic failure, deep sequencing was also performed at the first time point after virologic failure if a plasma/serum sample was available and HCV RNA was > 1000 IU/mL. Sequencing data were reported at a 15% assay cutoff.

Pharmacokinetics: A single pharmacokinetics (PK) blood sample was collected from all subjects at each on-treatment visit after baseline/Day 1 and the early termination visit, as applicable.

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

Statistical Methods:

Efficacy: The primary efficacy endpoint was the proportion of subjects with HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs (SVR12) 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 and overall.

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

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 the number and percentage of subjects who met the endpoint definitions.

Pharmacokinetics: Pharmacokinetics analyses were not conducted for this report.

Safety: All randomized/enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety data were analyzed by treatment group 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 (ie, treatment emergent). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 204 subjects were randomized in the study. All of the randomized subjects received at least 1 dose of SOF/VEL (101 subjects in the SOF/VEL group, and 103 subjects in the SOF/VEL+RBV group) and were included in the Safety Analysis Set and the FAS.

Demographics and baseline characteristics were generally balanced across the treatment groups. The mean age of subjects was 51 years (range: 31 to 85 years); the majority of subjects were male (79.4%), white (87.7%), and not Hispanic or Latino (90.7%). The mean baseline body mass index (BMI) for subjects was 27.1 kg/m^2 (range: 17.8 to 46.8 kg/m^2), and 23.0% had BMI $\geq$ 30 kg/m^2. All subjects had HCV genotype 3, including 93.6% with subtype 3a, 0.5% with subtype 3b, and 5.9% with an indeterminate subtype. Overall, 27% of subjects were treatment experienced, most of whom were previously treated with pegylated interferon and RBV. More subjects had the CC IL28B genotype (57.4%) than the CT (36.3%) and TT (5.9%) genotypes. All of the randomized subjects had cirrhosis. The mean baseline HCV RNA was 6.2 log_{10} IU/mL (range: 4.0 to 7.5 log_{10} IU/mL), and most subjects (72.5%) had baseline HCV RNA $\geq$ 800,000 IU/mL. Overall, 14.7% of subjects had confirmed HIV coinfection (15.8% in the SOF/VEL group and 13.6% in the SOF/VEL+RBV group).

Efficacy Results:

In the SOF/VEL group, 92 of 101 subjects achieved SVR12 (91.1%; 95% CI: 83.8% to 95.8%) following 12 weeks of treatment. Of the 9 subjects who did not achieve SVR12, 5 subjects relapsed, 1 subject had on-treatment virologic failure (nonresponder), 1 subject prematurely discontinued SOF/VEL on Day 1 due to AEs, and 2 subjects were lost to follow-up. A total of 93.1% (94 of 101 subjects) achieved SVR4. One of the 2 subjects with SVR4 who did not achieve SVR12 had virologic relapse determined at posttreatment Week 12; the other subject was lost to follow-up after the posttreatment Week 4 assessment. The high SVR12 rate and low number of subjects with virologic failure precluded meaningful conclusions being drawn from analyses of the evaluated subgroups. HCV RNA levels declined rapidly after initiation of SOF/VEL; at the end of treatment, the mean (SD) change from baseline in HCV RNA was −5.04 (0.640) log_{10} IU/mL.

In the SOF/VEL+RBV group, 99 of 103 subjects achieved SVR12 (96.1%; 95% CI: 90.4% to 98.9%) following 12 weeks of treatment. Of the 4 subjects who did not achieve SVR12, 2 subjects relapsed, 1 subject was lost to follow-up, and 1 subject prematurely discontinued SOF/VEL+RBV on Day 20 due to an AE and was subsequently lost to follow-up. A total of 97.1% (100 of 103 subjects) achieved SVR4; the 1 subject with SVR4 who did not achieve SVR12 was lost to follow-up after the posttreatment Week 4 assessment. The high SVR12 rate and low number of subjects with virologic failure precluded meaningful conclusions being drawn from analyses of the evaluated subgroups. HCV RNA levels declined rapidly after initiation of SOF/VEL+RBV; at the end of treatment, the mean (SD) change from baseline in HCV RNA was −5.13 (0.568) log_{10} IU/mL.

Virologic Resistance

Overall, 41 of 199 subjects (20.6%) in the Resistance Analysis Population had NS5A resistance-associated variants (RAVs) at baseline. In the SOF/VEL group 84.2% (16 of 19 subjects) with baseline NS5A RAVs and 96.2% (76 of 79 subjects) without baseline NS5A RAVs achieved SVR12. Two of the 4 subjects with Y93H at baseline (50.0%) achieved SVR12. Of the 5 subjects in the SOF/VEL group with virologic failure who had baseline and postbaseline sequencing data available, 3 subjects had emergent NS5A RAVs.

In the SOF/VEL+RBV group, 95.5% (21 of 22 subjects) with baseline NS5A RAVs, and 98.7% (78 of 79 subjects) without baseline NS5A RAVs achieved SVR12. Eight of the 9 subjects with Y93H at baseline (88.9%) achieved SVR12. Of the 2 subjects in the SOF/VEL+RBV group with virologic failure, 1 had emergent NS5A RAVs.

Pharmacokinetics/Pharmacodynamics Results: Pharmacokinetics analyses were not conducted for this report.

Safety Results:

Treatment with SOF/VEL ± RBV for 12 weeks was generally safe and well tolerated. A low number of SAEs, Grade 3 AEs, and Grade 3 or 4 laboratory abnormalities were reported. No Grade 4 AEs were reported. There were no notable changes in vital signs, and no subjects died during the study.

In the SOF/VEL group, 47.5% (48 of 101 subjects) experienced any AE, and 15.8% had an AE that was assessed as related to study drug. The 3 most common AEs were asthenia (11.9%, 12 subjects), headache (7.9%, 8 subjects), and back pain (6.9%, 7 subjects). Most of the AEs were Grade 1 (mild) or Grade 2 (moderate). Four subjects (4.0%) had SAEs, and all of the SAEs were assessed as unrelated to study drug. One subject prematurely discontinued SOF/VEL on Day 1 due to Grade 1 AEs of anxiety and dizziness after receiving 1 dose of SOF/VEL.

The number of Grade 3 or 4 hematology and chemistry laboratory abnormalities reported for the SOF/VEL group was low and included Grade 3 decreases in hemoglobin, lymphocytes, and platelets (1 subject each) and Grade 3 increases in glucose (1 subject with diabetes) and lipase (2 subjects; both asymptomatic). A Grade 4 increase in lipase was also reported (1 subject; asymptomatic). HIV RNA levels and CD4 cell counts remained stable for the 16 subjects with HIV coinfection.

In the SOF/VEL+RBV group, 74.8% (77 of 103 subjects) experienced any AE, and 50.5% had an AE that was assessed as related to study drug. The higher frequency of AEs observed in the SOF/VEL+RBV group relative to the SOF/VEL group was primarily due to AEs associated with RBV toxicity. The 3 most common AEs were asthenia (27.2%, 28 subjects), headache (24.3%, 25 subjects), and insomnia (11.7%, 12 subjects). Most of the AEs were Grade 1 (mild) or Grade 2 (moderate). Two subjects (1.9%) had a single SAE each, both of which were assessed as unrelated to study drug. One subject prematurely discontinued SOF/VEL+RBV on Day 20 due to an AE of Grade 1 abnormal blood bilirubin, and 1 subject prematurely discontinued RBV on Day 35 due to an AE of Grade 2 anemia.

The number of Grade 3 or 4 hematology and chemistry laboratory abnormalities reported for the SOF/VEL+RBV group was low and included Grade 3 decreases in hemoglobin (3 subjects) and platelets (1 subject) and Grade 3 increases in lipase (5 subjects; all asymptomatic), total bilirubin (2 subjects), urate (2 subjects), and glucose (2 subjects with diabetes). One subject had a Grade 3 increase in prothrombin time. One subject had a concurrent Grade 3 increase in AST and Grade 4 increase in ALT that were preceded by AEs of abdominal pain and resolved without discontinuation or interruption of study drugs. HIV RNA levels and CD4 cell counts remained stable for the 14 subjects with HIV coinfection.

CONCLUSIONS:

The conclusions of this study of subjects with genotype 3 HCV infection and compensated cirrhosis treated with SOF/VEL or SOF/VEL+RBV for 12 weeks are as follows:

- High SVR12 rates were observed following 12 weeks of treatment with SOF/VEL (91.1%) and SOF/VEL+RBV (96.1%).
- SOF/VEL and SOF/VEL+RBV were generally well tolerated. No treatment-emergent deaths, Grade 4 AEs, treatment-related SAEs, or clinically relevant laboratory abnormalities were observed.