FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/GS-5816/GS-9857 Fixed-Dose Combination with or without Ribavirin in Subjects with Chronic Genotype 1 HCV Infection Previously Treated with a Direct Acting Antiviral Regimen
Name of Test Drug:	Sofosbuvir (SOF)/Velpatasvir (VEL; GS-5816)/Voxilaprevir (VOX; GS-9857) Fixed-Dose Combination (FDC)
Dose and Formulation:	SOF/VEL/VOX FDC (400/100/100 mg) tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, DA 94404 USA
Study No.:	GS-US-367-1871 (TRILOGY-3)
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	125751 Not Applicable
ClinicalTrials.gov Identifier:	NCT02536313
Study Start Date:	29 July 2015 (First Subject Screened)
Study End Date:	28 June 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Eric Lawitz, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Luisa Stamm, MD, PhD Telephone: PPD Fax: PPD
Report Date:	24 August 2016

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-367-1871
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/GS-5816/GS-9857 Fixed-Dose Combination with or without Ribavirin in Subjects with Chronic Genotype 1 HCV Infection Previously Treated with a Direct Acting Antiviral Regimen

Investigators: Eric Lawitz, MD

Study Centers: 1 site in the US

Publications:

Lawitz E, Poordad F, Wells J, Hyland RH, Yang Y, Dvory-Sobol H, Stamm LM, Brainard DM, McHutchison JG, Landaverde C, Gutierrez J. High Efficacy of Sofosbuvir/Velpatasvir/GS-9857 With or Without Ribavirin for 12 Weeks in Direct Acting Antiviral-Experienced Patients With Genotype 1 HCV Infection [Presentation PS021]. J Hepatol 2016; 64: S146.

Study Period:

29 July 2015 (First Subject Screened)
28 June 2016 (Last Subject Observation)
28 March 2016 (Last Subject 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; GS-5816)/voxilaprevir (VOX; GS-9857) fixed dose combination (FDC) ± ribavirin (RBV) in subjects with chronic genotype 1 hepatitis C virus (HCV) infection and prior treatment experience with a direct-acting antiviral (DAA), 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 treatment with SOF/VEL/VOX

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

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), in subjects who provided their separate and specific consent

Methodology: This Phase 2, single-center, open-label study evaluated the safety and efficacy of SOF/VEL/VOX FDC with or without RBV in subjects with chronic genotype 1 HCV infection previously treated with a DAA regimen. Approximately 50% of the subjects had cirrhosis.

Approximately 80 subjects were planned to be enrolled into 1 of 2 treatment groups and randomized in equal proportions to receive:

- Group 1 (N = 40): SOF/VEL/VOX (400/100/100 mg) once daily with food for 12 weeks
- Group 2 (N = 40): SOF/VEL/VOX (400/100/100 mg) once daily with food + RBV (1000 or 1200 mg/day divided twice daily) with food for 12 weeks

Randomization was stratified by the presence of a nonstructural protein (NS) 5A inhibitor in the prior DAA regimens and the presence of cirrhosis.

Number of Subjects (Planned and Analyzed):
Planned: Approximately 80 subjects
Analyzed:

All Enrolled Subjects: 49 subjects

Full Analysis Set: 49 subjects

Safety Analysis Set: 49 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were DAA-experienced males and non-pregnant females aged ≥ 18 years with chronic genotype 1 HCV infection, screening HCV RNA ≥ 10^4 IU/mL, and body mass index (BMI) ≥ 18 kg/m^2, with or without cirrhosis.

Duration of Treatment: Subjects were treated for 12 weeks, with a 24-week follow-up period.

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

- SOF/VEL/VOX was administered orally with food at a dose of 400/100/100 mg (1 FDC tablet once daily).
- RBV was administered orally with food at a total daily dose of 1000 or 1200 mg (1000 mg for subjects weighing < 75 kg and 1200 mg for subjects weighing ≥ 75 kg) divided twice daily.

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

- SOF/VEL/VOX: ER1501B2
- RBV: AB7658Z

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, and at all subsequent on-treatment and posttreatment visits. The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to determine HCV RNA results in this study. The lower limit of quantification (LLOQ) of the assay was 15 IU/mL.

Pharmacokinetics: A single pharmacokinetic (PK) blood sample was collected from all subjects at Weeks 1, 2, 4, 8, and 12. Samples for PK analysis were also drawn at the early termination visit, as applicable.

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

Statistical Methods:

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of study drug) for the Full Analysis Set. A 2-sided 95% exact CI based on the Clopper-Pearson method was provided for the SVR12 rate in each treatment group.

Secondary efficacy endpoints included the proportion of subjects with SVR4 and SVR24, the proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline during treatment, and the proportion of subjects with virologic failure.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, 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.

Pharmacokinetics: No PK or pharmacodynamic analyses were performed for this report.

Safety: All enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety endpoints were analyzed by the number and percentage of subjects with events or abnormalities for categorical values and descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 49 subjects were enrolled into the study. All subjects were enrolled into 1 site in the United States. All subjects completed study treatment.

Demographics were generally balanced across treatment groups. Overall, the majority of subjects were male (65.3%), white (79.6%), and not Hispanic/Latino (67.3%), with a mean age of 54 years (range: 18–75 years). The mean baseline BMI value for subjects was 31.2 kg/m^2 (range: 19.5–55.4 kg/m^2), and 42.9% of subjects had BMI $\geq$ 30 kg/m^2.

Baseline disease characteristics were generally balanced across treatment groups. The majority of subjects had genotype 1a HCV infection (87.8%), and non-CC (CT or TT) IL28B alleles (85.7%). Overall, 51% of subjects had cirrhosis. Across groups, the mean baseline HCV RNA value was 6.3 $\log_{10}$ IU/mL (range: 5.2−7.1 $\log_{10}$ IU/mL), and most subjects had HCV RNA ≥ 800,000 IU/mL (81.6%).

All of the subjects were DAA experienced. Overall, 40.8% of subjects (20 of 49) had previously been treated an NS5A-containing regimen (the most common NS5A inhibitors were ledipasvir (LDV) [12 subjects] and daclatasvir [7 subjects]), 30.6% (15 of 49 subjects) had previously been treated with an NS3/4A inhibitor alone (the most common NS3/4A inhibitor used without another DAA was boceprevir [7 subjects]), and 28.6% (14 of 49 subjects) had previously been treated with an NS5B inhibitor alone or with an NS3/4A inhibitor (the most common NS5B inhibitor was SOF [11 subjects]). Most subjects had received only one prior treatment for HCV infection (87.8%).

Efficacy Results: All 24 subjects (100.0%) receiving SOF/VEL/VOX achieved SVR12, and 24 of 25 subjects (96.0%) receiving SOV/VEL/VOX+RBV achieved SVR12. All subjects who achieved SVR12 achieved SVR24.

SOF/VEL/VOX and SOF/VEL/VOX+RBV treatment led to rapid reduction of HCV RNA, and 100% of subjects had HCV RNA < LLOQ at the end of treatment. No subjects had on-treatment virologic failure. The 1 subject receiving SOF/VEL/VOX+RBV who did not achieve SVR12, completed the assigned treatment regimen and had virologic relapse at posttreatment Week 4. This subject had previously failed 24 weeks of LDV/SOF.

Virologic Resistance: Overall, the presence of baseline resistance-associated variants (RAVs) had no impact on SVR12 rates. In the SOF/VEL/VOX treatment group, all subjects achieved SVR12, including 54% with NS3 RAVs and 50% with NS5A RAVs. SOF/VEL/VOX+RBV treatment group, 67% subjects had NS3 RAVS and 38% had NS5A RAVs; all but 1 subject, who had NS5A RAVs at baseline achieved SVR12. The subject who relapsed had treatment-emergent NS3 RAVs and additional NS5A RAVs at the time of relapse.

Pharmacokinetics Results: Single plasma samples were collected at all scheduled on-treatment study visits after baseline/Day 1. Plasma concentration data from all PK samples collected in this study will be combined with data from other studies to develop a population PK model for SOF, GS-331007, VEL, and VOX, and will be presented in separate reports, as appropriate.

No PK or pharmacodynamic analyses were performed for this report.

Safety Results: SOF/VEL/VOX and SOF/VEL/VOX+RBV were generally safe and well tolerated. Across both treatment groups, most subjects had at least 1 AE (53.1%; 26 of 49 subjects). The majority of AEs reported were Grade 1 or 2 in severity. The most common AEs were fatigue (18.4%; 9 of 49 subjects) and anemia (8.2%; 4 of 49 subjects) reported in subjects receiving treatment with RBV.

No subject had an AE that led to permanent discontinuation of SOF/VEL/VOX. One subject receiving SOF/VEL/VOX+RBV experienced Grade 3 rash, which was considered to be related to study drug by the investigator and led to permanent discontinuation of RBV. Adverse events leading to permanent discontinuation of RBV were reported in 3 subjects, and included anemia, fatigue, and rash. None of these AEs were reported as serious and all were considered by the

investigator to be related to study drug.

No Grade 4 AEs, deaths, or pregnancies were reported. Pneumonia was the only treatment-emergent serious adverse event (SAE) reported in the study. Four of the 49 subjects (8.2%) had sulfa allergy and the AEs reported for these subjects were not meaningfully different than those reported for subjects without sulfa allergy; no urticaria or rash was reported.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. Grade 3 laboratory abnormalities were reported for 7 subjects (14.3%). No Grade 4 laboratory abnormalities were reported in this study.

Overall, hemoglobin levels were lower and reticulocyte levels were higher in subjects receiving SOF/VEL/VOX+RBV compared to those receiving SOF/VEL/VOX. Of the 25 subjects receiving SOF/VEL/VOX+RBV, Grade 3 decreased hemoglobin was reported in 4 subjects and Grade 3 decreased lymphocytes was reported in 1 subject. Grade 3 decreased platelets were reported in 2 of 49 subjects overall, with 1 subject in each treatment group. No other Grade 3 and no Grade 4 hematology laboratory abnormalities were observed. Three of the 4 Grade 3 decreased hemoglobin abnormalities were associated with AEs of anemia. No other hematology laboratory abnormality was reported as an AE.

Chemistry laboratory abnormalities included 1 subject who received SOF/VEL/VOX+RBV with Grade 3 increased alanine aminotransferase at the end of treatment and 1 subject with a history of diabetes who received SOF/VEL/VOX+RBV with Grade 3 increased glucose. No Grade 4 chemistry laboratory abnormalities were reported. None of the Grade 3 laboratory abnormalities were reported as AEs.

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

CONCLUSIONS:

- SOF/VEL/VOX administered daily with food for 12 weeks to DAA-experienced subjects with genotype 1 HCV infection was highly effective and the addition of RBV did not improve efficacy.
  - SVR12 rate was 100% in DAA-experienced subjects with or without cirrhosis treated with SOF/VEL/VOX for 12 weeks.
  - SVR12 rate was 96.0% in DAA-experienced subjects with or without cirrhosis treated with SOF/VEL/VOX+RBV for 12 weeks.
- Presence of baseline RAVs had no impact on SVR12 rates.
- SOF/VEL/VOX and SOF/VEL/VOX+RBV administered daily for 12 weeks were generally safe and well tolerated with few SAEs, Grade 3 AEs, discontinuations due to AEs, and Grade 3 laboratory abnormalities reported in the study overall. There were no Grade 4 AEs or laboratory abnormalities. Subjects receiving treatment with SOF/VEL/VOX+RBV reported more AEs and graded laboratory abnormalities than those receiving treatment with SOF/VEL/VOX alone.