FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Global, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of GS-9857 Plus Sofosbuvir/GS-5816 Fixed Dose Combination in Subjects with Chronic Non-Genotype 1 HCV Infection
Name of Test Drug:	Sofosbuvir (SOF)/Velpatasvir (VEL; GS-5816) Fixed-Dose Combination (FDC) + Voxilaprevir (VOX; GS-9857)
Dose and Formulation:	SOF/VEL FDC (400/100 mg) tablet VOX 100 mg tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-367-1169
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	119926 Not Applicable
ClinicalTrials.gov Identifier:	NCT02378961
Study Start Date:	16 February 2015 (First Subject Screened)
Study End Date:	26 January 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Edward Gane, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Luisa Stamm, MD, PhD Telephone: PPD Fax: PPD
Report Date:	14 June 2016

STUDY SYNOPSIS

Study GS-US-367-1169
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Global, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of GS-9857 Plus Sofosbuvir/GS-5816 Fixed Dose Combination in Subjects with Chronic Non-Genotype 1 HCV Infection

Investigators: Multicenter

Study Centers: This study was conducted at a total of 34 sites: 32 in the United States and 2 in New Zealand.

Publications:

Gane EJ, Nguyen M, Kwo P, Kowdley K, Reau N, Jacobson I, et al. Short-Duration Treatment With Sofosbuvir/Velpatasvir Plus GS-9857 in Treatment-Naïve Genotype 1–6 HCV-Infected Patients With or Without Cirrhosis [Poster SAT-138]. European Association for the Study of the Liver (EASL); 2016 13-17 April; Barcelona, Spain.

Lawitz E, Kowdley K, Curry M, Reau N, Nguyen M, Kwo P, et al. High Efficacy of Sofosbuvir/Velpatasvir Plus GS-9857 for 12 Weeks in Treatment-Experienced Genotype 1–6 HCV-Infected Patients, Including Those Previously Treated With Direct-Acting Antivirals [Presentation]. European Association for the Study of the Liver (EASL); 2016 13-17 April; Barcelona, Spain.

Study Period:

16 February 2015 (First Subject Screened)
26 January 2016 (Last Subject Observation)
21 September 2015 (Last Subject Observation for the Primary Endpoint)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were:

- To evaluate the efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL; GS-5816) fixed-dose combination (FDC) + voxilaprevir (VOX; GS-9857) in subjects with non-genotype 1 chronic hepatitis C virus (HCV) infection 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:

- 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
- To characterize steady-state pharmacokinetics (PK) of study drug

The exploratory objectives of this study were:

- 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 provide their separate and specific consent
- To assess the effect of treatment on health-related quality of life (QOL)

Methodology: This Phase 2, multicenter, nonrandomized, open-label study evaluated the safety and efficacy of SOF/VEL FDC (400/100 mg) + VOX 100 mg once daily for 6, 8, or 12 weeks in treatment-naive and treatment-experienced subjects with genotype 2, 3, 4, 5, or 6 HCV infection (ie, non-genotype 1) with or without cirrhosis.

A total of 128 subjects were enrolled into 1 of 4 treatment groups to receive SOF/VEL+VOX once daily with food as follows:

Cohort	Treatment Group	N	Treatment Duration (weeks)
1	Treatment naive, noncirrhotic	33	6
	Treatment naive, cirrhotic	30	8
2	Treatment experienced, noncirrhotic	36	12
	Treatment experienced, cirrhotic	29	12

Number of Subjects (Planned and Analyzed):
Planned: 210
Analyzed: 128

- All Enrolled Subjects: 128 subjects
- Full Analysis Set (FAS): 128 subjects
- Safety Analysis Set: 128 subjects
- PK Analysis Set: 128 subjects
- PK Substudy Analysis Set: 23 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were treatment-naive and treatment-experienced males and nonpregnant, nonnursing females aged ≥ 18 years with non-genotype 1 chronic 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: Treatment duration was 6, 8, or 12 weeks.

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

- **SOF/VEL** was administered orally with food at a dose of 400/100 mg (1 FDC tablet once daily).
- **VOX** was administered orally with food at a dose of 100 mg (1 tablet once daily).

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

- **SOF/VEL:** DU1404B1
- **VOX:** DY1408B1

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 blood sample for PK analysis was collected from all subjects at all on-treatment visits after baseline/Day 1. For single samples, plasma concentrations of SOF, SOF metabolites GS-566500 and GS-331007, VEL, and VOX were assessed.

For subjects who consented to participate in an optional PK substudy, intensive PK blood samples were collected for 24 hours postdose at the on-treatment Week 2 or 4 visit. For intensive PK samples, PK parameters of SOF, SOF metabolites GS-566500 and GS-331007, VEL, and VOX were assessed.

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

Quality of Life: Health-related QOL was assessed using the Short Form-36 (SF-36), the 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 SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of study drug) for the FAS. A 2-sided 95% exact confidence interval (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, 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.

Pharmacokinetics:

For subjects who participated in the PK substudy, plasma concentrations of SOF, GS-566500, GS-331007, VEL, and VOX were determined using validated bioanalytical assays. Pharmacokinetics parameters for these analytes (AUC_{tau}, C_{max}, C_{tau}, CL/F, $t_{1/2}$, T_{last}, T_{max}, and λ_z) were computed for all subjects with evaluable PK profiles. Descriptive statistics (sample size, mean, SD, percent coefficient of variation [%CV], median, Q1, Q3, minimum, and maximum by cirrhosis status (presence, absence) and overall were provided for PK data.

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 18.1.

Quality of Life:

Health-related QOL surveys (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C) were completed by subjects at baseline/Day 1, Week 4, end of treatment, early termination (if applicable), and posttreatment Weeks 4 and 12. A Wilcoxon signed rank test was used to explore within-treatment group changes from baseline to each postbaseline time point and from end of treatment to each posttreatment time point.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 128 subjects were enrolled into the study: 63 treatment-naive subjects (30 with cirrhosis and 33 without cirrhosis) and 65 treatment-experienced subjects (29 with cirrhosis and 36 without cirrhosis). Subjects were enrolled at 32 sites in the US (121 subjects) and 2 sites in New Zealand (7 subjects). Most subjects completed study treatment (125 subjects [97.7%]). Three subjects (2.3%) prematurely discontinued study treatment due to AEs. A total of 120 subjects (93.8%) completed the study and 8 subjects (6.3%) prematurely discontinued the study: 7 subjects (5.5%) discontinued due to lack of efficacy, and 1 subject (0.8%) died on posttreatment Day 97.

Demographics and baseline characteristics were generally balanced across treatment groups. Overall, the majority of subjects were male (62.5%), white (80.5%), and not Hispanic/Latino (86.7%), with a mean age of 56 years (range: 18–77 years). The mean baseline BMI value for subjects was 28.6 kg/m^2 (range: 18.4–52.6 kg/m^2), and 31.3% of subjects had BMI ≥ 30 kg/m^2. The majority of subjects had HCV genotype 3 (57.8%) or genotype 2 (25.8%), and non-CC (CT or TT) IL28B genotypes (61.7%). Across groups, the mean baseline HCV RNA value was 6.3 log_{10} IU/mL (range: 3.6−8.1 log_{10} IU/mL), and most subjects had HCV RNA ≥ 800,000 IU/mL (65.5%). The mean baseline alanine aminotransferase (ALT) value was 85 U/L (range: 10−309 U/L), and 54.7% of subjects had baseline ALT values > 1.5 × the upper limit of the normal range. Overall, the mean baseline creatinine clearance using the Cockcroft-Gault equation was 119.8 mL/min (range: 55.3−253.6 mL/min).

Of the treatment-experienced subjects, 29.2% (19 of 65) had previously been treated with pegylated interferon plus ribavirin; 9.2% (6 of 65) had been treated with an NS5A inhibitor; and 49.2% (32 of 65) had been treated with a non-NS5A inhibitor, primarily the NS5B inhibitor SOF. Most of the DAA-experienced subjects had received prior treatment with only 1 DAA (81.6%; 31 of 38).

Efficacy Results: Treatment with SOF/VEL+VOX led to rapid HCV RNA decline across all treatment groups. After 1 week of treatment, the mean change from baseline in HCV RNA levels ranged from −4.24 to −4.51 log_{10} IU/mL across groups. All subjects had HCV RNA < LLOQ at the end of treatment. No subjects experienced on-treatment virologic failure.

Treatment-naive subjects without cirrhosis who were treated with SOF/VEL+VOX for 6 weeks achieved an SVR12 rate of 87.9% (29 of 33 subjects); treatment-naive subjects with cirrhosis who were treated with SOF/VEL+VOX for 8 weeks achieved an SVR12 rate of 93.3% (28 of 30 subjects).

Treatment-experienced subjects, including DAA-experienced subjects and those with cirrhosis, who were treated with SOF/VEL+VOX for 12 weeks achieved an SVR12 rate of 98.5% (64 of 65 subjects).

A total of 7 subjects failed to achieve SVR12: 6 treatment-naive subjects, including 4 subjects in the 6-week group and 2 subjects in the 8-week group, and 1 treatment-experienced subject in the 12-week group. All 7 subjects experienced virologic relapse prior to posttreatment Week 12. Thus, SVR12 was 100.0% concordant with SVR24.

Virologic Resistance

Overall, the presence of baseline resistance-associated variants (RAVs) had no impact on SVR12 rates in the 8- and 12-week treatment groups. In the 6-week treatment group, there was a numeric, but not statistically significant, reduction in SVR12 rates for subjects who had RAVs (81.0%; 17 of 21 subjects) versus subjects without RAVs (100.0%; 12 of 12 subjects) (p-value = 0.27, Fisher's exact test). In treatment-experienced subjects, all but 1 subject with NS3, NS5A, and NS5B single or multiclass RAVs achieved SVR12.

None of the 7 subjects who relapsed had NS5A or NS5B treatment-emergent RAVs, and only 1 subject had an NS3 RAV (Q80R) emerge at the time of relapse. Q80R does not confer any reduced susceptibility to VOX in the genotype 3a replicon assay (0.8-fold shift in EC_{50} compared with wild type).

Pharmacokinetics: For 23 subjects who participated in the intensive PK substudy, administration of SOF/VEL+VOX resulted in SOF, GS-566500, GS-331007, and VEL exposures that were comparable in subjects regardless of cirrhosis status. Mean VOX exposure was modestly higher (approximately < 2-fold) in subjects with cirrhosis than subjects without cirrhosis (mean [%CV] AUC_{tau} 3755.6 [59.0] h•ng/mL vs 2097.8 [75.0] h•ng/mL and C_{max} 439.8 [70.6] ng/mL vs 264.7 [70.3] ng/mL, respectively). The impact of cirrhosis on VOX PK will be formally explored in population PK model development.

Safety Results: SOF/VEL+VOX was generally safe and well tolerated. Across treatment groups, most subjects had at least 1 AE (74.2%, 95 of 128 subjects). The majority of AEs were Grade 1 or Grade 2 in severity. The most common AEs were headache (25.0%, 32 subjects), diarrhea (22.7%, 29 subjects), fatigue (20.3%, 26 subjects), and nausea (18.8%, 24 subjects).

Three subjects (2.3%) each had a single Grade 3 AE (back pain, dizziness, gastroenteritis), all of which were assessed as unrelated to study drug by the investigator. Gastroenteritis was the only treatment-emergent SAE reported in the study. One subject died on posttreatment Day 97 of presumed sudden cardiac arrest. The death was assessed as unrelated to study drug by the investigator. Three subjects (2.3%) had at least 1 AE that led to premature discontinuation of SOF/VEL+VOX (fatigue; diarrhea, vomiting, and asthenia; gastritis). Five of the 128 subjects (3.9%) had a history of sulfa allergy. The AEs reported for these subjects were not meaningfully different than those reported for subjects without sulfa allergy, and no urticaria or rash was reported.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. Grade 3 and 4 laboratory abnormalities were reported for 5 subjects (3.9%) and 4 subjects (3.1%), respectively. No subject had more than 1 Grade 3 or 4 laboratory abnormality, and no Grade 3 or 4 laboratory abnormality was reported as an AE. The only Grade 3 or 4 laboratory abnormality experienced by > 1 subject was elevated lipase. All of the Grade 3 and Grade 4 lipase elevations (4 subjects, 3.1%) were transient, and none was associated with pancreatitis or any other AEs. No clinically meaningful changes in ALT or elevations in total bilirubin values were observed during treatment with SOF/VEL+VOX.

No clinically significant changes in vital signs or ECGs were reported during the study.

Quality-of-Life Questionnaires: Across treatment groups health-related QOL improved from baseline to the end of treatment, and improvements were maintained during posttreatment follow-up.

CONCLUSIONS:

- SOF/VEL+VOX administered once daily with food for 12 weeks to treatment-experienced subjects, including those who were DAA-experienced, was highly effective, with SVR12 rates > 98.0% for non-genotype 1 HCV infected subjects with or without cirrhosis.
- The SVR12 rate for treatment-naive subjects with cirrhosis treated with SOF/VEL+VOX for 8 weeks was 93.3%; the SVR12 rate was lower (87.9%) for treatment-naive subjects without cirrhosis treated for 6 weeks.
- The presence of baseline RAVs did not impact SVR12 rates for subjects who received SOF/VEL+VOX for 8 or 12 weeks.
- None of the subjects who experienced virologic relapse had NS5A or NS5B treatment-emergent RAVs, and only 1 subject had a treatment-emergent NS3 RAV (Q80R) at the time of relapse.
- SOF, GS-566500, GS-331007, and VEL exposures were comparable for all subjects in the intensive PK substudy, regardless of cirrhosis status; VOX exposure was modestly higher (approximately < 2-fold) for subjects with cirrhosis.
- SOF/VEL+VOX administered for 6, 8, or 12 weeks was generally safe and well tolerated with few SAEs, Grade 3 or 4 AEs, discontinuations due to AEs, and Grade 3 or 4 laboratory abnormalities.