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 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-367-1168
Phase of Development:	Phase 2
IND No.:	119926
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02378935
Study Start Date:	17 February 2015 (First Subject Screened)
Study End Date:	12 April 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:	03 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-367-1168
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 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:

17 February 2015 (First Subject Screened)
12 April 2016 (Last Subject Observation)
01 February 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) fixed dose combination (FDC) + voxilaprevir (VOX; GS-9857) ± ribavirin (RBV) in subjects with 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±RBV

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

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, open-label study evaluated the safety and efficacy of SOF/VEL FDC (400/100 mg) + VOX 100 mg once daily for 6, 8 (with or without RBV), or 12 weeks in treatment-naive and direct-acting antiviral (DAA)-experienced subjects with genotype 1 HCV infection with or without cirrhosis. DAA-experienced subjects had failed prior treatment with a nonstructural protein (NS)5A inhibitor or ≥ 2 classes of DAAs with or without interferon (IFN). Noncirrhotic subjects who had received a single dose of VOX 100 mg and 2 daily doses of SOF/VEL FDC (400/100 mg) + VOX 100 mg in the Phase 1b study GS-US-338-1121 were also eligible for enrollment with sponsor approval.

A total of 205 subjects were enrolled into 1 of the following treatment groups to receive SOF/VEL (400/100 mg) + VOX 100 mg once daily with food as follows:

Cohort	Treatment Group	N	Treatment Duration (weeks)
1	Treatment naive, noncirrhotic	34	6
	Treatment naive, noncirrhotic	36	8
	Treatment naive, cirrhotic	33	8
	Treatment naive, cirrhotic[a]	31	8
2	DAA-experienced, noncirrhotic	31	12
	DAA-experienced, cirrhotic	32	12
3	Subjects previously enrolled in Study GS-US-338-1121[b]	8	12

DAA = direct-acting antiviral; RBV = ribavirin
a Subjects were treated with SOF/VEL 400/100 mg +VOX 100 mg + RBV weight-based 1000 or 1200 mg divided daily dose.
b Subjects received a single dose of VOX 100 mg and 2 daily doses of SOF/VEL 400/100 mg +VOX 100 mg in Study GS-US-338-1121.

Number of Subjects (Planned and Analyzed):
Planned: 278
Analyzed: 205

- All Enrolled Subjects: 205 subjects
- Full Analysis Set (FAS): 205 subjects
- Safety Analysis Set: 205 subjects
- PK Analysis Set: 205 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were treatment-naive and DAA-experienced males and nonpregnant, nonnursing females aged ≥ 18 years with genotype 1 chronic HCV infection, screening HCV RNA ≥ 10^4 IU/mL (except subjects in Cohort 3 who must have had quantifiable HCV RNA), and body mass index (BMI) ≥ 18 kg/m^2, with or without cirrhosis.

Duration of Treatment: Treatment duration was 6, 8, or 12 weeks, with up to 24 weeks posttreatment follow-up.

Test Product, Dose, Mode of Administration, and Lot 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).
- **RBV** was administered orally with food at a total daily weight-based dose of 1000 or 1200 mg/day (5 or 6 × 200-mg tablets divided twice daily).

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

- **SOF/VEL:** DU1404B1, DU1405B1
- **VOX:** DY1408B1
- **RBV:** AB1933Z, AA2773Z

Reference Therapy, Dose, Mode of Administration, Lot 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 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 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, SVR24, proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through end of treatment (EOT), 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.

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. Pharmacokinetic parameters for these analytes (AUC_{tau}, C_{max}, CL/F, C_{tau}, $t_{1/2}$, T_{last}, T_{max}, and λ_z, as applicable) 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 19.

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, 6, 8, 12, and end of treatment, early termination (if applicable), and posttreatment Weeks 4, 12, and 24 (as applicable). 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 205 subjects were enrolled into the study: 134 treatment-naive subjects (64 with cirrhosis and 70 without cirrhosis) and 63 DAA-experienced subjects (32 with cirrhosis and 31 without cirrhosis); 8 subjects were enrolled in Cohort 3. Subjects were enrolled at 32 sites in the US (198 subjects) and 2 sites in New Zealand (7 subjects). All but 1 subject completed study treatment (204 subjects [99.5%]). One subject (0.5%) prematurely discontinued study treatment due to AEs.

Demographics and baseline characteristics were generally balanced across treatment groups. The majority of subjects enrolled in this study were male (65.4%), white (85.4%), and not Hispanic/Latino (79.5%), with a mean age of 56 years (range: 19–73 years). The mean baseline BMI value for subjects was 28.3 kg/m^2 (range: 18.4–51.7 kg/m^2), and 30.7% of subjects had BMI $\geq$ 30 kg/m^2. The majority of subjects had HCV genotype 1a (79.1% and 81.0% of treatment-naive and DAA-experienced subjects, respectively) and non-CC (CT or TT) IL28B genotypes (67.9% and 85.7% of treatment-naive and DAA-experienced subjects, respectively). Across the treatment-naive and DAA-experienced groups, the mean baseline HCV RNA values were similar (ranged from 6.0−6.5 $\log_{10}$ IU/mL) and a majority of subjects had HCV RNA $\geq$ 800,000 IU/mL (73.1% and 65.1% of treatment-naive and DAA-experienced subjects, respectively).

The majority of the DAA-experienced subjects were previously treated with at least 2 (73.0%; 46 of 63) DAA classes and 69.8% (44 of 63) of subjects had received only 1 prior HCV regimen. Of the DAA-experienced subjects, 54.0% (34 of 63) had previously been treated with a NS5B inhibitor and a NS3 inhibitor (the most common regimen was SOF and simeprevir [25 subjects]); 46.0% (29 of 63) had been treated with an NS5A inhibitor with or without another DAA (the most common NS5A inhibitors were daclatasvir [12 subjects] and ledipasvir [7 subjects]).

Efficacy Results: Among treatment-naive subjects without cirrhosis, treatment with SOF/VEL+VOX for 6 weeks led to an SVR12 rate of 70.6% (24 of 34 subjects), whereas treatment with SOF/VEL +VOX for 8 weeks led to an SVR12 rate of 100% (36 subjects). Among treatment-naive subjects with cirrhosis, treatment with SOF/VEL+VOX for 8 weeks led to an SVR12 rate of 93.9% (31 of 33 subjects) and treatment with SOF/VEL+VOX+RBV for 8 weeks led to an SVR12 rate of 80.6% (25 of 31 subjects).

All DAA-experienced subjects, including those with cirrhosis, treated with SOF/VEL+VOX for 12 weeks achieved SVR12 (100.0%, 63 subjects). All subjects in Cohort 3 also achieved SVR12 (100.0%, 8 subjects) with SOF/VEL+VOX for 12 weeks.

A total of 18 subjects, all of whom were treatment-naive, failed to achieve SVR12: 10 noncirrhotic subjects in the 6-week group, 2 cirrhotic subjects in the 8-week group, and 6 cirrhotic subjects in the RBV-containing 8-week group. All 18 subjects experienced virologic relapse prior to posttreatment Week 12. Thus, SVR12 was 100.0% concordant with SVR24.

For subjects with genotype 1 HCV infection, SOF/VEL+VOX with or without RBV treatment 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 −4.15 to −4.64 $\log_{10}$ IU/mL across the treatment-naive and DAA-experienced groups. All subjects had HCV RNA < LLOQ at the end of treatment. No subjects experienced on-treatment virologic failure.

Virologic Resistance:

Overall, the presence of baseline RAVs had no significant impact on SVR12 rates in the 6-, 8-, and 12-week treatment groups. All DAA-experienced subjects, with and without baseline RAVs, achieved SVR12 regardless of cirrhosis status.

None of the 18 subjects who relapsed had NS5A or NS5B treatment-emergent RAVs detected, and only 3 subjects had a treatment-emergent NS3 RAVs (Q41R, A156T, V170T, or V36M), each detected at low frequencies (< 1.8%) at the time of relapse. Of the treatment-emergent NS3 RAVs, only A156T confers high levels of resistance to VOX (> 581-fold shift in EC_{50} compared to genotype 1a WT replicon).

Pharmacokinetics/Pharmacodynamics Results: For 28 subjects who participated in the intensive PK substudy (5 of whom received SOF/VEL+VOX+RBV), administration of SOF/VEL+VOX resulted in SOF, GS-566500, GS-331007, and VEL exposures that were similar in subjects regardless of cirrhosis status. Mean VOX exposure was modestly higher (< 2-fold) in subjects with cirrhosis compared with subjects without cirrhosis.

Safety Results: SOF/VEL+VOX, with and without RBV, was generally safe and well tolerated. Across treatment groups, most subjects had at least 1 AE (64.4%, 132 of 205 subjects). The majority of AEs were Grade 1 or Grade 2 in severity. Grade 3 AEs were rare (2 subjects, 1.0%), and no Grade 4 AEs were reported. The most common AEs were headache (21.5%, 44 subjects), nausea (17.1%, 35 subjects), and fatigue (16.6%, 34 subjects).

Two subjects (1.0%) each had a single Grade 3 AE (atrial flutter, posttraumatic pain), both of which were assessed as unrelated to study drug by the investigator. Atrial flutter was also considered a serious AE (SAE), and was 1 of 2 SAEs reported in the study. Vertigo, the other reported SAE, occurred during posttreatment follow-up. Both SAEs were considered unrelated to study drug. One nontreatment-emergent death of an unknown cause occurred on posttreatment Day 175. The death was assessed as unrelated to study drug by the investigator. One subject receiving SOF/VEL+VOX+RBV met protocol-defined stopping criteria of elevated AST and ALT > 5 × baseline/Day 1 value and discontinued all study drugs on Day 24. No other subjects prematurely discontinued all study drugs during the study. Seven of the 205 subjects (3.4%) had a history of sulfa allergy. The AEs reported for these subjects were not 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 or Grade 4 laboratory abnormalities were reported for 19 (9.3%) and 2 (1.0%) subjects, respectively. Most of the Grade 3 and both of the Grade 4 laboratory abnormalities were transient. The most common Grade 3 laboratory abnormalities were elevated serum glucose (4 subjects, 3 of whom had a history of diabetes), asymptomatic elevated lipase (4 subjects), elevated total bilirubin (4 subjects, 3 of whom received RBV), decreased hemoglobin (3 subjects, all of whom received RBV), and low platelets (3 subjects, all of whom had cirrhosis). The only Grade 3 or 4 laboratory abnormality reported as an AE was the Grade 3 elevated ALT in the subject who met the protocol-defined stopping criteria.

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

Quality-of-Life Questionnaires: Across treatment groups, the health-related QOL improved from baseline to the end of treatment or were unchanged. In some instances, improvements were maintained during posttreatment follow-up. These results should be interpreted with caution as multiple endpoints were tested without adjusting for multiple comparisons, and the study was not powered to test these exploratory endpoints.

CONCLUSIONS:

- SOF/VEL+VOX administered once daily with food for 8 weeks to treatment-naive subjects with genotype 1 HCV infection or 12 weeks to DAA-experienced subjects with genotype 1 HCV infection was highly effective.
  - SVR12 rate was 97.0% in treatment-naive subjects with or without cirrhosis treated with SOF/VEL+VOX for 8 weeks
  - SVR12 rate was 100.0% in DAA-experienced subjects with or without cirrhosis treated with SOF/VEL+VOX for 12 weeks.
  - SVR12 rate was 70.6% for treatment-naive subjects without cirrhosis treated for 6 weeks with SOF/VEL+VOX
- The addition of RBV did not improve efficacy.
  - SVR12 rate was 80.6% in treatment-naive subjects with cirrhosis treated for 8 weeks with SOF/VEL+VOX+RBV
- The presence of baseline RAVs did not impact SVR12 rates in subjects who received SOF/VEL+VOX for 6, 8, or 12 weeks.
- None of the subjects who experienced virologic relapse had NS5A or NS5B treatment-emergent RAVs, and 3 subjects had treatment-emergent NS3 RAVs detected at low frequencies at the time of relapse.

- SOF, GS-566500, GS-331007, and VEL exposures were similar for all subjects in the intensive PK substudy, regardless of cirrhosis status; VOX exposure was modestly higher (< 2-fold) for subjects with cirrhosis.
- SOF/VEL+VOX, with or without RBV, administered for 6, 8, or 12 weeks was generally safe and well tolerated with few SAEs, Grade 3 AEs (no Grade 4 AEs were reported), discontinuations due to AEs, and Grade 3 or 4 laboratory abnormalities reported.