FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 3, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Coinfection
Name of Test Drug:	Sofosbuvir (SOF)/velpatasvir (VEL, GS-5816) fixed-dose combination (FDC)
Dose and Formulation:	SOF/VEL FDC (400/100 mg) tablet
Indication:	HCV infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Study No.:	GS-US-342-1202 (ASTRAL-5)
Phase of Development:	Phase 3
IND No.:	118605
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02480712
Study Start Date:	01 July 2015 (First Subject Screened)
Study End Date:	22 June 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: David L. Wyles, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Anu Osinusi, MD 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-342-1202
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Coinfection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 17 sites in the United States (US).

Publications: Wyles D, Brau N, Kottilil S, Daar E, Workowski K, Luetkemeyer A, et al. Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 Weeks in Patients Co-Infected with HCV and HIV-1: The Phase 3 ASTRAL-5 Study [Abstract PS104]. 2016 European Association for the Study of the Liver (EASL), Barcelona, Spain.

Study Period:

01 July 2015 (First Subject Screened)
22 June 2016 (Last Subject Observation)
19 April 2016 (Last Subject Observation for the Primary Endpoint)

Phase of Development: Phase 3

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) for 12 weeks in subjects with chronic HCV infection who were coinfected with HIV-1 as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of treatment with SOF/VEL for 12 weeks

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 kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To assess the proportion of subjects that maintained HIV-1 RNA < 50 copies/mL while on HCV treatment and at posttreatment Week 4

- To assess the change from baseline in CD4 T-cell count at the end of treatment and at posttreatment Week 4
- 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, response to therapy and/or tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics), in subjects who provided consent
- To assess the effect of treatment on health-related quality of life

Methodology: This Phase 3, multicenter, open-label study evaluated the antiviral efficacy, safety, and tolerability of SOF/VEL administered for 12 weeks in HCV treatment-naive and treatment-experienced (including treatment intolerant) subjects with chronic HCV infection who were coinfected with HIV-1.

Approximately 100 subjects were planned to be enrolled and treated with SOF/VEL FDC (400/100 mg) once daily for 12 weeks. Approximately 30% of subjects may have been treatment experienced and approximately 30% of subjects may have had cirrhosis.

All subjects were to complete the posttreatment Week 4 and 12 visits regardless of their treatment duration. Subjects who had HCV RNA less than the lower limit of quantitation (< LLOQ) at the posttreatment Week 12 visit were also to complete the posttreatment Week 24 visit unless a confirmed viral relapse occurred.

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

Subjects who do not achieve SVR may be eligible for enrollment in the Sequence Registry Study. Subjects who achieve SVR may be eligible for enrollment into the SVR Registry Study or SVR Cirrhosis Registry Study.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 100 subjects

Analyzed:

- All enrolled subjects: 107 subjects
- Full Analysis Set (FAS): 106 subjects
- Safety Analysis Set: 106 subjects
- Pharmacokinetic (PK) Analysis Set: 106 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were chronic HCV and HIV-1 coinfected males and nonpregnant/nonlactating females, aged 18 years or older. Subjects were HCV treatment-naive or treatment-experienced (including treatment intolerant), and had documentation of the presence or absence of cirrhosis, and a body mass index (BMI) ≥ 18 kg/m^2.

Subjects must have been on a stable, protocol-approved antiretroviral (ARV) regimen for ≥ 8 weeks prior to screening and must have been expected to maintain the same ARV regimen for the duration of the study. Subjects were required to have a CD4 T-cell count > 100 cells/mm^3 at screening and not have had an opportunistic infection within 6 months prior to screening.

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

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

- SOF/VEL FDC tablets were administered orally to subjects at a dose of 400/100 mg (1 FDC tablet) once daily with or without food.

The lot number of SOF/VEL administered in this study was DU1405B1.

Reference Therapy, Dose, Mode of Administration, and Lot No.: None

Criteria for Evaluation:

Efficacy: Blood samples to determine serum HCV RNA levels were collected from subjects at screening, baseline/Day 1 (predose), Weeks 1, 2, 4, 6, 8, 10, and 12 during treatment (or upon early termination), and posttreatment Weeks 4, 12, and 24 (if applicable). The COBAS® Ampliprep/ COBAS® TaqMan® HCV QuantitativeTest, v2.0 was used to quantify HCV RNA in this study. The LLOQ of the assay was 15 IU/mL.

Pharmacokinetics: A single PK blood sample was collected from all subjects at each on-treatment visit. The plasma concentrations of SOF, its metabolites GS-566500 and GS-331007, VEL, and tenofovir (TFV) may have been assessed.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, HIV RNA determinations, CD4 T-cell counts, electrocardiograms (ECGs), vital sign measurements, and physical examinations.

Quality of Life: Health-related quality of life was assessed with 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. The assessments were completed at baseline/Day 1, Weeks 4, 8, 12, posttreatment Weeks 4 and 12, and early termination (if applicable) visits.

Statistical Methods:

Efficacy: The primary efficacy endpoint was the proportion of subjects with SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the FAS. The primary efficacy endpoint analysis was conducted when all subjects completed the posttreatment Week 12 visit or prematurely discontinued from the study. The point estimate of the SVR12 rate was calculated and the 2-sided 95% exact confidence interval (CI) was constructed using the Clopper-Pearson method. Secondary efficacy endpoints included SVR4, SVR24, proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through end of treatment, and proportion of subjects with virologic failure.

Subgroup analyses were performed to assess the relationship between SVR12 and baseline demographic and disease characteristics. Point estimates and 95% exact CIs of the SVR12 rates were calculated for each subgroup by HCV genotype (1 [1a, 1b], 2, 3, 4) and overall.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and maximum). All categorical endpoints were summarized by number and percentage of subjects who met the endpoint definition.

Pharmacokinetics: The population PK model-derived PK parameters for SOF, GS-331007, VEL, and TFV were summarized by defined HIV ARV regimen at baseline, by treatment outcome (SVR12 success and failure), HCV genotype, and overall. Geometric mean ratio and its 90% CI were provided to compare the PK exposure between subjects who relapsed or achieved SVR12. Population PK model-derived PK parameters were also compared between the population from this study and relevant patient populations for each analyte (which included population PK-derived PK exposure data from Phase 2 and 3 studies) to compare PK exposure between HCV/HIV-coinfected subjects and HCV-monoinfected subjects.

Safety: All enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. The safety analysis was performed using the following subgroups:

- Subjects taking boosted tenofovir disoproxil fumarate (TDF) regimens, defined as regimens containing TDF and ritonavir (RTV) or cobicistat (COBI)-boosted protease inhibitors (PIs) or other agents (eg, elvitegravir [EVG]/COBI)
- Subjects taking non-boosted TDF-containing regimens, defined as regimens containing TDF and non-RTV or COBI-boosted PIs or other agents
- Subjects taking regimens that do not contain TDF

Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, HIV RNA determination, CD4 T-cell counts, ECGs, vital signs measurements, and physical examinations. Safety data 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 19.0.

Quality of Life: The health-related quality of life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C) were completed at baseline/Day 1, Weeks 4, 8, and 12 (during treatment (or upon early termination), and posttreatment Weeks 4 and 12. A Wilcoxon signed rank test explored within-treatment group changes in status 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 107 subjects were enrolled, of whom 106 subjects received at least 1 dose of study drug. Of the 106 enrolled and treated subjects, 4 subjects (3.8%) prematurely discontinued study treatment: 2 subjects (1.9%) were lost to follow-up and 2 subjects (1.9%) prematurely discontinued due to AEs.

The majority of subjects were male (85.8%), white (50.9%) or black (45.3%), and non-Hispanic or Latino (85.8%), with a mean age of 54 years (range: 25−72). The mean (SD) baseline BMI value for subjects was 27.2 (4.70) kg/m^2, and 21.7% had a BMI $\geq$ 30 kg/m^2. A total of

66 subjects (62.3%) had HCV genotype 1a, 12 subjects (11.3%) had HCV genotype 1b, 11 subjects (10.4%) had HCV genotype 2, 12 subjects (11.3%) had HCV genotype 3, and 5 subjects (4.7%) had HCV genotype 4. The majority of subjects had a non-CC (CT or TT) IL28B allele (77.4%, 82 subjects). Overall, 19 subjects (17.9%) had cirrhosis. The mean baseline HCV RNA was 6.3 $\log_{10}$ IU/mL (range: 5.0−7.4 $\log_{10}$ IU/mL), and most subjects (73.6%, 78 subjects) had baseline HCV RNA ≥ 800,000 IU/mL.

There were 31 (29.2%) HCV treatment-experienced subjects; the majority of these subjects (67.7%, 21 of 31) had failed prior treatment with a pegylated interferon (Peg-IFN) + ribavirin (RBV) regimen. Eight subjects (25.8%) had failed IFN ±RBV therapy, and 1 subject (3.2%) each had failed direct-acting antiviral (DAA) + Peg-IFN+RBV and DAA only therapy. At enrollment, subjects were on the following ARV regimens: boosted TDF-containing regimens (52.8%, 56 subjects), non-boosted TDF-containing regimens (33.0%, 35 subjects), and non-TDF-containing regimens (14.2%, 15 subjects). The overall mean CD4 T-count was 598 cells/µL (range: 183−1513 cells/µL) and 56.6% of subjects had CD4 counts > 500 cells/µL.

Efficacy Results:

The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the FAS. The overall SVR12 rate was 95.3% (95% CI: 89.3% to 98.5%). Across genotypes, SVR12 rates ranged from 91.7% for subjects with genotype 1b or genotype 3 HCV infection to 100.0% for subjects with genotype 2 or genotype 4 HCV infection. Of the 5 subjects who did not achieve SVR12, 2 subjects (1.9%) had virologic relapse, 2 subjects (1.9%) were lost to follow up, and 1 subject (0.9%) withdrew consent.

The SVR4 and SVR24 results were the same as the SVR12 results. Overall, all subjects who achieved SVR12 also achieved SVR24.

High SVR12 rates were achieved regardless of HCV genotype, prior HCV treatment experience, or cirrhosis status. The SVR12 rates in subjects with and without cirrhosis were 100.0% and 94.3%, respectively. The SVR12 rate in subjects with prior treatment failure was 96.8%, and 94.7% in treatment-naive subjects.

HCV RNA levels ($\log_{10}$ IU/mL) declined rapidly with similar decreases in HCV RNA observed across all HCV genotypes. Consistent with the rapid and sustained decline in HCV RNA, ≥ 80% of subjects had HCV RNA < LLOQ at Week 4. At Week 8, all subjects had HCV RNA < LLOQ, which was maintained through Week 12. Time to virologic suppression was not associated with treatment outcome overall or in any genotype.

Virologic Resistance Results:

Approximately 19% and 4% of subjects treated with SOF/VEL for 12 weeks had pretreatment NS5A and NS5B nucleoside inhibitor (NI) resistance-associated variants (RAVs) using a 1% assay cutoff, respectively. No subjects with baseline RAVs experienced virologic failure in this study. Two subjects with genotype 1a HCV infection experienced virologic relapse; 1 subject had low levels of N142D/S and C289R NS5B NI RAPs emerge posttreatment.

Pharmacokinetics Results: Population PK model-derived exposure parameters (AUC_{tau}, C_{max}, and C_{tau}) for SOF, GS-331007, VEL, and TFV were generated as applicable for all subjects with measureable plasma concentrations. Exposure of SOF, GS-331007, and VEL were generally

similar following administration with a variety of ARVs including unboosted and RTV- and COBI-boosted regimens. Of note, no difference in VEL exposure with RTV boosted ATV-containing regimens was observed in HCV/HIV-coinfected subjects, unlike the results of Study GS-US-342-1326, which showed a 142% increase in VEL AUC when administered with RTV boosted ATV+FTC/TDF in healthy subjects. The exposures of SOF, GS-331007, and VEL in the 2 subjects with virologic relapse were similar (N = 1) or modestly higher (N =1) than those who achieved SVR12. No significant differences in the exposure of SOF, GS-331007, and VEL were observed in HCV/HIV-coinfected subjects compared with subjects from the HCV-monoinfected Phase 2/3 US New Drug Application population. Tenofovir exposures were similar when TDF was administered as part of boosted (RTV- or COBI-containing; AUC: 3740 h•ng/mL) or unboosted (AUC: 3590 h•ng/mL) regimens. Tenofovir exposures following administration of boosted or unboosted TDF-containing regimens with SOF/VEL were also within the range of exposure observed in HIV-monoinfected subjects using boosted ARV regimens in the absence of SOF/VEL (mean TFV AUC range: 3110 to 4630 h•ng/mL).

Safety Results: Treatment with SOF/VEL was generally safe and well tolerated in subjects with HCV/HIV coinfection. The incidence of AEs was similar for subjects receiving boosted TDF-containing regimens, non-boosted TDF-containing regimens, or non-TDF-containing regimens. A total of 75 subjects (70.8%) experienced at least 1 AE. The majority of AEs (91.5%) were Grade 1 (mild) or Grade 2 (moderate) in severity. Treatment-related AEs were observed in a total of 50 subjects (47.2%).

Overall, 9 subjects (8.5%) had Grade 3 (severe) AEs, of which 2 were assessed as related to study drug by the investigator. No Grade 4 (life-threatening) AEs were reported. Two subjects (1.9%) had serious adverse events (SAEs): 1 subject had Grade 2 radial nerve palsy, and 1 subject had localized infection, sepsis, and urinary tract infection (all Grade 3). All SAEs were assessed as unrelated to study drug by the investigators. Overall, 2 subjects (1.9%) prematurely discontinued SOF/VEL due to AEs: 1 subject due to Grade 1 vomiting on Day 4, and 1 subject due to Grade 3 increased hepatic enzymes in the setting of recent hospitalization for infection with antibiotic use on Day 47.

One death was reported on posttreatment Day 162 from an unknown cause. No pregnancies were reported in the study.

The majority of laboratory abnormalities were Grade 1 or 2 in severity. A higher percentage of subjects receiving boosted TDF-containing regimens had Grade 3 laboratory abnormalities (20.4%, 11 subjects) compared with subjects receiving non-boosted TDF-containing regimens (11.4%, 4 subjects) or non-TDF-containing regimens (13.3%, 2 subjects). A significant proportion of subjects on RTV boosted ATV (85.0%, 17 of 20 subjects), were receiving boosted TDF-containing regimens, leading to the higher incidence of Grade 3 abnormalities (elevated bilirubin) observed in that group of subjects. Overall, few subjects had Grade 4 laboratory abnormalities (1.9%, 2 subjects). The most frequently occurring Grade 3 or 4 laboratory abnormality was increased total bilirubin, all secondary to RTV boosted ATV use.

With respect to renal safety, there were no Grade 3 or above AEs under the Renal and Urinary Disorders system organ class reported in any group. A total of 5 subjects (4 on boosted TDF-containing regimens) developed laboratory abnormalities consistent with changes in renal function during treatment; however, no changes were made to any ARV regimens. In the

majority of these cases (80%, 4 subjects), these abnormalities were transient and asymptomatic. One subject with persistent abnormalities had chronic kidney disease under the care of a nephrologist predating study treatment. This subject completed study treatment without modifications to his ARV regimen.

With respect to HIV-specific safety, no subjects experienced HIV virologic rebound, and CD4 T-cell counts were stable during treatment.

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) were reported during the study. No clinically significant abnormal 12-lead ECGs were captured postbaseline.

In summary, treatment with SOF/VEL for 12 weeks was safe and well tolerated in HCV treatment-naive and treatment-experienced subjects with genotype 1, 2, 3, or 4 HCV infection with HIV coinfection. The safety profile of SOF/VEL in these coinfected subjects was similar to that observed in the registrational Phase 3 studies of SOF/VEL in HCV-monoinfected subjects without cirrhosis or with compensated cirrhosis.

Other: Overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C quality of life questionnaires generally indicated that no on-treatment decrements in quality of life in subjects treated with SOF/VEL for 12 weeks occurred. During the treatment period, increases (improvement) from baseline were observed in all 8 domain scores and the physical component score for SF-36. The mean scores for most scales improved from end of treatment to 4 and 12 weeks after end of treatment. 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 for Study GS-US-342-1202 are as follows:

- Treatment with SOF/VEL for 12 weeks in HCV treatment-naive and treatment-experienced subjects with HCV/HIV coinfection, including those with and without cirrhosis, resulted in a high SVR12 rate (95.3%).
- High SVR12 rates were achieved across all HCV genotypes and subgroups.
  - Among subjects with cirrhosis, the SVR12 rate was 100.0%.
  - Among subjects with prior treatment failure, the SVR12 rate was 96.8%.
  - Among subjects with baseline NS5A resistance-associated variants, the SVR12 rate was 100.0%.
- The HCV virologic failure rate was low (1.9%) which is similar to rates observed in subjects with HCV monoinfection treated with SOF/VEL in other registrational studies.
- The presence of baseline NS5A or NS5B RAVs had no impact on treatment response. Two subjects with genotype 1a HCV infection experienced virologic relapse; 1 subject had low levels of N142D/S and C289R NS5B NI RAPs emerge posttreatment.
- There were no clinically relevant differences in SOF/VEL or TFV PK following coadministration of SOF/VEL with a variety of ARV regimens. The exposure of SOF/VEL and TFV in HCV/HIV-coinfected subjects was similar to that observed in HCV- and HIV-monoinfected populations, respectively.

- Treatment with SOF/VEL for 12 weeks was well tolerated and similar across all ARV regimens with a safety profile similar to that observed in subjects with HCV monoinfection. There was a low incidence of SAEs, discontinuations due to AEs, and no clinically relevant laboratory abnormalities.
- There was no effect of SOF/VEL treatment on CD4 T-cell count, CD4%, or HIV RNA levels.