FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Randomized, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir + GS-5816 for 12 Weeks in Treatment Experienced Subjects with Chronic HCV Infection	
Name of Test Drug:	Sofosbuvir (SOF), GS-5816	
Dose and Formulation:	SOF 400-mg tablet GS-5816 25-mg or 100-mg tablet	
Indication:	Hepatitis C virus infection	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA	
Study No.:	GS-US-342-0109	
Phase of Development:	Phase 2	
IND No.:	115670	
EudraCT No.:	Not applicable	
Study Start Date:	17 June 2013 (First Subject Screened)	
Study End Date	22 August 2014 (Last Subject Observation)	
Principal or Coordinating Investigator:	Name: Affiliation:	Stephen Pianko, MBBS, PhD, FRACP PPD
Gilead Responsible Medical Monitor:	Name: Telephone: Fax:	Diana Brainard, MD PPD PPD
Report Date:	27 March 2015	

STUDY SYNOPSIS
Study GS-US-342-0109
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Multicenter, Randomized, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir + GS-5816 for 12 Weeks in Treatment Experienced Subjects with Chronic HCV Infection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 7 sites in Australia, 2 sites in New Zealand, and 49 sites in the United States (US).

Publications:

Pianko S, Flamm SL, Shiffman ML, Kumar S, Strasser SI, Dore GJ, et al. High Efficacy of Treatment with Sofosbuvir+GS-5816±Ribavirin for 12 Weeks in Treatment-Experienced Patients with Genotype 1 or 3 HCV Infection [Abstract 197]. American Association for the Study of Liver Diseases (AASLD); 2014 November 7-11; Boston MA United States.

Study Period:

17 June 2013 (First Subject Screened)
22 August 2014 (Last Subject Observation)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To determine the antiviral efficacy of combination treatment with sofosbuvir (SOF) + GS-5816 with or without ribavirin (RBV) as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after completion of treatment (SVR12)
- To evaluate the safety and tolerability of each treatment regimen as assessed by review of the accumulated safety data

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attained SVR at 4 and 24 weeks after completion of treatment (SVR4 and SVR24)
- To evaluate the kinetics of circulating hepatitis C virus (HCV) RNA during treatment and after completion of treatment
- To evaluate the emergence of viral resistance to SOF and GS-5816 during treatment and after completion of treatment
- To characterize the steady-state pharmacokinetics (PK) of study drugs

The exploratory objective of this study was as follows:

- To identify or validate genetic markers that may have been predicative of the natural history of disease, virologic response to therapy, and/or tolerability of medical therapy through genetic discovery research (eg, pharmacogenomics), in subjects who provided their separate and specific consent

Methodology: This Phase 2, multicenter, randomized, open-label study assessed the safety, tolerability, and antiviral efficacy of SOF+GS-5816 with or without RBV administered for 12 weeks in treatment-experienced subjects with chronic HCV infection. A total of 323 subjects were randomized into 1 of 12 treatment groups as described below.

A total of 107 noncirrhotic subjects with genotype 3 HCV infection were randomized 1:1:1:1 to 1 of the following 4 treatment groups:

Group 1: SOF 400 mg + GS-5816 25 mg once daily for 12 weeks

Group 2: SOF 400 mg + GS-5816 25 mg once daily + RBV (1000 or 1200 mg/day divided twice daily [BID]) for 12 weeks

Group 3: SOF 400 mg + GS-5816 100 mg once daily for 12 weeks

Group 4: SOF 400 mg + GS-5816 100 mg once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks

A total of 104 cirrhotic subjects with genotype 3 HCV infection were randomized 1:1:1:1 to 1 of the following 4 treatment groups:

Group 5: SOF 400 mg + GS-5816 25 mg once daily for 12 weeks

Group 6: SOF 400 mg + GS-5816 25 mg once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks

Group 7: SOF 400 mg + GS-5816 100 mg once daily for 12 weeks

Group 8: SOF 400 mg + GS-5816 100 mg once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks

A total of 112 subjects with genotype 1 HCV infection were randomized 1:1:1:1 to 1 of the following 4 treatment groups:

Group 9: SOF 400 mg + GS-5816 25 mg once daily for 12 weeks

Group 10: SOF 400 mg + GS-5816 25 mg once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks

Group 11: SOF 400 mg + GS-5816 100 mg once daily for 12 weeks

Group 12: SOF 400 mg + GS-5816 100 mg once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks

Randomization into Groups 9 through 12 was stratified by HCV genotype (genotype 1a or 1b) and cirrhosis (presence or absence). For stratification, mixed genotype 1a/1b or genotype 1 was considered genotype 1a. Approximately 50% of the subjects with genotype 1 HCV infection were to have compensated cirrhosis.

All subjects were to complete posttreatment Week 4, 8, and 12 visits regardless of treatment duration. Subjects with HCV RNA < the lower limit of quantitation (LLOQ) at the posttreatment Week 12 visit were to complete a posttreatment Week 24 visit unless confirmed viral relapse occurred.

All subjects were eligible to participate in the PK substudy if written consent was obtained. An intensive 24-hour PK sample collection was performed at the on-treatment Week 2 or 4 visit to determine the steady-state PK of SOF, SOF metabolites GS-566500 and GS-331007, GS-5816, and RBV (if appropriate). Subjects providing separate and specific consent were eligible for participation in the pharmacogenomics substudy. A blood sample was drawn at the baseline/Day 1 visit or at any time during the study.

Subjects who did not achieve SVR were eligible for enrollment in the Sequence Registry Study (GS-US-248-0123) to monitor the persistence of resistance-associated mutations for up to 3 years. All subjects who achieved SVR24 were eligible for enrollment in the SVR Registry Study (GS-US-248-0122) to evaluate durability of SVR for up to 3 years posttreatment.

Number of Subjects (Planned and Analyzed):

Planned: 300 subjects

Analyzed:

- All randomized subjects: 323 subjects
- Full Analysis Set (FAS): 321 subjects
- Safety Analysis Set: 321 subjects
- PK Analysis Set: 174 subjects
- PK Substudy Analysis Set: 34 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females ≥ 18 years of age with chronic HCV infection, screening HCV RNA levels ≥ 10^4 IU/mL, body mass index (BMI) ≥ 18 kg/m^2, treatment experienced, with or without cirrhosis, and otherwise in general good health as determined by the investigator at screening.

Duration of Treatment: Treatment duration was 12 weeks.

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

- SOF was administered orally to all subjects at a dose of 400 mg (1 × 400-mg tablet once daily).
- GS-5816 was administered orally to all subjects at a dose of either 25 mg (Groups 1, 2, 5, 6, 9, 10) or 100 mg (Groups 3, 4, 7, 8, 11, 12) (1 × 25-mg tablet or 1 × 100-mg tablet once daily).
- RBV was administered orally to subjects in Groups 2, 4, 6, 8, 10, and 12 at a total daily dose of 1000 or 1200 mg/day (5 or 6 × 200-mg tablets divided BID).

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

- SOF: DC1211B1, DC1207B1, DC1209B1
- GS-5816: DL1301C1, DL1301C1-A, DL1301D1, DL1301D1-A, and DL1301D1-B
- RBV: A97943Z and AA2773Z

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, Day 1(predose), and at every subsequent on-treatment and posttreatment visit. The COBAS® TaqMan® HCV Test v2.0 for use with the High Pure System assay was used to quantify HCV RNA in this study. The LLOQ of the assay was 25 IU/mL.

Pharmacokinetics: A single PK blood sample was collected from all subjects at each on-treatment visit. For a subset of subjects who consented to participate in the optional PK substudy, intensive serial PK blood samples were collected at the on-treatment Week 2 or 4 visit. The PK of SOF, GS-566500, GS-331007, GS-5816, and RBV (if appropriate) 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.

Statistical Methods:

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the FAS. The 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method was provided for the SVR12 rates in each efficacy analysis group. Secondary efficacy endpoints included SVR4, SVR24, the proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through Week 12, 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 and stratification within group (as appropriate). All categorical endpoints were summarized by number and percentage of subjects who met the endpoint definition.

Pharmacokinetics: Steady-state PK over a 24-hour dosing interval was determined in subjects who participated in the PK substudy at the on-treatment Week 2 or 4 visit. Concentrations of SOF (and its metabolites GS-566500 and GS-331007), GS-5816, and RBV (if appropriate) in plasma were determined using validated bioanalytical assays. The PK parameters for these analytes were computed for all subjects with evaluable PK profiles. Descriptive statistics (sample size, mean, SD, coefficient of variation [%CV], median, Q1, Q3, minimum, maximum, and geometric mean and its 95% CI) were presented for PK concentration data and PK parameter data.

Safety: All randomized subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital sign measurements, ECGs, and physical examinations. Safety data included all data collected on or after the date of the first dose of any study drug through the date of the last dose of study drug plus 30 days. Safety endpoints were analyzed by the number and percentage of subjects with events or abnormalities for categorical values or descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data by GS-5816 dose and with or without RBV. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 323 subjects were randomized in the study: 107 noncirrhotic subjects with genotype 3 HCV infection, 104 cirrhotic subjects with genotype 3 HCV infection, and 112 subjects with genotype 1 HCV infection. All randomized and treated subjects were enrolled at 1 of 58 sites in Australia, New Zealand, and the US. Of these randomized subjects, 321 received at least 1 dose of study drug and were included in the Safety and Full Analysis Sets. Two subjects were randomized in the study but did not receive study drug resulting in a protocol deviation, and were excluded from both the Safety and Full Analysis Sets.

The majority of subjects (99.4%, 319 of 321 subjects) completed study treatment. Of the 321 enrolled subjects, 2 (0.6%) prematurely discontinued study treatment: 1 of 28 noncirrhotic subjects (3.6%) with genotype 3 HCV infection in the SOF + GS-5816 25 mg + RBV group discontinued study treatment due to elevated gamma glutamyltransferase (GGT) and alanine aminotransferase (ALT) and 1 of 25 cirrhotic subjects (4.0%) with genotype 3 HCV infection in the SOF + GS-5816 25 mg + RBV group was discontinued by the investigator due to noncompliance with study directions.

Across all treatment groups, the majority of subjects were male (68.8%), white (89.7%), and non-Hispanic/Latino (93.8%), with a mean age of 55 years (range: 22 to 72 years). The mean (SD) baseline BMI was 28.3 (5.06) kg/m^2, and 31.2% of subjects had a BMI $\geq$ 30 kg/m^2.

Of the 321 subjects across all treatment groups, 111 subjects had genotype 1 HCV infection (84 subjects [26.2%] were infected with HCV genotype 1a subtype, 26 subjects [8.1%] with the genotype 1b subtype, and 1 subject [0.3%] had no confirmed genotype 1 subtype) and 210 subjects (65.4%) had genotype 3 HCV infection. The majority of subjects did not have cirrhosis (54.5%) and 26.5% had IL28B CC alleles. The overall mean (SD) baseline HCV RNA was 6.6 (0.60) $\log_{10}$ IU/mL, and most subjects (85.7%) had baseline HCV RNA $\geq$ 800,000 IU/mL and baseline ALT values > 1.5 × upper limit of normal (62.6%). The overall mean (SD) baseline estimated glomerular filtration rate using the Cockcroft-Gault equation was 113.0 (30.26) mL/min. Subjects who had discontinued their prior HCV therapy due to an AE were prohibited from enrolling in this study; therefore, all subjects in this study were prior virologic failures, classified as either relapse/breakthrough (71.7%) or nonresponse (28.3%).

Efficacy Results: Noncirrhotic subjects with genotype 3 HCV infection who received SOF + GS-5816 25 mg or SOF + GS-5816 25 mg + RBV had SVR12 rates of 84.6% and 96.4%, respectively, and noncirrhotic subjects with genotype 3 HCV infection who received SOF + GS-5816 100 mg or SOF + GS-5816 100 mg + RBV had SVR12 rates of 100.0% in both treatment groups. Cirrhotic subjects with genotype 3 HCV infection who received SOF + GS-5816 25 mg or SOF + GS-5816 25 mg + RBV had SVR12 rates of 57.7% and 84.0%, respectively, and cirrhotic subjects with genotype 3 HCV infection who received SOF + GS-5816 100 mg or SOF + GS-5816 100 mg + RBV had SVR12 rates of 88.5% and 96.2%, respectively.

Most subjects with genotype 3 HCV infection who experienced virologic relapse did so by the posttreatment Week 4 visit. In subjects with genotype 3 HCV infection who received SOF + GS-5816 25 mg or SOF + GS-5816 25 mg + RBV, 17 of 19 subjects (89.5%) with virologic relapse had relapsed by the posttreatment Week 4 visit. In subjects with genotype 3 HCV infection who received SOF + GS-5816 100 mg or SOF + GS-5816 100 mg + RBV, 4 of 4 subjects (100.0%) with virologic relapse had relapsed by the posttreatment Week 4 visit.

Overall, all noncirrhotic and cirrhotic subjects with genotype 3 HCV infection who achieved SVR12 also achieved SVR24, resulting in a positive predictive value of 100.0% for all treatment groups.

Potent and rapid suppression of HCV RNA while on treatment was observed in all subjects across treatment groups. All subjects achieved HCV RNA < LLOQ on treatment.

HCV RNA levels ($\log_{10}$ IU/mL) declined rapidly in all treatment groups for noncirrhotic and cirrhotic subjects with genotype 3 HCV infection. After 1 week of treatment, mean (SD) changes from baseline ranged from −4.74 (0.324) to −4.36 (0.518) $\log_{10}$ IU/mL across treatment groups, demonstrating that similar decreases in HCV RNA were observed in all treatment groups, irrespective of cirrhosis status or inclusion of RBV in the treatment regimen. The decreases in HCV RNA were maintained from Week 2 through Week 12.

Subjects with genotype 1 HCV infection who received SOF + GS-5816 25 mg or SOF + GS-5816 25 mg + RBV had SVR12 rates of 100.0% and 96.6%, respectively, and subjects with genotype 1 HCV infection who received SOF + GS-5816 100 mg or SOF + GS-5816 100 mg + RBV had SVR12 rates of 100.0% and 96.6%, respectively.

Both subjects with genotype 1 HCV infection who experienced virologic relapse did so by the posttreatment Week 4 visit.

Across all treatment groups, subjects with genotype 1 HCV infection who achieved SVR12 also achieved SVR24, resulting in a positive predictive value of 100.0%.

HCV RNA levels ($\log_{10}$ IU/mL) declined rapidly in all treatment groups for subjects with genotype 1 HCV infection. After 1 week of treatment, mean (SD) changes from baseline ranged from −4.66 (0.450) to −4.48 (0.644) $\log_{10}$ IU/mL across treatment groups. The decreases in HCV RNA were maintained from Week 2 through Week 12.

The high SVR12 rates observed across all treatment groups preclude meaningful interpretation of subgroup analyses.

Virologic Resistance Results: Of the 210 subjects with genotype 3 HCV infection treated with SOF +GS-5816 25 mg or 100 mg ± RBV, 210 and 207 subjects had sequencing data available for HCV nonstructural protein (NS) 5A and NS5B, respectively. The prevalence of pretreatment NS5A resistance-associated polymorphisms (RAPS) detected at ≥ 15% of viral sequences was 17.1% (36 of 210 subjects) and of pretreatment NS5B RAPS was 3.9% (8 of 207 subjects).

Across all treatment groups of subjects with genotype 3 HCV infection, the SVR12 rate was similar in subjects with pretreatment NS5A RAPs compared to the SVR12 rate in subjects without pretreatment RAPs.

Of the 23 subjects with genotype 3 HCV infection who experienced virologic relapse, 7 subjects had pretreatment NS5A RAPs detected with a 1% cutoff. All 7 subjects had one or more NS5A RAP persist at virologic failure. All 16 subjects with no pretreatment NS5A RAPs had Y93H emerge at relapse, with Y93N also emerging in 1 subject.

Of the 111 subjects with genotype 1 HCV infection treated with SOF + GS-5816 25 mg or 100 mg ± RBV, 111 and 110 subjects had sequencing data available for HCV NS5A and NS5B, respectively. The prevalence of pretreatment NS5A RAPs detected at ≥ 15% of viral sequences was 15.3% (17 of 111 subjects) and of pretreatment NS5B RAPS was 2.7% (3 of 110 subjects). Sixteen of 17 subjects with NS5A RAPs achieved SVR.

Two subjects with genotype 1a HCV infection had virologic relapse after receiving either SOF + GS 5816 25 mg or 100mg + RBV. Both subjects had NS5A RAPs detected at >1% prevalence pretreatment, of which some RAPs were enriched posttreatment.

No S282T, L159F, or V321A was detected in any of the genotype 1 or 3 HCV-infected subjects who relapsed.

Pharmacokinetics Results: Administration of SOF + GS-5816 100 mg ± RBV resulted in modestly higher SOF (approximately 20%) and GS-566500 (approximately 26%) overall exposures (AUC) compared with administration of SOF + GS-5816 25 mg ± RBV. No notable difference in GS-331007 exposure was observed following administration of SOF with GS-5816 25 mg or 100 mg. GS-5816 exposure was not dose-proportional between GS-5816 25 mg and 100 mg, with a 6- to 8-fold exposure range observed (AUC, C_{max}, and C_{tau}).

Safety Results: The majority of subjects in each of the 4 treatment groups reported at least 1 AE with similar AE incidence across treatment groups (SOF + GS-5816 25 mg, 82.3%; SOF + GS-5816 25 mg + RBV, 80.5%; SOF + GS-5816 100 mg, 78.8%; SOF + GS-5816 100 mg + RBV, 86.3%).

Headache and fatigue were the only AEs occurring with > 10% incidence across all treatment groups. Types and percentages of AEs were similar in subjects treated with GS-5816 25 mg versus 100 mg with no discernible dose-related toxicity.

Most AEs reported in the study were Grade 1 or 2 in severity. A total of 1 subject (1.2%) in the SOF + GS-5816 25 mg + RBV group, 2 subjects (2.5%) in the SOF + GS-5816 100 mg group, and 4 subjects (5.0%) in the SOF + GS-5816 100 mg + RBV group had a Grade 3 or 4 AE. No Grade 3 or 4 AEs occurred in > 1 subject in any group. Two subjects (both in the SOF + GS-5816 100 mg + RBV group) experienced a Grade 3 AE (anemia in 1 subject and lipase increased in the other) that was assessed as related to study drug by the investigator.

Overall, SAEs were rare (2.5%, 8 of 321 subjects). A total of 1 subject (1.3%) in the SOF + GS-5816 25 mg group, 4 subjects (5.0%) in the SOF + GS-5816 100 mg group, and 3 subjects (3.8%) in the SOF + GS-5816 100 mg + RBV group experienced SAEs. No trends in SAE type or onset time were observed, as no SAE was reported in > 1 subject. All SAEs were assessed by the investigator to be not related to study drug and no SAEs led to treatment discontinuation.

Only 1 subject in the SOF + GS-5816 25 mg + RBV group permanently discontinued all study drugs due to AEs. This subject experienced elevated GGT on Day 74 and elevated ALT on Day 80. The subject discontinued study drugs on Day 81. The GGT and ALT elevations normalized by posttreatment Day 33. The investigator assessed the events as related to study drug.

The majority of laboratory abnormalities were Grade 1 or 2 in severity. Higher percentages of subjects had Grade 3 laboratory abnormalities in the RBV-containing groups (SOF + GS-5816 25 mg + RBV, 11.0% and SOF + GS-5816 100 mg + RBV, 10.0%) as compared with the RBV-free groups (SOF + GS-5816 25 mg, 3.8% and SOF + GS-5816 100 mg, 8.8%). This difference was accounted for primarily by the expected decreases in hemoglobin observed with RBV therapy; there was a higher incidence of Grade 3 decreased hemoglobin in RBV-treated subjects. No Grade 4 hematology laboratory abnormalities were reported. Grade 3 chemistry laboratory abnormalities were reported for ALT, aspartate aminotransferase, GGT, lipase (all transient and asymptomatic), serum glucose (hyperglycemia), serum sodium (hypernatremia), and total bilirubin (hyperbilirubinemia). Grade 4 chemistry laboratory abnormalities were reported for ALT, lipase (asymptomatic), and total bilirubin (hyperbilirubinemia). Grade 3 or 4 hyperbilirubinemia was only observed in RBV-containing treatment groups and was consistent with RBV-associated hemolysis.

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during the study. No clinically significant abnormal 12-lead ECGs were captured.

CONCLUSIONS: The conclusions for Study GS-US-342-0109 are as follows:

- Treatment with SOF + GS-5816 100 mg with or without RBV for 12 weeks resulted in high SVR12 rates in treatment-experienced subjects with genotype 1 or 3 HCV infection with or without cirrhosis. There were fewer virologic failures in treatment-experienced subjects with genotype 3 HCV infection who received SOF + GS-5816 100 mg ± RBV compared with those who received SOF + GS-5816 25 mg ± RBV.
- Administration of SOF + GS-5816 100 mg ± RBV resulted in modestly higher SOF (~20%) and GS-566500 (~26%) exposures compared with administration of SOF + GS-5816 25 mg ± RBV. GS-331007 exposure was similar regardless of GS-5816 dose. GS-5816 exposure was not dose-proportional between GS-5816 25 mg and GS-5816 100 mg.
- Treatment with SOF+GS-5816 ±RBV for 12 weeks resulted in high SVR12 rates in treatment-experienced, noncirrhotic or cirrhotic subjects with genotype 1 or 3 HCV infection regardless of the presence of NS5A RAPs. Subjects who experienced virologic relapse had NS5A RAPs, but not SOF genotypic resistance detected at relapse.
- Administration of SOF+GS-5816±RBV for 12 weeks was generally well tolerated. The addition of RBV to the regimen increased the incidence of AEs and laboratory abnormalities, but did not affect the overall high rates of treatment completion.