FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	An Open Label Study of Sofosbuvir/GS-5816 Fixed-Dose Combination in Subjects with Chronic HCV Infection
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:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-342-1446
Phase of Development:	Phase 3
IND No.:	118605
EudraCT No.:	2014-003898-42
ClinicalTrials.gov Identifier:	NCT02346721
Study Start Date:	23 February 2015 (First Subject Screened)
Study End Date:	15 June 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Tarik Asselah, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Anu Osinusi, MD Telephone: PPD Fax: PPD
Report Date:	21 February 2017

STUDY SYNOPSIS

Study GS-US-342-1446
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

An Open Label Study of Sofosbuvir/GS-5816 Fixed-Dose Combination in Subjects with Chronic HCV Infection
Investigators: This was a multicenter study.
Study Centers: Subjects were enrolled across 62 sites in the United States (including 1 site in Puerto Rico), France, the United Kingdom, Germany, Canada, Belgium, Hong Kong, and Italy.
Publications: Asselah T, Shafran S, Bourgeois S, Lai CL, Cramp M, Mathurin P, et al. Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 Weeks in HCV Infected Patients Previously Treated With Placebo: Results of the Deferred Treatment Study (GS-US-342-1446 Study) [Abstract SAT-279]. J Hepatology 2016;64:S827-8.
Study Period: 23 February 2015 (First Subject Screened) 23 March 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) for 12 weeks 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 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 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 and VEL during treatment and after cessation of treatment

Methodology: This Phase 3, international, multicenter, open-label study evaluated safety, tolerability, and antiviral efficacy of SOF/VEL for 12 weeks in subjects with chronic genotype 1, 2, 4, 6, or indeterminate HCV infection who received placebo in the Gilead Sciences, Inc. (Gilead) study GS-US-342-1138 (ASTRAL-1).

Approximately 100 subjects were planned for enrollment, and all were to receive SOF/VEL (400/100 mg) fixed-dose combination (FDC) once daily for 12 weeks without regard to food.

All subjects were required to complete the posttreatment Week 4 visit regardless of treatment duration. Subjects with HCV RNA less than the lower limit of quantitation (< LLOQ; 15 IU/mL) at posttreatment Week 4 were to complete posttreatment Week 12 and Week 24 visits unless confirmed viral relapse occurred. Subjects who prematurely discontinued study treatment for any reason were to complete an early termination visit. The assessments performed at each study visit are outlined in Appendix 2 of the study protocol (Appendix 16.1.1).

After completing all required study visits, subjects could enroll into a Gilead-sponsored SVR registry study if SVR12 was achieved or into a sequence registry study if SVR12 was not achieved. Subjects with cirrhosis who achieved SVR12 were eligible for participation in a cirrhosis registry study.

This final synoptic clinical study report (CSR) summarizes the results of the final analysis of data collected throughout the study, after all subjects had completed the posttreatment Week 24 visit or had prematurely discontinued from the study.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 100 subjects

Analyzed:

- All enrolled subjects: 111 subjects
- Full Analysis Set (FAS): 111 subjects
- Safety Analysis Set: 111 subjects

Diagnosis and Main Criteria for Inclusion: Subjects were HCV treatment-naive and treatment-experienced males and nonpregnant/nonlactating females ≥ 18 years with chronic HCV infection and HCV RNA > LLOQ with or without cirrhosis. All subjects had been administered placebo in Study GS-US-342-1138 (ASTRAL-1) and completed all on-treatment and posttreatment assessments in that study. A complete list of inclusion and exclusion criteria is available in the study protocol (Appendix 16.1.1, Section 4).

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 400/100 mg FDC tablets were administered orally once daily.

The lot numbers of SOF/VEL tablets administered in this study were DU1403B1 and DU1405B1.

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

Criteria for Evaluation:

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

Pharmacokinetics: A single pharmacokinetic (PK) blood sample was collected from all subjects at Weeks 1, 2, 4, 6, 8, 10, and 12 (and early termination, 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:

All tables, figures, and listings produced for this study are provided in Section 15.1 and Appendix 16.2.

Efficacy: The primary efficacy endpoint of the study was SVR12, defined as HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs for the FAS. Point estimates and 2-sided 95% exact confidence intervals (CIs) based on the Clopper-Pearson method were provided for the SVR12 rate by HCV genotype (1[further subtyped as 1a, 1b, 1g], 2, 4, 6) and overall.

Subgroup analyses were performed to assess the relationship between SVR12 and baseline demographic and disease characteristics and HCV treatment history. Point estimates and 95% exact CIs of the SVR12 rates were calculated for each subgroup by HCV genotype (1[further subtyped as 1a, 1b, 1g], 2, 4, 6) and overall for the FAS.

Secondary endpoints included SVR4 and SVR24, virologic outcomes (on-treatment virologic failure and relapse), HCV RNA < LLOQ through the end of treatment (EOT) by study visit, HCV RNA (log_{10} IU/mL), and change from baseline in HCV RNA (log_{10} IU/mL). The statistical methods used to evaluate the primary and secondary efficacy endpoints are detailed in Section 6 of the statistical analysis plan (Appendix 16.1.9).

Virologic Resistance

The NS5A and NS5B coding regions were amplified using standard reverse transcriptase polymerase chain reaction (PCR) technology. Following amplification, the PCR products were deep sequenced and analyzed using a 15% cutoff.

Pharmacokinetics: Pharmacokinetics was not assessed in this study.

Safety: All subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety data included all data collected on or after the date of the first dose of study drug up to the date of the last dose of study drug plus 30 days (ie, treatment emergent). All AEs and laboratory abnormalities discussed in this CSR were treatment emergent and are referred to as AEs and laboratory abnormalities, unless otherwise specified. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0; AEs and laboratory abnormalities were graded using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Version 15 April 2015.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 111 subjects were enrolled, received at least 1 dose of study drug, and were included in the FAS and the Safety Analysis Set. Overall, 110 subjects (99.1%) completed study treatment; 1 subject (0.9%) prematurely discontinued study treatment due to an AE of gallbladder adenocarcinoma (Tables 15.8.1.3 and 15.11.5.1).

The majority of subjects were male (58.6%), white (76.6%), and not Hispanic or Latino (95.5%) with a mean age of 54 years (range: 26-74 years). The mean baseline body mass index (BMI) value for subjects was 26.2 kg/m^2 (range: 17.6-43.4 kg/m^2), and 17.1% of subjects had BMI $\geq$ 30 kg/m^2 (Table 15.8.3.1).

A total of 63 subjects (56.8%) had HCV genotype 1 (43 subjects [38.7%] with genotype 1a, 19 subjects [17.1%] with genotype 1b, and 1 subject [0.9%] with genotype 1g); 20 subjects (18.0%) had HCV genotype 2 (9 subjects [8.1%] with genotype 2a/2c, 6 subjects [5.4%] with genotype 2b, and 5 subjects [4.5%] who did not have a determined genotype 2 subtype); 19 subjects (17.1%) had HCV genotype 4 (11 subjects [9.9%] with genotype 4a/4c/4d, 1 subject [0.9%] with genotype 4a, 1 subject [0.9%] with genotype 4e, and 6 subjects [5.4%] who did not have a determined genotype 4 subtype); 9 subjects (8.1%) had HCV genotype 6 (4 subjects [3.6%] with genotype 6c-1, 1 subject [0.9%] with genotype 6a, 3 subjects [2.7%] with genotype 6a/6b, and 1 subject [0.9%] with genotype 6e) (Table 15.8.3.2). The majority of subjects had a non-CC (CT or TT) IL28B allele (67.6%; 75 subjects). Overall, 19 subjects (17.1%) had cirrhosis. The mean (standard deviation [SD]) baseline HCV RNA value was 6.3 (0.55) $\log_{10}$ IU/mL, and most subjects (73.0%; 81 subjects) had baseline HCV RNA $\geq$ 800,000 IU/mL.

Thirty-one (27.9%) subjects were HCV treatment experienced, and the majority of those subjects (71.0%; 22 of 31 subjects) had failed prior treatment with pegylated interferon (Peg-IFN) + ribavirin (RBV); 16.1% (5 of 31 subjects) had prior treatment with a direct-acting antiviral + Peg-IFN+RBV.

Efficacy Results: Overall, 108 subjects (97.3%) achieved SVR12 following 12 weeks of treatment with SOF/VEL. Across genotypes, SVR12 rates ranged from 88.9% (8 of 9 subjects) for subjects with genotype 6 HCV infection to 100.0% for subjects with genotype 2 (20 of 20 subjects) or 4 (19 of 19 subjects) HCV infection.

	SOF/VEL 12 Weeks							
	Overall Study Total (N = 111)	**GT-1a (N = 43)**	**GT-1b (N = 19)**	**GT-1g (N = 1)**	**GT-1 Total (N = 63)**	**GT-2 (N = 20)**	**GT-4 (N =19)**	**GT-6 (N = 9)**
SVR12	108/111 (97.3%)	42/43 (97.7%)	19/19 (100.0%)	0/1	61/63 (96.8%)	20/20 (100.0%)	19/19 (100.0%)	8/9 (88.9%)
95% CI	92.3% to 99.4%	87.7% to 99.9%	82.4% to 100.0%	0.0% to 97.5%	89.0% to 99.6%	83.2% to 100.0%	82.4% to 100.0%	51.8% to 99.7%

GT = genotype
HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation 15 IU/mL.
SVR12 is sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.
The exact 95% CI for the proportion is based on the Clopper-Pearson method.
Source: Table 15.9.1

No subjects had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse). Overall, 3 subjects did not achieve SVR12 (Table 15.9.2.1.1), including 1 subject (0.9%) with virologic failure (a treatment-naive, 67 year-old-PPD male with genotype 1a HCV without cirrhosis who had relapse determined at posttreatment Week 4) and 2 subjects (1.8%) who were categorized as "Other" (ie, did not achieve SVR12 and did not meet criteria for virologic failure): 1 subject with HCV genotype 1g who prematurely discontinued study drug due to an AE of gallbladder adenocarcinoma after 72 days of dosing who had HCV RNA < LLOQ at the last on-study evaluation, and 1 subject with HCV genotype 6a/6b who withdrew consent after completing study treatment and achieving SVR4 (Listings 16.2.6.2 and 16.2.6.3). High SVR12 rates were achieved in all subgroups evaluated across all genotypes (Table 15.9.4.1).

Potent and rapid suppression of HCV RNA while on treatment was observed overall and for all HCV genotypes evaluated. By Week 4, 94.6% of subjects had HCV RNA < LLOQ. At Week 8, 100.0% of subjects had HCV RNA < LLOQ (Table 15.9.2.4). Overall, HCV RNA levels declined rapidly, with similar decreases in HCV RNA observed across all genotypes evaluated. After 1 week of treatment, the overall mean (SD) change from baseline in HCV RNA was −4.23 (0.592) $\log_{10}$ IU/mL. The decreases in HCV RNA were maintained from Week 2 through EOT, when mean (SD) HCV RNA was 1.15 (0.0) $\log_{10}$ IU/mL and mean (SD) change from baseline was −5.11 (0.566) $\log_{10}$ IU/mL (Table 15.9.2.5). Early viral response was not predictive of treatment outcome (Table 15.9.4.2).

All of the 107 evaluable subjects who achieved SVR12 also achieved SVR24 (Listing 16.2.6.1). Thus, the concordance rate between SVR12 and SVR24 was 100.0% (Table 15.9.2.3).

Virologic Resistance Results: Baseline NS5A deep-sequencing data were obtained for 108 of 109 subjects with a virologic outcome. NS5A amplification failed in 1 subject (Virology Listing 1). Baseline NS5B deep-sequencing data were obtained for 106 of 109 subjects. Population sequencing of a short-length NS5B fragment that included amino acid position S282 was obtained for the 1 subject who did not have NS5B deep-sequencing data (Virology Listing 2).

Prevalence of Pretreatment NS5A and NS5B NI RAVs (15% cutoff)

	Overall Study Total (N = 111)	GT-1a (N = 44)[a]	GT-1b (N = 20)[b]	GT-1 Total (N = 64)[b]	GT-2 (N = 20)	GT-4 (N = 19)	GT-6 (N = 8)[b]
Subjects with Pretreatment NS5A Sequence Data and Virologic Outcome, n/N (% of subjects with NS5A RAVs)	39/108 (36.1%)	4/43 (9.3%)	2/19 (10.5%)	6/62 (9.7%)	16/20 (80%)	13/19 (68.4%)	4/7 (57.1%)
Subjects with Pretreatment NS5B Sequence Data and Virologic Outcome, n/N (% of subjects with NS5B RAVs)	12/107 (11.2%)	0/43	5/19 (26.3%)	5/62 (8.1%)	1/19 (5.3%)	2/19 (10.5%)	4/7 (57.1%)

GT = genotype by sequencing analyses; NI = nucleoside inhibitor; RAV = resistance-associated variant
a Includes Subject PPD who was determined to have genotype 1g at screening and an indeterminate genotype 1 subtype (non-1b) by subsequent sequencing-based BLAST analysis.
b Subject PPD was determined to have genotype 6e at screening and genotype 1b by subsequent sequencing-based BLAST analysis.
Source: Virology Listings 1 and 2

Pretreatment NS5A RAVs were detected above the 15% cutoff in 39 of 108 subjects (36.1%) with NS5A sequence data and virologic outcome (Virology Listing 1). Pretreatment NS5B nucleoside (NI) RAVs were detected above the 15% cutoff in 12 of 107 subjects (11.2%) with NS5B deep sequence data and virologic outcome (Virology Listing 2). All subjects with pretreatment NS5A or NS5B NI RAVs achieved SVR12.

One subject with genotype 1a relapsed after treatment with SOF/VEL for 12 weeks. No pretreatment NS5A or NS5B NI RAVs were detected in this subject using a 15% cutoff. NS5A RAV Y93H was detected in > 99% of the viral population at the relapse time point (Virology Listing 3). No NS5B NI RAVs emerged at relapse (Virology Listing 4).

Pharmacokinetic/Pharmacodynamics Results: Pharmacokinetics and pharmacodynamics were not assessed.

Safety Results

Adverse Events and Serious Adverse Events

The majority of subjects had at least 1 AE (71.2%; 79 subjects). Most AEs were Grade 1 or 2 in severity. The most commonly reported AEs were headache (21.6%; 24 subjects), fatigue (16.2%; 18 subjects), and nausea (10.8%, 12 subjects) (Tables 15.11.2.1.2 and 15.11.2.1.3). Grade 3 or 4 AEs were reported for 4 subjects (3.6%): 1 subject with Grade 3 vertigo on Day 8 that was assessed as related to study drug and resolved on the same day; 1 subject with Grade 3 AEs of cellulitis and lymphangitis on Day 51, both of which were assessed as SAEs and unrelated to study drug and resolved on Day 66; 1 subject with a Grade 3 AE of hepatocellular carcinoma on Day 79 that was assessed as an SAE and unrelated to study drug and resolved on posttreatment Day 22 following tumor resection; and 1 subject with a Grade 4 AE of gallbladder adenocarcinoma on Day 70 that was assessed as an SAE and unrelated to study drug and led to premature discontinuation of study drug (Listings 16.2.7.2 and 16.2.7.5). This subject died 261 days after discontinuing study drug and was the only death reported in the study (Listing 16.2.7.3). Five subjects (4.5%) had SAEs (Table 15.11.4.1). In addition to the 3 subjects with SAEs reported above, 1 subject had an SAE of meniscus injury (Grade 2) on Day 36 that resolved on Day 38, and 1 subject had an SAE of lower limb fracture (Grade 2) on Day 69 that resolved on posttreatment Day 122. None of the SAEs was assessed as related to study drug (Listing 16.2.7.4). One subject interrupted dosing of SOF/VEL for 1 day (Day 73) due to Grade 1 ventricular extrasystoles with onset on Day 67. The event was assessed as unrelated to study drug and resolved on Day 75 (Listing 16.2.7.6). Complete subject narratives for all SAEs, the discontinuation due to AEs, and the death are provided in Section 15.2.

Clinical Laboratory Results

A total of 64.9% (72 subjects) had at least 1 clinical laboratory abnormality. For most subjects the maximum grade laboratory abnormality was Grade 1 (42.3%; 47 subjects) or Grade 2 (15.3%; 17 subjects). Grade 3 was the maximum grade for 6.3% (7 subjects), and 0.9% (1 subject) had a Grade 4 laboratory abnormality (Table 15.11.6.2). The only Grade 3 laboratory abnormalities reported for ≥ 2 subjects were increased lipase (2.7%; 3 subjects) and increased glucose (hyperglycemia; 1.8%; 2 subjects). Lipase elevations were not associated with any AEs or pancreatitis (Listing 16.2.8.1.3.3). Both of the subjects with Grade 3 hyperglycemia had a history of diabetes and were taking medication for diabetes (Listing 16.2.8.1.3.2). One subject had Grade 3 increased bilirubin at Week 10 (4.6 mg/dL) and was subsequently diagnosed with

gallbladder adenocarcinoma (Listing 16.2.8.1.3.1); at follow-up subsequent to discontinuation of study drug total bilirubin had increased to 8.4 mg/dL (Grade 4), accounting for the only Grade 4 laboratory abnormality. All clinical laboratory results are provided in Tables 15.9.3, 15.11.6.1.1 through 15.11.6.1.12; Figures 15.11.6.1 through 15.11.6.10; and Listings 16.2.8.1.4 through 16.2.8.1.9.

Vital Signs Measurements

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) and no clinically significant ECG abnormalities were reported during the study (Listings 16.2.8.2.1 through 16.2.8.2.3.2). No subject pregnancies were reported (Listing 16.2.8.3).

CONCLUSIONS:

- Treatment with SOF/VEL for 12 weeks in treatment-naive and treatment-experienced subjects resulted in a high SVR12 rate (97.3%). High SVR12 rates were achieved across all HCV genotypes and subgroups, and the overall SVR12 rate was similar to that observed in subjects who received SOF/VEL for 12 weeks in the parent study (Study GS-US-342-1138 [99.0%; 618 of 624 subjects]).
- All subjects with pretreatment NS5A or NS5B NI RAVs achieved SVR12. Virologic relapse in a single subject with genotype 1a infection was associated with emergence of the NS5A RAV Y93H. No NS5B NI RAVs emerged at relapse.
- SOF/VEL was generally well tolerated with low rates of Grade 3 and 4 AEs, SAEs, discontinuations due to AEs and Grade 3 and 4 laboratory abnormalities.