FINAL CLINICAL STUDY REPORT

Study Title:	An Open Label Study to Evaluate The Efficacy And Safety Of Sofosbuvir/GS-5816 Fixed Dose Combination With Ribavirin For 24 Weeks In Chronic HCV Infected Subjects Who Participated In A Prior Gilead Sponsored HCV Treatment Study
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-342-1553
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	118605 Not Applicable
ClinicalTrials.gov Identifier:	NCT023000103
Study Start Date:	01 December 2014 (First Subject Screened)
Study End Date:	15 September 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Edward Gane, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Anu Osinusi, MD Telephone: PPD Fax: PPD Email: PPD
Report Date:	26 January 2017

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-342-1553
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: An Open Label Study to Evaluate The Efficacy And Safety Of Sofosbuvir/GS-5816 Fixed Dose Combination With Ribavirin For 24 Weeks In Chronic HCV Infected Subjects Who Participated In A Prior Gilead Sponsored HCV Treatment Study

Investigators: Multicenter

Study Centers: Subjects were enrolled at 31 sites (25 in the United States, 4 in Australia, and 2 in New Zealand)

Publications: Gane EJ, Shiffman ML, Etzkorn K, Morelli G, Stedman C, Davis MN, et al. Sofosbuvir/Velpatasvir in Combination With Ribavirin for 24 Weeks is Effective Retreatment for Patients Who Failed Prior NS5A Containing DAA Regimens: Results of the GS-US-342-1553 Study [Abstract PS024]. J Hepatology 2016;64:S147-S8.

Study Period:

01 December 2014 (First Subject Screened)
15 September 2016 (Last Subject Observation)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To evaluate efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL; GS-5816) with ribavirin (RBV) for 24 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

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attain 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 2, open-label, multicenter study evaluated the efficacy, safety, and tolerability of SOF/VEL+RBV in subjects with chronic HCV infection who did not achieve SVR following treatment with a direct-acting-antiviral (DAA) regimen in a prior Gilead Sciences, Inc. (Gilead)-sponsored HCV study. All enrolled subjects were to receive SOF/VEL (400/100 mg) + RBV (1000 or 1200 mg) daily for 24 weeks.

Number of Subjects (Planned and Analyzed):

Planned: 150 subjects
Enrolled: 69 subjects
Analyzed: 69 subjects

- 69 subjects in the Safety Analysis Set
- 69 subjects in the Full Analysis Set (FAS)

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males and nonpregnant/nonlactating females with chronic HCV infection who did not achieve SVR in a prior Gilead-sponsored HCV treatment study.

Duration of Treatment: 24 weeks of treatment and up to 24 weeks of follow-up

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

- **SOF/VEL** was administered orally without regard to food at a dose of 400/100 mg (1 tablet once daily).
- **RBV** was administered orally with food at a dose of 1000 or 1200 mg/day (5 or 6 × 200 mg tablets divided into 2 doses).

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

SOF/VEL: DU1403B1, DU1405B1

RBV: AA6551Z

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 (predose); Weeks 1, 2, 4, 6, 8, 12, 16, 20, and 24 of treatment (or early termination, as applicable); and posttreatment Weeks 4, 12, and 24 (if applicable). The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study. The lower limit of quantitation (LLOQ) of the assay is 15 IU/mL.

Virologic Resistance

Baseline deep-sequencing analysis of HCV nonstructural (NS) protein 3 (NS3), NS5A, and NS5B coding regions was performed for all subjects. For all subjects with virologic failure, deep sequencing of the NS5A and NS5B genes was performed at the first time point after virologic failure if the plasma/serum sample was available and HCV RNA was > 1000 IU/mL.

Pharmacokinetics: No pharmacokinetics (PK) assessments were conducted.

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 the proportion of subjects with HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs (SVR12) in the FAS. Two-sided 95% exact confidence intervals (CIs) based on the Clopper-Pearson method were provided for SVR12 overall and by HCV genotype (1[1a, 1b], 2, and 3).

Pharmacokinetics: No PK assessments were conducted.

Safety: All subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety analyses 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 (ie, treatment emergent). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 69 subjects were enrolled into the study. All of the enrolled subjects received at least 1 dose of study drug and were included in both the Safety Analysis Set and the FAS. Overall, 66 subjects (95.7%) completed study treatment. Three subjects prematurely discontinued study treatment: 1 subject due to an AE of irritability, 1 subject due to lack of efficacy, and 1 subject due to a protocol violation.

The majority of subjects were male (76.8%), white (88.4%), and not Hispanic/Latino (92.8%), with a mean age of 57 years (range: 31−74 years). The mean baseline body mass index (BMI) value for subjects was 28.0 kg/m^2 (range: 19.2−43.7 kg/m^2), and 29.0% of the subjects had BMI ≥ 30 kg/m^2. A total of 32 subjects (46.4%) had HCV genotype 1a, 5 subjects (7.2%) had HCV genotype 1b, 14 subjects (20.3%) had HCV genotype 2, and 18 subjects (26.1%) had HCV genotype 3. The majority of subjects had a non-CC (CT or TT) IL28B allele (66.7%; 46 subjects). Overall, 18 subjects (26.1%) had cirrhosis. The mean (SD) baseline HCV RNA value was 6.4 (0.67) $\log_{10}$ IU/mL and most subjects (78.3%) had baseline HCV RNA ≥ 800,000 IU/mL.

All of the subjects had been treated with a DAA regimen in a Gilead-sponsored study. The median time from completion of prior treatment to baseline/Day 1 of the current study was 356 days (range 101–600 days). Overall, 40.6% (28 subjects) had been treated with SOF/VEL+VOX (NS5A/5B inhibitor+ NS3/4A PI), 39.1% (28 subjects) had been treated with SOF/VEL, and 20.3% (14 subjects) had been treated with SOF/VEL+RBV, for different durations.

Efficacy Results: Overall, 91.3% of subjects achieved SVR12 following 24 weeks of treatment with SOF/VEL+RBV. Across genotypes, SVR12 rates ranged from 77.8 % for subjects with genotype 3 HCV infection to 97.3% for subjects with genotype 1 HCV infection.

Overall, 6 subjects (8.7%) did not achieve SVR12, 5 of whom had virologic failure (7.2%) and 1 of whom (1.4%) withdrew consent after achieving SVR4. Of the 5 subjects with virologic

failure, 3 subjects had relapse, 1 subject had nonresponse, and 1 subject had virologic rebound. One subject who achieved SVR12 had virologic relapse determined at posttreatment Week 24; at the time of virologic failure, the subject had virus that was distinct from the virus at baseline.

HCV RNA levels (log_{10} IU/mL) declined rapidly, with similar decreases observed across all HCV genotypes. Consistent with the rapid and sustained decline in HCV RNA, ≥ 90% of subjects had HCV RNA < LLOQ at Week 4. Time to virologic suppression was not associated with treatment outcome overall or genotype.

Virologic Resistance

Using a 15% assay cutoff, 39.7% of subjects had baseline NS5A resistance-associated variants (RAVs). For genotype 1, 5 of 5 subjects (100.0%) with NS5A RAVs achieved SVR12. For genotype 2, 8 of 9 subjects (88.9%) with NS5A RAVs achieved SVR12. For subjects with genotype 3 infection, the SVR12 rate was 76.9% (10 of 13 subjects) for subjects with RAVs compared with an SVR12 rate of 100.0% (4 of 4 subjects) for subjects without RAVs. Nine of 11 subjects (81.9%) with genotype 3 and Y93H achieved SVR12.

The 2 subjects with on-treatment virologic failure developed treatment-emergent NS5A and NS5B RAVs; 1 subject with nonresponse and genotype 3a infection had the emergent NS5A RAVs A30R (4.1%), L31F (3.1%), and Y93H (72.1%), and 1 subject with virologic rebound and genotype 1a infection had an emergent NS5A P32L (1.6%). For both subjects, NS5B nucleoside inhibitor (NI) RAVs emerged at low frequency (< 2.5%).

Among the 3 subjects who relapsed, 2 subjects with genotype 3a had enrichment of NS5A RAV Y93H and 1 of the 2 had emergent NS5A RAV L31M at a low level at relapse. One subject with genotype 2b had L31M at baseline and at relapse, without treatment-emergent NS5A RAVs.

Pharmacokinetics/Pharmacodynamics Results: No PK assessments were conducted.

Safety Results: Treatment with SOF/VEL+RBV was generally well tolerated by subjects. A total of 61 subjects (88.4%) experienced at least 1 AE. The majority of AEs (95.7%) were Grade 1 (mild) or Grade 2 (moderate) in severity. Treatment-related AEs were observed in 52 subjects (75.4%). Grade 3 (severe) AEs were rare (4.3%) and no Grade 4 (life-threatening) AEs were reported. One subject (1.4%) had a serious adverse event (SAE; Grade 3 nephrolithiasis). Overall, only 1 subject (1.4%) prematurely discontinued SOF/VEL, due to a Grade 2 event of irritability on Day 11. Three subjects (4.3%) prematurely discontinued RBV only, due to AEs of cough (Day 15), vomiting (Day 54), and depressed mood (Day 55) (1 subject each). Nine subjects (13.0%) had AEs that led to modification and/or interruption of RBV. The only AEs that led to modification and/or interruption of RBV for ≥ 2 subjects were hemolytic anemia and nausea (4.3%; 3 subjects each) and fatigue (2.9%; 2 subjects). No deaths or pregnancies were reported during the study.

The majority of laboratory abnormalities were Grade 1 or 2 in severity. Most subjects had at least 1 laboratory abnormality reported, with the majority of subjects having a maximum severity of Grade 1 (39.1%; 27 subjects) or Grade 2 (40.6%; 28 subjects). A smaller percentage of subjects had a maximum Grade 3 laboratory abnormality (11.6%; 8 subjects), and 4.3% (3 subjects) had a Grade 4 laboratory abnormality. The most common Grade 3 and 4

hematologic and chemistry laboratory abnormalities (decreased hemoglobin and increased total bilirubin) were consistent with RBV-associated hemolysis. Grade 3 decreased hemoglobin was reported for 7.2% (5 subjects) and resolved following completion of study drug. The only other Grade 3 hematologic abnormality reported was Grade 3 decreased lymphocytes. No Grade 4 hematologic abnormalities were reported. The most common Grade 3 and 4 chemistry abnormalities were Grade 3 increased glucose (2.9%; 2 subjects both with a history of diabetes), Grade 3 or 4 increased lipase (2.9%; 1 subject each, with no clinical signs or pancreatitis), and Grade 3 and 4 increased total bilirubin (5.8%; 2 subjects each).

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) or ECGs were reported during the study.

CONCLUSIONS: The conclusions from this study are as follows:

- Treatment with SOF/VEL+RBV for 24 weeks in subjects who had failed prior treatment with SOF+VEL ± VOX ± RBV resulted in a high SVR12 rate (91.3%)
  - For subjects with genotype 1 HCV infection, the SVR12 rate was 97.3%
  - For subjects with genotype 2 HCV infection, the SVR12 rate was 92.9%
  - For subjects with genotype 3 HCV infection, the SVR12 rate was 77.8%.
- The presence of baseline RAVs had an impact on the SVR12 rate in subjects with genotype 3 HCV infection, with an SVR12 rate of 76.9% for subjects with RAVs compared with an SVR12 rate of 100.0% for subjects without RAVs. Virologic relapse in subjects with genotype 3 was associated with enrichment or emergence of NS5A RAVs.
- Treatment with SOF/VEL+RBV for 24 weeks was safe and well tolerated. There was a low incidence of Grade 3 or 4 AEs, SAEs, and discontinuations due to AEs. Most Grade 3 and 4 laboratory abnormalities were consistent with the known effects of RBV.