FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) infection
Name of Test Drug:	Sofosbuvir (SOF)/Velpatasvir (VEL) 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 Dr. Foster City, CA 94404 USA
Study No.:	GS-US-342-1521
Phase of Development:	Phase 3
IND No.:	This is a non-IND study
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT03074331
Study Start Date:	23 March 2017 (First Subject Screened)
Study End Date:	07 February 2018 (Last Subject Last Observation for the Primary Endpoint)
Principal or Coordinating Investigator:	Name: Ajit Sood, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Luisa M. Stamm, MD, PhD Telephone: PPD Fax: PPD
Report Date:	14 May 2018

STUDY SYNOPSIS

Study GS-US-342-1521

Gilead Sciences, Inc.
333 Lakeside Dr.
Foster City, CA 94404
USA

Title of Study: A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) Infection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 16 study sites in India.

Publications: Sood A, Duseja A, Kabrawala M, Amrose P, Goswami B, Chowdhury A, et al. The sofosbuvir/velpatasvir single tablet regimen administered for 12 weeks with minimal monitoring in India [Abstract O-HCV-12] Asian Pacific Association for the Study of the Liver (APASL); 2018 14-18 March; New Delhi, India. p. S240.

Study Period:

23 March 2017 (First Subject Screened)
07 February 2018 (Last Subject Last 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; GS-7977)/velpatasvir (VEL; GS-5816) fixed-dose combination (FDC) for 12 weeks in subjects with chronic HCV infection 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 FDC for 12 weeks

Methodology: This Phase 3, open-label, multicenter study evaluated the antiviral efficacy, safety, and tolerability of SOF/VEL for 12 weeks in subjects with chronic HCV infection.

Approximately 125 subjects were to be enrolled to receive SOF/VEL FDC (400/100 mg) once daily with or without food for 12 weeks. Up to 20% of subjects enrolled in the study were to have been treatment experienced and up to approximately 20% were to have compensated cirrhosis at baseline.

All subjects were to complete the screening, baseline/Day 1, and Week 12 visits, and posttreatment Week 4 and 12 visits. In addition, subjects were to return at Weeks 4 and 8 for drug dispensing.

Number of Subjects (Planned and Analyzed):
Planned: 125 subjects
Analyzed: 130 subjects
All Enrolled Analysis Set: 130 subjects
Full Analysis Set (FAS): 129
Safety Analysis Set: 129

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males and nonpregnant, nonlactating females ≥ 18 years of age, with chronic HCV infection, with or without cirrhosis.

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

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

SOF/VEL (1 × 400/100 mg tablet) was administered by mouth once daily with or without food for 12 weeks

The lot number of SOF/VEL administered in this study was DU1501B1.

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), Week 12 during treatment (or upon early termination), and posttreatment Week 12. 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 this assay is 15 IU/mL.

Virology: For all subjects with virologic failure, deep sequencing analysis of HCV nonstructural protein (NS) 5A, and NS5B coding regions was performed at baseline and at the first time point after virologic failure if a plasma sample was available and HCV RNA was > 1000 IU/mL. All data are reported at a 15% assay cutoff.

Pharmacokinetics: No pharmacokinetic (PK) assessments were performed for this report.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital signs measurements, 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. In the primary efficacy analysis, the SVR12 rate was compared to the prespecified performance goal of 85% by using a 2-sided exact 1-sample binomial test at the 0.05 significance level. The SVR12 rates for all subjects were calculated along with 2-sided 95% exact confidence interval (CI) and p-value based on the Clopper-Pearson method. The point estimates and 95% exact CIs of the SVR12 rates were displayed by genotype for key demographic and baseline characteristic subgroups. A Forest plot graphically presented estimates and 95% CIs in SVR12 rates for each of the subgroups.

Secondary efficacy endpoints included the proportion of subjects with virologic failure.

All continuous endpoints were summarized using descriptive statistics (sample size [n], 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: No PK assessments were performed for this report.

Safety: All enrolled 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 signs, and physical examinations. Safety data were analyzed and included all data collected on and after the date of the first dose of 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 20.1.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Of the 130 enrolled subjects, 129 received at least 1 dose of study drug and were included in the Safety Analysis Set and FAS. One subject was enrolled into the study but withdrew consent and did not receive study drug. This subject was excluded from both the Safety Analysis Set and the FAS. There were 128 subjects who completed study treatment, of whom 123 subjects (95.3%) had HCV RNA results at posttreatment Week 12 and completed the study. One subject was lost to follow-up and prematurely discontinued study treatment and the study. Five subjects completed study treatment but did not complete the study (4 were lost to follow-up and 1 withdrew consent).

All subjects were Asian and the majority of subjects were male (58.9%), non-Hispanic or Latino (99.2%), with a mean age of 43 years (range: 19–75 years). The mean (range) baseline BMI was 23.6 (15.3–39.5) kg/m^2, and 35.7% of subjects had BMI $\geq$ 25 kg/m^2.

The majority of subjects had genotype 3 (69.8%) or genotype 1 (21.7% [1a = 4.7%, 1b = 17.1%]) HCV infection; 5.4% of subjects had genotype 4, 0.8% had genotype 6, and 2.3% had indeterminate HCV infection. Overall, 32.6% of subjects had cirrhosis and 8.5% of subjects were treatment experienced, 81.8% of whom had prior treatment with Peg-IFN +RBV.

The mean (SD) baseline HCV RNA value was 5.9 (0.96) log_{10} IU/mL, and most subjects (57.4%) had HCV RNA $\geq$ 800,000 IU/mL. The mean (SD) baseline eGFR using the Cockcroft-Gault equation was 100.6 (25.78) mL/min.

Efficacy Results:

The overall SVR12 rate was 93.0% (95% CI: 87.2% to 96.8%). The study met the primary endpoint of an SVR12 rate that was statistically superior relative to the prespecified SVR12 performance goal of 85% (p = 0.009).

Nine of 129 subjects (6.9%) did not achieve SVR12: 1 subject was a nonresponder at the EOT, 2 subjects relapsed, and 6 subjects were categorized as “Other”. Of the 2 subjects who relapsed, 1 had an exclusionary prior treatment history of SOF+DCV for 12 weeks. All 6 subjects categorized as “Other” missed their posttreatment Week 12 visit (1 withdrew consent and 5 were lost to follow-up). The majority of subjects who did not achieve SVR12 did so for non-virologic reasons precluding meaningful subgroup analysis.

The SVR12 rates were > 90.0% for all subtype groups with greater than 1 subject, including rare subtypes of genotype 3. None of the 3 subjects who failed to achieve SVR12 had treatment-emergent NS5A or NS5B NI RAVs.

Pharmacokinetics Results: No PK analyses were performed for this report.

Safety Results: Overall, 14.7% of subjects (19 of 129) experienced at least 1 AE. The 3 most commonly reported AEs were headache (3.1%, 4 of 129 subjects), upper abdominal pain (2.3%, 3 of 129 subjects), and pyrexia (2.3%, 3 of 129 subjects). No subjects had AEs that led to premature discontinuation or interruption of study drug. No subjects died during the study. Most AEs were Grade 1 (mild) in severity. One Grade 3 AE was reported for 1 of 129 subjects (0.8%). This Grade 3 AE of rectal hemorrhage was also the only SAE in the study and was assessed as unrelated to study drug. No Grade 4 AEs were reported.

The majority of subjects who had graded laboratory abnormalities had a maximum grade of Grade 1 (20.6%) or Grade 2 (8.7%). Grade 3 and 4 laboratory abnormalities were reported for 6.3% (8 of 126) and 3.2% (4 of 126) of subjects, respectively. No clinically meaningful laboratory abnormalities were noted.

CONCLUSIONS:

The conclusions from Study GS-US-342-1521 conducted in India are as follows:

- Treatment with SOF/VEL for 12 weeks resulted in an SVR12 rate of 93.0%, which was statistically superior to the performance goal of 85% at the pre-specified 0.05 significance level ($p = 0.009$), meeting the primary efficacy endpoint.
- Treatment with SOF/VEL for 12 weeks was generally safe and well tolerated, with no deaths, no permanent discontinuations of study drug due to AEs, and SAEs and Grade 3 or 4 AEs were rare. No clinically meaningful laboratory abnormalities were noted.
- When compared with the initial registrational global Phase 3 studies, SVR rates were comparable and rates of reported AEs were lower in this study than previously observed.