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 Drive Foster City, CA 94404 USA
Study No.:	GS-US-342-1522
Phase of Development:	Phase 3
IND No.:	This is a non-IND study
EudraCT No.:	2015-003001-42
ClinicalTrials.gov Identifier:	NCT02722837
Study Start Date:	04 April 2016 (First Subject Screened)
Study End Date:	26 June 2017 (Last Subject Last Observation for the Primary Endpoint) 13 September 2017 (Last Subject Last Observation)
Principal or Coordinating Investigator:	Name: Vasily Isakov, MD, DMSc, Professor Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Brian McNabb, MD Telephone: PPD Fax: PPD
Report Date:	11 December 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-342-1522

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/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 15 study sites in the Russian Federation and Sweden.

Publications: Weiland O, Zhdanov K, Chulanov VP, McNabb BL, Lu S, Svarovskaia EU, et al. Safety and Efficacy of Sofosbuvir/Velpatasvir in a Genotype 1-3 HCV Infected Russian and Swedish Population: Results from a Phase 3, Prospective Trial [Abstract 1186]. Hepatology 2017;66 (1):639A.

Study Period:

04 April 2016 (First Subject Screened)
26 June 2017 (Last Subject Last Observation for the Primary Endpoint)
13 September 2017 (Last Subject Last Observation)

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 virologic 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 attain 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 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 provide their separate and specific consent
- To assess the effect of treatment on health-related quality of life (QOL)

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

Approximately 120 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 cirrhosis at baseline and up to approximately 20% were to have been treatment experienced.

All subjects were to complete the screening, Day 1, on-treatment visits at the end of Weeks 1, 2, 4, 8, and 12, and posttreatment visits at Weeks 4, 12, and 24 following the last dose of study drug. Subjects who achieved SVR4 were to complete the posttreatment Week 12 and Week 24 visits unless confirmed viral relapse occurred.

Number of Subjects (Planned and Analyzed):
Planned: 120

Analyzed: 119

Full Analysis Set (FAS): 119

Safety Analysis Set: 119

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.

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 numbers of SOF/VEL administered in this study were DU1405B1 and 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), Weeks 1, 2, 4, 8, and 12 during treatment (or upon early termination) 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 this assay is 15 IU/mL.

Virology: Baseline deep sequencing analysis of HCV nonstructural protein (NS)5A, and NS5B coding regions was performed for all subjects. For all subjects with virologic failure, deep sequencing was performed at the first time point after virologic failure if the 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, electrocardiograms (ECGs), and physical examinations.

Quality of Life: Health-related QOL was assessed with the Short Form-36 (Health Survey) (SF-36) questionnaire.

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. The SVR12 rate in each HCV genotype was calculated along with 2-sided 95% exact confidence interval (CI) based on 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 SVR4 and SVR24, HCV RNA < LLOQ while on treatment by study visit, HCV RNA absolute values and changes from baseline through the end of treatment (EOT), virologic failure, and characterization of HCV drug resistance substitutions at baseline and during and after treatment with SOF/VEL.

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 20.0.

Other: The health-related QOL questionnaire, SF-36, was completed at baseline/Day 1, Week 4, Week 12, EOT, posttreatment Week 4, and posttreatment Week 12 and changes from baseline, change from EOT to posttreatment were presented for each of the 8 domains of the SF-36 (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), and for the physical component score and mental component summary. A Wilcoxon signed rank test was used to explore changes in status from baseline to each of the time points, and from EOT to posttreatment time points. Plots of mean ± SD of change from baseline in SF-36 summary scores were presented.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Of the 119 enrolled subjects, 119 received at least 1 dose of study drug and were included in the Safety Analysis Set and FAS. The 119 subjects were enrolled across 15 sites: 13 sites in Russia (103 subjects) and 2 sites in Sweden (16 subjects). All subjects (100.0%) completed study treatment and had HCV RNA results at posttreatment Weeks 4 and 12. There were 8 subjects (6.7%) who discontinued from the study after completing the posttreatment Week 12 assessment: 7 subjects (5.9%) were lost to follow up and 1 subject (0.8%) discontinued due to lack of efficacy.

Overall, the numbers of male (50.4%) and female (49.6%) subjects in the study were approximately even. All subjects were non-Hispanic/Latino and the majority of subjects were white (98.3%), with a mean age of 44 years (range: 18-71 years). The mean (range) baseline body mass index (BMI) was 25.9 (17.5–35.5) kg/m^2, and 12.6% of subjects had BMI ≥ 30 kg/m^2.

The majority of subjects had genotype 1 (65.5% [1a = 6.7%, 1b = 58.8%]) or genotype 3 (28.6% [3a = 27.7%, 3 no confirmed subtype = 0.8%]) HCV infection; 5.9% of subjects had genotype 2 (2a/2c = 1.7%, 2b = 4.2%) HCV infection. Most of the subjects (75.6%) had a non-CC IL28B genotype (CT = 60.5%, TT = 15.1%).

Overall, 29 of 119 subjects (24.4%) were treatment experienced and 22 of 119 subjects (18.5%) had cirrhosis. The mean (SD) baseline HCV RNA value was 6.1 (0.54) $\log_{10}$ IU/mL, and most subjects had HCV RNA ≥ 800,000 IU/mL (68.1%). The mean (SD) baseline alanine aminotransferase (ALT) value was 72 (61.3) U/L, and 43.7% of subjects had baseline ALT values > 1.5 × ULN. The mean (SD) baseline estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation was 118.1 (28.77) mL/min.

Efficacy Results: The SVR12 rate was 99.2% (95% CI: 95.4% to 100.0%). All of the 119 subjects in the FAS achieved SVR12, except 1 treatment-experienced subject with genotype 3 HCV infection without cirrhosis who experienced virologic relapse after completing treatment. No subjects had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse). Overall, SVR4 results were the same as the SVR12 and SVR24 results, with the exception of 1 subject with genotype 3 HCV infection who achieved SVR4 but had relapsed by the posttreatment Week 12 visit. All subjects who achieved SVR12 also achieved SVR24. Thus, SVR12 was 100.0% concordant with SVR24.

Host and viral factors that have historically been predictive of or associated with lower sustained virologic response (SVR) rates (eg, older age, prior HCV treatment, high BMI, cirrhosis, high viral load, non-CC IL28B genotypes) did not affect SVR12 rates in this study. The single virologic failure precludes meaningful subgroup analyses.

Potent and rapid suppression of HCV RNA while on treatment was observed in all subjects. HCV RNA levels ($\log_{10}$ IU/mL) declined rapidly with similar decreases in HCV RNA observed in all subjects and across HCV genotypes. After 1 week of treatment, the overall mean (SD) change from baseline in HCV RNA levels was −4.17 (0.502) $\log_{10}$ IU/mL. The decreases in HCV RNA were maintained from Week 2 through the EOT Week 12, with mean HCV RNA levels ranging from 1.37 to 1.15 $\log_{10}$ IU/mL and mean changes from baseline ranging from –4.70 to –4.93 $\log_{10}$ IU/mL.

Virologic Resistance: Approximately 29% (35 of 119) and 24% (29 of 119) of subjects who received SOF/VEL for 12 weeks had baseline NS5A and NS5B nucleoside inhibitor (NI) resistance-associated variants (RAVs) using a 15% assay cut off, respectively. The common baseline NS5A RAVs were A30K/T/L/S (10 subjects), L31M/F/I (10 subjects), and Y93H (8 subjects). The most common baseline NS5B NI RAV was L159F (26 subjects). All subjects with baseline RAVs achieved SVR12. The 1 subject with genotype 3a HCV infection who experienced virologic relapse had NS5A RAV Y93H emerge posttreatment.

Pharmacokinetics/Pharmacodynamics Results: No PK or pharmacodynamics analyses were performed for this report.

Safety Results: Overall, 41.2% (49 of 119 subjects) experienced at least 1 AE. The most common AEs were headache (16.0%, 19 of 119 subjects), fatigue (6.7%, 8 of 119 subjects), and asthenia (5.9%, 7 of 119 subjects). No subject experienced any AE leading to interruption, or discontinuation of study drug, during this study. Most AEs were Grade 1 or 2 in severity. No Grade 4 AEs were reported. Grade 3 AEs were reported for 2 of 119 subjects (1.7%); neither of the Grade 3 AEs (nausea and spinal compression fracture) occurred in > 1 subject. The Grade 3 AE of nausea was non-serious and was considered related to study drug by the investigator. The Grade 3 of spinal compression fracture was assessed as a serious adverse event (SAE) and was assessed as unrelated to study drug.

Overall, 4 SAEs (3.4%, 4 of 119 subjects) were reported in this study. No trends in SAEs were observed, and no SAE was reported for > 1 subject. All SAEs were assessed as unrelated to study drug.

The majority of subjects who had graded laboratory abnormalities had a maximum grade of Grade 1 (29.4%, 35 of 119 subjects) or Grade 2 (14.3%, 17 of 119 subjects) in severity. Overall, the incidence of Grade 3 laboratory abnormalities was 5.0% (6 of 119 subjects) and no Grade 4 laboratory abnormalities were reported for this study. Grade 3 hematology laboratory abnormalities were reported for decreased lymphocytes (0.8%, 1 of 119 subjects) and neutrophils (3.4%, 4 of 119 subjects). In general, Grade 3 decreases in lymphocytes and neutrophils were either isolated events or intermittent and transient and none were assessed as AEs. The only Grade 3 chemistry laboratory abnormality reported was increased lipase (1.7%, 2 of 119 subjects) and no coagulation laboratory abnormalities were reported in this study. The Grade 3 lipase elevations were isolated events or intermittent and transient, and were not associated with clinical symptoms.

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during this study. A single subject who had sinus tachycardia at baseline had a significant ECG finding of sinus tachycardia at the EOT that was assessed as clinically significant; however, it was not assessed by the investigators as being an AE.

Other: Overall, results from the SF-36 questionnaire indicated that QOL parameters improved during treatment with SOF/VEL for subjects with chronic HCV infection. The mean scores for most scales continued to improve from EOT to posttreatment Weeks 4 and 12. 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 from Study GS-US-342-1522 conducted in Russia and Sweden are as follows:

- SOF/VEL for 12 weeks resulted in high SVR12 rates (99.2%) irrespective of genotype, prior treatment history, the presence of cirrhosis, or baseline RAVs.
- Treatment with SOF/VEL for 12 weeks was generally well tolerated in this study, with no deaths, no permanent discontinuations of study drug due to AEs, few SAEs, only two Grade 3 AEs, no Grade 4 AEs, and no clinically meaningful laboratory abnormalities.
- When compared with the Phase 3 conducted studies in the United States (US) and Europe, SVR rates were comparable and rates of reported AEs were lower in this study than previously observed.