FINAL CLINICAL STUDY REPORT

Study Title:	An Open-Label Study to Evaluate the Safety And Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir Fixed-Dose Combination for 12 Weeks in Subjects who Participated in a Prior Gilead-Sponsored HCV Treatment Study
Name of Test Drug:	Sofosbuvir (SOF)/Velpatasvir (VEL)/Voxilaprevir (VOX) Fixed-Dose Combination (FDC)
Dose and Formulation:	SOF/VEL/VOX FDC (400/100/100 mg) tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-367-4181
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	125751 2017-000179-98
ClinicalTrials.gov Identifier:	NCT03118843
Study Start Date:	25 April 2017 (First Subject Screened)
Study End Date:	19 March 2018 (Last Subject Last Observation for the Primary Endpoint)
Principal or Coordinating Investigator:	Name: Peter Ruane, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Luisa Stamm, MD, PhD Telephone: PPD Fax: PPD
Report Date:	05 July 2018

STUDY SYNOPSIS

Study GS-US-367-4181

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

Title of Study: An Open-Label Study to Evaluate the Safety And Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir Fixed-Dose Combination for 12 Weeks in Subjects who Participated in a Prior Gilead-Sponsored HCV Treatment Study

Investigators: Multicenter study

Study Centers: This study was conducted across 27 sites in the United States (US) (17 sites), New Zealand (2 sites), Australia (2 sites), Canada (2 sites), Germany (2 sites), France (1 site), and the United Kingdom (1 site)

Publications: Ruane P, Strasser SJ, Gane EJ, Hyland RH, Shao J, Dvory-Sobol H, et al. Retreatment with Sofosbuvir/Velpatasvir/Voxilaprevir for 12 weeks is safe and effective for patients who have previously received Sofosbuvir/Velpatasvir or Sofosbuvir/Velpatasvir/Voxilaprevir [Abstract LBO-06]. 16th International Symposium on Viral Hepatitis and Liver Diseases (ISVHLD); 2018 14-17 June; Toronto, Canada

Study Period:

25 April 2017 (First Subject Screened)
19 March 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 determine the efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL)/voxilaprevir (VOX) fixed-dose combination (FDC) for 12 weeks 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/VOX FDC

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attain SVR at 4 weeks after cessation of treatment (SVR4)
- 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, VEL, and VOX during treatment and after cessation of treatment

Methodology: This Phase 3, open-label study evaluated the safety and efficacy of SOF/VEL/VOX treatment for 12 weeks in subjects with chronic HCV infection who did not achieve a sustained virologic response (SVR) in a prior Gilead-sponsored HCV treatment study.

All eligible subjects were enrolled to receive the SOF/VEL/VOX FDC (400/100/100 mg) once daily with food for 12 weeks.

All subjects completed the screening, Day 1, and on-treatment visits at the end of Weeks 2, 4, 8, and 12. Posttreatment visits occurred at Weeks 4 and 12 after the last dose of study drug.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 50 subjects
Analyzed: 31 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were chronically HCV-infected male and nonpregnant/nonlactating female subjects aged 18 years or older who did not achieve SVR in a prior Gilead-sponsored HCV treatment study. Each subject previously received SOF/VEL/VOX for 8 weeks or SOF/VEL for 12 weeks in GS-US-367-1172 (POLARIS-2), GS-US-367-1173 (POLARIS-3), or GS-US-367-1170 (POLARIS-4), or treatment with another HCV direct-acting antiviral (DAA)-based regimen in a Gilead-sponsored study, with approval from Gilead. Each subject must have completed the protocol-mandated treatment and posttreatment assessments in the prior Gilead-sponsored study.

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/VOX FDC (400/100/100 mg) tablets were administered once daily with food for 12 weeks.

The lot number of the SOF/VEL/VOX FDC (400/100/100 mg) tablets administered in this study was ER1602B1.

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 2, 4, 8, and 12 (or upon early termination); and posttreatment Weeks 4 and 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.

Pharmacokinetics: No pharmacokinetics (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.

Statistical Methods:

Efficacy: The primary efficacy endpoint was SVR12 defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after cessation of treatment in the Full Analysis Set (FAS). No inferential statistics were provided, and no statistical comparison was conducted. The point estimate of SVR12 rate and 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method are provided for all subjects, and for each subgroup specified in the SAP.

Secondary efficacy endpoints included the proportion of subjects with SVR4, the proportion of subjects with HCV RNA < LLOQ while on treatment, HCV RNA (log_{10} IU/mL) and change from baseline in HCV RNA (log_{10} IU/mL) through the end of treatment (EOT), and the proportion of subjects with virologic failure. The 2-sided 95% exact CI based on Clopper-Pearson method is provided for the percentage of subjects with SVR4 and for the percentages of subjects with HCV RNA < LLOQ at each postbaseline visit for the FAS. Summary statistics are presented for absolute values and changes from baseline in HCV RNA (log_{10} IU/mL) by visit through EOT.

Pharmacokinetics: No PK analyses 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 measurements, ECGs, and physical examinations. Safety data included all data collected on or after 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.

Analysis results are presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category were presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum are presented.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 31 subjects were enrolled into the study. All enrolled subjects received at least 1 dose of study drug and were included in the Full Analysis Set and Safety Analysis Set. All 31 subjects enrolled completed study treatment.

The majority of subjects were male (74.2%), white (80.6%), and non-Hispanic/Latino (93.5%). Mean age was 60 years (range: 34-74). Mean baseline body mass index (BMI) was 27.7 (range: 19.7−39.5) kg/m^2; 29.0% of subjects had a BMI ≥ 30 kg/m^2.

Most subjects had genotype 1 (61.3% [1a, 48.4%; 1b, 12.9%]) or genotype 3 (25.8%) HCV infection. Approximately half of the subjects (48.4%) had cirrhosis. Most subjects (90.3%) had a non-CC IL28B genotype. The mean (SD) baseline HCV RNA value was 6.5 (0.56) log_{10} IU/mL, and most subjects (80.6%) had HCV RNA ≥ 800,000 IU/mL.

Most subjects had been previously treated with SOF/VEL/VOX for 8 weeks (54.8%) or SOF/VEL for 12 weeks (35.5%).

Efficacy Results: All 31 subjects (100.0%) achieved SVR4 and SVR12.

HCV RNA levels (log_{10} IU/mL) declined rapidly. The decreases in HCV RNA at Week 2 were maintained from Weeks 4 through 12. At Week 12, mean HCV RNA level was 1.15 log_{10} IU/mL, and changes from baseline ranged from −6.16 to −3.76 log_{10} IU/mL.

Consistent with the rapid and sustained decline in HCV RNA, 96.8% of subjects had HCV RNA < LLOQ at Week 4, and 100.0% of subjects had HCV RNA < LLOQ at Weeks 8 and 12. Time to virologic suppression was not associated with treatment outcome.

Overall, 58.1% of subjects had nonstructural protein 3 (NS3) and/or nonstructural protein 5A (NS5A) resistance-associated variants (RAVs). The presence of baseline RAVs did not impact the SVR12 rate.

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

Safety Results: Treatment with SOF/VEL/VOX for 12 weeks was generally safe and well tolerated. At least 1 AE was reported in 19 subjects (61.3%), and AEs considered related to study drug were reported in 13 subjects (41.9%).

The most commonly reported AEs were fatigue or nausea (each 5 subjects, 16.1%), and headache (4 subjects, 12.9%). No other AEs were reported for more than 10% of subjects.

Most AEs reported in the study were Grade 1 or 2 in severity. Four Grade 3 AEs were reported in 1 subject with a history of Dieulafoy lesion who was hospitalized with a Grade 3 gastrointestinal hemorrhage; 2 of the 4 Grade 3 AEs in this subject (the Grade 3 gastrointestinal hemorrhage and a Grade 3 event of asthenia) were reported as serious adverse events (SAEs). None of this subject's AEs were related to study drug. No Grade 3 or higher AEs or SAEs were reported in any other subject. No deaths were reported during the study, and no subject discontinued study drug or the study due to an AE.

Most subjects had at least 1 laboratory abnormality; most laboratory abnormalities were Grade 1 or 2 in severity. Grade 3 decreased hemoglobin and Grade 3 decreased neutrophils were reported in the subject who was hospitalized with Grade 3 gastrointestinal hemorrhage. Grade 3 increased serum glucose was reported in 2 subjects. Both subjects had a medical history of diabetes. No other Grade 3 or 4 chemistry or coagulation laboratory abnormalities were reported.

There were no notable changes from baseline in vital signs, and no pregnancies were reported during this study.

CONCLUSIONS: The conclusions from Study GS-US-367-4181 are as follows:

- Treatment with SOF/VEL/VOX for 12 weeks in subjects with chronic HCV infection who were previously treated with a SOF/VEL-containing regimen resulted in an SVR12 rate of 100.0%.
- Treatment with SOF/VEL/VOX for 12 weeks was generally safe and well tolerated. Few Grade 3 or higher AEs or SAEs were reported. No deaths or discontinuations due to AEs, and no clinically meaningful laboratory abnormalities were observed.