FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination in Subjects with Chronic HCV Infection who have received a Liver Transplant
Name of Test Drug:	Sofosbuvir/Velpatasvir Fixed-Dose Combination (SOF/VEL 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-342-2104
Phase of Development:	Phase 2
IND No.:	Not Applicable
EudraCT No.:	2016-000416-15
ClinicalTrials.gov Identifier:	NCT02781571
Study Start Date:	27 July 2016 (First Subject Screened)
Study End Date:	28 July 2017 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Xavier Forns, MD, PhD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Brian McNabb, MD Telephone: PPD Fax: PPD
Report Date:	06 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-342-2104
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination in Subjects with Chronic HCV Infection who have received a Liver Transplant

Investigators: Multicenter study

Study Centers: 15 Sites in Spain (8 sites), Switzerland (2 sites), and the United Kingdom (5 sites)

Publications: Agarwal K, Castells L, Mullhaupt B, Rosenberg WM, McNabb BL, Arterburn S, et al. Sofosbuvir/Velpatasvir for 12 Weeks in Genotype 1-4 HCV-Infected Liver Transplant Recipients [Poster 1069]. American Association for the Study of Liver Diseases (AASLD) 68th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting; 2017 October 20-October 24, Washington, DC. Hepatology 66: S1 2017 (suppl; abstract 1069)

Study Period:

27 July 2016 (First Subject Screened)
28 July 2017 (Last Subject Last Observation for the Primary Endpoint and Study)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To evaluate the efficacy of study treatment with sofosbuvir/velpatasvir fixed-dose combination (SOF/VEL FDC) for 12 weeks as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after cessation of study treatment regimen (SVR12)
- To evaluate the safety and tolerability of the study treatment regimen

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attained SVR at 4 weeks after cessation of the study treatment regimen (SVR4)
- To evaluate the kinetics of circulating HCV RNA during study treatment and after cessation of the study treatment regimen
- To evaluate the emergence of viral resistance to SOF and VEL during study treatment and after cessation of study treatment regimen

The exploratory objective was:

- To identify or validate genetic markers that were 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 provided their separate and specific consent

Methodology: This was a Phase 2, multicenter, open-label study that evaluated the safety, tolerability and efficacy of SOF/VEL FDC administered for 12 weeks in subjects with chronic HCV post-liver transplant. Approximately 80 subjects with chronic hepatitis C virus (HCV) infection who had received a liver transplant were planned for enrollment and all were to receive SOF/VEL FDC [400/100 mg] tablet once daily for 12 weeks.

Number of Subjects (Planned and Analyzed):
Planned: 80 subjects
Analyzed: 79 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were chronic HCV infected, post-liver transplant, male and non-pregnant/non-lactating female subjects without cirrhosis or with compensated cirrhosis, ages 18 years or older.

Duration of Treatment: Enrolled subjects received study treatment for 12 weeks. The end of study occurred at the posttreatment Week 4 visit for subjects with confirmed (2 consecutive HCV RNA measurements ≥ LLOQ) virologic failure who did not achieve SVR4; or at the posttreatment Week 12 visit in the case of patients who did achieve SVR4. Subjects with HCV RNA ≥ LLOQ at the posttreatment Week 12 visit were to have a confirmatory HCV RNA sample collected.

Test Product, Dose, Mode of Administration, and Batch No.: SOF/VEL was manufactured as a 400/100mg FDC tablet for oral administration. Subjects took 1 tablet once daily with or without food for 12 weeks by mouth.

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

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 2, 4, 8, and 12 while on treatment (or early termination, as applicable); and at posttreatment Weeks 4 and 12 (if applicable). Efficacy was evaluated using scheduled assessments of HCV RNA performed using COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Virologic Resistance: Baseline deep-sequencing analysis of HCV nonstructural (NS) protein 5A (NS5A), and NS5B coding regions was performed at baseline for all subjects. For all subjects with virologic failure, deep sequencing 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: A single PK blood sample was collected postdose at each on-treatment visit (excluding Day 1) for all subjects.

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 discontinuation of study drug for subjects in the Full Analysis Set (FAS). The estimate of the proportion of subjects with SVR12 and a 2-sided 95% exact CI based on the Clopper-Pearson method was provided for the overall "SOF/VEL 12 Weeks" group and by HCV genotype (1 total [and further broken down for 1a and 1b], 2, 3, 4, 5, and 6, as applicable).

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

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 20.0.

Other: No analyses of exploratory objectives were performed for this report.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Overall, the majority of subjects were male (81.0%), white (82.3%), and not Hispanic/Latino (97.5%), with a mean age of 62 years (range: 45–81 years). The mean baseline BMI value for subjects was 27.6 kg/m^2 (range: 18.3−38.6 kg/m^2), and 27.8% of the subjects had BMI ≥ 30 kg/m^2.

Of the 79 enrolled subjects, 47 subjects (59.5%) were treatment experienced and 14 subjects (17.7%) had cirrhosis. A total of 15 subjects (19.0%) subjects had HCV genotype 1a, 22 subjects (27.8%) subjects had HCV genotype 1b, 3 subjects (3.8%) subjects had HCV genotype 2, 35 subjects (44.3%) had HCV genotype 3, and 4 subjects (5.1%) subjects had HCV genotype 4. No subjects with genotype 5 or 6 HCV infection were enrolled. Mean (range) time since transplant was 8.7 (0.3-23.9) years. At baseline, all 79 subjects were on at least one immunosuppressant. The most common immunosuppressants were tacrolimus (55 subjects, 69.6%), mycophenolate mofetil (15 subjects, 19.0%), cyclosporine (11 subjects, 13.9%), and azathioprine (9 subjects, 11.4%). Mean (SD) ALT value was 60 (49.2) U/L and 27 of 79 subjects (34.2%) had ALT values > 1.5 × ULN. Mean (SD) CL_{cr} value was 77.2 (25.42) mL/min. The mean (SD) baseline HCV RNA value was 6.4 (0.55) log_{10} IU/mL and 61 subjects (77.2%) had baseline HCV RNA ≥ 800,000 IU/mL. Forty subjects (50.6%) had a non-CC (CT or TT) IL28B genotype.

Efficacy Results: SVR12 was achieved by 76 of 79 subjects (96.2%) of subjects following 12 weeks of treatment with SOF/VEL. The SVR12 rates were 93.3% for subjects with genotype 1a HCV infection, 95.5% for subjects with genotype 1b infection, 100% for subjects with genotype 2 infection, 97.1% for subjects with genotype 3 infection, and 100% for genotype 4 HCV infection.

Three subjects (3.8%) did not achieve SVR12: 2 subjects (2.5%) subjects had virologic failure and 1 subject (1.3%) subject discontinued therapy due to an AE of hyperglycemia and classified as other. Both of the subjects with virologic failure experienced relapse: 1 treatment-naïve subject with genotype 1a infection without cirrhosis who relapsed at posttreatment Week 4, and 1 treatment-experienced subject with genotype 3b infection without cirrhosis who relapsed at posttreatment Week 12.

Due to the high overall SVR rate, no meaningful differences between subgroups, including those defined by cirrhosis status or prior treatment experience were observed.

Virologic Resistance: Overall, 24 of 78 subjects (30.8%) subjects with a virologic outcome had NS5A resistance-associated variants (RAVs) at baseline. The SVR12 rate was 22 of 24 subjects (91.7%) for subjects with baseline NS5A RAVs who received 12 weeks of SOF/VEL, and 54 of 54 subjects (100.0%) without baseline NS5A RAVs. All six subjects with NS5B RAVs at baseline achieved SVR12. Of the 2 subjects who experienced virologic relapse, the subject with genotype 1a infection had NS5A K24R at baseline and relapse and treatment-emergent NS5A RAV L31V, the subject with genotype 3b had NS5A RAVs A30K+L30M at baseline and relapse and treatment-emergent NS5B RAV S282T.

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

Safety Results: Treatment with SOF/VEL was generally well tolerated by subjects. A total of 62 subjects (78.5%) experienced at least 1 AE. The 3 most frequently reported AEs were headache (19 subjects [24.1%]), fatigue (16 subjects [20.3%]), and cough (8 subjects [10.1%]). Grade 3 (severe) AEs were rare (3.8%), and no Grade 4 (life-threatening) AEs were reported. Three subjects (3.8%) had serious adverse events (SAEs; hepatocellular carcinoma, joint swelling, and *Pneumonia klebsiella*). None of the Grade 3 or Grade 4 AEs or SAEs were assessed by the investigator as treatment-related. One subject (1.4%) prematurely discontinued SOF/VEL on Day 7 due to a Grade 1 AE of hyperglycemia. No subjects experienced acute rejection during the study and no subjects required adjustment of immunosuppression to manage rejection or for suspected drug-drug interaction.

At least one graded laboratory abnormality occurred in 65 subjects (82.3%), and the majority (56 subjects [70.9%]) of laboratory abnormalities were Grade 1 or Grade 2. Grade 3 laboratory abnormalities occurred in 8 subjects (10.1%) and 1 (1.3%) subject had a Grade 4 laboratory abnormality. The Grade 3 laboratory abnormalities were Grade 3 increased glucose (3 subjects [3.8%], all with a history of diabetes), hyperuricemia (4 subjects [5.1%]), and proteinuria (1 subject [1.3%]). One subject had an isolated grade 4 lymphocyte decrease.

CONCLUSIONS: The conclusions from this study are as follows:

- Treatment with SOF/VEL for 12 weeks in liver transplant recipients with recurrent HCV infection resulted in an SVR12 rate of 96.2%.
- Treatment with SOF/VEL for 12 weeks was safe and well tolerated. There was a low incidence of Grade 3 or 4 AEs, SAEs, and discontinuations due to AE. There were no clinically meaningful laboratory abnormalities. There were no episodes of acute liver rejection.