FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 1 Relative Bioavailability and Food Effect Study of a Pediatric Oral Granule Formulation of SOF/VEL in Healthy Adult Subjects
Name of Test Drug:	Sofosbuvir/velpatasvir (SOF/VEL)
Dose and Formulation:	SOF/VEL 400/100 mg oral granules
Indication:	Hepatitis C Virus Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-342-1142
Phase of Development:	Phase 1
IND No.: **EudraCT No.:**	118605 Not Applicable
ClinicalTrials.gov Identifier:	Not Applicable
Study Start Date:	27 March 2017 (First Subject Screened)
Study End Date:	16 October 2017 (Last Subject Last Observation for the Primary Endpoint)
Principal or Coordinating Investigator:	Name: Troy Borema, MD Affiliation: PPD
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Report Date:	05 July 2018

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-342-1142
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 1 Relative Bioavailability and Food Effect Study of a Pediatric Oral Granule Formulation of SOF/VEL in Healthy Adult Subjects

Investigators: Troy Borema, MD

Study Centers: 1 site in United States (US)

Publications: At the time of this report, these data have not been published.

Study Period:

27 March 2017 (First Subject Screened)
16 October 2017 (Last Subject Last Observation for the Primary Endpoint)

Phase of Development: Phase 1

Objectives:

The primary objectives of this study were as follows:

- To evaluate the relative bioavailability (BA) of a pediatric oral granule formulation of sofosbuvir/velpatasvir (SOF/VEL) relative to the tablet formulation
- To evaluate the effect of concomitant food intake on the pharmacokinetics (PK) of a pediatric oral granule formulation of SOF/VEL

The secondary objectives of this study were as follows:

- To evaluate the safety and tolerability of a pediatric oral granule formulation of SOF/VEL following single-dose administration to healthy subjects
- To evaluate the palatability of a pediatric oral granule formulation of SOF/VEL

Methodology: This Phase 1, randomized, open-label, single-center, single-dose, multiple-period, crossover study evaluated the BA of pediatric oral granule formulations of SOF/VEL relative to the adult tablet formulation in healthy adult subjects. The safety and tolerability of the pediatric oral granule formulations of SOF/VEL, as well as the effect of food on its PK, were evaluated.

Following screening procedures and Day −1 assessments, a total of 112 eligible subjects were enrolled in 1 of 2 cohorts and randomized 1:1 to 1 of 2 treatment sequences (ie, AB or BA, ACG or CAG) within the cohort, as follows:

Cohort 1:

- **Treatment A**: Single dose tablet of SOF/VEL 400/100 mg (1 × 400/100 mg) administered orally under fasted conditions
- **Treatment B:** Single dose of fixed-dose combination 1 (FDC1) SOF/VEL oral granules 400/100 mg (8 × 50/12.5 mg packets) administered orally under fasted conditions

Adaptive Cohort 2 (referred to as Cohort 2 throughout):

- **Treatment A:** Single dose tablet of SOF/VEL 400/100 mg (1 × 400/100 mg) administered orally under fasted conditions
- **Treatment C:** Single dose of SOF/VEL FDC2 oral granules 400/100 mg (8 × 50/12.5 mg packets) administered orally under fasted conditions
- **Treatment G:** Single dose of SOF/VEL FDC2 oral granules 400/100 mg (8 × 50/12.5 mg packets) administered orally under fed conditions

Cohort 1 was enrolled first. Following evaluation of Cohort 1 PK data, Cohort 2 was enrolled.

Two formulations of SOF/VEL FDC oral granules were used in this study, as follows: FDC1 (Treatment B) and FDC2 (Treatments C and G). The active and inactive ingredients in FDC1 and FDC2 were identical; the only difference in the formulations was the amount of taste-mask coating, which was 20% for FDC1and 5% for FDC2.

There was also a protocol-specified option to enroll Adaptive Cohorts 3 and 4 to evaluate alternative formulations of SOF and VEL oral granules, and food effect, respectively. Adaptive Cohorts 3 and 4 were not introduced in the study. Evaluation of the food effect of SOF/VEL oral granules was added to Cohort 2.

Number of Subjects (Planned and Analyzed):

Planned: 194 subjects

Analyzed: 112 subjects (28 subjects each for AB, BA, ACG, and CAG treatment sequences)
PK Analysis Set: 28 subjects for each analyte of interest (VEL, SOF, GS-331007 and GS-566500)

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males and nonpregnant, nonlactating females, 18 to 45 years of age (inclusive) with body mass index (BMI) ≥ 19.0 and ≤ 30.0 kg/m2, 12-lead electrocardiogram (ECG) without clinically significant abnormalities, estimated creatinine clearance (CLcr, calculated using the Cockcroft-Gault equation) ≥ 90 mL/min, no significant medical history, and in good general health as determined by the investigator at the screening evaluation.

Duration of Treatment: All subjects received a single dose of study drug on Days 1 and 10; subjects in Cohort 2 also received a single dose of study drug on Day 19.

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

SOF/VEL 400/100 mg oral granules were administered orally, with liquid. The batch numbers of SOF/VEL oral granules administered in this study were:

- FDC1: FH1701B1
- FDC2: FH1701C1

Reference Therapy, Dose, Mode of Administration, and Batch No.:

SOF/VEL 400/100 mg tablets were administered orally. The batch number of SOF/VEL 400/100 mg tablets administered in this study was DU1404B1.

SOF/VEL 400/100 mg FDC2 oral granules were administered orally. The batch number of SOF/VEL FDC2 oral granules administered in this study was FH1701C1.

Criteria for Evaluation:

Efficacy: No efficacy assessments were performed for this study.

Pharmacokinetics: Intensive PK sampling occurred relative to dosing of SOF/VEL at the following time points on Days 1, 10, and 19 (Cohort 2 only), as applicable:

- 0 (≤ 5 min predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, 96, and 120 hours postdose

The following plasma PK parameters were calculated for SOF, its metabolites GS-331007 and GS-566500, and VEL, as applicable: AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, C_{max}, T_{max}, C_{last}, T_{last}, λ_z, CL/F, $t_{1/2}$, and V_z/F.**Safety:** Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital signs measurements, ECGs, and physical examinations.

Palatability: Palatability was assessed by questionnaire within 15 minutes after study drug administration on Days 1, 10, and 19 (Cohort 2 only).

Statistical Methods:

Efficacy: No efficacy analyses were performed for this study.

Pharmacokinetics: The primary analyses assessed the relative BA of SOF/VEL oral granule formulations compared to the tablet formulation and evaluated the effect of food on the PK of the SOF/VEL oral granule formulation. Analyses were conducted using mixed-effects statistical models with treatment, sequence, and treatment period as fixed effects, and subject within sequence as a random effect.

Plasma concentrations and PK parameters were listed and summarized by treatment using descriptive statistics. An analysis of variance (ANOVA) was performed for the natural logarithms of PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) for SOF and its metabolites (GS-331007 and GS-566500), and VEL. The test-to-reference ratios and associated 90% CIs

were calculated by taking the exponential of the point estimate and the corresponding lower and upper limits, which is consistent with the using a two 1-sided tests approach. For the formulation test, bioequivalence was concluded if the geometric least-squares mean (GLSM) ratios and corresponding 90% CIs for VEL and GS-331007 AUC_{inf}, AUC_{last}, and C_{max} were within the prespecified boundaries of 80% to 125%. For the evaluation of food effect, analyses were conducted for the primary PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) of VEL, SOF, GS-331007 and GS-566500.

Safety: The Safety Analysis Set included all enrolled subjects who received at least 1 dose of study drug. Safety data were analyzed by treatment and included all data collected on or 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.

Palatability: Categorical palatability data were collected on dosing days and summarized (number and percentage of subjects) using descriptive statistics by cohort and treatment sequence and overall by treatment.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 112 subjects were enrolled and randomized into the study across 4 treatment sequences, with 56 subjects in each cohort, and 28 subjects in each treatment sequence. All subjects were included in the SOF, GS-331007, GS-566500, and VEL PK analysis sets. All subjects received study drug and completed the study.

The majority of subjects were male (61.6%, 69 subjects), white (64.3%, 72 subjects), and were Hispanic or Latino (75%, 84 subjects). Subjects had a mean (SD) age of 34 (7.3) years (range: 19 to 45 years). Mean (SD) BMI was 25.7 (2.98) kg/m^2, and mean (SD) CL_{cr}, as calculated by Cockcroft-Gault, was 122.0 (21.15) mL/min at baseline.

Efficacy Results: Efficacy was not evaluated in this study.

Pharmacokinetics Results: The descriptive summary and statistical comparison of PK parameters for VEL, GS-331007, SOF and GS-566500 following the administration of single oral doses of SOF/VEL as a tablet (1× 400/100 mg tablet) and as oral granules (400/100 mg; 8 × 50/12.5 mg packets) as FDC1 or FDC2 under fasted or fed conditions are presented in the table below.

Statistical Comparison	GLSM Ratio (90% CI) AUC_{last} (h*ng/mL) (N=56)	GLSM Ratio (90% CI) AUC_{inf} (h*ng/mL) (N=56)	GLSM Ratio (90% CI) C_{max} (ng/mL) (N=56)
FDC1 Oral Granule Formulation versus Tablet Formulation, Fasted			
VEL	67.19 (60.23, 74.96)	67.47 (60.57, 75.16)	66.10 (59.23, 73.76)
GS-331007	94.80 (91.79, 97.91)	95.19 (92.24, 98.24)	118.00 (112.02, 124.30)
SOF	62.11 (55.98, 68.91)	62.97 (56.79, 69.82)	55.00 (48.19, 62.78)
GS-566500	71.63 (66.26, 77.44)	72.23 (66.95, 77.93)	70.13 (65.30, 75.31)
FDC2 Oral Granule Formulation versus Tablet Formulation, Fasted			
VEL	93.56 (82.00, 106.74)	94.01 (82.75, 106.81)	97.25 (85.83, 110.19)
GS-331007	102.26 (99.55, 105.05)	101.83 (99.29, 104.45)	109.43 (103.95, 115.20)
SOF	93.86 (86.41, 101.95)	94.01 (86.36, 102.33)	80.36 (71.91, 89.80)
GS-566500	97.46 (91.99, 103.27)	97.24 (91.92, 102.86)	95.61 (89.41, 102.23)
FDC2 Oral Granule Formulation, Fasted, versus FDC2 Oral Granule Formulation, Fed			
VEL	122.33 (101.35, 147.65)	121.16 (101.06, 145.25)	100.88 (84.94, 119.81)
GS-331007	103.80 (100.23, 107.51)	103.82 (100.45, 107.31)	63.59 (60.57, 66.76)
SOF	167.69 (150.62, 186.70)	164.11 (147.95, 182.03)	105.26 (91.41, 121.20)
GS-566500	154.39 (142.37, 167.43)	153.19 (141.65, 165.68)	118.91 (109.19, 129.49)

GLSM = geometric least-squares mean, FDC = fixed-dose combination
Two formulations of SOF/VEL oral granules (FDC1 and FDC2) were used in this study. The active and inactive ingredients in FDC1 and FDC2 were identical; the only difference in the formulations was the amount of taste-mask coating, which was 20% for FDC1and 5% for FDC2.

Administration of the SOF/VEL FDC1 oral granule formulation resulted in approximately 30% lower VEL exposure compared with the tablet formulation. GS-331007 exposures were bioequivalent between the tablet formulation and SOF/VEL FDC1 oral granules. The exposures of SOF and GS-566500 were also lower (approximately 30% to 45%) following administration of the FDC1 oral granule formulation compared with the tablet formulation.

As assessed by VEL and GS-331007 PK parameters, the SOF/VEL FDC2 oral granule formulation was bioequivalent to the SOF/VEL tablet formulation under fasted conditions with the GLSM and 90% CIs for VEL and GS-331007 AUC_{inf}, AUC_{last} and C_{max} contained within the prespecified bioequivalence boundaries of 80% to 125%. The AUC_{inf} and AUC_{last} of SOF, and the AUC_{inf}, AUC_{last} and C_{max} of GS-566500 were also bioequivalent between the SOF/VEL FDC2 oral granule formulation and the tablet formulation. The SOF C_{max} in the SOF/VEL FDC2 oral granule formulation was comparable to the tablet formulation with a GLSM ratio [90% CI] of 80.36% [71.91, 89.80].

Administration of SOF/VEL FDC2 oral granule formulation following a high fat meal resulted in an approximately 20% increase in VEL AUC, with no change in C_{max}, no change in GS-331007 AUC, with a 37% decrease in C_{max}, an approximately 65% increase in SOF AUC, with no change in C_{max}, and an approximately 53% increase in GS-566500 AUC, with a 19% increase in C_{max}. This effect of food on the PK of the SOF/VEL FDC2 oral granule formulation was similar

to that observed with the approved tablet formulation. As these are not considered clinically relevant changes in exposure, these data support administration of SOF/VEL FDC2 oral granules without regard to food.

Safety Results: No deaths, SAEs, Grade 2, 3 or 4 AEs, or AEs that led to study drug discontinuation were reported. All AEs were Grade 1 in severity. Constipation and headache (5 subjects [4.5%] each), and gastritis (2 subjects [1.8%]) were the only AEs reported in 2 or more subjects. One subject had a Grade 1 AE of headache assessed by the investigator to be related to study drug. A total of 73 subjects (65.2%) experienced a graded laboratory abnormality during the study. Most laboratory abnormalities were either Grade 1 or 2 in severity. A total of 5 subjects had Grade 3 laboratory abnormalities: 2 subjects (1.8%) had Grade 3 elevated LDL levels, both with elevated LDL (Grade 2) at Screening, and 3 female subjects (2.7%) had occult blood in the urine, all with menses at the time of urinalysis. There were no Grade 4 laboratory abnormalities. Overall, there were no notable changes in vital signs (heart rate, respiration rate, blood pressure, and temperature).

Palatability: Most subjects rated the SOF/VEL tablet (81.3%) and the SOF/VEL oral granule formulations (range: 85.7% to 96.4%) as palatable (ie, subjects chose either 'Neither dislike nor like', 'Like slightly', 'Like moderately', or 'Like very much').

CONCLUSIONS:

The conclusions from this final analysis of Study GS-US-342-1142 are as follows:

- As assessed by VEL and GS-331007 PK parameters, the SOF/VEL FDC2 oral granule formulation was bioequivalent to the SOF/VEL tablet formulation.
- The SOF/VEL FDC2 oral granule formulation can be administered without regard to food.
- All formulations of SOF/VEL were generally safe and well-tolerated following single-dose administration in healthy subjects.
- Most subjects rated the taste of the SOF/VEL FDC2 oral granule formulation as palatable, whether taken under fasted (85.7%) or fed (92.9%) conditions.