FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 1, Open-Label, Drug Interaction Study Evaluating the Effect of Sofosbuvir/Velpatasvir/GS-9857 Fixed-Dose Combination on the Pharmacokinetics of a Representative Hormonal Contraceptive Medication, Norgestimate/Ethinyl Estradiol
Name of Test Drug:	Sofosbuvir (SOF)/Velpatasvir (VEL)/Voxilaprevir (VOX; GS-9857) Fixed-Dose Combination (FDC) + VOX
Dose and Formulation:	SOF/VEL/VOX FDC (400/100/100 mg) tablet VOX 100 mg tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-367-1909
Phase of Development:	Phase 1
IND No.:	125751
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02533427
Study Start Date:	29 October 2015 (First Subject Screened)
Study End Date:	18 March 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Richard Robson, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Luisa Stamm, MD, PhD Telephone: PPD Fax: PPD
Report Date:	09 September 2016

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-367-1909

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

Title of Study: A Phase 1, Open-Label, Drug Interaction Study Evaluating the Effect of Sofosbuvir/Velpatasvir/GS-9857 Fixed-Dose Combination on the Pharmacokinetics of a Representative Hormonal Contraceptive Medication, Norgestimate/Ethinyl Estradiol

Investigators: Richard Robson, MD

Study Centers: 1 site in New Zealand

Publications: There are no publications at the time of this clinical study report (CSR).

Study Period:

29 October 2015 (First Subject Screened)
18 March 2016 (Last Subject Observation)
18 March 2016 (Last Subject Observation for the Primary Endpoint)

Phase of Development: Phase 1

Objectives:

The primary objectives of this study were as follows:

- To determine the effect of sofosbuvir (SOF)/velpatasvir (VEL)/voxilaprevir (VOX; GS-9857) + VOX on the pharmacokinetics (PK) of a representative hormonal contraceptive medication, norgestimate (NGM) 0.180 mg/0.215 mg/0.25 mg/ethinyl estradiol (EE) 0.025 mg (Ortho Tri-Cyclen® Lo)
- To assess the effect of NGM/EE on the PK of SOF/VEL/VOX+VOX

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of administration of SOF/VEL/VOX+VOX when given with a representative hormonal contraceptive medication, NGM/EE

Methodology: This Phase 1, open-label, single-center, fixed-sequence, multiple-dose study evaluated the PK, safety, and tolerability of SOF/VEL/VOX+VOX when administered with a representative hormonal contraceptive medication, NGM/EE, in healthy females of childbearing potential. Following screening procedures, eligible subjects were either enrolled in a 28-day lead-in period (Part A), during which they completed dosing with NGM/EE prior to initiation of Study Day 1 in Cycle 1 (Part B), or for subjects with a documented history of taking NGM/EE for at least 1 menstrual cycle, directly enrolled into Part B of the study within 28 days of screening.

If enrolled in the lead-in period, subjects were admitted to the study center on Day L –1 and confined until completion of NGM/EE dosing on Day L 1. Daily dosing with NGM/EE continued for 28 days. For Part B, all subjects returned to the study center on Study Day –1, where they remained until completion of NGM/EE dosing on Study Day 1. Subjects continued daily dosing with NGM/EE through Study Day 56 (2 full 28-day menstrual cycles). Subjects were administered SOF/VEL/VOX+VOX during Cycle 2 on Study Days 36 to 42. Subjects received a follow-up telephone call 7 to 10 days after the last dose of NGM/EE to monitor any adverse events (AEs) and concomitant medications.

Study drug was administered as shown in the table below.

	Part A	**Part B**			
	Lead-In	**Cycle 1**	**Cycle 2**		
Study Day	L 1-L 28	1-28	29-35	36-42	43-56
Cycle Day	1-28	1-28	1-7	8-14	15-28
NGM/EE	X	X	X	X	X
SOF/VEL/VOX+VOX				X	

Number of Subjects (Planned and Analyzed):

Planned: 15 subjects to obtain 12 evaluable subjects

Analyzed:

- 15 subjects enrolled in the lead-in period (Part A)
- 15 subjects in the Safety Analysis Set
- 15 subjects in each PK Analysis Set
- 15 subjects in each Pharmacodynamic (PD) Analysis Set

Diagnosis and Main Criteria for Inclusion: Eligible subjects were nonpregnant, nonlactating, nonsmoking, premenopausal females between 18 and 45 years of age (inclusive), with body mass index (BMI) from 19.0 to 30.0 kg/m^2 (inclusive), 12-lead electrocardiogram (ECG) without clinically significant abnormalities, normal renal function, creatinine clearance (CL_{cr}) ≥ 80 mL/min (calculated using the Cockcroft-Gault method), no significant medical history, and good general health.

Duration of Treatment: Up to 84 days treatment duration and 94 days study duration

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

Cycle 2: SOF/VEL/VOX FDC (1 × 400/100/100-mg tablet) + VOX (1 × 100-mg tablet) + NGM 0.180 mg/0.215 mg/0.250 mg/EE 0.025 mg once daily, administered orally in the morning with food

The test product batch numbers were ER1501B2 (SOF/VEL/VOX), DY1502B1 (VOX), and 15BM277B (NGM/EE).

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

Cycle 1: NGM 0.180 mg/0.215 mg/0.250 mg/EE 0.025 mg once daily, administered orally in the morning with food

The reference product batch number was 15BM277B (NGM/EE).

Criteria for Evaluation:

Efficacy: No efficacy analyses were performed.

Pharmacokinetics: Serial blood samples were collected predose and at prespecified time points through 24 hours postdose on Study Days 14 and 42. Plasma concentrations of NGM, norelgestromin (NGMN) and norgestrel (NG) (metabolites of NGM), and EE were determined and PK parameters were estimated (Study Days 14 and 42). Plasma concentrations of SOF, GS-566500 and GS-331007 (metabolites of SOF), VEL, and VOX were determined and PK parameters were estimated (Study Day 42).

Blood samples for luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were collected predose on Study Days 14 and 42. Blood samples for progesterone were collected predose on Study Days 21 and 49.

Safety: Safety assessments were performed at prespecified time points during the study and included monitoring of AEs, concomitant medications, clinical laboratory analyses, vital sign measurements, ECGs, and physical examinations.

Statistical Methods:

Efficacy: No efficacy analyses were performed.

Pharmacokinetics: Concentration data and PK parameters for SOF, GS-566500, GS-331007, VEL, VOX, NGM, NGMN, NG, and EE were listed by subject and summarized using descriptive statistics by treatment. Ninety percent confidence intervals (CIs) were constructed for the ratios of geometric means of NGM, NGMN, NG, and EE PK parameters (AUC_{tau}, C_{max}, C_{tau}) for the test treatment (NGM/EE + SOF/VEL/VOX+VOX) versus the reference treatment (NGM/EE alone), where possible. A lack of PK interaction was concluded if the resulting 90% CIs were within the interval of 70% to 143%. The PK parameters for SOF, GS-566500, GS-331007, VEL, and VOX were compared with historical data.

Descriptive summary statistics were presented for progesterone, LH, and FSH concentrations by treatment.

Safety: Adverse event data were listed by subject. Treatment-emergent AEs, AEs assessed as related to study drug or study procedure, serious adverse events (SAEs), and AEs that led to permanent discontinuation of study drug or study were summarized by treatment, system organ class, and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0.

Listings of individual subject laboratory results were provided. Laboratory results and changes from predose values for selected laboratory tests were summarized by treatment at scheduled visits. Vital signs, ECG data, and the incidence of treatment-emergent laboratory abnormalities were summarized by treatment.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 15 subjects were enrolled in the lead-in period (Part A) of the study. All 15 subjects continued to Part B, received study drug in Part B, were included in each PK and PD analysis set, and completed study drug and the study. Overall, the mean age was 24 years (range: 19 to 37). All 15 subjects were female, non-Hispanic or Latino, and the majority were white (14 subjects, 93.3%).

Efficacy Results: No efficacy analyses were performed.

Pharmacokinetics/Pharmacodynamics Results: Similar systemic exposures (AUC_{tau}, C_{max}, and C_{tau}) of NGMN and NG (active metabolites of NGM) and EE were observed following administration of NGM/EE alone or in combination with SOF/VEL/VOX+VOX. All 90% CIs of the GLSM ratios for AUC_{tau}, C_{max}, and C_{tau} were within the lack of PK alteration boundaries of 70% to 143%.

	Mean (%CV)		
	NGM/EE (Reference) (N = 15)	**NGM/EE + SOF/VEL/VOX+VOX (Test) (N = 15)**	**%GLSM Ratio (90% CI) Test/Reference**
NGMN PK Parameter			
AUC_{tau} (h•pg/mL)	13,757.4 (18.0)	14,690.4 (14.4)	107.36 (103.19, 111.69)
C_{max} (pg/mL)	1080.9 (20.5)	1162.2 (18.0)	107.71 (97.78, 118.65)
C_{tau} (pg/mL)	364.1 (21.1)	413.9 (17.8)	114.19 (107.40, 121.39)
NG PK Parameter			
AUC_{tau} (h•ng/mL)	41.1 (26.9)	47.3 (27.9)	115.14 (106.49, 124.50)
C_{max} (ng/mL)	2.0 (26.1)	2.3 (26.3)	115.02 (108.12, 122.37)
C_{tau} (ng/mL)	1.5 (24.5)	1.8 (29.6)	121.62 (110.85, 133.44)
EE PK Parameter			
AUC_{tau} (h•pg/mL)	835.2 (44.0)	871.4 (40.8)	105.43 (96.95, 114.66)
C_{max} (pg/mL)	68.4 (45.4)	80.6 (35.3)	121.06 (106.10, 138.12)
C_{tau} (pg/mL)	19.7 (55.0)	18.2 (57.1)	92.86 (82.55, 104.45)

Systemic exposures of VOX, VEL, SOF, GS-566500, and GS-331007 were within the ranges of exposures observed in historical data (reference treatments for healthy subjects receiving multiple-dose SOF/VEL/VOX+VOX in Studies GS-US-380-1999 and GS-US-367-1905).

Luteinizing hormone, FSH, and progesterone serum concentrations were similar across both treatments. Median concentrations of LH and FSH were lower than those expected for the ovulatory phase, consistent with decreased LH and FSH serum concentrations caused by oral hormonal contraceptives. Progesterone median values were substantially lower than those expected for the luteal phase, consistent with absence of ovulation.

Safety Results: Overall, 14 of 15 subjects (93.3%) experienced at least 1 AE. All AEs were Grade 1 or 2 in severity; no Grade 3 or 4 AEs, no SAEs, no AEs leading to permanent discontinuation of study drug or study, and no deaths were reported during the study. Headache was reported at similar frequencies during both treatments (each 40.0%) while gastrointestinal disorders were more frequently reported during treatment with NGM/EE + SOF/VEL/VOX+VOX (66.7%) compared with NGM/EE alone (20.0%).

Overall, 13 of 15 subjects (86.7%) experienced at least 1 laboratory abnormality. Most laboratory abnormalities were Grade 1 in severity, and no Grade 4 laboratory abnormalities were reported. Grade 3 laboratory abnormalities were reported for 2 subjects (13.3%) and included increased ALT, increased LDL, and occult blood in the urine.

No notable changes in vital signs or clinically significant ECG abnormalities were observed.

CONCLUSIONS: The conclusions from this study are as follows:

- No PK interaction was observed following administration of SOF/VEL/VOX+VOX with NGM/EE.
- The exposures of VOX, VEL, SOF, GS-566500, and GS-331007 were within the ranges of exposures observed in historical data.
- No loss of contraceptive efficacy is expected upon coadministration of SOF/VEL/VOX with oral contraceptives.
- The coadministration of SOF/VEL/VOX+VOX with NGM/EE was generally safe and well tolerated.