FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 1 Relative Bioavailability and Food Effect Study of a Pediatric Oral Granule Formulation of Ledipasvir/Sofosbuvir in Healthy Adult Subjects
Name of Test Drug:	Ledipasvir (LDV)/sofosbuvir (SOF) oral granules
Dose and Formulation:	Ledipasvir/sofosbuvir 90/400 mg (8 × 11.25/50 mg units, LDV/SOF oral granules)
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Study No.:	GS-US-337-2091
Phase of Development:	Phase 1
IND No.:	115268
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	Not Applicable
Study Start Date:	24 May 2016 (First Subject Screened)
Study End Date:	27 July 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Stuart I Harris, MD PhD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Kathryn Kersey, MSc Telephone: PPD Fax: PPD
Report Date:	22 February 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-337-2091
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 Ledipasvir/Sofosbuvir in Healthy Adult Subjects

Investigators: Stuart I Harris, MD PhD

Study Centers: Single center in the United States (US)

Publications: At the time of this report, the results of this study have not been published.

Study Period:

24 May 2016 (First Subject Screened)
27 July 2016 (Last Subject Observation)

Phase of Development: Phase 1

Objectives:

The primary objectives of this study were as follows:

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

The secondary objectives of this study were as follows:

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

Methodology: This Phase 1, randomized, open-label, single-center, single-dose, 3-period, crossover study evaluated the bioavailability of a pediatric oral granule formulation of LDV/SOF relative to the adult tablet formulation in healthy adult subjects. The safety and tolerability of the pediatric oral granule formulation of LDV/SOF and the effect of food on its PK were also evaluated.

Following screening procedures and Day −1 assessments, a total of 42 eligible subjects were randomized to 1 of 6 treatment sequences using a Williams design, with a 9-day washout interval between each treatment, as follows:

- **Treatment A:** Single dose of LDV/SOF tablet (90/400 mg; 1 × 90/400 mg tablet) administered orally under fasted conditions
- **Treatment B:** Single dose of LDV/SOF oral granules (90/400 mg; 8 × 11.25/50 mg units) administered orally under fasted conditions
- **Treatment C:** Single dose of LDV/SOF oral granules (90/400 mg; 8 × 11.25/50 mg units) administered orally under fed conditions

Number of Subjects (Planned and Analyzed):
Planned: 42 subjects
Analyzed: 42 subjects (All Randomized Analysis, PK Analysis, and Safety Analysis Sets)

Diagnosis and Main Criteria for Inclusion: Eligible subjects were healthy male and nonpregnant, nonlactating female subjects, 18 to 45 years of age (inclusive), with a body mass index (BMI) of ≥ 19.0 and ≤ 30.0 kg/m^2, 12-lead electrocardiogram (ECG) without clinically significant abnormalities, estimated creatinine clearance (CL_{cr}, 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 which was performed no more than 28 days prior to the scheduled first dose of study drug.

Duration of Treatment: Subjects received single doses of study drug on Days 1, 11, and 21.

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

- Treatment B: LDV/SOF oral granules (90/400 mg; 8 × 11.25/50 mg units) were administered orally as a single dose under fasted conditions.
- Treatment C: LDV/SOF oral granules (90/400 mg; 8 × 11.25/50 mg units) were administered orally as a single dose under fed conditions.

The batch number of LDV/SOF oral granules administered in this study was EL1601C2.

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

- Treatment A: LDV/SOF tablet (90/400 mg; 1 × 90/400 mg tablet) was administered orally as a single dose under fasted conditions.
- Treatment B: LDV/SOF oral granules (90/400 mg; 8 × 11.25/50 mg units) were administered orally as a single dose under fasted conditions.

The batch number of LDV/SOF oral granules administered in this study was EL1601C2.

The lot number of LDV/SOF tablets administered in this study was DK1303B1.

Criteria for Evaluation:

Efficacy: No efficacy assessments were performed for this study.

Pharmacokinetics: Serial PK sampling occurred relative to dosing of LDV/SOF on the following time points on Days 1, 11, and 21:

- Predose (≤ 5 minutes), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, 120, and 144 hours postdose

The following single-dose plasma PK parameters of LDV, SOF, and SOF metabolites (GS-566500 and GS-331007) were calculated: AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, C_{max}, T_{max}, C_{last}, T_{last}, λ_z, CL/F, V_z/F, and $t_{1/2}$ as appropriate.

Safety: Safety was assessed during the study by clinical laboratory tests, physical examinations including vital signs and ECG at various time points during the study, and by documentation of adverse events (AEs) and concomitant medications throughout the study.

Palatability: Palatability was assessed by a questionnaire administered to study subjects within 15 minutes after study drug administration.

Statistical Methods:

Efficacy: No efficacy assessments were performed for this study.

Pharmacokinetics: The primary analysis was to assess the relative bioavailability of a pediatric oral granule formulation of LDV/SOF relative to the approved tablet formulation (formulation test) and to evaluate the effect of concomitant food intake on PK of the oral granule formulation of LDV/SOF (food effect test). Analyses were conducted using mixed-effects statistical models with fixed effects of treatment, period, and sequence and random subject effect.

Plasma concentrations and PK parameters were listed and summarized using descriptive statistics by treatment for LDV, SOF, and SOF metabolites (GS-566500 and GS-331007). An analysis of variance (ANOVA) was performed for the natural logarithms of PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) for LDV, SOF, GS-566500, and GS-331007. The ANOVA model included fixed effects for sequence, period, and treatment. The subjects were viewed as a random sample. The 2 one-sided test procedure was performed on the ratio of the central value of the test treatment to the central value of the reference treatment. This was done via a 90% CI for the ratio obtained in the framework of the ANOVA for the logarithms. The endpoints of the CI were obtained by exponentiation of the endpoints of the 90% CI for the difference of logarithm means.

For the formulation test, bioequivalence between the test treatment (oral granule formulation [Treatment B]) and the reference treatment (tablet formulation [Treatment A]) was concluded if the 90% CI from the analyses of the logarithms of LDV and GS-331007 AUC_{last}, AUC_{inf}, and C_{max} were within the 80% to 125% range. In accordance with the FDA guidance for Bioavailability and Bioequivalence Studies, the primary PK analysis set excluded subjects who had predose concentrations > 5% of C_{max}. A sensitivity analysis was also performed which included PK data from all subjects, in all periods, of the study. Exploratory analyses were conducted for the PK parameters of SOF and GS-566500.

For the food effect test, PK equivalence between the test treatment (oral granule formulation administered under fed conditions [Treatment C]) and the reference treatment (oral granule formulation administered under fasted conditions [Treatment B]) was concluded if the 90% CI

from the analyses of the logarithms of AUC_{last} and AUC_{inf} were within the 80% to 125% range for GS-331007 and within the 70% to 143% range for LDV. In addition, exploratory analyses may have been conducted on the natural logarithms of C_{max} for GS-331007 and LDV, as well as the PK parameters for SOF and GS-566500.

Safety: The Safety Analysis Set included all randomized subjects who received at least 1 dose of study drug. Treatment-emergent AEs (hereafter referred to as AEs) were summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19. All AEs, serious adverse events (SAEs), and AEs leading to discontinuation of study drug were listed by subject. The frequency of subjects who experienced AEs, SAEs, and discontinuations were summarized by treatment. The AEs were also summarized by relationship to study drug and severity by treatment. The incidence of treatment-emergent graded laboratory abnormalities was summarized by treatment. Vital signs and clinical laboratory results and changes from predose were summarized by treatment sequence. Individual data for vital signs measurements and 12-lead safety ECG results (ie, normal, not clinically significant abnormal, and clinically significant abnormal) were listed by subject.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: All 42 randomized subjects received study drug and completed the study and are included in the Safety and PK Analysis Sets.

The majority of subjects were male (71.4% male, 30 subjects), white (54.8% white, 23 subjects), and of Hispanic or Latino ethnicity (66.7% Hispanic or Latino, 28 subjects). Subjects had a mean (SD) age of 29 (6.0) years (range: 19 to 44 years), mean (SD) BMI of 25.0 (2.81) kg/m^2, and mean (SD) $CL_{cr,}$ as calculated by Cockcroft-Gault, of 117.17 (21.142) mL/min at baseline.

Efficacy Results: No efficacy assessments were performed for this study.

Pharmacokinetic Results: The descriptive summary and statistical comparison of PK parameters for LDV, SOF, GS-566500, and GS-331007 following the administration of single oral doses of LDV/SOF as a tablet (90/400 mg; 1 × 90/400 mg tablet) and as oral granules (90/400 mg; 8 × 11.25/50 mg units) under fasted conditions are presented in the table below.

PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI)
	Treatment A	Treatment B	
	LDV/SOF Tablet Formulation (1 × 90/400 mg) fasted (Reference)	LDV/SOF Oral Granule Formulation (8 × 11.25/50 mg units) fasted (Test)	LDV/SOF Oral Granules vs LDV/SOF FDC Tablet
LDV (N = 42 reference/N = 39 test)[a]			
AUC_{last} (ng*h/mL)	7362.3 (48.3)	6242.5 (40.7)	87.76 (77.94, 98.82)
AUC_{inf} (ng*h/mL)	8467.5 (54.4)	7088.4 (46.3)	88.36 (78.43, 99.54)
C_{max} (ng/mL)	261.3 (43.5)	214.8 (38.2)	84.59 (74.69, 95.81)
GS-331007 (N = 42 reference/N = 42 test)			
AUC_{last} (ng*h/mL)	11146.3 (26.9)	11525.8 (26.3)	103.14 (96.71, 110.00)
AUC_{inf} (ng*h/mL)	11720.0 (26.1)	12095.0 (24.4)	103.64 (98.48, 109.07)
C_{max} (ng/mL)	833.9 (23.6)	951.9 (27.0)	112.81 (104.12, 122.22)
SOF (N = 42 reference/N = 42 test)			
AUC_{last} (ng*h/mL)	1559.8 (40.5)	1676.9 (43.7)	102.13 (87.16, 119.67)
AUC_{inf} (ng*h/mL)	1580.8 (40.2)	1684.1 (43.5)	101.60 (86.67, 119.10)
C_{max} (ng/mL)	1221.0 (38.5)	1266.7 (46.6)	95.98 (78.00, 118.11)
GS-566500 (N = 42 reference/N = 42 test)			
AUC_{last} (ng*h/mL)	1846.6 (31.4)	1952.9 (33.5)	100.59 (88.89, 113.83)
AUC_{inf} (ng*h/mL)	1894.9 (30.8)	2009.7 (33.0)	101.37 (90.17, 113.96)
C_{max} (ng/mL)	475.1 (33.9)	511.3 (34.9)	103.04 (91.06, 116.60)

a Subjects PPD PPD and PPD in Treatment B were excluded since their LDV predose plasma concentration was > 5% of C_{max}.

In accordance with the FDA guidance for Bioavailability and Bioequivalence Studies, the primary PK analysis set excluded the LDV data from 3 subjects who had predose LDV concentrations > 5% of C_{max} in the LDV/SOF oral granule formulation under fasted conditions (Treatment B).

Data from the primary analysis demonstrated modestly lower LDV exposure (approximately 12%) in the LDV/SOF oral granules compared with the LDV/SOF tablet formulation, with the lower bounds of the 90% CI being approximately 75% to 78%. When assessed relative to the previously established maximum PD effect (E_{max}) model, LDV plasma exposures continued to reside in the near-maximal portion of the exposure-response curve. Considering the lack of an exposure/efficacy relationship for LDV, these modest decreases in exposure are not considered to be clinically relevant.

GS-331007 exposure in the LDV/SOF oral granules was bioequivalent to the LDV/SOF tablets. Exploratory analyses showed that the AUC and C_{max} of SOF and GS-566500 were also

comparable between the 2 formulations, with the 90% CIs for the %GLSM ratios contained within the range of 78% to 120% and 89% to 117%, respectively. Taken together, these results support further evaluation of LDV/SOF oral granule formulation.

The descriptive summary and statistical comparison of PK parameters for LDV, SOF, GS-566500, and GS-331007 following the administration of single oral doses of LDV/SOF as oral granules (90/400 mg; 8 × 11.25/50 mg units) under fasted and fed conditions are presented in the table below.

PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI)
	Treatment B	Treatment C	
	LDV/SOF Oral Granule Formulation (8 × 11.25/50 mg units) fasted (Reference)	LDV/SOF Oral Granule Formulation (8 × 11.25/50 mg units) fed (Test)	LDV/SOF Oral Granules High-Fat Meal vs Fasted
LDV (N = 39 reference/N = 40 test)[a,b]			
AUC_{last} (ng*h/mL)	6242.5 (40.7)	5149.6 (26.2)	87.62 (79.65, 96.39)
AUC_{inf} (ng*h/mL)	7088.4 (46.3)	5748.3 (29.0)	87.06 (78.95, 96.00)
C_{max} (ng/mL)	214.8 (38.2)	159.8 (28.9)	78.15 (71.26, 85.71)
GS-331007 (N = 42 reference/N = 42 test)			
AUC_{last} (ng*h/mL)	11525.8 (26.3)	11653.6 (18.9)	103.12 (97.61, 108.94)
AUC_{inf} (ng*h/mL)	12095.0 (24.4)	12220.6 (18.3)	102.26 (98.18, 106.52)
C_{max} (ng/mL)	951.9 (27.0)	583.1 (24.2)	62.01 (56.90, 67.59)
SOF (N = 42 reference/N = 42 test)			
AUC_{last} (ng*h/mL)	1676.9 (43.7)	2577.2 (33.1)	166.11 (145.00, 190.30)
AUC_{inf} (ng*h/mL)	1684.1 (43.5)	2597.7 (32.9)	166.18 (145.56, 189.71)
C_{max} (ng/mL)	1266.7 (46.6)	1236.3 (49.0)	100.32 (84.83, 118.65)
GS-566500 (N = 42 reference/N = 42 test)			
AUC_{last} (ng*h/mL)	1952.9 (33.5)	2931.7 (19.1)	163.23 (144.62, 184.23)
AUC_{inf} (ng*h/mL)	2009.7 (33.0)	2988.8 (18.7)	160.65 (143.40, 179.99)
C_{max} (ng/mL)	511.3 (34.9)	593.9 (31.0)	122.12 (108.28, 137.73)

a Subjects PPD PPD and PPD in Treatment B were excluded since their LDV predose plasma concentration was > 5% of C .

b Subjects PPD and PPD in Treatment C were excluded since their LDV predose plasma concentration was > 5% of C_{max}.

With regards to food effect, the primary analysis demonstrated that the prespecified equivalence criteria for AUC of LDV (70% to 143%) and GS-331007 (80% to 125%) after administration of LDV/SOF oral granules under fed conditions compared with fasted conditions were met. Exploratory analyses showed the administration of the oral granules formulation under fed conditions compared with fasted conditions resulted in < 2-fold increase in AUC of SOF, and AUC and C_{max} of GS-566500, with no alteration in SOF C_{max}. These observations are consistent

with historical data (Study GS-US-337-0101) on the effect of a high-fat/high-calorie meal on the LDV/SOF tablet formulation, which can be administered without regard to food. Taken together, these results indicate that the oral granule formulation of LDV/SOF can be administered without regard to food.

Safety Results: No deaths, SAEs, Grade 3 or 4 AEs, or AEs that led to study drug discontinuation were reported. All AEs were Grade 1 or 2 in severity. Headache and constipation were the only AEs reported in > 1 subject. One subject receiving LDV/SOF oral granule formulation under fasted conditions experienced Grade 1 AEs of abdominal pain and diarrhea that were assessed related to study drug by the investigator. A total of 18 subjects (42.9%) experienced a graded laboratory abnormality during the study. Most laboratory abnormalities were either Grade 1 or 2 in severity. One subject with a medical history of elevated lipase or amylase values had a Grade 4 laboratory abnormality of increased lipase 10 days after administration of the second dose of LDV/SOF (1 day prior to the third dose) that was asymptomatic and no action was taken. Repeat assessments 2 and 21 days later revealed Grade 3 increased lipase with no associated AEs. Overall, there were no notable changes in vital signs (temperature, pulse, systolic blood pressure, diastolic blood pressure, and respiration rate), and no clinically significant ECG abnormalities were observed.

Palatability Results: Most subjects rated the taste of the granule formulation as palatable whether taken with (92.9%) or without (95.2%) food; the tablet formulation was rated as palatable by 92.9% of subjects.

CONCLUSIONS:

The conclusions of this study are as follows:

- Relative to the LDV/SOF tablet, no clinically significant differences in the PK of LDV/SOF oral granule formulation were observed, supporting further clinical evaluation of this formulation in patients.
- The LDV/SOF oral granule formulation can be administered without regard to food.
- The existing LDV/SOF tablet formulation (1 × 90/400-mg tablet) and the LDV/SOF oral granule formulation (8 × 11.25/50 mg units) were generally well tolerated.