FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 1 Relative Bioavailability and Food Effect Study of a Pediatric Granules Formulation of Ledipasvir/Sofosbuvir in Healthy Adult Subjects
Name of Test Drug:	Ledipasvir (LDV, GS-5885)/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-337-1115
Phase of Development:	Phase 1
IND No.:	115268
EudraCT No.:	2015-003570-32
ClinicalTrials.gov Identifier:	Not Applicable.
Study Start Date:	13 May 2015 (First Subject Screened)
Study End Date:	30 June 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Audrey E. Martinez, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Bittoo Kanwar, MD Telephone: PPD Fax: PPD
Report Date:	21 December 2015

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-337-1115
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 Granules Formulation of Ledipasvir/Sofosbuvir in Healthy Adult Subjects

Investigators: Audrey E. Martinez, MD

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

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

Study Period:

13 May 2015 (First Subject Screened)
30 June 2015 (Last Subject Observation)
28 June 2015 (Last Subject 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 of a pediatric granules formulation of ledipasvir/sofosbuvir (LDV/SOF) relative to tablet formulation in healthy subjects.
- To evaluate the effect of concomitant food intake on the pharmacokinetics (PK) of a pediatric granules formulation of LDV/SOF.

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of a pediatric granules formulation of LDV/SOF following single-dose administration in healthy subjects.

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

A total of 42 subjects were randomized and enrolled to 1 of 6 treatment sequences, with a 9-day washout interval between each treatment, as follows:

- **Treatment A:** Single dose of LDV/SOF (90/400 mg) (1 × 90/400 mg tablet) administered orally under fasted conditions

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

Treatment Sequence	Day 1	Days 2-10	Day 11	Days 12-20	Day 21
ABC (n = 7)	A	Washout	B	Washout	C
ACB (n = 7)	A	Washout	C	Washout	B
BCA (n = 7)	B	Washout	C	Washout	A
BAC (n = 7)	B	Washout	A	Washout	C
CBA (n = 7)	C	Washout	B	Washout	A
CAB (n = 7)	C	Washout	A	Washout	B

Following screening and Day -1 procedures, eligible subjects were confined to the clinic from Day -1 until completion of procedures on Day 27. All subjects were contacted by telephone 7 to 10 days after the last dose of study drug, including subjects who discontinued the study early, to assess any adverse events (AEs) and concomitant medication usage.

Each assigned study treatment was administered in the morning at approximately the same time each day with 240 mL of water. Treatments A and B were administered under fasted conditions (no food or liquids, except water for at least 10 hours prior to dosing), Treatment C was administered with 240 mL of water under fed conditions (no food or liquids, except water for at least 10 hours prior to breakfast). A meal was initiated 30 minutes prior to study drug administration and should have been completed in 30 minutes or less. The study drug was administered at or within 5 minutes after the subjects completing a standardized high-calorie/high-fat meal (approximately 1000 calories, approximately 50% fat).

The evening prior to the days of PK assessments (Days 1, 11, and 21), subjects underwent an overnight fast (no food or liquids, except water, for at least 10 hours prior to dosing or breakfast per treatment). Following dosing (Treatments A and B: fasted; Treatment C: fed), subjects were restricted from food intake until after collection of the 4-hour blood draw, relative to study drug dosing. On days of PK assessments (Days 1, 11, and 21), other than the water provided with dosing, water and other fluids were withheld for 1 hour before and 2 hours after study drug administration. Water may have been freely consumed by all subjects following the 2-hour blood draw for the remainder of the collection period. A meal (standardized lunch) was provided to subjects after the 4-hour postdose blood draw.

Number of Subjects (Planned and Analyzed):
Planned: 42
Analyzed:

All Randomized Analysis Set: 42 subjects

PK Analysis Set: 42 subjects

Safety Analysis Set: 42 subjects

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) ≥ 19.0 and ≤ 30.0 kg/m^2, had either a normal 12-lead electrocardiogram (ECG) or an ECG with abnormalities that were considered clinically insignificant by the investigator, normal renal function, no significant medical history, and be in good general health as determined by the investigator at screening evaluation performed no more than 28 days prior to the scheduled first dose.

Duration of Treatment: Subjects were treated for 21 days on Days 1, 11, and 21 with a 9-day washout interval between each treatment.

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

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

The lot number of LDV/SOF (90/400 mg) (8 × 11.25/50 mg units, LDV/SOF oral granules) administered in this study was EL1502C1.

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

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

The lot number of LDV/SOF (90/400 mg) (8 × 11.25/50 mg units, LDV/SOF oral granules) administered in this study was EL1502C1.

The lot number of LDV/SOF (90/400 mg) (1 × 90/400 mg tablet) administered in this study was DK1208B1R.

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 days and time points:

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, and $t_{1/2}$ as appropriate.

Safety: Safety assessments included monitoring of AEs and concomitant medications, physical examinations, vital sign measurements, clinical laboratory tests, and 12-lead ECGs.

Further details on study assessments are provided in the clinical study protocol (Appendix 16.1.1).

Statistical Methods:

All tables, figures, and listings produced for this study are provided in Section 15.1 and Appendix 16.2. Further details on statistical methods are provided in the statistical analysis plan (Appendix 16.1.9).

Efficacy: No efficacy assessments were performed for this study.

Pharmacokinetics: The primary analysis was to assess the relative bioavailability of a pediatric granules formulation of LDV/SOF relative to tablet formulation, and to evaluate the effect of concomitant food intake on PK of a pediatric granules formulation of LDV/SOF. 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, 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, and SOF metabolites (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 tests 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 formulation test, bioequivalence between the test treatment (Treatment B) and the reference treatment (Treatment A) were 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 0.80 to 1.25 range. Exploratory analyses were conducted for the PK parameters of SOF and GS-566500. For food effect test, PK equivalence between the test treatment (Treatment C) and the reference treatment (Treatment B) were concluded if the 90% CI from the analyses of the logarithms of AUC_{last} and AUC_{inf} were within the 0.80 to 1.25 range for GS-331007 and within the 0.70 to 1.43 range for LDV. In addition, the 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. Additional analyses may have been performed if useful and appropriate.

Safety: All randomized 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 were listed by subject and treatment and summarized by treatment and 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. Adverse events were coded using the Medical Dictionary for Regulatory Activities, Version 18.0.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 42 subjects were enrolled and randomized, included in the Safety and PK Analysis Sets, and all subjects completed the study.

The mean age was 36 years with a range of 24 to 45 years and sex was evenly distributed in the study (50% of subjects were male). The majority of subjects were white (92.9%) and Hispanic or Latino (97.6%). The mean (SD) baseline BMI was 26.6 (2.11) kg/m^2.

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

Pharmacokinetic Results: Statistical comparisons of the PK parameters for LDV, SOF, GS-566500, and GS-331007 following the administration of single doses of LDV/SOF (90/400 mg) fixed-dose combination (FDC) tablet and LDV/SOF (90/400 mg) (8 × 11.25/50 mg units) pediatric oral granules under fasted conditions are presented in the table below.

PK Parameter	GLSM		%GLSM Ratio (90% CI)
	LDV/SOF FDC Tablet (Reference) (N = 42)	LDV/SOF Oral Granules (Test) (N = 40)[a]	LDV/SOF Oral Granules vs LDV/SOF FDC Tablet
SOF			
AUC_{last} (h·ng/mL)	1411.75	1257.88	89.10 (81.65, 97.23)
AUC_{inf} (h·ng/mL)	1417.85	1264.13	89.16 (81.73, 97.26)
C_{max} (ng/mL)	1082.23	1064.00	98.32 (87.89, 109.98)
GS-566500			
AUC_{last} (h·ng/mL)	1431.12	1369.13	95.67 (89.17, 102.64)
AUC_{inf} (h·ng/mL)	1482.94	1419.16	95.70 (89.38, 102.46)
C_{max} (ng/mL)	354.86	363.97	102.57 (95.81, 109.81)
GS-331007			
AUC_{last} (h·ng/mL)	10,418.46	10,770.39	103.38 (99.63, 107.27)
AUC_{inf} (h·ng/mL)	10,958.37	11,301.92	103.13 (99.50, 106.90)
C_{max} (ng/mL)	826.84	953.41	115.31 (109.31, 121.64)
LDV			
AUC_{last} (h·ng/mL)	7939.81	4839.98	60.96 (54.72, 67.91)
AUC_{inf} (h·ng/mL)	9257.04	5726.54	61.86 (55.38, 69.10)
C_{max} (ng/mL)	274.41	163.37	59.53 (52.71, 67.24)

a Subjects PPD and PPD were excluded from the PK analysis for SOF, GS-566500, GS-331007, and LDV.
Source: Section 15.1, Table 5

Similar plasma exposures of SOF and its metabolites, GS-566500 and GS-331007, were achieved upon administration of LDV/SOF FDC and LDV/SOF oral granules. The 90% CI of the GLSM ratios for the AUC and C_{max} of SOF, GS-566500, and GS-331007 were within the bioequivalence bounds of 80% to 125%. The AUC and C_{max} of LDV within LDV/SOF oral granules were approximately 38% to 40% lower when compared with LDV/SOF FDC; the predefined bioequivalence criteria were not met and as such the oral granule formulation is not considered bioequivalent to the FDC tablet formulations.

Statistical comparisons of the PK parameters for LDV, SOF, GS-566500, and GS-331007 following the administration LDV/SOF (90/400 mg) (8 × 11.25/50 mg units) pediatric oral granules in the fasted state compared with the fed state (high-fat meal) are presented in the table below.

PK Parameter	GLSM		%GLSM Ratio (90% CI)
	LDV/SOF Oral Granules Fasted (Reference) (N = 40)[a]	LDV/SOF Oral Granules + High-Fat Meal (Test) (N = 42)	High-Fat Meal vs Fasted
SOF			
AUC_{last} (h·ng/mL)	1258.29	2726.80	216.71 (198.60, 236.46)
AUC_{inf} (h·ng/mL)	1264.60	2736.79	216.42 (198.42, 236.04)
C_{max} (ng/mL)	1072.08	1598.65	149.12 (129.31, 171.95)
GS-566500			
AUC_{last} (h·ng/mL)	1369.49	2670.58	195.01 (179.77, 211.53)
AUC_{inf} (h·ng/mL)	1419.05	2727.53	192.21 (177.64, 207.97)
C_{max} (ng/mL)	364.66	590.21	161.85 (146.62, 178.67)
GS-331007			
AUC_{last} (h·ng/mL)	10,807.19	11,999.48	111.03 (106.44, 115.83)
AUC_{inf} (h·ng/mL)	11,341.78	12,640.46	111.45 (106.89, 116.21)
C_{max} (ng/mL)	958.21	537.61	56.11 (52.28, 60.21)
LDV			
AUC_{last} (h·ng/mL)	4786.45	6451.57	134.79 (123.55, 147.05)
AUC_{inf} (h·ng/mL)	5657.42	7553.43	133.51 (122.31, 145.75)
C_{max} (ng/mL)	162.23	215.97	133.12 (118.97, 148.96)

a Subjects PPD and PPD were excluded from the PK analysis for SOF, GS-566500, GS-331007, and LDV.
Source: Section 15.1, Table 5

Administration of LDV/SOF oral granules with a high-fat meal increased exposures of SOF (AUC_{last} and AUC_{inf} increased by 116% to 117% and C_{max} by 49%) and GS-566500 (AUC_{last} and AUC_{inf} increased by 92% to 95% and C_{max} by 62%) compared with administration in the fasted state. For GS-331007, a 44% lower C_{max} was observed with no change in AUC. The 90% CI of the GLSM ratios for the AUC of GS-331007 remained within the lack of PK alteration bounds of 70% to 143%. Since the AUC parameters of GS-331007 met the PK equivalence criteria, the effect of food on GS-331007 PK was not considered clinically significant. For LDV, administration of LDV/SOF oral granules with a high-fat meal increased LDV AUC_{last} and AUC_{inf} by 34% to 35% and C_{max} by 33% compared with administration in the fasted state.

These results were consistent with the data from a previous Phase 1 study with LDV/SOF (90/400 mg) FDC (Study GS-US-337-0101), which demonstrated that LDV/SOF could be administered without regard to food.

Safety Results: No deaths, serious adverse events (SAEs), pregnancies, or discontinuations of study drug due to an AE were reported.

The only AE reported in > 1 subject was syncope (2 subjects). All AEs were Grade 1 in severity. There were no AEs considered related to study drug. No Grade 4 laboratory abnormalities were observed. One Grade 3 laboratory abnormality of occult blood (3+) was observed in a 33-year old female subject on Day 21. Grade 2 laboratory abnormalities were observed in 3 subjects (high total cholesterol and high low-density lipoprotein cholesterol); all other laboratory abnormalities were Grade 1. There were no clinically significant trends in vital signs, 12-lead ECGs, or laboratory abnormalities.

CONCLUSIONS:

The conclusions of this study are as follows:

- The LDV/SOF oral granule formulation was not bioequivalent to the existing LDV/SOF FDC tablet formulation.
- The LDV/SOF oral granule formulation can be administered without regard to food.
- The LDV/SOF FDC tablet and pediatric oral granule formulation were generally well tolerated in healthy subjects.