Clinical trial results:
A Phase 1 Relative Bioavailability and Food Effect Study of a Pediatric Oral Granule Formulation of Ledipasvir/Sofosbuvir in Healthy Adult Subjects

Summary

EudraCT number	2017-003956-22
Trial protocol	Outside EU/EEA
Global end of trial date	27 July 2016

Results information

Result version number	v1 (current)
This version publication date	06 December 2017
First version publication date	06 December 2017

Trial information

Trial identification

Sponsor protocol code	GS-US-337-2091

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Clinical Trials Mailbox , Gilead Sciences International Ltd , ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trials Mailbox , Gilead Sciences International Ltd , ClinicalTrialDisclosures@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001411-PIP01-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 July 2016
Global end of trial reached?	Yes
Global end of trial date	27 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were to evaluate the relative bioavailability of a pediatric oral granule formulation of ledipasvir/sofosbuvir (LDV/SOF) relative to tablet formulation in healthy participants and to evaluate the effect of concomitant food intake on the pharmacokinetics (PK) of a pediatric oral granule formulation of LDV/SOF.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	24 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	42
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	42
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at one study site in the United States. The first participant was screened on 24 May 2016. The last study visit occurred on 27 July 2016.

Pre-assignment

Screening details:

58 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment ABC

Arm description:

Treatment A, 9-day washout, Treatment B, 9-day washout, and then Treatment C.

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	LDV/SOF, Harvoni®, GS-5885/GS-7977
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment A = Single dose of LDV/SOF (90/400 mg tablet) under fasted condition
Treatment B = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition
Treatment C = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition

Arm title	Treatment ACB

Arm description:

Treatment A, 9-day washout, Treatment C, 9-day washout, and then Treatment B.

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	LDV/SOF, Harvoni®, GS-5885/GS-7977
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment A = Single dose of LDV/SOF (90/400 mg tablet) under fasted condition
Treatment C = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition
Treatment B = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition

Arm title	Treatment BCA

Arm description:

Treatment B, 9-day washout, Treatment C, 9-day washout, and then Treatment A.

Arm type	Experimental

Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	LDV/SOF, Harvoni®, GS-5885/GS-7977
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment B = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition
Treatment C = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition
Treatment A = Single dose of LDV/SOF (90/400 mg tablet) under fasted condition

Arm title	Treatment BAC

Arm description:

Treatment B, 9-day washout, Treatment A, 9-day washout, and then Treatment C.

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	LDV/SOF, Harvoni®, GS-5885/GS-7977
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment B = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition
Treatment A = Single dose of LDV/SOF (90/400 mg tablet) under fasted condition
Treatment C = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition

Arm title	Treatment CBA

Arm description:

Treatment C, 9-day washout, Treatment B, 9-day washout, and then Treatment A.

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	LDV/SOF, Harvoni®, GS-5885/GS-7977
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment C = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition
Treatment B = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition
Treatment A = Single dose of LDV/SOF (90/400 mg tablet) under fasted condition

Arm title	Treatment CAB

Arm description:

Treatment C, 9-day washout, Treatment A, 9-day washout, and then Treatment B.

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	LDV/SOF, Harvoni®, GS-5885/GS-7977
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment C = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition
Treatment A = Single dose of LDV/SOF (90/400 mg tablet) under fasted condition
Treatment B = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition

Number of subjects in period 1	Treatment ABC	Treatment ACB	Treatment BCA
Started	7	7	7
Completed	7	7	7

Number of subjects in period 1	Treatment BAC	Treatment CBA	Treatment CAB
Started	7	7	7
Completed	7	7	7

Baseline characteristics

Reporting groups	
Reporting group title	Treatment ABC
Reporting group description:	
Treatment A, 9-day washout, Treatment B, 9-day washout, and then Treatment C.	

Reporting group title	Treatment ACB
Reporting group description:	
Treatment A, 9-day washout, Treatment C, 9-day washout, and then Treatment B.	

Reporting group title	Treatment BCA
Reporting group description:	
Treatment B, 9-day washout, Treatment C, 9-day washout, and then Treatment A.	
Reporting group title	Treatment BAC
Reporting group description:	
Treatment B, 9-day washout, Treatment A, 9-day washout, and then Treatment C.	
Reporting group title	Treatment CBA
Reporting group description:	
Treatment C, 9-day washout, Treatment B, 9-day washout, and then Treatment A.	
Reporting group title	Treatment CAB
Reporting group description:	
Treatment C, 9-day washout, Treatment A, 9-day washout, and then Treatment B.	

Reporting group values	Treatment ABC	Treatment ACB	Treatment BCA
Number of subjects	7	7	7
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	32	29	29
standard deviation	± 7.4	± 6.3	± 4.8
Gender categorical Units: Subjects			
Female	1	2	2
Male	6	5	5
Race Units: Subjects			
Black or African American	3	3	3
Native Hawaiian or Pacific Islander	0	0	0
White	4	4	4
Ethnicity Units: Subjects			
Hispanic or Latino	5	6	4
Not Hispanic or Latino	2	1	3

Reporting group values	Treatment BAC	Treatment CBA	Treatment CAB
Number of subjects	7	7	7

Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	29	26	31
standard deviation	± 6.4	± 4.0	± 6.3
Gender categorical Units: Subjects			
Female	2	3	2
Male	5	4	5
Race Units: Subjects			
Black or African American	2	4	3
Native Hawaiian or Pacific Islander	0	1	0
White	5	2	4
Ethnicity Units: Subjects			
Hispanic or Latino	5	4	4
Not Hispanic or Latino	2	3	3

Reporting group values	Total		
Number of subjects	42		
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	12		
Male	30		
Race Units: Subjects			
Black or African American	18		
Native Hawaiian or Pacific Islander	1		
White	23		
Ethnicity Units: Subjects			
Hispanic or Latino	28		
Not Hispanic or Latino	14		

End points

End points reporting groups

Reporting group title	Treatment ABC

Reporting group description:

Treatment A, 9-day washout, Treatment B, 9-day washout, and then Treatment C.

Reporting group title	Treatment ACB

Reporting group description:

Treatment A, 9-day washout, Treatment C, 9-day washout, and then Treatment B.

Reporting group title	Treatment BCA

Reporting group description:

Treatment B, 9-day washout, Treatment C, 9-day washout, and then Treatment A.

Reporting group title	Treatment BAC

Reporting group description:

Treatment B, 9-day washout, Treatment A, 9-day washout, and then Treatment C.

Reporting group title	Treatment CBA

Reporting group description:

Treatment C, 9-day washout, Treatment B, 9-day washout, and then Treatment A.

Reporting group title	Treatment CAB

Reporting group description:

Treatment C, 9-day washout, Treatment A, 9-day washout, and then Treatment B.

Subject analysis set title	Treatment A
Subject analysis set type	Per protocol

Subject analysis set description:

Single dose of LDV/SOF (90/400 mg tablet) under fasted condition (Treatment A)

Subject analysis set title	Treatment B
Subject analysis set type	Per protocol

Subject analysis set description:

Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition (Treatment B).

Subject analysis set title	Treatment C
Subject analysis set type	Per protocol

Subject analysis set description:

Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition (Treatment C)

Primary: Pharmacokinetic (PK) Parameter: Cmax of SOF, GS-566500, and GS-331007

End point title	Pharmacokinetic (PK) Parameter: Cmax of SOF, GS-566500, and GS-331007

End point description:

Cmax is defined as the maximum concentration of drug.

End point type	Primary

End point timeframe:

Predose, 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

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	42	42	
Units: ng/mL				
arithmetic mean (standard deviation)				
SOF	1221.0 (± 469.99)	1266.7 (± 589.77)	1236.3 (± 605.60)	
GS-566500	475.1 (± 160.89)	511.3 (± 178.63)	593.9 (± 184.38)	
GS-331007	833.9 (± 197.11)	951.9 (± 257.01)	583.1 (± 141.01)	

Statistical analyses

Statistical analysis title	GLSM ratio of SOF (Treatment B vs A)

Statistical analysis description:

Percentage geometric least-squares mean (GLSM) ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	95.98
Confidence interval	
level	90 %
sides	2-sided
lower limit	78
upper limit	118.11

Notes:

[1] - Statistical Comparison

Statistical analysis title	GLSM ratio of SOF (Treatment C vs B)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

Comparison groups	Treatment C v Treatment B
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	100.32

Confidence interval	
level	90 %
sides	2-sided
lower limit	84.83
upper limit	118.65

Notes:

[2] - Statistical Comparison

Statistical analysis title	GLSM ratio of GS-566500 (Treatment B vs A)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	103.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	91.06
upper limit	116.6

Notes:

[3] - Statistical Comparison

Statistical analysis title	GLSM ratio of GS-566500 (Treatment C vs B)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

Comparison groups	Treatment C v Treatment B
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	122.12
Confidence interval	
level	90 %
sides	2-sided
lower limit	108.28
upper limit	137.73

Notes:

[4] - Statistical Comparison

Statistical analysis title	GLSM ratio of GS-331007 (Treatment B vs A)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	112.81
Confidence interval	
level	90 %
sides	2-sided
lower limit	104.12
upper limit	122.22

Notes:

[5] - Statistical Comparison

Statistical analysis title	GLSM ratio of GS-331007 (Treatment C vs B)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

Comparison groups	Treatment C v Treatment B
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	62.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	56.9
upper limit	67.59

Notes:

[6] - Statistical Comparison

Primary: PK Parameter: Cmax of LDV

End point title	PK Parameter: Cmax of LDV

End point description:

Cmax is defined as the maximum concentration of drug.

End point type	Primary

End point timeframe:

Predose, 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

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	39[7]	40[8]	
Units: ng/mL				
arithmetic mean (standard deviation)	261.3 (± 113.55)	214.8 (± 82.05)	159.8 (± 46.17)	

Notes:

[7] - 3 participants were excluded since their LDV predose plasma concentration was > 5% of Cmax.

[8] - 2 participants were excluded since their LDV predose plasma concentration was > 5% of Cmax.

Statistical analyses

Statistical analysis title	GLSM ratio of LDV (Treatment B vs A)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 81; however, only 42 unique participants were analyzed, each reported for Treatment B (N = 39) and Treatment A (N = 42).

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	84.59
Confidence interval	
level	90 %
sides	2-sided
lower limit	74.69
upper limit	95.81

Notes:

[9] - Statistical comparison

Statistical analysis title	GLSM ratio of LDV (Treatment C vs B)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 81; however, only 40 unique participants were analyzed, each reported for Treatment C (N = 40) and Treatment B (N = 39).

Comparison groups	Treatment C v Treatment B
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	78.15
Confidence interval	
level	90 %
sides	2-sided
lower limit	71.26
upper limit	85.71

Notes:

[10] - Statistical comparison

Primary: PK Parameter: AUClast of SOF, GS-566500, and GS-331007

End point title	PK Parameter: AUClast of SOF, GS-566500, and GS-331007

End point description:

AUClast is defined as the concentration of drug from time zero to the last observable concentration.

End point type	Primary

End point timeframe:

Predose, 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

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	42	42	
Units: h*ng/mL				
arithmetic mean (standard deviation)				
SOF	1559.8 (± 632.08)	1676.9 (± 732.07)	2577.2 (± 852.76)	
GS-566500	1846.6 (± 579.71)	1952.9 (± 654.54)	2931.7 (± 559.29)	
GS-331007	11146.3 (± 2999.47)	11525.8 (± 3037.01)	11653.6 (± 2197.58)	

Statistical analyses

Statistical analysis title	GLSM ratio of SOF (Treatment B vs A)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	102.13
Confidence interval	
level	90 %
sides	2-sided
lower limit	87.16
upper limit	119.67

Notes:

[11] - Statistical Comparison

Statistical analysis title	GLSM ratio of SOF (Treatment C vs B)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

Comparison groups	Treatment C v Treatment B

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	166.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	145
upper limit	190.3

Notes:

[12] - Statistical Comparison

Statistical analysis title	GLSM ratio of GS-566500 (Treatment B vs A)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[13]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	100.59
Confidence interval	
level	90 %
sides	2-sided
lower limit	88.89
upper limit	113.83

Notes:

[13] - Statistical Comparison

Statistical analysis title	GLSM ratio of GS-566500 (Treatment C vs B)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

Comparison groups	Treatment C v Treatment B
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[14]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	163.23
Confidence interval	
level	90 %
sides	2-sided
lower limit	144.62
upper limit	184.23

Notes:

[14] - Statistical Comparison

Statistical analysis title	GLSM ratio of GS-331007 (Treatment B vs A)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[15]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	103.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	96.71
upper limit	110

Notes:

[15] - Statistical Comparison

Statistical analysis title	GLSM ratio of GS-566500 (Treatment C vs B)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

Comparison groups	Treatment C v Treatment B
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[16]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	103.12
Confidence interval	
level	90 %
sides	2-sided
lower limit	97.61
upper limit	108.94

Notes:

[16] - Statistical Comparison

Primary: PK Parameter: AUClast of LDV

End point title	PK Parameter: AUClast of LDV

End point description:

AUClast is defined as the concentration of drug from time zero to the last observable concentration.

End point type	Primary

End point timeframe:

Predose, 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

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	39[17]	40[18]	
Units: h*ng/mL				
arithmetic mean (standard deviation)	7362.3 (± 3557.92)	6242.5 (± 2542.34)	5149.6 (± 1349.23)	

Notes:

[17] - 3 participants were excluded since their LDV predose plasma concentration was > 5% of Cmax.

[18] - 2 participants were excluded since their LDV predose plasma concentration was > 5% of Cmax.

Statistical analyses

Statistical analysis title	GLSM ratio of LDV (Treatment B vs A)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 81; however, only 42 unique participants were analyzed, each reported for Treatment B (N = 39) and Treatment A (N = 42).

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other[19]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	87.76
Confidence interval	
level	90 %
sides	2-sided
lower limit	77.94
upper limit	98.82

Notes:

[19] - Statistical Comparison

Statistical analysis title	GLSM ratio of LDV (Treatment C vs B)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 79; however, only 40 unique participants were analyzed, each reported for Treatment C (N = 40) and Treatment B (N = 39).

Comparison groups	Treatment C v Treatment B
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other[20]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	87.62
Confidence interval	
level	90 %
sides	2-sided
lower limit	79.65
upper limit	96.39

Notes:

[20] - Statistical Comparison

Primary: PK Parameter: AUCinf of SOF, GS-566500, and GS-331007

End point title	PK Parameter: AUCinf of SOF, GS-566500, and GS-331007

End point description:

AUCinf is defined as the concentration of drug extrapolated to infinite time.

End point type	Primary

End point timeframe:

Predose, 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

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	42	42	
Units: h*ng/mL				
arithmetic mean (standard deviation)				
SOF	1580.8 (± 634.96)	1684.1 (± 733.08)	2597.7 (± 853.35)	
GS-566500	1894.9 (± 584.25)	2009.7 (± 663.88)	2988.8 (± 558.28)	
GS-331007	11720.0 (± 3058.58)	12095.0 (± 2947.17)	12220.6 (± 2238.27)	

Statistical analyses

Statistical analysis title	GLSM ratio of SOF (Treatment B vs A)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[21]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	101.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	86.67
upper limit	119.1

Notes:

[21] - Statistical Comparison

Statistical analysis title	GLSM ratio of SOF (Treatment C vs B)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

Comparison groups	Treatment C v Treatment B

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[22]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	166.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	145.56
upper limit	189.71

Notes:

[22] - Statistical Comparison

Statistical analysis title	GLSM ratio of GS-566500 (Treatment B vs A)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[23]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	101.37
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.17
upper limit	113.96

Notes:

[23] - Statistical Comparison

Statistical analysis title	GLSM ratio of GS-566500 (Treatment C vs B)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

Comparison groups	Treatment C v Treatment B
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[24]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	160.65
Confidence interval	
level	90 %
sides	2-sided
lower limit	143.4
upper limit	179.99

Notes:

[24] - Statistical Comparison

Statistical analysis title	GLSM ratio of GS-331007 (Treatment B vs A)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[25]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	103.64
Confidence interval	
level	90 %
sides	2-sided
lower limit	98.48
upper limit	109.07

Notes:

[25] - Statistical Comparison

Statistical analysis title	GLSM ratio of GS-331007 (Treatment C vs B)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

Comparison groups	Treatment C v Treatment B
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[26]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	102.26
Confidence interval	
level	90 %
sides	2-sided
lower limit	98.18
upper limit	106.52

Notes:

[26] - Statistical Comparison

Primary: PK Parameter: AUCinf of LDV

End point title	PK Parameter: AUCinf of LDV

End point description:

AUCinf is defined as the concentration of drug extrapolated to infinite time.

End point type	Primary

End point timeframe:

Predose, 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

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	39[27]	40[28]	
Units: h*ng/mL				
arithmetic mean (standard deviation)	8467.5 (± 4605.87)	7088.4 (± 3279.03)	5748.3 (± 1669.51)	

Notes:

[27] - 3 participants were excluded since their LDV predose plasma concentration was > 5% of Cmax.

[28] - 2 participants were excluded since their LDV predose plasma concentration was > 5% of Cmax.

Statistical analyses

Statistical analysis title	GLSM ratio of LDV (Treatment B vs A)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 81; however, only 42 unique participants were analyzed, each reported for Treatment B (N = 39) and Treatment A (N = 42).

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other[29]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	88.36
Confidence interval	
level	90 %
sides	2-sided
lower limit	78.43
upper limit	99.54

Notes:

[29] - Statistical Comparison

Statistical analysis title	GLSM ratio of LDV (Treatment C vs B)

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 79; however, only 40 unique participants were analyzed, each reported for Treatment C (N = 40) and Treatment B (N = 39).

Comparison groups	Treatment C v Treatment B
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other[30]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	87.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	78.95
upper limit	96

Notes:

[30] - Statistical Comparison

Secondary: PK Parameter: Tmax of SOF, GS-566500, and GS-331007

End point title	PK Parameter: Tmax of SOF, GS-566500, and GS-331007

End point description:

Tmax is defined as the time (observed time point) of Cmax.

End point type	Secondary

End point timeframe:

Predose, 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

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	42	42	
Units: hours				
median (inter-quartile range (Q1-Q3))				
SOF	0.51 (0.50 to 1.50)	2.00 (1.00 to 2.50)	1.50 (1.00 to 3.00)	
GS-566500	1.76 (1.00 to 2.00)	2.50 (2.00 to 3.00)	3.00 (2.50 to 4.00)	
GS-331007	3.00 (2.00 to 4.00)	3.00 (2.50 to 3.50)	4.50 (4.00 to 5.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Tmax of LDV

End point title	PK Parameter: Tmax of LDV

End point description:

Tmax is defined as the time (observed time point) of Cmax.

End point type	Secondary

End point timeframe:

Predose, 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

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	39[31]	40[32]	
Units: hours				
median (inter-quartile range (Q1-Q3))	4.50 (4.50 to 4.55)	4.50 (4.50 to 5.00)	5.00 (4.50 to 6.00)	

Notes:

[31] - 3 participants were excluded since their LDV predose plasma concentration was > 5% of Cmax.

[32] - 2 participants were excluded since their LDV predose plasma concentration was > 5% of Cmax.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Adverse Events

End point title	Incidence of Adverse Events

End point description:

The percentage of participants experiencing treatment-emergent adverse events was summarized.

End point type	Secondary

End point timeframe:

From Baseline up to Day 21 plus 30 days

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	42	42	
Units: percentage of participants				
number (not applicable)	9.5	9.5	14.3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: For Serious Adverse Events: From Screening until 30 days after last administration of study drug. For Non-Serious Adverse Events: From Baseline until 30 days after last administration of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	Treatment A
Reporting group description: Single dose of LDV/SOF (90/400 mg tablet) under fasted condition (Treatment A)	
Reporting group title	Treatment B
Reporting group description: Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition (Treatment B)	
Reporting group title	Treatment C
Reporting group description: Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition (Treatment C)	

Serious adverse events	Treatment A	Treatment B	Treatment C
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 42 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment A	Treatment B	Treatment C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 42 (4.76%)	3 / 42 (7.14%)	6 / 42 (14.29%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 42 (2.38%)	3 / 42 (7.14%)	3 / 42 (7.14%)
occurrences (all)	1	3	4
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	3 / 42 (7.14%)
occurrences (all)	1	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported