Clinical trial results:
A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir+RBV for 24 Weeks in Genotype 1 or 3 and Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablet for 12 weeks in Genotype 1 or 4 HCV-Infected Subjects with Renal Insufficiency

Summary

EudraCT number	2013-002897-30
Trial protocol	DE AT NL
Global end of trial date	19 October 2017

Results information

Result version number	v1 (current)
This version publication date	23 August 2018
First version publication date	23 August 2018

Trial information

Trial identification

Sponsor protocol code	GS-US-334-0154

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01958281
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS00006432: German Clinical Trials Register

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	19 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2017
Global end of trial reached?	Yes
Global end of trial date	19 October 2017
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 safety and efficacy of sofosbuvir (SOF) plus ribavirin (RBV) for 24 weeks and ledipasvir/sofosbuvir (LDV/SOF) for 12 weeks, and to evaluate the steady state pharmacokinetics (PK) of SOF and its metabolites and LDV in participants with genotype (GT) 1, 3, or 4 HCV infection who have chronic renal insufficiency (impaired kidney function).

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	07 October 2013
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	New Zealand: 14
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	38
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)	30
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States and New Zealand. The first participant was screened on 07 October 2013. The last study visit occurred on 19 October 2017.

Pre-assignment

Screening details:

32 participants were screened for Cohorts 1 and 2 and 33 participants were screened for Cohort 3.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	SOF 200 mg + RBV 200 mg (Cohort 1)

Arm description:

Participants with genotype 1 or 3 HCV infection received SOF 200 mg + RBV for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Sofosbuvir
Investigational medicinal product code	
Other name	Sovaldi®, SOF, GS-7977
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg tablet or 2 x 100 mg tablets administered once daily

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	RBV
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg administered once daily

Arm title	SOF 400 mg + RBV 200 mg (Cohort 2)

Arm description:

Participants with genotype 1 or 3 HCV infection received SOF 400 mg + RBV for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Sofosbuvir
Investigational medicinal product code	
Other name	Sovaldi®, SOF, GS-7977
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg tablet or 4 x 100 mg tablets administered once daily

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	RBV
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

200 mg administered once daily

Arm title	LDV/SOF (Cohort 3)

Arm description:

Participants with genotype 1 HCV infection received LDV/SOF for 12 weeks.

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

Dosage and administration details:

90/400 mg fixed-dose combination (FDC) tablet administered once daily

Number of subjects in period 1	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)	LDV/SOF (Cohort 3)
Started	10	10	18
Completed	4	6	18
Not completed	6	4	0
Withdrew Consent	1	-	-
Adverse event, non-fatal	-	2	-
Lack of efficacy	5	2	-

Baseline characteristics

Reporting groups	
Reporting group title	SOF 200 mg + RBV 200 mg (Cohort 1)
Reporting group description:	
Participants with genotype 1 or 3 HCV infection received SOF 200 mg + RBV for 24 weeks.	
Reporting group title	SOF 400 mg + RBV 200 mg (Cohort 2)
Reporting group description:	
Participants with genotype 1 or 3 HCV infection received SOF 400 mg + RBV for 24 weeks.	
Reporting group title	LDV/SOF (Cohort 3)
Reporting group description:	
Participants with genotype 1 HCV infection received LDV/SOF for 12 weeks.	

Reporting group values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)	LDV/SOF (Cohort 3)
Number of subjects	10	10	18
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62	58	57
standard deviation	± 6.5	± 9.0	± 7.5
Gender categorical Units: Subjects			
Female	4	2	12
Male	6	8	6
Ethnicity Units: Subjects			
Hispanic or Latino	2	1	4
Not Hispanic or Latino	8	9	14
Race Units: Subjects			
Black or African American	5	4	10
White	2	5	8
Asian	1	0	0
Hawaiian or Pacific Islander	0	1	0
Other	2	0	0
HCV genotype Units: Subjects			
Genotype 1a	7	6	14
Genotype 1b	2	2	4
Genotype 3a	1	2	0
IL28b Status			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	2	5	1
CT	6	4	11
TT	2	1	6

HCV RNA Category Units: Subjects			
< 6 log10 IU/ mL	3	4	5
≥ 6 log10 IU/ mL	7	6	13
HCV RNA (log10 IU/mL) Units: log10 IU/mL			
arithmetic mean	6.4	6.3	6.2
standard deviation	± 0.47	± 0.50	± 0.54

Reporting group values	Total		
Number of subjects	38		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	18		
Male	20		
Ethnicity Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	31		
Race Units: Subjects			
Black or African American	19		
White	15		
Asian	1		
Hawaiian or Pacific Islander	1		
Other	2		
HCV genotype Units: Subjects			
Genotype 1a	27		
Genotype 1b	8		
Genotype 3a	3		
IL28b Status			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	8		
CT	21		
TT	9		
HCV RNA Category Units: Subjects			
< 6 log10 IU/ mL	12		
≥ 6 log10 IU/ mL	26		
HCV RNA (log10 IU/mL) Units: log10 IU/mL			
arithmetic mean			

standard deviation	-		

End points

End points reporting groups

Reporting group title	SOF 200 mg + RBV 200 mg (Cohort 1)
Reporting group description:	
Participants with genotype 1 or 3 HCV infection received SOF 200 mg + RBV for 24 weeks.	
Reporting group title	SOF 400 mg + RBV 200 mg (Cohort 2)
Reporting group description:	
Participants with genotype 1 or 3 HCV infection received SOF 400 mg + RBV for 24 weeks.	
Reporting group title	LDV/SOF (Cohort 3)
Reporting group description:	
Participants with genotype 1 HCV infection received LDV/SOF for 12 weeks.	

Primary: Percentage of Participants With Sustained Virologic Response (SVR) 12 Weeks After Discontinuation of Therapy (SVR12)

End point title	Percentage of Participants With Sustained Virologic Response (SVR) 12 Weeks After Discontinuation of Therapy (SVR12)[1]
End point description:	
SVR12 was defined as HCV RNA < the lower limit of quantitation (LLOQ; ie, 15 IU/mL) at 12 weeks after stopping study treatment. Participants in the Full Analysis Set (participants who were enrolled and took at least 1 dose of study drug) were analyzed.	
End point type	Primary
End point timeframe:	
Posttreatment Week 12	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)	LDV/SOF (Cohort 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	18	
Units: percentage of participants				
number (confidence interval 95%)	40.0 (12.2 to 73.8)	60.0 (26.2 to 87.8)	100.0 (81.5 to 100.0)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Experiencing Treatment-Emergent Adverse Events

End point title	Percentage of Participants Experiencing Treatment-Emergent Adverse Events[2]
End point description:	
Participants in the Safety Analysis Set (participants who took at least 1 dose of study drug) were analyzed.	

End point type	Primary

End point timeframe:

Up to 24 weeks plus 30 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)	LDV/SOF (Cohort 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	18	
Units: percentage of participants				
number (not applicable)	100.0	90.0	72.2	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Experiencing Treatment-Emergent Laboratory Abnormalities

End point title	Percentage of Participants Experiencing Treatment-Emergent Laboratory Abnormalities[3]

End point description:

Treatment-emergent laboratory abnormalities were defined as values that increased by at least 1 toxicity grade from baseline at any time postbaseline up to the date of last dose of study drug plus 30 days. Participants in the Safety Analysis Set were analyzed.

End point type	Primary

End point timeframe:

Up to 24 weeks plus 30 days

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)	LDV/SOF (Cohort 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	18	
Units: percentage of participants				
number (not applicable)	100.0	100.0	100.0	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Experiencing Clinically Significant 12-lead Electrocardiogram (ECG) Abnormalities

End point title	Percentage of Participants Experiencing Clinically Significant 12-lead Electrocardiogram (ECG) Abnormalities[4]

End point description:

Participant in the Safety Analysis Set were analyzed.

End point type	Primary

End point timeframe:

Up to 24 weeks plus 30 days

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)	LDV/SOF (Cohort 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	18	
Units: percentage of participants				
number (not applicable)	0	0	5.6	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Experiencing Treatment-Emergent Adverse Events Associated with Vital Sign Abnormalities

End point title	Percentage of Participants Experiencing Treatment-Emergent Adverse Events Associated with Vital Sign Abnormalities[5]

End point description:

Participants in the Safety Analysis Set were analyzed.

End point type	Primary

End point timeframe:

Up to 24 weeks plus 30 days

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)	LDV/SOF (Cohort 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	18	
Units: percentage of participants				
number (not applicable)	10.0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter: AUCtau of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)

End point title	PK Parameter: AUCtau of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)[6][7]

End point description:

AUCtau is defined as concentration of drug over time (the area under the concentration verses time curve over the dosing interval). Participants in the PK Analysis Set (all enrolled participants who took at least 1 dose of study drug and have at least 1 nonmissing postdose PK concentration value) from Cohorts 1 and 2 with available data were analyzed.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: h*ng/mL				
arithmetic mean (standard deviation)				
SOF (Cohort 1: N = 8; Cohort 2: N = 10)	1093.9 (± 703.03)	1630.5 (± 851.33)		
GS-566500 (Cohort 1: N = 10; Cohort 2: N = 10)	2120.2 (± 837.51)	4026.2 (± 1848.50)		
GS-331007 (Cohort 1: N = 10; Cohort 2: N = 10)	31859.4 (± 12621.62)	51989.6 (± 29461.91)		
RBV (Cohort 1: N = 10; Cohort 2: N = 10)	22253.9 (± 6860.72)	23595.5 (± 9636.77)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter: AUCtau of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)

End point title	PK Parameter: AUCtau of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)[8][9]

End point description:

AUCtau is defined as concentration of drug over time (the area under the concentration verses time curve over the dosing interval). Participants in the PK Analysis Set from Cohorts 1 and 2 with available data were analyzed.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 12

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: h*ng/mL				
arithmetic mean (standard deviation)				
SOF (Cohort 1: N = 9; Cohort 2: N = 8)	1302.7 (± 652.18)	1571.3 (± 944.71)		
GS-566500 (Cohort 1: N = 10; Cohort 2: N = 8)	2223.2 (± 877.20)	3213.9 (± 1221.71)		
GS-331007 (Cohort 1: N = 10; Cohort 2: N = 8)	31078.3 (± 16745.94)	46810.1 (± 25249.07)		
RBV (Cohort 1: N = 8; Cohort 2: N = 8)	45341.9 (± 8712.71)	50471.2 (± 23077.43)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter: AUCtau of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)

End point title	PK Parameter: AUCtau of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)[10][11]

End point description:

AUCtau is defined as concentration of drug over time (the area under the concentration verses time curve over the dosing interval). Participants in the PK Analysis Set from Cohort 3 with available data were analyzed.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2 or 4

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohorts 1 and 2 are presented as a separate endpoint because the time frames are different.

End point values	LDV/SOF (Cohort 3)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
SOF	3536.8 (± 2040.59)			
GS-566500	7716.6 (± 3534.76)			
GS-331007	71463.3 (± 28979.92)			
LDV	18460.1 (± 19999.95)			

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter: Cmax of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)

End point title	PK Parameter: Cmax of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)[12][13]

End point description:

Cmax is defined as the maximum concentration of drug. Participants in the PK Analysis Set from Cohorts 1 and 2 were analyzed.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: ng/mL				
arithmetic mean (standard deviation)				
SOF	575.9 (± 487.66)	976.8 (± 712.04)		
GS-566500	308.3 (± 132.60)	538.3 (± 241.51)		
GS-331007	1750.0 (± 578.56)	2721.4 (± 1452.86)		
RBV	1373.1 (± 496.37)	1373.8 (± 550.23)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter: Cmax of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)

End point title	PK Parameter: Cmax of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)[14][15]

End point description:

Cmax is defined as the maximum concentration of drug. Participants in the PK Analysis Set from Cohorts 1 and 2 with available data were analyzed.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 12

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: ng/mL				
arithmetic mean (standard deviation)				
SOF (Cohort 1: N = 10; Cohort 2: N = 8)	903.9 (± 598.55)	1422.9 (± 1390.47)		
GS-566500 (Cohort 1: N = 10; Cohort 2: N = 8)	352.2 (± 127.83)	509.1 (± 216.71)		
GS-331007 (Cohort 1: N = 10; Cohort 2: N = 8)	1727.0 (± 775.37)	2645.0 (± 1482.10)		
RBV (Cohort 1: N = 8; Cohort 2: N = 8)	2458.8 (± 437.54)	2589.4 (± 1159.66)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter: Cmax of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)

End point title	PK Parameter: Cmax of SOF, Its Metabolites (GS-566500 and

	GS-331007), and LDV at Week 2 or 4 (Cohort 3)[16][17]

End point description:

Cmax is defined as the maximum concentration of drug. Participants in the PK Analysis Set from Cohort 3 with available data were analyzed.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2 or 4

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohorts 1 and 2 are presented as a separate endpoint because the time frames are different.

End point values	LDV/SOF (Cohort 3)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: ng/mL				
arithmetic mean (standard deviation)				
SOF	2018.1 (± 1110.56)			
GS-566500	1021.6 (± 359.13)			
GS-331007	3570.0 (± 1325.31)			
LDV	903.4 (± 844.70)			

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter: Ctau of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)

End point title	PK Parameter: Ctau of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)[18][19]

End point description:

Ctau is defined as the observed drug concentration at the end of the dosing interval. Participants in the PK Analysis Set from Cohorts 1 and 2 were analyzed. PK data for SOF are not presented because all values were below the limit of quantitation.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are

different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: ng/mL				
arithmetic mean (standard deviation)				
GS-566500	3.7 (± 7.88)	20.8 (± 20.51)		
GS-331007	1023.0 (± 477.15)	1736.1 (± 1110.41)		
RBV	759.1 (± 240.04)	818.8 (± 323.67)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter: Ctau of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)

End point title	PK Parameter: Ctau of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)[20][21]

End point description:

Ctau is defined as the observed drug concentration at the end of the dosing interval. Participants in the PK Analysis Set from Cohorts 1 and 2 with available data were analyzed. PK data for SOF are not presented because all values were below the limit of quantitation.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 12

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: ng/mL				
arithmetic mean (standard deviation)				
GS-566500 (Cohort 1: N = 10; Cohort 2: N = 9)	2.3 (± 7.12)	10.4 (± 11.07)		
GS-331007 (Cohort 1: N = 10; Cohort 2: N = 9)	952.5 (± 586.51)	1356.0 (± 681.23)		
RBV (Cohort 1: N = 10; Cohort 2: N = 9)	1567.5 (± 529.35)	1968.6 (± 884.99)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter: Ctau of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)

End point title	PK Parameter: Ctau of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)[22][23]

End point description:

Ctau is defined as the observed drug concentration at the end of the dosing interval. Participants in the PK Analysis Set from Cohort 3 with available data were analyzed.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2 or 4

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohorts 1 and 2 are presented as a separate endpoint because the time frames are different.

End point values	LDV/SOF (Cohort 3)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ng/mL				
arithmetic mean (standard deviation)				
SOF	2.9 (± 1.57)			
GS-566500	59.3 (± 88.08)			
GS-331007	2568.2 (± 1106.81)			
LDV	705.0 (± 876.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With SVR at 4 Weeks After Discontinuation of Therapy (SVR4)

End point title	Percentage of Participants With SVR at 4 Weeks After Discontinuation of Therapy (SVR4)

End point description:

SVR4 was defined as HCV RNA < LLOQ at 4 weeks after stopping study treatment. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Posttreatment Week 4

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)	LDV/SOF (Cohort 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	18	
Units: percentage of participants				
number (confidence interval 95%)	40.0 (12.2 to 73.8)	60.0 (26.2 to 87.8)	100.0 (81.5 to 100.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With SVR at 24 Weeks After Discontinuation of Therapy (SVR24)

End point title	Percentage of Participants With SVR at 24 Weeks After Discontinuation of Therapy (SVR24)

End point description:

SVR4 was defined as HCV RNA < LLOQ at 24 weeks after stopping study treatment. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Posttreatment Week 24

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)	LDV/SOF (Cohort 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	18	
Units: percentage of participants				
number (confidence interval 95%)	40.0 (12.2 to 73.8)	60.0 (26.2 to 87.8)	100.0 (81.5 to 100.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Overall Virologic Failure

End point title	Percentage of Participants With Overall Virologic Failure

End point description:

Virologic failure was defined as:
• On-treatment virologic failure:
• Breakthrough (confirmed HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while on treatment), or
• Rebound (confirmed > 1 log10 IU/mL increase in HCV RNA from nadir while on treatment), or • Non-response (HCV RNA persistently ≥ LLOQ through 8 weeks of treatment)
• Virologic relapse:
• Confirmed HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at last on-treatment visit.

Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to Posttreatment Week 24

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)	LDV/SOF (Cohort 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	18	
Units: percentage of participants				
number (not applicable)	50.0	40.0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: AUClast of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)

End point title	PK Parameter: AUClast of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)[24]

End point description:

AUClast is defined as the concentration of drug from time zero to the last observable concentration. Participants in the PK Analysis Set from Cohorts 1 and 2 were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: h*ng/mL				
arithmetic mean (standard deviation)				
SOF	885.0 (± 710.72)	1607.7 (± 854.70)		
GS-566500	1973.3 (± 851.52)	3965.7 (± 1900.25)		
GS-331007	31859.4 (± 12621.62)	51989.6 (± 29461.91)		
RBV	22253.9 (± 6860.72)	23595.5 (± 9636.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: AUClast of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)

End point title	PK Parameter: AUClast of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)[25]

End point description:

AUClast is defined as the concentration of drug from time zero to the last observable concentration. Participants in the PK Analysis Set from Cohorts 1 and 2 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 12

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: h*ng/mL				
arithmetic mean (standard deviation)				
SOF (Cohort 1: N = 10; Cohort 2: N = 8)	1177.7 (± 674.86)	1548.1 (± 955.12)		
GS-566500 (Cohort 1: N = 10; Cohort 2: N = 8)	1867.1 (± 839.39)	3133.0 (± 1230.39)		
GS-331007 (Cohort 1: N = 10; Cohort 2: N = 8)	31078.3 (± 16745.94)	46810.1 (± 25249.07)		
RBV (Cohort 1: N = 10; Cohort 2: N = 10)	45341.9 (± 8712.71)	50471.2 (± 23077.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: AUClast of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)

End point title	PK Parameter: AUClast of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)[26]

End point description:

AUClast is defined as the concentration of drug from time zero to the last observable concentration. Participants in the PK Analysis Set from Cohort 3 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2 or 4

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohorts 1 and 2 are presented as a separate endpoint because the time frames are different.

End point values	LDV/SOF (Cohort 3)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
SOF	3519.3 (± 2045.64)			
GS-566500	7657.6 (± 3555.57)			
GS-331007	69177.7 (± 31267.56)			
LDV	18044.3 (± 20210.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Clast of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)

End point title	PK Parameter: Clast of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)[27]

End point description:

Clast is defined as the last observable concentration of drug. Participants in the PK Analysis Set from Cohorts 1 and 2 were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: ng/mL				
arithmetic mean (standard deviation)				
SOF	68.0 (± 100.22)	21.3 (± 22.22)		
GS-566500	37.6 (± 18.84)	35.8 (± 21.06)		
GS-331007	1023.0 (± 477.15)	1736.1 (± 1110.41)		
RBV	759.1 (± 240.04)	818.8 (± 323.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Clast of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)

End point title	PK Parameter: Clast of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)[28]

End point description:

Clast is defined as the last observable concentration of drug. Participants in the PK Analysis Set from Cohorts 1 and 2 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 12

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: ng/mL				
arithmetic mean (standard deviation)				
SOF (Cohort 1: N = 10; Cohort 2: N = 8)	100.7 (± 158.83)	22.7 (± 30.15)		

GS-566500 (Cohort 1: N = 10; Cohort 2: N = 8)	72.2 (± 80.16)	32.1 (± 22.04)		
GS-331007 (Cohort 1: N = 10; Cohort 2: N = 8)	952.5 (± 586.51)	1412.9 (± 705.06)		
RBV (Cohort 1: N = 10; Cohort 2: N = 8)	1741.3 (± 417.42)	2040.9 (± 917.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Clast of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)

End point title	PK Parameter: Clast of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)[29]

End point description:

Clast is defined as the last observable concentration of drug. Participants in the PK Analysis Set from Cohort 3 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2 or 4

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohorts 1 and 2 are presented as a separate endpoint because the time frames are different.

End point values	LDV/SOF (Cohort 3)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: ng/mL				
arithmetic mean (standard deviation)				
SOF	56.3 (± 216.91)			
GS-566500	70.5 (± 97.14)			
GS-331007	2570.6 (± 1071.71)			
LDV	700.6 (± 848.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Tmax of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)

End point title	PK Parameter: Tmax of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)[30]

End point description:

Tmax is defined as the time (observed time point) of Cmax. Participants in the PK Analysis Set from Cohorts 1 and 2 were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: hours				
median (inter-quartile range (Q1-Q3))				
SOF	1.00 (0.50 to 2.00)	1.50 (1.00 to 2.13)		
GS-566500	2.17 (2.00 to 3.97)	4.00 (2.00 to 4.00)		
GS-331007	4.00 (4.00 to 4.00)	6.00 (4.00 to 6.00)		
RBV	2.00 (1.00 to 2.00)	2.00 (1.00 to 2.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Tmax of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)

End point title	PK Parameter: Tmax of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)[31]

End point description:

Tmax is defined as the time (observed time point) of Cmax. Participants in the PK Analysis Set from Cohorts 1 and 2 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 12

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: hours				
median (inter-quartile range (Q1-Q3))				
SOF (Cohort 1: N = 10; Cohort 2: N = 8)	1.04 (1.00 to 2.00)	0.50 (0.50 to 1.50)		
GS-566500 (Cohort 1: N = 10; Cohort 2: N = 8)	2.17 (1.93 to 4.00)	2.00 (1.50 to 4.00)		
GS-331007 (Cohort 1: N = 10; Cohort 2: N = 8)	5.11 (4.00 to 6.05)	5.00 (4.00 to 6.00)		
RBV (Cohort 1: N = 8; Cohort 2: N = 8)	2.00 (1.00 to 2.17)	1.50 (1.00 to 3.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Tmax of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)

End point title	PK Parameter: Tmax of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)[32]

End point description:

Tmax is defined as the time (observed time point) of Cmax. Participants in the PK Analysis Set from Cohort 3 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2 or 4

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohorts 1 and 2 are presented as a separate endpoint because the time frames are different.

End point values	LDV/SOF (Cohort 3)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: hours				
median (inter-quartile range (Q1-Q3))				
SOF	1.00 (0.50 to 1.10)			
GS-566500	2.00 (2.00 to 2.02)			
GS-331007	4.02 (4.00 to 6.02)			
LDV	6.00 (4.00 to 8.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Tlast of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)

End point title	PK Parameter: Tlast of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)[33]

End point description:

Tlast is defined as the time (observed time point) of Clast. Participants in the PK Analysis Set from Cohorts 1 and 2 were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: hours				
median (inter-quartile range (Q1-Q3))				
SOF	4.00 (3.92 to 4.13)	6.00 (4.00 to 8.13)		
GS-566500	12.00 (11.97 to 12.00)	24.00 (12.00 to 24.00)		
GS-331007	24.00 (24.00 to 24.00)	24.00 (24.00 to 24.00)		
RBV	24.00 (24.00 to 24.00)	24.00 (24.00 to 24.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Tlast of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)

End point title	PK Parameter: Tlast of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)[34]

End point description:

Tlast is defined as the time (observed time point) of Clast. Participants in the PK Analysis Set from Cohorts 1 and 2 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 12

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: hours				
median (inter-quartile range (Q1-Q3))				
SOF (Cohort 1: N = 10; Cohort 2: N = 8)	4.00 (2.33 to 4.00)	4.03 (4.00 to 6.00)		
GS-566500 (Cohort 1: N = 10; Cohort 2: N = 8)	12.00 (10.00 to 12.02)	24.00 (12.00 to 24.00)		
GS-331007 (Cohort 1: N = 10; Cohort 2: N = 8)	24.00 (24.00 to 24.00)	24.00 (24.00 to 24.00)		
RBV (Cohort 1: N = 8; Cohort 2: N = 8)	24.00 (24.00 to 24.00)	24.00 (24.00 to 24.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Tlast of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)

End point title	PK Parameter: Tlast of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)[35]

End point description:

Tlast is defined as the time (observed time point) of Clast. Participants in the PK Analysis Set from Cohort 3 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2 or 4
Analysis Population

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohorts 1 and 2 are presented as a separate endpoint because the time frames are different.

End point values	LDV/SOF (Cohort 3)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: hours				
median (inter-quartile range (Q1-Q3))				
SOF	12.00 (12.00 to 12.00)			
GS-566500	24.00 (24.00 to 24.00)			

GS-331007 LDV	24.00 (24.00 to 24.00) 24.00 (24.00 to 24.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: λz of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)

End point title	PK Parameter: λz of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)[36]

End point description:

λz is defined as the terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma concentration of drug versus time curve of the drug. Participants in the PK Analysis Set from Cohorts 1 and 2 were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: 1/hour				
arithmetic mean (standard deviation)				
SOF	1.0419 (± 0.28621)	1.0155 (± 0.33118)		
GS-566500	0.2078 (± 0.04748)	0.1771 (± 0.05802)		
GS-331007	0.0275 (± 0.01331)	0.0273 (± 0.01711)		
RBV	0.0165 (± 0.00524)	0.0141 (± 0.00658)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: λz of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)

End point title	PK Parameter: λz of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)[37]

End point description:

λz is defined as the terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma concentration of drug versus time curve of the drug. Participants in the PK Analysis Set from Cohorts 1 and 2 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 12

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: 1/hour				
arithmetic mean (standard deviation)				
SOF (Cohort 1: N = 9; Cohort 2: N = 8)	1.4002 (± 0.29086)	1.2154 (± 0.24100)		
GS-566500 (Cohort 1: N = 10; Cohort 2: N = 8)	0.2232 (± 0.05244)	0.1818 (± 0.06121)		
GS-331007 (Cohort 1: N = 10; Cohort 2: N = 8)	0.0332 (± 0.01388)	0.0313 (± 0.02100)		
RBV (Cohort 1: N = 8; Cohort 2: N = 8)	0.0124 (± 0.00580)	0.0085 (± 0.02100)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: λz of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)

End point title	PK Parameter: λz of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)[38]

End point description:

λz is defined as the terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma concentration of drug versus time curve of the drug. Participants in the PK Analysis Set from Cohort 3 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2 or 4

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohorts 1 and 2 are presented as a separate endpoint because the time frames are different.

End point values	LDV/SOF (Cohort 3)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: 1/hour				
arithmetic mean (standard deviation)				
SOF	0.6033 (± 0.24057)			
GS-566500	0.1705 (± 0.04602)			
GS-331007	0.0214 (± 0.01222)			
LDV	0.0305 (± 0.01226)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: t1/2 of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)

End point title	PK Parameter: t1/2 of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 2 (Cohorts 1 and 2)[39]

End point description:

t1/2 is defined as the estimate of the terminal elimination half-life of the drug. Participants in the PK Analysis Set from Cohorts 1 and 2 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: hours				
median (inter-quartile range (Q1-Q3))				
SOF (Cohort 1: N = 8; Cohort 2: N = 10)	0.67 (0.59 to 0.75)	0.67 (0.57 to 0.87)		
GS-566500 (Cohort 1: N = 10; Cohort 2: N = 10)	3.31 (2.95 to 3.98)	3.88 (3.17 to 4.44)		
GS-331007 (Cohort 1: N = 10; Cohort 2: N = 10)	30.53 (19.14 to 43.25)	29.05 (17.29 to 35.15)		
RBV (Cohort 1: N = 10; Cohort 2: N = 10)	46.89 (41.03 to 47.87)	56.43 (43.06 to 71.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: t1/2 of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)

End point title	PK Parameter: t1/2 of SOF, Its Metabolites (GS-566500 and GS-331007), and RBV at Week 12 (Cohorts 1 and 2)[40]

End point description:

t1/2 is defined as the estimate of the terminal elimination half-life of the drug. Participants in the PK Analysis Set from Cohorts 1 and 2 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 12

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 3 are presented as a separate endpoint because the time frames are different.

End point values	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: hours				
median (inter-quartile range (Q1-Q3))				
SOF (Cohort 1: N = 9; Cohort 2: N = 8)	0.48 (0.45 to 0.49)	0.57 (0.48 to 0.67)		
GS-566500 (Cohort 1: N = 10; Cohort 2: N = 8)	3.03 (2.72 to 3.96)	3.88 (2.93 to 4.79)		
GS-331007 (Cohort 1: N = 10; Cohort 2: N = 8)	22.03 (18.76 to 27.96)	33.54 (13.61 to 45.15)		
RBV (Cohort 1: N = 8; Cohort 2: N = 8)	61.25 (45.37 to 88.73)	91.62 (54.00 to 171.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: t1/2 of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)

End point title	PK Parameter: t1/2 of SOF, Its Metabolites (GS-566500 and GS-331007), and LDV at Week 2 or 4 (Cohort 3)[41]

End point description:

t1/2 is defined as the estimate of the terminal elimination half-life of the drug. Participants in the PK Analysis Set from Cohort 3 with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose at Week 2 or 4

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for Cohorts 1 and 2 are presented as a separate endpoint because the time frames are different.

End point values	LDV/SOF (Cohort 3)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (inter-quartile range (Q1-Q3))				
SOF	1.18 (1.11 to 1.47)			
GS-566500	4.02 (3.57 to 4.68)			
GS-331007	39.30 (30.38 to 54.89)			
LDV	25.96 (18.25 to 31.89)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to end of treatment (Week 12 or Week 24) plus 30 days

Adverse event reporting additional description:

Safety Analysis Set: participants who took at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	SOF 200 mg + RBV 200 mg (Cohort 1)
Reporting group description:	
Participants with genotype 1 or 3 HCV infection received SOF 200 mg + RBV for 24 weeks.	
Reporting group title	SOF 400 mg + RBV 200 mg (Cohort 2)
Reporting group description:	
Participants with genotype 1 or 3 HCV infection received SOF 400 mg + RBV for 24 weeks.	
Reporting group title	LDV/SOF (Cohort 3)
Reporting group description:	
Participants with genotype 1 HCV infection received LDV/SOF for 12 weeks.	

Serious adverse events	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)	LDV/SOF (Cohort 3)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	4 / 18 (22.22%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome			

subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	SOF 200 mg + RBV 200 mg (Cohort 1)	SOF 400 mg + RBV 200 mg (Cohort 2)	LDV/SOF (Cohort 3)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	9 / 10 (90.00%)	12 / 18 (66.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Extranodal marginal zone B-cell lymphoma (MALT type)			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	4 / 18 (22.22%)
occurrences (all)	1	1	4
Chills			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Peripheral swelling			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Cough			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Irritability			
subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Anxiety			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Depressed mood			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Tearfulness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Investigations			
Weight decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Overdose			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Hypertensive heart disease			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 10 (40.00%)	0 / 10 (0.00%)	4 / 18 (22.22%)
occurrences (all)	4	0	6
Dizziness			
subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	1 / 18 (5.56%)
occurrences (all)	1	2	1
Hypoaesthesia			

subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Lethargy			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Hyperaesthesia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 10 (30.00%)	3 / 10 (30.00%)	0 / 18 (0.00%)
occurrences (all)	3	3	0
Haemolytic anaemia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	2 / 18 (11.11%)
occurrences (all)	1	1	2
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Constipation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Abdominal pain			

subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Abdominal wall haematoma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Breath odour			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Retching			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Swollen tongue			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Rash pruritic			
subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Dry skin			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Pruritus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Rash erythematous			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rash generalised			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Rash papular			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Nocturia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Renal failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	2 / 18 (11.11%)
occurrences (all)	1	1	2
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Muscle spasms			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal pain			

subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Joint swelling			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Ear infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eczema infected			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Herpes virus infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Pharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	2
Hyperkalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
Gout			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 18 (5.56%)
occurrences (all)	0	1	2
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2013	• The study design was changed from a randomized study to reflect a 2-part step-wise design to allow a full review of safety, efficacy, and PK data through posttreatment Week 4 of both doses of SOF (200 mg or 400 mg) + RBV in subjects with creatinine clearance < 30 mL/min before proceeding to the cohort of subjects on dialysis. • The assay to assess the HCV RNA levels was changed to the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. • Additional echocardiogram assessments and cardiac parameters were added to the study procedures, inclusion/exclusion criteria, treatment discontinuation criteria, medical history requirements, safety procedures, and stopping rules for toxicity. • Inclusion Criterion 5h was updated to clarify the creatinine clearance laboratory parameter values allowed for inclusion in the study. • Hematologic stimulating agents were added to the concomitant medications list as prohibited medications.
20 February 2014	• Exclusion criteria for electrocardiograms (ECG) were updated to reflect the QTcF interval • The RBV dosage and administration was modified to allow the investigator to modify the dose of RBV if he/she felt it was medically necessary • An external Data Monitoring Committee (DMC) was added to this protocol to review the progress of the study and evaluate the safety, efficacy, and PK data • Exclusion Criterion 8d was updated to include clarification on cardiac exclusion criteria: subjects with significant cardiac disease resulting in pulmonary hypertension within 1 year of screening were excluded from the study • Clarification of when echocardiograms in Part B will be performed • Updated safety language for the reporting of adverse events (AEs) and serious adverse events (SAEs).
23 February 2015	• Removed Part 2 dose group scheduled to receive SOF+RBV for 24 weeks in HCV-infected subjects on dialysis. Added Cohort 3 to include subjects with genotype 1 or 4 HCV infection with severe renal impairment (estimated glomerular filtration rate [eGFR] calculated using the Cockcroft-Gault equation < 30 mL/min) to receive LDV/SOF (90/400 mg) for 12 weeks. • Updated the approximate number of planned subjects from 40 to 30
23 April 2015	• Amiodarone was moved to the "Agents Disallowed" list based on risk of symptomatic bradycardia with coadministration of amiodarone with LDV/SOF. Postmarketing cases of symptomatic bradycardia have been reported in patients receiving amiodarone who were coadministered Harvoni (LDV/SOF). • For Cohort 3, increased the number of enrolled subjects to 15 subjects to obtain 10 evaluable subjects. • Updated the approximate number of planned subjects to approximately 35 from 30 • The grading scale for severity of AEs and laboratory abnormalities was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported