Clinical trial results:
A Phase 2, Multicenter, Open-Label, Randomized Study to Investigate the Safety and Efficacy of GS-7977 and Ribavirin Administered for 48 Weeks in Patients Infected With Chronic HCV With Cirrhosis and Portal Hypertension With or Without Liver Decompensation

Summary

EudraCT number	2012-002457-29
Trial protocol	ES
Global end of trial date	06 October 2015

Results information

Result version number	v1 (current)
This version publication date	21 August 2016
First version publication date	21 August 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-334-0125

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01687257
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 Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@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	06 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the antiviral efficacy of combination therapy with sofosbuvir (SOF) + ribavirin (RBV) for 48 weeks in compensated and decompensated subjects with chronic hepatitis C virus (HCV) infection, as measured by sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12 defined as HCV RNA < the lower limit of quantitation [LLOQ] 12 weeks posttreatment).

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	27 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	Australia: 5
Worldwide total number of subjects	50
EEA total number of subjects	17

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	45
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States, Europe, Australia, and New Zealand. The first participant was screened on 27 November 2012. The last study visit occurred on 06 October 2015.

Pre-assignment

Screening details:

63 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	SOF+RBV (Group 1)

Arm description:

SOF+RBV for up to 48 weeks

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

Dosage and administration details:

Sofosbuvir (SOF) 400 mg once daily

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

Dosage and administration details:

Ribavirin (RBV) tablets administered in a divided daily dose based on weight (< 75 kg = 1000 mg and ≥ 75 kg = 1200 mg)

Arm title	Observation/SOF+RBV (Group 2; Received Treatment)

Arm description:

Participants completed 24 weeks of observation and then received SOF+RBV for up to 48 weeks.

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

Dosage and administration details:

SOF 400 mg once daily

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RBV tablets administered in a divided daily dose based on weight (< 75 kg = 1000 mg and ≥ 75 kg = 1200 mg)

Number of subjects in period 1[1]	SOF+RBV (Group 1)	Observation/SOF+RBV (Group 2; Received Treatment)
Started	25	21
Completed	17	15
Not completed	8	6
Subject Withdrew Consent	1	1
Adverse event, non-fatal	1	-
Efficacy Failure	6	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 4 subjects who were randomized to the Observation/SOF+RBV group discontinued study during the Observation period prior to receiving study drug and are not included in the Subject Disposition. Reasons for discontinuation were as follows: Subject Withdrew Consent (N = 1) and Investigator's Discretion (N = 3).

Baseline characteristics

Reporting groups	
Reporting group title	SOF+RBV (Group 1)
Reporting group description: SOF+RBV for up to 48 weeks	
Reporting group title	Observation/SOF+RBV (Group 2; Received Treatment)
Reporting group description: Participants completed 24 weeks of observation and then received SOF+RBV for up to 48 weeks.	

Reporting group values	SOF+RBV (Group 1)	Observation/SOF+RBV (Group 2; Received Treatment)	Total
Number of subjects	25	21	46
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	55	56	
standard deviation	± 7.2	± 7	-
Gender categorical Units: Subjects			
Female	7	5	12
Male	18	16	34
Race Units: Subjects			
Black or African American	1	1	2
White	22	20	42
Asian	1	0	1
Other	1	0	1
HCV Genotype Units: Subjects			
Genotype 1a	10	8	18
Genotype 1b	9	5	14
Genotype 2a/2c	1	0	1
Genotype 2b	1	1	2
Genotype 3a	2	6	8
Genotype 4	1	1	2
Genotype 4h	1	0	1
IL28b Status			
CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	3	6	9
CT	14	10	24
TT	8	5	13
HCV RNA Category Units: Subjects			
< 800,000 IU/mL	10	5	15

≥ 800,000 IU/mL	15	16	31
Child-Pugh-Turcotte (CPT) Score Category			
CPT scores, widely used to grade the severity of cirrhosis and to determine the need for liver transplantation, are calculated based on a combination of laboratory values and clinical features. CPT scores can range from 5 to 15, with higher scores indicating a greater severity of disease.			
Units: Subjects			
CPT A (5-6)	8	10	18
CPT B (7-10)	17	11	28
Model for End-Stage Liver Disease (MELD) Score			
MELD scores, used to assess prognosis and suitability for transplant, are calculated based on laboratory values only and can range from 6 to 40, with higher scores indicating greater disease severity.			
Units: Subjects			
MELD Score 6	1	2	3
MELD Score 7	0	3	3
MELD Score 8	5	2	7
MELD Score 9	3	1	4
MELD Score 10	5	4	9
MELD Score 11	0	4	4
MELD Score 12	4	1	5
MELD Score 13	2	1	3
MELD Score 15	3	3	6
MELD Score 16	2	0	2
HCV RNA			
Units: log10 IU/mL			
arithmetic mean	6.1	6.2	
standard deviation	± 0.49	± 0.79	-
Hepatic Venous Pressure Gradient (HVPG)			
Units: mmHg			
arithmetic mean	17.4	16.4	
standard deviation	± 4.7	± 4.88	-

End points

End points reporting groups

Reporting group title	SOF+RBV (Group 1)
Reporting group description: SOF+RBV for up to 48 weeks	
Reporting group title	Observation/SOF+RBV (Group 2; Received Treatment)
Reporting group description: Participants completed 24 weeks of observation and then received SOF+RBV for up to 48 weeks.	
Subject analysis set title	Observation Period (Group 2)
Subject analysis set type	Per protocol
Subject analysis set description: 24 weeks of observation	
Subject analysis set title	All SOF+RBV (Groups 1 and 2)
Subject analysis set type	Per protocol
Subject analysis set description: This group includes participants who received SOF+RBV for up to 48 weeks in both Groups 1 and 2.	

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, 25 IU/mL) at 12 weeks after stopping study treatment. For the Observation/SOF+RBV group, SVR12 during the observational period was defined as HCV RNA < LLOQ for 12 consecutive weeks, any time during the observational period.

Participants who were randomized to the study were analyzed.

End point type	Primary

End point timeframe:

Posttreatment Week 12 (SOF+RBV) and up to 24 weeks (Observation)

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+RBV (Group 1)	Observation/SOF+RBV (Group 2; Received Treatment)	Observation Period (Group 2)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25	21	25	
Units: percentage of participants				
number (not applicable)	72	71.4	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With SVR at 4, 24, and 48 Weeks After Discontinuation of Therapy (SVR4, SVR24, and SVR48)

End point title	Percentage of Participants With SVR at 4, 24, and 48 Weeks After Discontinuation of Therapy (SVR4, SVR24, and SVR48)

End point description:

SVR4, SVR24, and SVR48 were defined as HCV RNA < LLOQ at 4, 24, and 48 weeks after stopping study treatment, respectively.

Participants who were randomized and received at least 1 dose of study drug with available data were analyzed.

End point type	Secondary

End point timeframe:

Posttreatment Weeks 4, 24, and 48

End point values	SOF+RBV (Group 1)	Observation/SOF+RBV (Group 2; Received Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	21		
Units: percentage of participants				
number (not applicable)				
SVR4 (Group 1: N = 25; Group 2: N = 21)	72	76.2		
SVR24 (Group 1: N = 25; Group 2: N = 21)	68	71.4		
SVR48 (Group 1: N = 17; Group 2: N = 13)	94.1	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing On-Treatment Virologic Failure

End point title	Percentage of Participants Experiencing On-Treatment Virologic Failure

End point description:

On-treatment virologic failure was defined as:
• 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).

Participants who were randomized and received at least 1 dose of study drug were analyzed.

End point type	Secondary

End point timeframe:

Up to 48 weeks

End point values	SOF+RBV (Group 1)	Observation/SOF+RBV (Group 2; Received Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	21		
Units: percentage of participants				
number (not applicable)	8	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Viral Relapse

End point title	Percentage of Participants Experiencing Viral Relapse

End point description:

Viral relapse was defined as HCV RNA ≥ LLOQ during the post-treatment period having achieved HCV RNA < LLOQ at end of treatment, confirmed with 2 consecutive values or last available post-treatment measurement.

Participants who were randomized and received at least 1 dose of study drug with available data were analyzed.

End point type	Secondary

End point timeframe:

Up to Posttreatment Week 24

End point values	SOF+RBV (Group 1)	Observation/SOF+RBV (Group 2; Received Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: percentage of participants				
number (not applicable)	17.4	23.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hepatic Venous Pressure Gradient (HVPG) at End of Treatment

End point title	Change From Baseline in Hepatic Venous Pressure Gradient (HVPG) at End of Treatment

End point description:

HVPG closely reflects the degree of portal hypertension in patients with cirrhosis. The end of treatment for the Observation group was defined as the end of the observation period.

Baseline values were the last available values on or prior to first dose date of any study drug.

Participants who were randomized to the study with available data at baseline and end of observation or end of treatment were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24 (Observation) and Week 48 (SOF+RBV)

End point values	SOF+RBV (Group 1)	Observation/SOF+RBV (Group 2; Received Treatment)	Observation Period (Group 2)	All SOF+RBV (Groups 1 and 2)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	19	18	21	37
Units: mmHg				
arithmetic mean (standard deviation)	-1.6 (± 4.9)	-0.4 (± 2.69)	0.5 (± 2.52)	-1 (± 3.97)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Child-Pugh-Turcotte (CPT) Score

End point title	Change From Baseline in Child-Pugh-Turcotte (CPT) Score

End point description:

CPT scores, widely used to grade the severity of cirrhosis and to determine the need for liver transplantation, are calculated based on a combination of laboratory values and clinical features. CPT scores can range from 5 to 15, with higher scores indicating a greater severity of disease. Data are presented as improvement, no change, or worsening in CPT scores at Week 24 (Observation) and Posttreatment Week 4 (SOF+RBV groups).

Improvement in CPT score was defined as having a decrease in CPT score from baseline, no change in CPT score was defined as having no change in CPT score from baseline, and worsening in CPT score was defined as having an increase in CPT score from baseline.

Baseline values were the last available values on or prior to first dose date of any study drug.

Participants who were randomized to the study with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24 (Observation) and Posttreatment Week 4 (SOF+RBV)

End point values	SOF+RBV (Group 1)	Observation/SOF+RBV (Group 2; Received Treatment)	Observation Period (Group 2)	All SOF+RBV (Groups 1 and 2)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	23	18	20	41
Units: percentage of participants				
number (not applicable)				
Improvement in CPT Score	65.2	38.9	10	53.7
No Change in CPT Score	26.1	50	75	36.6
Worsening in CPT Score	8.7	11.1	15	9.8

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Model for End Stage Liver Disease (MELD) Scores

End point title	Change From Baseline in Model for End Stage Liver Disease (MELD) Scores

End point description:

MELD scores, used to assess prognosis and suitability for transplant, are calculated based on laboratory values only and can range from 6 to 40, with higher scores indicating greater disease severity. Data are presented as improvement, no change, or worsening in MELD scores at Week 24 (Observation) and Posttreatment Week 4 (SOF+RBV groups).

Improvement in MELD score was defined as having a baseline MELD score of 11-15 or 16-20 that changed to 0-10, or a baseline MELD score of 16-20 that changed to 11-15; no change in MELD score was defined as having no change in score group (0-10, 11-15, or 16-20) from baseline; and worsening in MELD score was defined as having a baseline MELD score of 0-10 that changed to 11-15 or 16-20, or a baseline MELD score of 11-15 that changed to 16-20.

Baseline values were the last available values on or prior to first dose date of any study drug.

Participants who were randomized to the study with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24 (Observation) and Posttreatment Week 4 (SOF+RBV)

End point values	SOF+RBV (Group 1)	Observation/SOF+RBV (Group 2; Received Treatment)	Observation Period (Group 2)	All SOF+RBV (Groups 1 and 2)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	24	17	20	41
Units: percentage of participants				
number (not applicable)				
Improvement in MELD Score	33.3	5.9	20	22
No Change in MELD Score	54.2	88.2	75	68.3
Worsening in MELD Score	12.5	5.9	5	9.8

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 48 weeks plus 30 days	
Adverse event reporting additional description:	
Adverse event data includes all participants who were randomized to the study.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	SOF+RBV (Group 1)
Reporting group description:	
SOF+RBV for up to 48 weeks	
Reporting group title	Observation Period Only (Group 2)
Reporting group description:	
This reporting group includes participants who were randomized to the Observation/SOF+RBV group and received up to 24 weeks of observation.	
Reporting group title	SOF+RBV Treatment Only (Group 2)
Reporting group description:	
This reporting group includes participants who completed observation and received SOF+RBV for up to 48 weeks.	

Serious adverse events	SOF+RBV (Group 1)	Observation Period Only (Group 2)	SOF+RBV Treatment Only (Group 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 25 (16.00%)	3 / 25 (12.00%)	6 / 21 (28.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic cancer			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 21 (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
Injury, poisoning and procedural complications			

Femur fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye swelling			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Drug abuse			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
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+RBV (Group 1)	Observation Period Only (Group 2)	SOF+RBV Treatment Only (Group 2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 25 (92.00%)	10 / 25 (40.00%)	20 / 21 (95.24%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	7 / 21 (33.33%)
occurrences (all)	2	1	14
Dizziness			
subjects affected / exposed	4 / 25 (16.00%)	0 / 25 (0.00%)	3 / 21 (14.29%)
occurrences (all)	4	0	3
Hepatic encephalopathy			
subjects affected / exposed	2 / 25 (8.00%)	3 / 25 (12.00%)	2 / 21 (9.52%)
occurrences (all)	3	3	2
Disturbance in attention			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Encephalopathy			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Memory impairment			

subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Syncope			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	5 / 21 (23.81%)
occurrences (all)	2	0	5
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 25 (24.00%)	1 / 25 (4.00%)	9 / 21 (42.86%)
occurrences (all)	7	1	10
Asthenia			
subjects affected / exposed	7 / 25 (28.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
occurrences (all)	9	0	1
Oedema peripheral			
subjects affected / exposed	0 / 25 (0.00%)	3 / 25 (12.00%)	5 / 21 (23.81%)
occurrences (all)	0	3	5
Pyrexia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	4 / 21 (19.05%)
occurrences (all)	4	1	7
Peripheral swelling			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 25 (36.00%)	1 / 25 (4.00%)	6 / 21 (28.57%)
occurrences (all)	11	1	6
Diarrhoea			
subjects affected / exposed	3 / 25 (12.00%)	1 / 25 (4.00%)	6 / 21 (28.57%)
occurrences (all)	3	1	7
Abdominal pain upper			

subjects affected / exposed	3 / 25 (12.00%)	0 / 25 (0.00%)	2 / 21 (9.52%)
occurrences (all)	3	0	2
Abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	4 / 21 (19.05%)
occurrences (all)	0	1	7
Ascites			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	2 / 21 (9.52%)
occurrences (all)	2	1	2
Vomiting			
subjects affected / exposed	3 / 25 (12.00%)	1 / 25 (4.00%)	1 / 21 (4.76%)
occurrences (all)	3	1	1
Constipation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	4
Dyspepsia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Melaena			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	3
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 25 (16.00%)	0 / 25 (0.00%)	3 / 21 (14.29%)
occurrences (all)	4	0	3
Dyspnoea			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	2 / 21 (9.52%)
occurrences (all)	3	1	2
Epistaxis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			

subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	8 / 25 (32.00%)	1 / 25 (4.00%)	3 / 21 (14.29%)
occurrences (all)	9	1	3
Rash			
subjects affected / exposed	6 / 25 (24.00%)	3 / 25 (12.00%)	0 / 21 (0.00%)
occurrences (all)	8	3	0
Dry skin			
subjects affected / exposed	3 / 25 (12.00%)	0 / 25 (0.00%)	2 / 21 (9.52%)
occurrences (all)	3	0	2
Alopecia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Skin ulcer			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 25 (24.00%)	0 / 25 (0.00%)	7 / 21 (33.33%)
occurrences (all)	7	0	7
Anxiety			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	3 / 21 (14.29%)
occurrences (all)	1	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	3 / 21 (14.29%)
occurrences (all)	1	0	3
Back pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	1 / 21 (4.76%)
occurrences (all)	3	0	1
Muscle spasms			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Musculoskeletal pain			

subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 25 (12.00%)	0 / 25 (0.00%)	4 / 21 (19.05%)
occurrences (all)	3	0	4
Influenza			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Urinary tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	2 / 21 (9.52%)
occurrences (all)	0	1	3
Gastroenteritis viral			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 21 (0.00%)
occurrences (all)	0	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2012	• Update of background, safety, and concomitant medication data • Modification of subject stopping rules pertaining to alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) and bilirubin • Modification of inclusion criteria relating to birth control • Addition of exclusion criteria for bilirubin and imaging evidence or history of portal vein thrombosis • Addition of erythropoiesis-stimulating agents • Addition of guidance surrounding HVPG measurements • Clarification of self-monitoring of pregnancy
21 February 2013	• Extension of SOF+RBV treatment from 24 to 48 weeks for both treatment groups • Clarification that HPVG measurements were to be taken at screening and Week 48 for subjects in the SOF+RBV group, and at screening and Weeks 24 and 72 for subjects in the Observation/SOF+RBV group • Update of MELD definition
04 June 2013	• Addition of laboratory assessments associated with collection of CPT score during the posttreatment follow-up period • Addition of MELD score to all posttreatment follow-up visits • Clarification on collection of pharmacokinetic (PK) sample draw times • Clarification on the posttreatment follow-up period for subjects who terminate study treatment early
02 May 2014	• Incorporation of additional monitoring for subjects with elevated total bilirubin and an additional stopping criterion for subjects with elevated direct bilirubin, based on recommendations of the safety review committee
04 March 2015	• Addition of an HVPG measurement at the posttreatment Week 48 visit for subjects who achieved SVR12 to determine the effect of SVR on HVPG

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported