Clinical trial results:
A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of GS-7977 and Ribavirin for 24 Weeks in Subjects with Recurrent Chronic HCV Post Liver Transplant

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-002417-19
Trial protocol	DE ES
Global end of trial date	14 August 2014

Results information

Result version number	v1 (current)
This version publication date	20 February 2016
First version publication date	20 February 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-334-0126

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01687270
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 Information Desk, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial Information Desk, 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	14 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was an open-label, single-arm study of sofosbuvir (SOF; GS-7977) and ribavirin (RBV) in adults who had a liver transplant which became re-infected with hepatitis C. The treatment period was 24 weeks with up to 48 weeks of follow up. The total time in this study lasted up to 72 weeks not including the screening visit.

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	26 October 2012
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: 3
Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	40
EEA total number of subjects	9

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	33
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at a total of 12 study sites in the United States, Europe, and New Zealand. The first participant was screened on 26 October 2012. The last participant observation occurred on 14 August 2014.

Pre-assignment

Screening details:

49 participants were screened.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	SOF+RBV

Arm description:

Sofosbuvir (SOF) + ribavirin (RBV) for 24 weeks

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

Dosage and administration details:

Sofosbuvir (SOF) 400 mg tablet administered orally once daily

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

Dosage and administration details:

Ribavirin (RBV) 200-mg tablet(s) administered orally in a divided daily dose starting at 400 mg, subsequently adjusted (range: 200 to 1200 mg in a divided daily dose) based upon a number of factors including hemoglobin value, creatinine clearance, and weight.

Number of subjects in period 1	SOF+RBV
Started	40
Completed	28
Not completed	12
Lost to follow-up	1
Lack of efficacy	11

Baseline characteristics

Reporting groups	
Reporting group title	Overall study
Reporting group description:	
SOF+RBV for 24 weeks	

Reporting group values	Overall study	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59		
standard deviation	± 6.3	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	31	31	
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	39	39	
Unknown or Not Reported	0	0	
Race Units: Subjects			
White	34	34	
Black	3	3	
Asian	2	2	
Other	1	1	
HCV RNA Category Units: Subjects			
< 6 log10 IU/mL	8	8	
6 to 7 log10 IU/mL	20	20	
> 7 log10 IU/mL	12	12	
Prior HCV Treatment Units: Subjects			
No	5	5	
Yes	35	35	
HCV Genotype Units: Subjects			
Genotype 1A	22	22	
Genotype 1B	11	11	
Genotype 3A	5	5	
Genotype 3B	1	1	
Genotype 4	1	1	
IL28b Status			

CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	13	13	
CT	16	16	
TT	11	11	
HCV RNA			
Units: log10 IU/mL			
arithmetic mean	6.55		
standard deviation	± 0.751	-	

End points

End points reporting groups

Reporting group title	SOF+RBV
Reporting group description: Sofosbuvir (SOF) + ribavirin (RBV) for 24 weeks	

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

End point title	Percentage of Participants With Sustained Virologic Response 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) 12 weeks following the last dose of study drug.	
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 intergroup analysis was performed because the study was single-arm, and no analysis against a historic rate was performed because the study was not designed to demonstrate superiority or noninferiority.

End point values	SOF+RBV			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)	70			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Discontinue Study Drug Due to an Adverse Event

End point title	Percentage of Participants Who Discontinue Study Drug Due to an Adverse Event[2]
End point description:	
End point type	Primary
End point timeframe: Baseline to Week 24	

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 intergroup analysis was performed because the study was single-arm, and no analysis

against a historic rate was performed because the study was not designed to demonstrate superiority or noninferiority.

End point values	SOF+RBV			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)	5			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

SVR4, SVR 24, and SVR 48 were defined as HCV RNA < LLOQ 4, 24, and 48 weeks following the last dose of study
drug, respectively.

End point type	Secondary

End point timeframe:

Posttreatment Weeks 4, 24, and 48

End point values	SOF+RBV			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)				
SVR4	72.5			
SVR24	70			
SVR48	70			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HCV RNA < LLOQ at Weeks 12 and 24

End point title	Percentage of Participants With HCV RNA < LLOQ at Weeks 12 and 24

End point description:

End point type	Secondary
End point timeframe:	
Weeks 12 and 24	

End point values	SOF+RBV			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)				
Week 12 (n = 40)	100			
Week 24 (n = 38)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: HCV RNA and Change From Baseline at Weeks 2, 4, and 8

End point title	HCV RNA and Change From Baseline at Weeks 2, 4, and 8
End point description:	

End point type	Secondary
End point timeframe:	
Baseline; Weeks 2, 4, and 8	

End point values	SOF+RBV			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Week 2 (n = 39)	1.65 (± 0.37)			
Change from baseline at Week 2 (n = 39)	-4.89 (± 0.692)			
Week 4 (n = 40)	1.38 (± 0)			
Change from baseline at Week 4 (n = 40)	-5.17 (± 0.751)			
Week 8 (n = 40)	1.38 (± 0.005)			
Change from baseline at Week 8 (n = 40)	-5.17 (± 0.752)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Virologic Failure

End point title	Percentage of Participants With Virologic Failure

End point description:

Virologic failure was defined as on-treatment virologic failure or virologic relapse.

• On-treatment virologic failure: HCV RNA < LLOQ during treatment with subsequent detectable HCV RNA while
continuing treatment

• Virologic relapse: HCV RNA < LLOQ at last observed on-treatment HCV RNA measurement and HCV RNA ≥
LLOQ after stopping treatment (2 consecutive HCV RNA measurements or last available HCV RNA measurement)

End point type	Secondary

End point timeframe:

Up to Posttreatment Week 24

End point values	SOF+RBV			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)				
On-treatment virologic failure	0			
Virologic relapse	30			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 24 weeks plus 30 days	
Adverse event reporting additional description:	
Safety Analysis set	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	SOF+RBV
Reporting group description:	
SOF + RBV for 24 weeks	

Serious adverse events	SOF+RBV		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 40 (15.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Compression fracture			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Jaundice			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hallucination			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SOF+RBV		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 40 (95.00%)		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Fatigue subjects affected / exposed occurrences (all)	12 / 40 (30.00%) 13		
Oedema peripheral subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Pyrexia subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 7		
Dyspnoea subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 6		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 5		
Depression subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Insomnia subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 5		
Irritability subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 5		
Investigations Blood creatinine increased subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Laceration			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	10 / 40 (25.00%)		
occurrences (all)	11		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	8		
Lymphopenia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Diarrhoea			

subjects affected / exposed	11 / 40 (27.50%)		
occurrences (all)	12		
Dyspepsia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	9		
Oral lichen planus			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 40 (22.50%)		
occurrences (all)	12		
Back pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Candida infection			

subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2		
Metabolism and nutrition disorders Hypomagnesaemia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all) Increased appetite subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 August 2012	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin criteria for discontinuation of study treatment (ie, stopping rules) were modified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25304641