Clinical trial results:
A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks with Ribavirin or for 24 Weeks Without Ribavirin in Treatment-Experienced Cirrhotic Subjects with Chronic Genotype 1 HCV Infection

Summary

EudraCT number	2013-002296-17
Trial protocol	FR
Global end of trial date	12 November 2014

Results information

Result version number	v1 (current)
This version publication date	19 June 2016
First version publication date	19 June 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-337-0121

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01965535
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	12 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 November 2014
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 determine the antiviral efficacy of combination treatment with ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) for 24 weeks and LDV/SOF + ribavirin (RBV) for 12 weeks as measured by the proportion of subjects with sustained viral response (SVR) 12 weeks after discontinuation of therapy (SVR12), and to evaluate the safety and tolerability of each regimen as assessed by review of the accumulated safety data.

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 September 2013
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	France: 155
Worldwide total number of subjects	155
EEA total number of subjects	155

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)	123
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled study sites in France. The first participant was screened on 26 September 2013. The last study visit occurred on 12 November 2014.

Pre-assignment

Screening details:

172 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	LDV/SOF 24 Weeks

Arm description:

LDV/SOF plus placebo to match RBV in a divided daily dose for 24 weeks

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

Dosage and administration details:

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

Investigational medicinal product name	Placebo to match RBV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match RBV administered in a divided daily dose

Arm title	LDV/SOF+RBV 12 Weeks

Arm description:

Placebo to match LDV/SOF + placebo to match RBV for 12 weeks, followed by LDV/SOF + RBV for 12 weeks

Arm type	Experimental
Investigational medicinal product name	Placebo to match LDV/SOF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match LDV/SOF once daily

Investigational medicinal product name	Placebo to match RBV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match RBV administered in a divided daily dose

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

Dosage and administration details:

LDV/SOF (90/400 mg) FDC tablet 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 (200 mg tablets) administered in a divided daily dose based on weight (1000 mg per day for participants weighing < 75 kg; 1200 mg per day for participants weighing ≥ 75 kg)

Number of subjects in period 1	LDV/SOF 24 Weeks	LDV/SOF+RBV 12 Weeks
Started	78	77
Completed	76	76
Not completed	2	1
Lack of efficacy	2	1

Baseline characteristics

Reporting groups	
Reporting group title	LDV/SOF 24 Weeks
Reporting group description:	
LDV/SOF plus placebo to match RBV in a divided daily dose for 24 weeks	
Reporting group title	LDV/SOF+RBV 12 Weeks
Reporting group description:	
Placebo to match LDV/SOF + placebo to match RBV for 12 weeks, followed by LDV/SOF + RBV for 12 weeks	

Reporting group values	LDV/SOF 24 Weeks	LDV/SOF+RBV 12 Weeks	Total
Number of subjects	78	77	155
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57	56	
standard deviation	± 10.7	± 7.4	-
Gender categorical Units: Subjects			
Female	22	19	41
Male	56	58	114
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	4
Not Hispanic or Latino	76	75	151
Race Units: Subjects			
Black or African American	3	1	4
White	75	76	151
HCV Genotype Units: Subjects			
Genotype 1 (no confirmed subtype)	1	1	2
Genotype 1a	50	48	98
Genotype 1b	27	28	55
Hepatitic C Virus (HCV) RNA Units: log10 IU/mL			
arithmetic mean	6.5	6.5	
standard deviation	± 0.59	± 0.47	-

End points

End points reporting groups

Reporting group title	LDV/SOF 24 Weeks
Reporting group description:	
LDV/SOF plus placebo to match RBV in a divided daily dose for 24 weeks	
Reporting group title	LDV/SOF+RBV 12 Weeks
Reporting group description:	
Placebo to match LDV/SOF + placebo to match RBV for 12 weeks, followed by LDV/SOF + RBV 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)
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. 1 participant who was randomized to the LDV/SOF + RBV group who received placebo discontinued prior to receiving LDV/SOF + RBV and is excluded from the Full Analysis Set. 1 participant who was randomized to the LDV/SOF + RBV group received LDV/SOF + placebo, and is counted in the LDV/SOF group for the safety analysis, and in the LDV/SOF+RBV group for the efficacy analysis (ie, in the Full Analysis Set). Full Analysis Set: participant with genotype 1 HCV infection who were randomized and received at least 1 dose of active study drug.	
End point type	Primary
End point timeframe:	
Posttreatment Week 12	

End point values	LDV/SOF 24 Weeks	LDV/SOF+RBV 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	77		
Units: percentage of participants				
number (not applicable)	97.4	96.1		

Statistical analyses

Statistical analysis title	Statistical Analysis of SVR12
Statistical analysis description:	
A sample size of 75 subjects in each treatment group would provide 80% power to detect a difference of 15% in SVR12 rates (80% vs 95%) between the 2 treatment groups.	
Comparison groups	LDV/SOF 24 Weeks v LDV/SOF+RBV 12 Weeks

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Difference in proportions
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	8.6

Notes:

[1] - The 2-sided 95% confidence interval (CI) on the difference in SVR12 rates between the 2 treatment groups was constructed based on stratum-adjusted Mantel-Haenszel (MH) proportions.

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

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

End point description:

SVR4 and SVR24 were defined as HCV RNA < LLOQ at 4 and 24 weeks following the last dose of study drug, respectively.

Full Analysis Set

End point type	Secondary

End point timeframe:

Posttreatment Weeks 4 and 24

End point values	LDV/SOF 24 Weeks	LDV/SOF+RBV 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	77		
Units: percentage of participants				
number (not applicable)				
SVR4	97.4	97.4		
SVR24	97.4	96.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HCV RNA < LLOQ (ie, < 25 IU/mL) at Weeks 1, 2, 4, 8, 12, and 24

End point title	Percentage of Participants With HCV RNA < LLOQ (ie, < 25 IU/mL) at Weeks 1, 2, 4, 8, 12, and 24

End point description:

Full Analysis Set

End point type	Secondary

End point timeframe:

Weeks 1, 2, 4, 8, 12, and 24

End point values	LDV/SOF 24 Weeks	LDV/SOF+RBV 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	77		
Units: percentage of participants				
number (not applicable)				
Week 1	7.8	9.1		
Week 2	50.6	59.7		
Week 4	97.4	97.4		
Week 8	98.7	100		
Week 12	100	100		
Week 24	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HCV RNA at Weeks 1, 2, 4, 8, and 12

End point title	Change From Baseline in HCV RNA at Weeks 1, 2, 4, 8, and 12
End point description:	
Participants in Full Analysis Set with available data were analyzed.	
End point type	Secondary
End point timeframe:	
Baseline; Weeks 1, 2, 4, 8, and 12	

End point values	LDV/SOF 24 Weeks	LDV/SOF+RBV 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	77		
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Week 1 (LDV/SOF: n = 75; LDV/SOF + RBV: n = 75)	-4.1 (± 0.558)	-4.27 (± 0.547)		
Week 2 (LDV/SOF: n = 77; LDV/SOF + RBV: n = 77)	-4.74 (± 0.926)	-4.94 (± 0.452)		
Week 4 (LDV/SOF: n = 77; LDV/SOF + RBV: n = 77)	-5.1 (± 0.582)	-5.19 (± 0.433)		
Week 8 (LDV/SOF: n = 77; LDV/SOF + RBV: n = 77)	-5.11 (± 0.597)	-5.2 (± 0.448)		
Week 12 (LDV/SOF: n = 77; LDV/SOF + RBV: n = 77)	-5.11 (± 0.595)	-5.2 (± 0.448)		

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

End point type	Secondary

End point timeframe:

Up to Posttreatment Week 24

End point values	LDV/SOF 24 Weeks	LDV/SOF+RBV 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	77		
Units: percentage of participants				
number (not applicable)				
On-Treatment Virologic Failure	0	0		
Virologic Relapse	2.6	3.9		

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: participants who were randomized and received at least 1 dose of study drug	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	LDV/SOF
Reporting group description:	
LDV/SOF plus placebo to match RBV for 24 weeks	
Reporting group title	LDV/SOF+RBV
Reporting group description:	
Placebo to match LDV/SOF plus placebo to match RBV for 12 weeks, followed by LDV/SOF+RBV for 12 weeks	

Serious adverse events	LDV/SOF	LDV/SOF+RBV	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 78 (10.26%)	4 / 77 (5.19%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic encephalopathy			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Mitral valve disease			

subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			

subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LDV/SOF	LDV/SOF+RBV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 78 (85.90%)	72 / 77 (93.51%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 78 (8.97%)	7 / 77 (9.09%)	
occurrences (all)	7	7	
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 78 (39.74%)	21 / 77 (27.27%)	
occurrences (all)	41	29	
Dizziness			
subjects affected / exposed	5 / 78 (6.41%)	1 / 77 (1.30%)	
occurrences (all)	5	1	
Disturbance in attention			

subjects affected / exposed	0 / 78 (0.00%)	4 / 77 (5.19%)	
occurrences (all)	0	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	35 / 78 (44.87%)	45 / 77 (58.44%)	
occurrences (all)	37	52	
Fatigue			
subjects affected / exposed	15 / 78 (19.23%)	7 / 77 (9.09%)	
occurrences (all)	17	7	
Influenza like illness			
subjects affected / exposed	5 / 78 (6.41%)	5 / 77 (6.49%)	
occurrences (all)	5	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 78 (10.26%)	14 / 77 (18.18%)	
occurrences (all)	8	15	
Diarrhoea			
subjects affected / exposed	9 / 78 (11.54%)	9 / 77 (11.69%)	
occurrences (all)	13	10	
Abdominal pain upper			
subjects affected / exposed	7 / 78 (8.97%)	5 / 77 (6.49%)	
occurrences (all)	7	8	
Constipation			
subjects affected / exposed	5 / 78 (6.41%)	5 / 77 (6.49%)	
occurrences (all)	5	6	
Abdominal distension			
subjects affected / exposed	3 / 78 (3.85%)	4 / 77 (5.19%)	
occurrences (all)	4	4	
Dyspepsia			
subjects affected / exposed	3 / 78 (3.85%)	4 / 77 (5.19%)	
occurrences (all)	3	5	
Abdominal pain			
subjects affected / exposed	5 / 78 (6.41%)	2 / 77 (2.60%)	
occurrences (all)	7	2	
Gastrooesophageal reflux disease			

subjects affected / exposed	3 / 78 (3.85%)	4 / 77 (5.19%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 78 (14.10%)	10 / 77 (12.99%)	
occurrences (all)	13	10	
Dyspnoea			
subjects affected / exposed	3 / 78 (3.85%)	9 / 77 (11.69%)	
occurrences (all)	3	10	
Dyspnoea exertional			
subjects affected / exposed	2 / 78 (2.56%)	4 / 77 (5.19%)	
occurrences (all)	2	5	
Epistaxis			
subjects affected / exposed	5 / 78 (6.41%)	1 / 77 (1.30%)	
occurrences (all)	5	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	7 / 78 (8.97%)	12 / 77 (15.58%)	
occurrences (all)	7	12	
Dry skin			
subjects affected / exposed	4 / 78 (5.13%)	12 / 77 (15.58%)	
occurrences (all)	4	12	
Rash			
subjects affected / exposed	2 / 78 (2.56%)	5 / 77 (6.49%)	
occurrences (all)	2	7	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 78 (16.67%)	17 / 77 (22.08%)	
occurrences (all)	14	17	
Irritability			
subjects affected / exposed	9 / 78 (11.54%)	7 / 77 (9.09%)	
occurrences (all)	9	7	
Sleep disorder			
subjects affected / exposed	8 / 78 (10.26%)	5 / 77 (6.49%)	
occurrences (all)	8	5	
Musculoskeletal and connective tissue disorders			

Myalgia			
subjects affected / exposed	9 / 78 (11.54%)	8 / 77 (10.39%)	
occurrences (all)	10	8	
Arthralgia			
subjects affected / exposed	12 / 78 (15.38%)	6 / 77 (7.79%)	
occurrences (all)	14	6	
Back pain			
subjects affected / exposed	11 / 78 (14.10%)	4 / 77 (5.19%)	
occurrences (all)	13	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	13 / 78 (16.67%)	4 / 77 (5.19%)	
occurrences (all)	13	5	
Nasopharyngitis			
subjects affected / exposed	5 / 78 (6.41%)	4 / 77 (5.19%)	
occurrences (all)	5	4	
Rhinitis			
subjects affected / exposed	2 / 78 (2.56%)	4 / 77 (5.19%)	
occurrences (all)	2	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 78 (6.41%)	6 / 77 (7.79%)	
occurrences (all)	5	6	
Vitamin D deficiency			
subjects affected / exposed	3 / 78 (3.85%)	4 / 77 (5.19%)	
occurrences (all)	3	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2014	Clinical assessment of weight was added at every on-treatment study visit and physical examinations were removed from on-treatment study visits at Weeks 1, 2, 4, 8, 13, 14, 16, and 20.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There were no limitations affecting the analysis or results.

Notes: