Clinical trial results:
A Phase 2, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination in Treatment-Naive and Treatment-Experienced Subjects with Chronic Genotype 4 or 5 HCV Infection

Summary

EudraCT number	2013-003978-27
Trial protocol	FR
Global end of trial date	17 February 2015

Results information

Result version number	v1 (current)
This version publication date	15 May 2016
First version publication date	15 May 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-337-1119

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02081079
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	17 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was to evaluate the efficacy, safety, and tolerability of ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) in participants with chronic genotype 4 or 5 hepatitis C virus (HCV) infection as measured by the proportion of subjects with sustained virologic response (SVR12), defined as HCV RNA < lower limit of quantification (LLOQ) 12 weeks after discontinuation of therapy.

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 March 2014
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	France: 85
Worldwide total number of subjects	85
EEA total number of subjects	85

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)	62
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in France. The first participant was screened on 07 March 2014. The last study visit occurred on 17 February 2015.

Pre-assignment

Screening details:

91 participants were screened.

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	Genotype 4

Arm description:

LDV/SOF FDC for up to 12 weeks in participants with genotype 4 HCV infection

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:

Ledipasvir/sofosbuvir (90/400 mg) FDC once daily

Arm title	Genotype 5

Arm description:

LDV/SOF FDC for up to 12 weeks in participants with genotype 5 HCV infection

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:

Ledipasvir/sofosbuvir (90/400 mg) FDC once daily

Number of subjects in period 1	Genotype 4	Genotype 5
Started	44	41
Completed	40	39
Not completed	4	2
Lost to follow-up	1	-

Lack of efficacy	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Genotype 4
Reporting group description:	
LDV/SOF FDC for up to 12 weeks in participants with genotype 4 HCV infection	
Reporting group title	Genotype 5
Reporting group description:	
LDV/SOF FDC for up to 12 weeks in participants with genotype 5 HCV infection	

Reporting group values	Genotype 4	Genotype 5	Total
Number of subjects	44	41	85
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	51	63	
standard deviation	± 8.9	± 9.6	-
Gender categorical Units: Subjects			
Female	16	20	36
Male	28	21	49
Race Units: Subjects			
Black or African American	8	0	8
White	36	41	77
HCV Genotype Units: Subjects			
Genotype 4	44	0	44
Genotype 5	0	41	41
Cirrhosis Status Units: Subjects			
Absence	34	32	66
Presence	10	9	19
IL28b Status			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	8	19	27
CT	27	18	45
TT	9	4	13
HCV RNA Units: log10 copies/mL			
arithmetic mean	6.2	64	
standard deviation	± 0.47	± 0.47	-

Subject analysis sets

Subject analysis set title	Genotype 4: Treatment-naive
Subject analysis set type	Sub-group analysis

Subject analysis set description:

LDV/SOF FDC for up to 12 weeks in treatment-naive participants with genotype 4 HCV infection

Subject analysis set title	Genotype 4: Treatment-experienced
Subject analysis set type	Sub-group analysis

Subject analysis set description:

LDV/SOF FDC for up to 12 weeks in treatment-experienced participants with genotype 4 HCV infection

Subject analysis set title	Genotype 5: Treatment-naive
Subject analysis set type	Sub-group analysis

Subject analysis set description:

LDV/SOF FDC for up to 12 weeks in treatment-naive participants with genotype 5 HCV infection

Subject analysis set title	Genotype 5: Treatment-experienced
Subject analysis set type	Sub-group analysis

Subject analysis set description:

LDV/SOF FDC for up to 12 weeks in treatment-experienced participants with genotype 5 HCV infection

Reporting group values	Genotype 4: Treatment-naive	Genotype 4: Treatment-experienced	Genotype 5: Treatment-naive
Number of subjects	22	22	21
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52	50	61
standard deviation	± 9.2	± 8.8	± 10.4
Gender categorical Units: Subjects			
Female	11	5	10
Male	11	17	11
Race Units: Subjects			
Black or African American	3	5	0
White	19	17	21
HCV Genotype Units: Subjects			
Genotype 4	22	22	0
Genotype 5	0	0	21
Cirrhosis Status Units: Subjects			
Absence	21	13	18
Presence	1	9	3
IL28b Status			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	7	1	13

CT	11	16	7
TT	4	5	1

HCV RNA			
Units: log10 copies/mL			
arithmetic mean	6	6.3	6.2
standard deviation	± 0.4	± 0.48	± 0.48

Reporting group values	Genotype 5: Treatment-experienced		
Number of subjects	20		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	64		
standard deviation	± 8.6		
Gender categorical			
Units: Subjects			
Female	10		
Male	10		
Race			
Units: Subjects			
Black or African American	0		
White	20		
HCV Genotype			
Units: Subjects			
Genotype 4	0		
Genotype 5	20		
Cirrhosis Status			
Units: Subjects			
Absence	14		
Presence	6		
IL28b Status			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	6		
CT	11		
TT	3		
HCV RNA			
Units: log10 copies/mL			
arithmetic mean	6.6		
standard deviation	± 0.39		

End points

End points reporting groups

Reporting group title	Genotype 4
Reporting group description: LDV/SOF FDC for up to 12 weeks in participants with genotype 4 HCV infection	
Reporting group title	Genotype 5
Reporting group description: LDV/SOF FDC for up to 12 weeks in participants with genotype 5 HCV infection	
Subject analysis set title	Genotype 4: Treatment-naive
Subject analysis set type	Sub-group analysis
Subject analysis set description: LDV/SOF FDC for up to 12 weeks in treatment-naive participants with genotype 4 HCV infection	
Subject analysis set title	Genotype 4: Treatment-experienced
Subject analysis set type	Sub-group analysis
Subject analysis set description: LDV/SOF FDC for up to 12 weeks in treatment-experienced participants with genotype 4 HCV infection	
Subject analysis set title	Genotype 5: Treatment-naive
Subject analysis set type	Sub-group analysis
Subject analysis set description: LDV/SOF FDC for up to 12 weeks in treatment-naive participants with genotype 5 HCV infection	
Subject analysis set title	Genotype 5: Treatment-experienced
Subject analysis set type	Sub-group analysis
Subject analysis set description: LDV/SOF FDC for up to 12 weeks in treatment-experienced participants with genotype 5 HCV infection	

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. Full Analysis Set: participants were enrolled and received at least 1 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 statistical analysis was planned or performed.

End point values	Genotype 4: Treatment-naive	Genotype 4: Treatment-experienced	Genotype 5: Treatment-naive	Genotype 5: Treatment-experienced
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	22	21	20
Units: percentage of participants				
number (not applicable)	95.5	90.9	95.2	95

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Permanently Discontinued LDV/SOF Due to an Adverse Event

End point title	Percentage of Participants Who Permanently Discontinued LDV/SOF Due to an Adverse Event[2]

End point description:

Safety Analysis Set: participants were enrolled and received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Up to 12 weeks

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 analysis was planned or performed.

End point values	Genotype 4	Genotype 5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	41		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

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 SVR 24 were defined as HCV RNA < LLOQ at 4 and 24 weeks after stopping study treatment, respectively.

Full Analysis Set

End point type	Secondary

End point timeframe:

Posttreatment Weeks 4 and 24

End point values	Genotype 4: Treatment-naive	Genotype 4: Treatment-experienced	Genotype 5: Treatment-naive	Genotype 5: Treatment-experienced
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	22	21	20
Units: percentage of participants				
number (not applicable)				
SVR4	95.5	90.9	95.2	95
SVR24	95.5	90.9	95.2	95

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Virologic Failure

End point title	Percentage of Patients With Virologic Failure

End point description:

Virologic failure was defined as either:
• On-treatment virologic failure:
o Breakthrough (confirmed HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while on treatment), or
o Rebound (confirmed > 1 log10 IU/mL increase in HCV RNA from nadir while on treatment), or
o Non-response (HCV RNA persistently ≥ LLOQ through 8 weeks of treatment); OR
• Relapse:
o HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at end of treatment, confirmed with 2 consecutive values or last available posttreatment measurement

Full Analysis Set

End point type	Secondary

End point timeframe:

Up to posttreatment Week 24

End point values	Genotype 4: Treatment-naive	Genotype 4: Treatment-experienced	Genotype 5: Treatment-naive	Genotype 5: Treatment-experienced
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	22	21	20
Units: percentage of participants				
number (not applicable)				
On-treatment Virologic Failure	0	0	0	0
Relapse	4.5	9.1	4.8	5

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in HCV RNA at Weeks 2, 4, 8, and 12
End point description: Full Analysis Set	
End point type	Secondary
End point timeframe: Baseline; Weeks 2, 4, 8, and 12	

End point values	Genotype 4: Treatment-naive	Genotype 4: Treatment-experienced	Genotype 5: Treatment-naive	Genotype 5: Treatment-experienced
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	22	21	20
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Change at Week 2	-4.65 (± 0.397)	-4.77 (± 0.495)	-4.97 (± 0.479)	-4.94 (± 0.477)
Change at Week 4	-4.86 (± 0.396)	-5.17 (± 0.49)	-5.07 (± 0.474)	-5.39 (± 0.381)
Change at Week 8	-4.88 (± 0.401)	-5.18 (± 0.484)	-5.07 (± 0.474)	-5.45 (± 0.387)
Change at Week 12	-4.88 (± 0.401)	-5.18 (± 0.484)	-5.07 (± 0.474)	-5.45 (± 0.387)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 12 weeks plus 30 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Genotype 4

Reporting group description:

Ledipasvir/sofosbuvir (LDV/SOF) (90/400 mg) fixed-dose combination (FDC) for up to 12 weeks in participants with genotype 4 hepatitis C virus (HCV) infection

Reporting group title	Genotype 5

Reporting group description:

LDV/SOF (90/400 mg) FDC for up to 12 weeks in participants with genotype 5 HCV infection

Serious adverse events	Genotype 4	Genotype 5	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)	1 / 41 (2.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 44 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Genotype 4	Genotype 5	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 44 (70.45%)	31 / 41 (75.61%)	
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	3 / 44 (6.82%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			

Headache			
subjects affected / exposed	11 / 44 (25.00%)	11 / 41 (26.83%)	
occurrences (all)	14	13	
Dizziness			
subjects affected / exposed	0 / 44 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 44 (22.73%)	16 / 41 (39.02%)	
occurrences (all)	10	18	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 44 (6.82%)	1 / 41 (2.44%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 44 (9.09%)	3 / 41 (7.32%)	
occurrences (all)	4	3	
Nausea			
subjects affected / exposed	4 / 44 (9.09%)	1 / 41 (2.44%)	
occurrences (all)	4	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 44 (9.09%)	2 / 41 (4.88%)	
occurrences (all)	4	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 44 (9.09%)	1 / 41 (2.44%)	
occurrences (all)	4	1	
Arthralgia			
subjects affected / exposed	1 / 44 (2.27%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Myalgia			
subjects affected / exposed	1 / 44 (2.27%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Musculoskeletal pain			

subjects affected / exposed	0 / 44 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 44 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Urinary tract infection			
subjects affected / exposed	0 / 44 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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: