Clinical trial results:
A Phase 2, Open Label Study to Evaluate The Safety and Efficacy of Ledipasvir/Sofosbuvir (LDV/SOF) Fixed Dose Combination (FDC) Tablet for 12 or 24 Weeks in Kidney Transplant Recipients with Chronic HCV Infection

Summary

EudraCT number	2014-002121-35
Trial protocol	IT DE AT
Global end of trial date	16 June 2016

Results information

Result version number	v1 (current)
This version publication date	26 May 2017
First version publication date	26 May 2017

Trial information

Trial identification

Sponsor protocol code	GS-US-337-1406

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02251717
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	16 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 June 2016
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 ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) as measured by the proportion of participants who attain SVR at 12 weeks after discontinuation of therapy (SVR12) and to evaluate the safety and tolerability of each treatment 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	14 October 2014
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	Austria: 24
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 49
Worldwide total number of subjects	114
EEA total number of subjects	114

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)	99
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Europe. The first participant was screened on 14 October 2014. The last study visit occurred on 16 June 2016.

Pre-assignment

Screening details:

130 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	LDV/SOF 12 Weeks

Arm description:

LDV/SOF for 12 weeks in participants with chronic genotype 1 or 4 HCV infection who have had a kidney transplant

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

Dosage and administration details:

90/400 mg FDC tablet administered orally once daily

Arm title	LDV/SOF 24 Weeks

Arm description:

LDV/SOF for 24 weeks in participants with chronic genotype 1 or 4 HCV infection who have had a kidney transplant

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

Dosage and administration details:

90/400 mg FDC tablet administered orally once daily

Number of subjects in period 1	LDV/SOF 12 Weeks	LDV/SOF 24 Weeks
Started	57	57
Completed	56	56
Not completed	1	1
Withdrew Consent	1	-
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	LDV/SOF 12 Weeks
Reporting group description:	
LDV/SOF for 12 weeks in participants with chronic genotype 1 or 4 HCV infection who have had a kidney transplant	
Reporting group title	LDV/SOF 24 Weeks
Reporting group description:	
LDV/SOF for 24 weeks in participants with chronic genotype 1 or 4 HCV infection who have had a kidney transplant	

Reporting group values	LDV/SOF 12 Weeks	LDV/SOF 24 Weeks	Total
Number of subjects	57	57	114
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54	53	
standard deviation	± 8.3	± 10	-
Gender categorical Units: Subjects			
Female	24	24	48
Male	33	33	66
Ethnicity Units: Subjects			
Hispanic or Latino	1	4	5
Not Hispanic or Latino	56	53	109
Race Units: Subjects			
Black or African American	2	2	4
White	54	53	107
Asian	1	1	2
Other	0	1	1
HCV genotype Units: Subjects			
Genotype 1	51	53	104
Genotype 4	6	4	10
Cirrhosis Status Units: Subjects			
No	49	48	97
Yes	8	9	17
IL28b Status			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	14	18	32
CT	34	34	68
TT	9	5	14

HCV RNA Category Units: Subjects			
< 800,000 IU/mL	11	16	27
≥ 800,000 IU/mL	46	41	87
Prior HCV Treatment Status Units: Subjects			
Treatment-Naive	40	39	79
Treatment- Experienced	17	18	35
Years From Most Recent Kidney Transplant Units: years			
arithmetic mean	12.1	14.4	
standard deviation	± 9.51	± 9.66	-
HCV RNA Units: log10 IU/mL			
arithmetic mean	6.3	6.2	
standard deviation	± 0.63	± 0.53	-

End points

End points reporting groups

Reporting group title	LDV/SOF 12 Weeks
Reporting group description:	
LDV/SOF for 12 weeks in participants with chronic genotype 1 or 4 HCV infection who have had a kidney transplant	
Reporting group title	LDV/SOF 24 Weeks
Reporting group description:	
LDV/SOF for 24 weeks in participants with chronic genotype 1 or 4 HCV infection who have had a kidney transplant	

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.	
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	LDV/SOF 12 Weeks	LDV/SOF 24 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: percentage of participants				
number (confidence interval 95%)	100 (93.7 to 100)	100 (93.7 to 100)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Permanently Discontinued Any Study Drug Due to an Adverse Event

End point title	Percentage of Participants Who Permanently Discontinued Any Study Drug Due to an Adverse Event[2]
End point description:	
End point type	Primary
End point timeframe:	
Up to 24 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 comparison was planned or performed.

End point values	LDV/SOF 12 Weeks	LDV/SOF 24 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: percentage of participants				
number (not applicable)	1.8	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 SVR24 were defined as HCV RNA < LLOQ at 4 and 24 weeks after stopping study treatment, respectively.

End point type	Secondary

End point timeframe:

Posttreatment Weeks 4 and 24

End point values	LDV/SOF 12 Weeks	LDV/SOF 24 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: percentage of participants				
number (confidence interval 95%)				
SVR4	100 (93.7 to 100)	100 (93.7 to 100)		
SVR24	100 (93.7 to 100)	100 (93.7 to 100)		

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:

• 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 ontreatment visit.

End point type	Secondary

End point timeframe:

Up to Posttreatment Week 24

End point values	LDV/SOF 12 Weeks	LDV/SOF 24 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: percentage of participants				
number (not applicable)	0	0		

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	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	LDV/SOF 12 Weeks
Reporting group description:	
LDV/SOF for 12 weeks in participants with chronic genotype 1 or 4 HCV infection who have had a kidney transplant	
Reporting group title	LDV/SOF 24 Weeks
Reporting group description:	
LDV/SOF for 24 weeks in participants with chronic genotype 1 or 4 HCV infection who have had a kidney transplant	

Serious adverse events	LDV/SOF 12 Weeks	LDV/SOF 24 Weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 57 (8.77%)	8 / 57 (14.04%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Incisional hernia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Shunt thrombosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Arteriovenous shunt operation			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
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			
Pulmonary embolism			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Intervertebral disc protrusion			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
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	LDV/SOF 12 Weeks	LDV/SOF 24 Weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 57 (40.35%)	36 / 57 (63.16%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 57 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	3	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 57 (15.79%)	13 / 57 (22.81%)	
occurrences (all)	9	14	
Somnolence			
subjects affected / exposed	1 / 57 (1.75%)	3 / 57 (5.26%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 57 (1.75%)	3 / 57 (5.26%)	
occurrences (all)	1	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 57 (14.04%)	8 / 57 (14.04%)	
occurrences (all)	8	9	
Fatigue			
subjects affected / exposed	4 / 57 (7.02%)	7 / 57 (12.28%)	
occurrences (all)	4	9	
Oedema peripheral			
subjects affected / exposed	0 / 57 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 57 (0.00%)	4 / 57 (7.02%)	
occurrences (all)	0	5	
Diarrhoea			
subjects affected / exposed	3 / 57 (5.26%)	5 / 57 (8.77%)	
occurrences (all)	3	5	
Nausea			
subjects affected / exposed	3 / 57 (5.26%)	3 / 57 (5.26%)	
occurrences (all)	3	3	
Vomiting			
subjects affected / exposed	3 / 57 (5.26%)	1 / 57 (1.75%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 57 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	3	
Dyspnoea			
subjects affected / exposed	1 / 57 (1.75%)	4 / 57 (7.02%)	
occurrences (all)	1	4	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	4 / 57 (7.02%)	0 / 57 (0.00%)	
occurrences (all)	4	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 57 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	5	
Nasopharyngitis			
subjects affected / exposed	0 / 57 (0.00%)	5 / 57 (8.77%)	
occurrences (all)	0	5	
Urinary tract infection			
subjects affected / exposed	4 / 57 (7.02%)	4 / 57 (7.02%)	
occurrences (all)	4	7	
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	2 / 57 (3.51%)	5 / 57 (8.77%)	
occurrences (all)	2	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2014	Text was updated to ensure clear direction to investigators on the possible methods to manage study drug in the event that a subject requires treatment adjustments due to changes in creatinine clearance.
17 April 2015	- A safety update regarding disallowed medication. Amiodarone has been added to the "Agents Disallowed" list based on risk of symptomatic bradycardia with coadministration of amiodarone with ledipasvir/sofosbuvir. Postmarketing cases of symptomatic bradycardia have been reported in patients receiving amiodarone who were coadministered Harvoni® (ledipasvir/sofosbuvir) or Sovaldi® (sofosbuvir) in combination with another direct acting antiviral. - Alignment in Gilead protocols for clarification of requirements for use of abstinence as a form of contraception based on a UK competent authority request - Minor administrative changes made to Italian Amendment 1, dated 29 September 2014 based on request from the competent Italian authority, AIFA.
19 June 2015	Updated the information related to the interaction of LDV/SOF with dabigatran, in line with the approved SmPC of Harvoni based on request from VHP.

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:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27842383