



## Clinical trial results:

### Open-Label Study to Evaluate the Safety and Efficacy of Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) for 6 Weeks in Subjects with Acute Genotype 1 or 4 Hepatitis C Virus (HCV) and Chronic Human Immunodeficiency Virus (HIV)-1 Co-Infection

#### Summary

EudraCT number	2014-004812-12
Trial protocol	DE GB
Global end of trial date	08 January 2016

#### Results information

Result version number	v1 (current)
This version publication date	23 January 2017
First version publication date	23 January 2017

#### Trial information

##### Trial identification

Sponsor protocol code	GS-US-337-1612
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02457611
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 Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trials 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	08 January 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 January 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of this study are to determine the antiviral efficacy, safety, and tolerability of ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) in adults with acute genotype 1 or 4 hepatitis C virus (HCV) and chronic human immunodeficiency virus (HIV)-1 co-infection.

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	11 June 2015
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	United Kingdom: 11
Country: Number of subjects enrolled	Germany: 15
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	26
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at study sites in Germany and the United Kingdom. The first participant was screened on 11 June 2015. The last study visit occurred on 8 January 2016.

### Pre-assignment

Screening details:

34 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

<b>Arm title</b>	LDV/SOF
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Arm description:

Ledipasvir/sofosbuvir (Harvoni®; LDV/SOF) (90/400 mg) fixed-dose combination (FDC) tablet administered once daily for 6 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:

90/400 mg FDC administered once daily

Number of subjects in period 1	LDV/SOF
Started	26
Completed	23
Not completed	3
Lost to follow-up	3

## Baseline characteristics

### Reporting groups

Reporting group title	LDV/SOF
Reporting group description:	
Ledipasvir/sofosbuvir (Harvoni®; LDV/SOF) (90/400 mg) fixed-dose combination (FDC) tablet administered once daily for 6 weeks	

Reporting group values	LDV/SOF	Total	
Number of subjects	26	26	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	41		
standard deviation	± 8.8	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	26	26	
Race			
Units: Subjects			
Black or African American	1	1	
White	24	24	
Asian	1	1	
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	22	22	
Not Disclosed	3	3	
IL28b Status			
Units: Subjects			
CC	12	12	
CT	11	11	
TT	3	3	
HCV Genotype			
Units: Subjects			
Genotype 1a	19	19	
Genotype 4	7	7	
HCV RNA Category			
Units: Subjects			
< 800,000 IU/mL	14	14	
≥ 800,000 IU/mL	12	12	
HCV RNA			
Units: log10 IU/mL			
arithmetic mean	5.4		
standard deviation	± 1.6	-	
CD4 Counts			

Units: cells/uL			
arithmetic mean	675		
standard deviation	± 251.3	-	

## End points

### End points reporting groups

Reporting group title	LDV/SOF
Reporting group description: Ledipasvir/sofosbuvir (Harvoni®; LDV/SOF) (90/400 mg) fixed-dose combination (FDC) tablet administered once daily for 6 weeks	

### Primary: Percentage of Participants With Sustained Virologic Response 12 Weeks After Completion of Treatment (SVR12)

End point title	Percentage of Participants With Sustained Virologic Response 12 Weeks After Completion of Treatment (SVR12) <sup>[1]</sup>
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End point description:

SVR12 was defined as HCV RNA < the lower limit of quantitation (LLOQ) 12 weeks following the last dose of study drug.

Full Analysis Set: participants with genotype 1 or 4 HCV infection who were enrolled into the study and received at least 1 dose of study drug

End point type	Primary
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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.

<b>End point values</b>	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Percentage of participants				
number (confidence interval 95%)	76.9 (56.4 to 91)			

### 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 <sup>[2]</sup>
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End point description:

Safety Analysis Set: participants who received at least 1 dose of study drug

End point type	Primary
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End point timeframe:

Up to 6 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.

<b>End point values</b>	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Percentage of participants				
number (not applicable)	0			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Sustained Virologic Response 4 Weeks After Discontinuation of Study Treatment (SVR4)

End point title	Percentage of Participants With Sustained Virologic Response 4 Weeks After Discontinuation of Study Treatment (SVR4)
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End point description:

SVR4 was defined as HCV RNA < LLOQ 4 weeks after the last dose of study drug.

Full Analysis Set

End point type	Secondary
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End point timeframe:

Posttreatment Week 4

<b>End point values</b>	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Percentage of Participants				
number (confidence interval 95%)	84.6 (65.1 to 95.6)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With HCV RNA < LLOQ on Treatment

End point title	Percentage of Participants With HCV RNA < LLOQ on Treatment
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End point description:

Full Analysis Set

End point type	Secondary
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End point timeframe:

Weeks 2, 4, and 6



End point values	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 2	73.1 (52.2 to 88.4)			
Week 4	88.5 (69.8 to 97.6)			
Week 6	96.2 (80.4 to 99.9)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in HCV RNA at Weeks 2, 4, and 6

End point title	Change From Baseline in HCV RNA at Weeks 2, 4, and 6
End point description:	Participants in the Full Analysis Set with available data were analyzed.
End point type	Secondary
End point timeframe:	Baseline; Weeks 2, 4, and 6

End point values	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Change at Week 2 (N=26)	-4.01 (± 1.497)			
Change at Week 4 (N= 25)	-4.16 (± 1.583)			
Change at Week 6 (N= 25)	-4.17 (± 1.583)			

### 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	
confirmed HCV RNA $\geq$ LLOQ after having previously had HCV RNA $<$ LLOQ, while on treatment (ie, breakthrough),	
confirmed $> 1$ log <sub>10</sub> IU/mL increase in HCV RNA from nadir while on treatment (ie, rebound),	
HCV RNA persistently $\geq$ LLOQ through end of treatment (ie, nonresponse)	
Relapse	
HCV RNA $\geq$ LLOQ during the posttreatment period having achieved HCV RNA $<$ LLOQ at end of treatment, confirmed with 2 consecutive values or last available posttreatment measurement	
End point type	Secondary
End point timeframe:	
Up to Posttreatment Week 12	

<b>End point values</b>	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Percentage of participants				
number (not applicable)	15.4			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in HIV RNA From Day 1 to End of Treatment as Assessed by Proportion of Participants Who Had Confirmed HIV Virologic Rebound During the Study.

End point title	Change in HIV RNA From Day 1 to End of Treatment as Assessed by Proportion of Participants Who Had Confirmed HIV Virologic Rebound During the Study.
End point description:	
Participants with HIV virologic rebound was defined as participants with at least two HIV RNA $\geq 400$ copies/mL at 2 consecutive post-baseline visits which are at least 2 weeks apart based on actual dates.	
Safety Analysis Set	
End point type	Secondary
End point timeframe:	
Day 1; Week 6	

<b>End point values</b>	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: log <sub>10</sub> IU/mL				
number (not applicable)	0			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants That Maintain HIV-1 RNA < 50 Copies/mL While on HCV Treatment and at Posttreatment Week 4

End point title	Percentage of Participants That Maintain HIV-1 RNA < 50 Copies/mL While on HCV Treatment and at Posttreatment Week 4
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End point description:

Participants in the Safety Analysis Set who had HIV-1 RNA < 50 copies/mL at Baseline were analyzed.

End point type	Secondary
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End point timeframe:

Weeks 2, 4, 6, and Posttreatment Week 4

End point values	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Percentage of participants				
number (confidence interval 95%)				
Week 2	100 (83.9 to 100)			
Week 4	100 (83.9 to 100)			
Week 6	95.2 (76.2 to 99.9)			
Posttreatment Week 4	100 (83.9 to 100)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline on CD4 T-cell Count at the End of Treatment and at Posttreatment Week 4

End point title	Percent Change From Baseline on CD4 T-cell Count at the End of Treatment and at Posttreatment Week 4
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End point description:

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary
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End point timeframe:

Baseline; Week 6; Posttreatment Week 4

<b>End point values</b>	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Percent change				
arithmetic mean (standard deviation)				
Change at Week 6 (N = 24)	-0.3 (± 4.91)			
Change at Posttreatment Week 4 (N = 23)	0.4 (± 4.08)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 6 weeks plus 30 days

Adverse event reporting additional description:

Safety Analysis Set

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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### Reporting groups

Reporting group title	LDV/SOF
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Reporting group description:

LDV/SOF 90/400 mg FDC tablet administered once daily for 6 weeks

Serious adverse events	LDV/SOF		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 26 (3.85%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 26 (3.85%)		
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	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Pneumonia aspiration			
subjects affected / exposed	1 / 26 (3.85%)		
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 %

<b>Non-serious adverse events</b>	LDV/SOF		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 26 (76.92%)		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 26 (23.08%)		
occurrences (all)	8		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 26 (26.92%)		
occurrences (all)	9		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 26 (26.92%)		
occurrences (all)	7		
Oral herpes			

subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Syphilis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2015	<ul style="list-style-type: none"><li>• Additional exclusion period for the use of investigational drugs or devices to meet German regulatory preferences.</li><li>• Clarification of contraceptive requirements.</li></ul>
05 March 2015	Clarification that subjects may not have antiretroviral regimens changed to support entry to the trial.
30 March 2015	Added amiodarone 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.

Notes:

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### 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: