Clinical trial results:
A Phase 3, Global, Multicenter, Randomized, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir/GS-9857 Fixed-Dose Combination for 8 Weeks and Sofosbuvir/Velpatasvir for 12 Weeks in Subjects with Chronic Genotype 3 HCV Infection and Cirrhosis

Summary

EudraCT number	2015-002996-12
Trial protocol	DE GB FR
Global end of trial date	02 January 2017

Results information

Result version number	v1 (current)
This version publication date	16 December 2017
First version publication date	16 December 2017

Trial information

Trial identification

Sponsor protocol code	GS-US-367-1173

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02639338
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	02 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy, safety, and tolerability of treatment with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) fixed-dose combination (FDC) for 8 weeks and of treatment with sofosbuvir/velpatasvir (SOF/VEL) FDC for 12 weeks in participants naive to direct-acting antivirals (DAA) with chronic genotype 3 HCV infection and cirrhosis.

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	23 December 2015
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	United Kingdom: 15
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	United States: 96
Worldwide total number of subjects	220
EEA total number of subjects	59

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)	204
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America, Europe, and Asia Pacific. The first participant was screened on 23 December 2015. The last study visit occurred on 02 January 2017.

Pre-assignment

Screening details:

315 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	SOF/VEL/VOX 8 Weeks

Arm description:

SOF/VEL/VOX (400/100/100 mg) FDC tablet orally once daily with food for 8 weeks

Arm type	Experimental
Investigational medicinal product name	Sofosbuvir/Velpatasvir/Voxilaprevir
Investigational medicinal product code	
Other name	Vosevi®, SOF/VEL/VOX
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400/100/100 mg once daily with food for 8 weeks

Arm title	SOF/VEL 12 Weeks

Arm description:

SOF/VEL (400/100 mg) FDC tablet orally once daily without regard to food for 12 weeks

Arm type	Experimental
Investigational medicinal product name	Sofosbuvir/Velpatasvir
Investigational medicinal product code	
Other name	Epclusa®, SOF/VEL
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400/100 mg once daily without regard to food for 12 weeks

Number of subjects in period 1[1]	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks
Started	110	109
Completed	106	105
Not completed	4	4
Withdrew Consent	1	2

Death	1	-
Lost to follow-up	2	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1 participant in SOF/VEL group who was randomized but not treated is not included in the subject disposition table.

Baseline characteristics

Reporting groups	
Reporting group title	SOF/VEL/VOX 8 Weeks
Reporting group description:	
SOF/VEL/VOX (400/100/100 mg) FDC tablet orally once daily with food for 8 weeks	
Reporting group title	SOF/VEL 12 Weeks
Reporting group description:	
SOF/VEL (400/100 mg) FDC tablet orally once daily without regard to food for 12 weeks	

Reporting group values	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks	Total
Number of subjects	110	109	219
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54	55	
standard deviation	± 8.5	± 8.4	-
Gender categorical Units: Subjects			
Female	36	26	62
Male	74	83	157
IL28b Status			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	41	52	93
CT	57	44	101
TT	12	13	25
HCV RNA Category Units: Subjects			
< 800,000 IU/mL	40	28	68
≥ 800,000 IU/mL	70	81	151
Race Units: Subjects			
White	100	97	197
Asian	8	9	17
American Indian or Alaska Native	1	1	2
Black or African American	0	1	1
Native Hawaiian or Pacific Islander	0	1	1
Other	1	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	9	8	17
Not Hispanic or Latino	101	101	202
HCV RNA Units: log10 IU/mL			
arithmetic mean	6.0	6.3	

standard deviation	± 0.8	± 0.63	-

End points

End points reporting groups

Reporting group title	SOF/VEL/VOX 8 Weeks
Reporting group description:	
SOF/VEL/VOX (400/100/100 mg) FDC tablet orally once daily with food for 8 weeks	
Reporting group title	SOF/VEL 12 Weeks
Reporting group description:	
SOF/VEL (400/100 mg) FDC tablet orally once daily without regard to food 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)[1]
End point description:	
1) SVR12 was defined as HCV RNA < the lower limit of quantitation (LLOQ) at 12 weeks after stopping study treatment. 2) Full Analysis Set: all randomized/enrolled participants who took at least 1 dose of the 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: The statistical analysis of this primary efficacy endpoint is provided in the attachment.

End point values	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	109		
Units: percentage of participants				
number (confidence interval 95%)	96.4 (91.0 to 99.0)	96.3 (90.9 to 99.0)		

Attachments (see zip file)	Primary Efficacy Endpoint Analysis.pdf

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants Who Permanently Discontinue Study Drug Due to an Adverse Event[2]
End point description:	
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 comparison was planned or performed.

End point values	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	109		
Units: percentage of participants				
number (not applicable)	0	0.9		

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:

1) SVR4 and SVR24 were defined as HCV RNA < LLOQ at 4 and 24 weeks after stopping study treatment, respectively.
2) Full Analysis Set

End point type	Secondary

End point timeframe:

Posttreatment Weeks 4 and 24

End point values	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	109		
Units: percentage of participants				
number (confidence interval 95%)				
SVR4	97.3 (92.2 to 99.4)	97.2 (92.2 to 99.4)		
SVR24	96.4 (91.0 to 99.0)	96.3 (90.9 to 99.0)		

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

End point description:

1) Percentage of participants in Full Analysis Set with on-treatment data were analyzed.
2) 999 = Not Applicable (NA) (The treatment for this group was only 8 weeks.)

End point type	Secondary

End point timeframe:

Weeks 1, 2, 4, 8 and 12

End point values	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	109		
Units: percentage of participants				
number (confidence interval 95%)				
Week 1 (SOF/VEL/VOX: N = 110; SOF/VEL: N= 109)	17.3 (10.7 to 25.7)	10.1 (5.1 to 17.3)		
Week 2 (SOF/VEL/VOX: N = 110; SOF/VEL: N= 108)	56.4 (46.6 to 65.8)	50.9 (41.1 to 60.7)		
Week 4 (SOF/VEL/VOX: N = 110; SOF/VEL: N= 108)	87.3 (79.6 to 92.6)	85.2 (77.1 to 91.3)		
Week 8 (SOF/VEL/VOX: N = 110; SOF/VEL: N= 108)	97.3 (92.2 to 99.4)	99.1 (94.9 to 100.0)		
Week 12 (SOF/VEL/VOX: N = NA; SOF/VEL: N= 107)	999 (999 to 999)	100.0 (96.6 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HCV RNA

End point title	Change From Baseline in HCV RNA

End point description:

1) Participants in the Full Analysis Set with available data were analyzed.
2) 999 = Not Applicable (NA) (The treatment for this group was only 8 weeks.)

End point type	Secondary

End point timeframe:

Weeks 1, 2, 4, 8 and 12

End point values	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	109		
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Week 1 (SOF/VEL/VOX: N = 106; SOF/VEL: N= 105)	-4.06 (± 0.716)	-4.09 (± 0.653)		

Week 2 (SOF/VEL/VOX: N = 109; SOF/VEL: N= 107)	-4.60 (± 0.825)	-4.73 (± 0.783)		
Week 4 (SOF/VEL/VOX: N = 109; SOF/VEL: N= 108)	-4.84 (± 0.789)	-5.00 (± 0.781)		
Week 8 (SOF/VEL/VOX: N = 107; SOF/VEL: N= 108)	-4.9 (± 0.801)	-5.09 (± 0.832)		
Week 12 (SOF/VEL/VOX: N = NA; SOF/VEL: N= 107)	999 (± 999)	-5.14 (± 0.630)		

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:

1) Virologic failure was defined as either ontreatment virologic failure or virologic relapse. Ontreatment virologic failure = either breakthrough (confirmed HCV RNA ≥ LLOQ after having previously had HCV RNA <
LLOQ on 2 consecutive measurements while on treatment), or rebound (confirmed > 1 log10 IU/mL increase in HCV RNA from nadir while on treatment). Virologic relapse = confirmed HCV RNA ≥ LLOQ during
the posttreatment period having achieved HCV RNA < LLOQ at last ontreatment visit.
2) Full Analysis Set

End point type	Secondary

End point timeframe:

Up to Posttreatment Week 24

End point values	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	109		
Units: percentage of participants				
number (not applicable)	1.8	1.8		

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	
Adverse event reporting additional description:	
Safety Analysis Set	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	SOF/VEL/VOX 8 Weeks
Reporting group description:	
SOF/VEL/VOX (400/100/100 mg) FDC tablet orally once daily with food for 8 weeks	
Reporting group title	SOF/VEL 12 Weeks
Reporting group description:	
SOF/VEL (400/100 mg) FDC tablet once daily without regard to food for 12 weeks	

Serious adverse events	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 110 (1.82%)	3 / 109 (2.75%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (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			
Costochondritis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudarthrosis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
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	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 110 (61.82%)	61 / 109 (55.96%)	
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 110 (24.55%)	32 / 109 (29.36%)	
occurrences (all)	28	34	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 110 (25.45%)	31 / 109 (28.44%)	
occurrences (all)	28	31	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	23 / 110 (20.91%)	10 / 109 (9.17%)	
occurrences (all)	23	10	
Diarrhoea			
subjects affected / exposed	17 / 110 (15.45%)	5 / 109 (4.59%)	
occurrences (all)	17	5	
Abdominal pain			
subjects affected / exposed	9 / 110 (8.18%)	5 / 109 (4.59%)	
occurrences (all)	9	5	
Abdominal pain upper			
subjects affected / exposed	2 / 110 (1.82%)	7 / 109 (6.42%)	
occurrences (all)	2	7	
Vomiting			
subjects affected / exposed	7 / 110 (6.36%)	1 / 109 (0.92%)	
occurrences (all)	7	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 110 (5.45%)	5 / 109 (4.59%)	
occurrences (all)	6	5	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	7 / 110 (6.36%)	2 / 109 (1.83%)	
occurrences (all)	7	2	
Back pain			
subjects affected / exposed	1 / 110 (0.91%)	6 / 109 (5.50%)	
occurrences (all)	1	7	
Myalgia			
subjects affected / exposed	1 / 110 (0.91%)	6 / 109 (5.50%)	
occurrences (all)	1	6	

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

None reported