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 12 Weeks and Sofosbuvir/Velpatasvir for 12 Weeks in Direct-Acting Antiviral-Experienced Subjects with Chronic HCV Infection who Have Not Received an NS5A Inhibitor

Summary

EudraCT number	2015-003167-10
Trial protocol	DE FR GB
Global end of trial date	18 January 2017

Results information

Result version number	v1 (current)
This version publication date	01 February 2018
First version publication date	01 February 2018

Trial information

Trial identification

Sponsor protocol code	GS-US-367-1170

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02639247
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., GileadClinicalTrials@gilead.com
Scientific contact	Clinical Trials Mailbox, Gilead Sciences International Ltd., GileadClinicalTrials@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	18 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 October 2016
Global end of trial reached?	Yes
Global end of trial date	18 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy, safety, and tolerability of treatment with sofosbuvir/velpatasvir/voxilaprevir (Vosevi®; SOF/VEL/VOX) fixed-dose combination (FDC) for 12 weeks and of sofosbuvir/velpatasvir (Epclusa®; SOF/VEL) FDC for 12 weeks in direct-acting antiviral (DAA)-experienced adults with chronic hepatitis C virus (HCV) infection with or without cirrhosis who have not received prior treatment with a regimen containing an inhibitor of the HCV NS5A protein.

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: 12
Country: Number of subjects enrolled	France: 45
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	United States: 188
Country: Number of subjects enrolled	New Zealand: 3
Worldwide total number of subjects	333
EEA total number of subjects	81

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)	284
From 65 to 84 years	48
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled across 101 study sites in North America, Europe, and Asia Pacific. The first participant was screened on 23 December 2015. The last study visit occurred on 18 January 2017.

Pre-assignment

Screening details:

397 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 12 Weeks

Arm description:

SOF/VEL/VOX (400/100/100 mg) fixed-dose combination (FDC) tablet orally once daily for 12 weeks

Arm type	Experimental
Investigational medicinal product name	SOF/VEL/VOX
Investigational medicinal product code	
Other name	Vosevi®, GS-7977/GS-5816/GS-9857
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400/100/100 mg FDC tablet administered orally once daily with food

Arm title	SOF/VEL 12 Weeks

Arm description:

SOF/VEL (400/100 mg) FDC tablet orally once daily for 12 weeks

Arm type	Experimental
Investigational medicinal product name	SOF/VEL
Investigational medicinal product code	
Other name	Epclusa®, GS-7977/GS-5816
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400/100 mg FDC tablet administered orally once daily without regard to food

Number of subjects in period 1	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks
Started	182	151
Completed	177	149
Not completed	5	2
Withdrew Consent	-	1

Death	2	-
Protocol Violation	1	-
Lost to follow-up	2	1

Baseline characteristics

Reporting groups	
Reporting group title	SOF/VEL/VOX 12 Weeks
Reporting group description:	
SOF/VEL/VOX (400/100/100 mg) fixed-dose combination (FDC) tablet orally once daily for 12 weeks	
Reporting group title	SOF/VEL 12 Weeks
Reporting group description:	
SOF/VEL (400/100 mg) FDC tablet orally once daily for 12 weeks	

Reporting group values	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks	Total
Number of subjects	182	151	333
Age categorical Units: Subjects			
Age continuous			
Safety Analysis Set: all participants who received at least 1 dose of study drug			
Units: years			
arithmetic mean	57	57	
standard deviation	± 9.0	± 7.3	-
Gender categorical Units: Subjects			
Female	39	37	76
Male	143	114	257
Race/Ethnicity Units: Subjects			
White	160	131	291
Black or African American	16	13	29
Asian	2	4	6
Other	2	1	3
American Indian or Alaska Native	2	0	2
Native Hawaiian or Pacific Islander	0	2	2
Race/Ethnicity Units: Subjects			
Hispanic or Latino	19	8	27
Not Hispanic or Latino	163	143	306
IL28b Status			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	33	29	62
CT	107	95	202
TT	42	27	69
HCV RNA Category Units: Subjects			
< 800,000 IU/mL	46	38	84
≥ 800,000 IU/mL	136	113	249

HCV RNA			
Units: log10 IU/mL			
arithmetic mean	6.3	6.3	
standard deviation	± 0.56	± 0.66	-

End points

End points reporting groups

Reporting group title	SOF/VEL/VOX 12 Weeks
Reporting group description:	
SOF/VEL/VOX (400/100/100 mg) fixed-dose combination (FDC) tablet orally once daily for 12 weeks	
Reporting group title	SOF/VEL 12 Weeks
Reporting group description:	
SOF/VEL (400/100 mg) FDC tablet orally once daily 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:	
SVR12 is defined as HCV RNA < the lower limit of quantitation (LLOQ) at 12 weeks after stopping study treatment. Full Analysis Set (FAS) included all randomized or enrolled participants who took 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: The statistical analysis of this primary endpoint is provided in the attachment.

End point values	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	151		
Units: percentage of participants				
number (confidence interval 95%)	97.8 (94.5 to 99.4)	90.1 (84.1 to 94.3)		

Attachments (see zip file)	Primary_Endpoint_StatsAnalysis/Primary_Endpoint_StatsAnalys

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:	
Safety Analysis Set included participants who took 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	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	151		
Units: percentage of participants				
number (not applicable)	0	0.7		

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 are 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	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	151		
Units: percentage of participants				
number (confidence interval 95%)				
SVR4	98.4 (95.3 to 99.7)	91.4 (85.7 to 95.3)		
SVR24	97.8 (94.5 to 99.4)	90.1 (84.1 to 94.3)		

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:	
Full Analysis Set	
End point type	Secondary
End point timeframe:	
Weeks 1, 2, 4, 8 and 12	

End point values	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	151		
Units: percentage of participants				
number (confidence interval 95%)				
Week 1	15.9 (10.9 to 22.1)	17.2 (11.6 to 24.2)		
Week 2	62.6 (55.2 to 69.7)	56.3 (48.0 to 64.3)		
Week 4	88.5 (82.9 to 92.7)	90.7 (84.9 to 94.8)		
Week 8	100.0 (98.0 to 100.0)	98.7 (95.3 to 99.8)		
Week 12	98.9 (96.1 to 99.9)	99.3 (96.3 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:	
Participants in the Full Analysis Set with available data were analyzed.	
End point type	Secondary
End point timeframe:	
Weeks 1, 2, 4, 8, and 12	

End point values	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	151		
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Change at Wk 1 (SOF/VEL/VOX:N=181, SOF/VEL:N=148)	-4.29 (± 0.627)	-4.17 (± 0.651)		
Change at Wk 2 (SOF/VEL/VOX:N=180, SOF/VEL:N=151)	-4.93 (± 0.604)	-4.78 (± 0.677)		
Change at Wk 4 (SOF/VEL/VOX:N=182, SOF/VEL:N=151)	-5.13 (± 0.561)	-5.06 (± 0.66)		

Change at Wk 8 (SOF/VEL/VOX:N=182, SOF/VEL:N=150)	-5.17 (± 0.562)	-5.08 (± 0.759)		
Change at Wk 12 (SOF/VEL/VOX:N=180,	-5.17 (± 0.559)	-5.09 (± 0.727)		

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:

- 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 on-treatment visit.

End point type	Secondary

End point timeframe:

Up to Posttreatment Week 24

End point values	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	151		
Units: percentage of participants				
number (not applicable)	0.5	9.9		

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: all participants who received at least 1 dose of study drug	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	SOF/VEL/VOX 12 Weeks
Reporting group description:	
SOF/VEL/VOX (400/100/100 mg) fixed-dose combination (FDC) tablet orally once daily for 12 weeks	
Reporting group title	SOF/VEL 12 Weeks
Reporting group description:	
SOF/VEL (400/100 mg) FDC tablet orally once daily for 12 weeks	

Serious adverse events	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 182 (2.20%)	4 / 151 (2.65%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 182 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 182 (0.55%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 182 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure congestive			
subjects affected / exposed	1 / 182 (0.55%)	0 / 151 (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			
Cerebrovascular accident			
subjects affected / exposed	0 / 182 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 182 (0.55%)	0 / 151 (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	1 / 182 (0.55%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 182 (0.00%)	1 / 151 (0.66%)	
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 12 Weeks	SOF/VEL 12 Weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 182 (60.99%)	88 / 151 (58.28%)	
Nervous system disorders			
Headache			
subjects affected / exposed	50 / 182 (27.47%)	43 / 151 (28.48%)	
occurrences (all)	55	43	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	43 / 182 (23.63%)	43 / 151 (28.48%)	
occurrences (all)	43	45	
Asthenia			
subjects affected / exposed	10 / 182 (5.49%)	9 / 151 (5.96%)	
occurrences (all)	11	9	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	36 / 182 (19.78%)	7 / 151 (4.64%)	
occurrences (all)	41	7	
Nausea			
subjects affected / exposed	22 / 182 (12.09%)	12 / 151 (7.95%)	
occurrences (all)	25	13	
Abdominal pain			
subjects affected / exposed	3 / 182 (1.65%)	9 / 151 (5.96%)	
occurrences (all)	3	12	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 182 (6.59%)	3 / 151 (1.99%)	
occurrences (all)	12	3	
Irritability			
subjects affected / exposed	4 / 182 (2.20%)	8 / 151 (5.30%)	
occurrences (all)	4	8	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	12 / 182 (6.59%)	8 / 151 (5.30%)	
occurrences (all)	12	8	

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