Clinical trial results:
A Phase 3, Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir/GS-9857 Fixed-Dose Combination for 12 Weeks in Direct-Acting Antiviral-Experienced Subjects with Chronic HCV Infection

Summary

EudraCT number	2015-003455-21
Trial protocol	DE GB FR
Global end of trial date	21 June 2017

Results information

Result version number	v1
This version publication date	01 July 2018
First version publication date	01 July 2018

Trial information

Trial identification

Sponsor protocol code	GS-US-367-1171

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02607735
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, 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	21 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 October 2016
Global end of trial reached?	Yes
Global end of trial date	21 June 2017
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 evaluate the safety and efficacy of treatment with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) in adults with chronic Hepatitis C Virus (HCV) infection who have previously received treatment with direct-acting antiviral 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	11 November 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: 9
Country: Number of subjects enrolled	France: 72
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	United States: 237
Country: Number of subjects enrolled	Canada: 42
Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	New Zealand: 7
Worldwide total number of subjects	416
EEA total number of subjects	104

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)	344
From 65 to 84 years	72
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 11 November 2015. The last study visit occurred on 21 June 2017.

Pre-assignment

Screening details:

520 participants were screened.

Period 1

Period 1 title	Primary Study
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	SOF/VEL/VOX (Primary Study)

Arm description:

SOF/VEL/VOX for 12 weeks

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

Dosage and administration details:

400/100/100 mg fixed-dose combination (FDC) tablet administered orally once daily with food

Arm title	Placebo (Primary Study)

Arm description:

Placebo 12 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet administered orally once daily with food

Number of subjects in period 1[1]	SOF/VEL/VOX (Primary Study)	Placebo (Primary Study)
Started	263	152
Completed	257	152
Not completed	6	0
Withdrew Consent	2	-
Lost to follow-up	4	-

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 the SOF/VEL/VOX (Primary Study) group who was randomized but never treated is not included in the subject disposition table.

Period 2

Period 2 title	Deferred Treatment Substudy
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	SOF/VEL/VOX (Deferred Treatment Substudy)

Arm description:

Participants who completed placebo treatment were eligible to enroll in to the open-label Deferred Treatment Substudy to receive SOF/VEL/VOX (400/100/100 mg) FDC tablet orally once daily with food for 12 weeks.

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

Dosage and administration details:

400/100/100 mg fixed-dose combination (FDC) tablet administered orally once daily with food

Number of subjects in period 2[2]	SOF/VEL/VOX (Deferred Treatment Substudy)
Started	147
Completed	142
Not completed	5
Withdrew Consent	1
Lost to follow-up	4

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only participants who completed placebo treatment and continued to meet the treatment criteria were eligible to enroll in to the open-label Deferred Treatment Substudy.

Baseline characteristics

Reporting groups	
Reporting group title	SOF/VEL/VOX (Primary Study)
Reporting group description: SOF/VEL/VOX for 12 weeks	
Reporting group title	Placebo (Primary Study)
Reporting group description: Placebo 12 weeks	

Reporting group values	SOF/VEL/VOX (Primary Study)	Placebo (Primary Study)	Total
Number of subjects	263	152	415
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58	59	
standard deviation	± 8.5	± 8.0	-
Gender categorical Units: Subjects			
Female	63	31	94
Male	200	121	321
Race Units: Subjects			
White	211	124	335
Black or African American	38	22	60
Asian	8	6	14
Native Hawaiian or Pacific Islander	3	0	3
Not Disclosed	1	0	1
American Indian or Alaska Native	1	0	1
Other	1	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	15	10	25
Not Hispanic or Latino	247	142	389
Not Disclosed	1	0	1
IL28b Status			
The CC, CT, and TT alleles are different forms of the IL28b gene			
Units: Subjects			
CC	47	27	74
CT	165	93	258
TT	51	32	83
HCV RNA Category Units: Subjects			
< 800,000 IU/mL	73	36	109
≥ 800,000 IU/mL	190	116	306

HCV RNA			
Units: log10 IU/mL			
arithmetic mean	6.3	6.3	
standard deviation	± 0.68	± 0.63	-

End points

End points reporting groups

Reporting group title	SOF/VEL/VOX (Primary Study)
Reporting group description: SOF/VEL/VOX for 12 weeks	
Reporting group title	Placebo (Primary Study)
Reporting group description: Placebo 12 weeks	
Reporting group title	SOF/VEL/VOX (Deferred Treatment Substudy)
Reporting group description: Participants who completed placebo treatment were eligible to enroll in to the open-label Deferred Treatment Substudy to receive SOF/VEL/VOX (400/100/100 mg) FDC tablet orally once daily with food for 12 weeks.	

Primary: Percentage of Participants With Sustained Virologic Response (SVR) 12 Weeks After Discontinuation of Therapy (SVR12) (Primary Study)

End point title	Percentage of Participants With Sustained Virologic Response (SVR) 12 Weeks After Discontinuation of Therapy (SVR12) (Primary Study)[1]
End point description: SVR12 was defined as HCV RNA < the lower limit of quantitation (LLOQ) at 12 weeks after stopping study treatment. Participants in the Full Analysis Set (all randomized/enrolled participants who took at least 1 dose of study drug) were analyzed.	
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 (Primary Study)	Placebo (Primary Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	152		
Units: percentage of participants				
number (confidence interval 95%)	96.2 (93.1 to 98.8)	0 (0.0 to 2.4)		

Attachments (see zip file)	367-1171_PrimaryEndpoint_StatsAnalysis.pdf

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants Who Permanently Discontinued Study Drug Due to an Adverse Event (Primary Study)[2]

End point description:

Participants in the Full Analysis Set (all randomized/enrolled participants who took at least 1 dose of study drug) were analyzed.

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 (Primary Study)	Placebo (Primary Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	152		
Units: percentage of participants				
number (not applicable)	0.4	2.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With SVR at 4 Weeks After Discontinuation of Therapy (SVR4) (Primary Study)

End point title	Percentage of Participants With SVR at 4 Weeks After Discontinuation of Therapy (SVR4) (Primary Study)

End point description:

SVR4 was defined as HCV RNA < LLOQ at 4 weeks after stopping study treatment, respectively. Participants in the Full Analysis Set (all randomized/enrolled participants who took at least 1 dose of study drug) were analyzed.

End point type	Secondary

End point timeframe:

Posttreatment Week 4

End point values	SOF/VEL/VOX (Primary Study)	Placebo (Primary Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	152		
Units: percentage of participants				
number (confidence interval 95%)	97.7 (95.1 to 99.2)	0 (0.0 to 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HCV RNA < LLOQ On Treatment (Primary Study)

End point title	Percentage of Participants With HCV RNA < LLOQ On Treatment (Primary Study)

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 (Primary Study)	Placebo (Primary Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	152		
Units: percentage of participants				
number (confidence interval 95%)				
Week 1 (SOF/VEL/VOX: N = 263; Placebo: N = 152)	15.6 (11.4 to 20.5)	0 (0.0 to 2.4)		
Week 2 (SOF/VEL/VOX: N = 263; Placebo: N = 150)	56.7 (50.4 to 62.7)	0 (0.0 to 2.4)		
Week 4 (SOF/VEL/VOX: N = 262; Placebo: N = 150)	92.7 (88.9 to 95.6)	0 (0.0 to 2.4)		
Week 8 (SOF/VEL/VOX: N = 262; Placebo: N = 150)	100.0 (98.6 to 100.0)	0 (0.0 to 2.4)		
Week 12 (SOF/VEL/VOX: N = 261; Placebo: N = 149)	99.6 (97.9 to 100.0)	0 (0.0 to 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HCV RNA (Primary Study)

End point title	Change From Baseline in HCV RNA (Primary Study)

End point description:

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

End point type	Secondary

End point timeframe:

Baseline; Weeks 1, 2, 4, 8 and 12

End point values	SOF/VEL/VOX (Primary Study)	Placebo (Primary Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	150		
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Week 1 (SOF/VEL/VOX: N = 258; Placebo: N = 150)	-4.20 (± 0.733)	0.02 (± 0.300)		
Week 2 (SOF/VEL/VOX: N = 261; Placebo: N = 148)	-4.81 (± 0.704)	0.02 (± 0.322)		
Week 4 (SOF/VEL/VOX: N = 261; Placebo: N = 150)	-5.07 (± 0.677)	-0.01 (± 0.441)		
Week 8 (SOF/VEL/VOX: N = 262; Placebo: N = 149)	-5.11 (± 0.678)	0.05 (± 0.434)		
Week 12 (SOF/VEL/VOX: N = 261; Placebo: N = 138)	-5.10 (± 0.690)	0.03 (± 0.430)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With SVR at 24 Weeks After Discontinuation of Therapy (SVR24) (Primary Study)

End point title	Percentage of Participants With SVR at 24 Weeks After Discontinuation of Therapy (SVR24) (Primary Study)[3]

End point description:

SVR24 was defined as HCV RNA < LLOQ at 24 weeks after stopping study treatment. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Posttreatment Week 24

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: SVR24 was not assessed for the placebo group.

End point values	SOF/VEL/VOX (Primary Study)			
Subject group type	Reporting group			
Number of subjects analysed	263			
Units: percentage of participants				
number (confidence interval 95%)	96.2 (93.1 to 98.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Virologic Failure (Primary Study)

End point title	Percentage of Participants With Virologic Failure (Primary Study)[4]

End point description:

Virologic failure is 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.
Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to Posttreatment Week 24

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Virological failure was not assessed for the placebo group.

End point values	SOF/VEL/VOX (Primary Study)			
Subject group type	Reporting group			
Number of subjects analysed	263			
Units: percentage of participants				
number (not applicable)	2.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With SVR at 4, 12, and 24 Weeks After Discontinuation of Therapy (Deferred Treatment Substudy)

End point title	Percentage of Participants With SVR at 4, 12, and 24 Weeks After Discontinuation of Therapy (Deferred Treatment Substudy)

End point description:

SVR4, SVR12 and SVR24 was defined as HCV RNA < LLOQ at 4, 12 and 24 weeks after stopping study treatment respectively. Participants in the Full Analysis Set (all enrolled participants who took at least 1 dose of study drug) from the Deferred Treatment Substudy were analyzed.

End point type	Secondary

End point timeframe:

Posttreatment Weeks 4, 12, and 24 (Deferred Treatment Substudy)

End point values	SOF/VEL/VOX (Deferred Treatment Substudy)			
Subject group type	Reporting group			
Number of subjects analysed	147			
Units: percentage of participants				
number (confidence interval 95%)				
SVR4	98.6 (95.2 to 99.8)			
SVR12	97.3 (93.2 to 99.3)			
SVR24	97.3 (93.2 to 99.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HCV RNA < LLOQ On Treatment (Deferred Treatment Substudy)

End point title	Percentage of Participants With HCV RNA < LLOQ On Treatment (Deferred Treatment Substudy)

End point description:

Participants in the Full Analysis Set of the Deferred Treatment Substudy were analyzed.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 4, 8 and 12 (Deferred Treatment Substudy)

End point values	SOF/VEL/VOX (Deferred Treatment Substudy)			
Subject group type	Reporting group			
Number of subjects analysed	147			
Units: percentage of participants				
number (confidence interval 95%)				
Week 1	14.3 (9.1 to 21.0)			
Week 2	62.6 (54.2 to 70.4)			
Week 4	93.2 (87.8 to 96.7)			
Week 8	100.0 (97.5 to 100.0)			
Week 12	100.0 (97.5 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HCV RNA (Deferred Treatment Substudy)

End point title	Change From Baseline in HCV RNA (Deferred Treatment Substudy)

End point description:

Participants with available data in the Full Analysis Set of the Deferred Treatment Substudy were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Weeks 1, 2, 4, 8, and 12 (Deferred Treatment Substudy)

End point values	SOF/VEL/VOX (Deferred Treatment Substudy)			
Subject group type	Reporting group			
Number of subjects analysed	147			
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Week 1 (N = 139)	-4.30 (± 0.626)			
Week 2 (N = 145)	-4.93 (± 0.602)			
Week 4 (N = 147)	-5.16 (± 0.512)			
Week 8 (N=147)	-5.20 (± 0.532)			
Week 12 (N= 147)	-5.20 (± 0.532)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Virologic Failure (Deferred Treatment Substudy)

End point title	Percentage of Participants With Virologic Failure (Deferred Treatment Substudy)

End point description:

Participants in the Full Analysis Set of the Deferred Treatment Substudy were analyzed.

End point type	Secondary

End point timeframe:

Up to Posttreatment Week 24 (Deferred Treatment Substudy)

End point values	SOF/VEL/VOX (Deferred Treatment Substudy)			
Subject group type	Reporting group			
Number of subjects analysed	147			
Units: percentage of participants				
number (not applicable)	2.7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Primary Study: Up to 12 Weeks + 30 days; Deferred Treatment Substudy: Up to 12 Weeks + 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	20.0

Reporting groups	
Reporting group title	SOF/VEL/VOX (Primary Study)
Reporting group description:	
SOF/VEL/VOX (400/100/100 mg) FDC tablet orally once daily with food for 12 weeks	
Reporting group title	Placebo (Primary Study)
Reporting group description:	
Placebo tablet orally once daily with food for 12 weeks	
Reporting group title	SOF/VEL/VOX (Deferred Treatment Substudy)
Reporting group description:	
Participants who completed placebo treatment were eligible for open-label Deferred Treatment Substudy. SOF/VEL/VOX (400/100/100 mg) FDC tablet orally once daily with food for 12 weeks	

Serious adverse events	SOF/VEL/VOX (Primary Study)	Placebo (Primary Study)	SOF/VEL/VOX (Deferred Treatment Substudy)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 263 (1.90%)	7 / 152 (4.61%)	6 / 147 (4.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal neoplasm			
subjects affected / exposed	1 / 263 (0.38%)	0 / 152 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 263 (0.00%)	1 / 152 (0.66%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			

subjects affected / exposed	1 / 263 (0.38%)	0 / 152 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 263 (0.00%)	1 / 152 (0.66%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 263 (0.00%)	0 / 152 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteritis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 152 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 263 (0.00%)	0 / 152 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 263 (0.00%)	1 / 152 (0.66%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 263 (0.00%)	1 / 152 (0.66%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			

subjects affected / exposed	1 / 263 (0.38%)	0 / 152 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 263 (0.00%)	0 / 152 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 263 (0.38%)	0 / 152 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 152 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 263 (0.00%)	1 / 152 (0.66%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 263 (0.38%)	0 / 152 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 152 (0.66%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	0 / 263 (0.00%)	0 / 152 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 152 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal infection			
subjects affected / exposed	0 / 263 (0.00%)	1 / 152 (0.66%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 152 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	SOF/VEL/VOX (Primary Study)	Placebo (Primary Study)	SOF/VEL/VOX (Deferred Treatment Substudy)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	206 / 263 (78.33%)	107 / 152 (70.39%)	87 / 147 (59.18%)
Nervous system disorders			
Headache			
subjects affected / exposed	66 / 263 (25.10%)	26 / 152 (17.11%)	29 / 147 (19.73%)
occurrences (all)	72	32	30
Dizziness			
subjects affected / exposed	11 / 263 (4.18%)	14 / 152 (9.21%)	7 / 147 (4.76%)
occurrences (all)	11	14	7
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	56 / 263 (21.29%)	30 / 152 (19.74%)	31 / 147 (21.09%)
occurrences (all)	58	30	31
Asthenia			

subjects affected / exposed	20 / 263 (7.60%)	9 / 152 (5.92%)	3 / 147 (2.04%)
occurrences (all)	22	9	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	48 / 263 (18.25%)	19 / 152 (12.50%)	28 / 147 (19.05%)
occurrences (all)	58	24	32
Nausea			
subjects affected / exposed	37 / 263 (14.07%)	12 / 152 (7.89%)	21 / 147 (14.29%)
occurrences (all)	41	13	24
Psychiatric disorders			
Insomnia			
subjects affected / exposed	19 / 263 (7.22%)	8 / 152 (5.26%)	5 / 147 (3.40%)
occurrences (all)	19	8	5
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 263 (4.18%)	8 / 152 (5.26%)	7 / 147 (4.76%)
occurrences (all)	11	8	7
Arthralgia			
subjects affected / exposed	8 / 263 (3.04%)	8 / 152 (5.26%)	9 / 147 (6.12%)
occurrences (all)	8	8	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 October 2015	• The definition of treatment experience for eligibility has been revised from DAA-experienced to NS5A inhibitor-experienced. • Participants with DAA experience that did not include an NS5A inhibitor will be eligible for screening in a separate protocol Study GS-US-367-1170. • The total number of study centers participating has been increased from 100 to 120. • Revisions have been made to the approximate number of participants by genotype to be randomized or enrolled into each group • The randomization ratio for Group 1 subjects with genotype 1 has been revised from 2:1 to 1:1 • Updates have been made to Section 1 including Rationale for This Study, Rationale for the Study Design, and Risk/Benefit Assessment for the Study to account for study changes and provide clarification. • Section 6 Procedures has been revised to now include procedures for breaking treatment code/unblinding of subjects for medical emergencies. • Additional formatting, minor grammatical corrections and updates were made throughout the document.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28564569