



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 Compared to Sofosbuvir/Velpatasvir for 12 Weeks in Direct-Acting Antiviral-Naive Subjects with Chronic HCV Infection

Summary

EudraCT number	2015-003460-36
Trial protocol	DE GB FR
Global end of trial date	11 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-367-1172
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02607800
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	11 January 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 January 2017
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 compare the efficacy, safety, and tolerability of treatment with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) fixed dose combination (FDC) for 8 weeks with that of SOF/VEL FDC for 12 weeks in direct-acting antiviral-naïve participants with chronic HCV 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	16 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: 47
Country: Number of subjects enrolled	France: 187
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	New Zealand: 26
Country: Number of subjects enrolled	Canada: 60
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	United States: 554
Worldwide total number of subjects	943
EEA total number of subjects	279

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)	849
From 65 to 84 years	94
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 16 November 2015. The last study visit occurred on 11 January 2017.

Pre-assignment

Screening details:

1116 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
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Arm description:

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

Number of subjects in period 1^[1]	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks
Started	501	440
Completed	492	430
Not completed	9	10
Withdrew Consent	2	-

Lost to follow-up	7	10
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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: 2 participants (one in each treatment group) who were randomized but not treated are 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 with or without food for 12 weeks	

Reporting group values	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks	Total
Number of subjects	501	440	941
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	53	52	
standard deviation	± 11.1	± 11.9	-
Gender categorical			
Units: Subjects			
Female	246	203	449
Male	255	237	492
Race			
Units: Subjects			
White	391	365	756
Black or African American	48	47	95
Asian	51	22	73
Other	5	2	7
American Indian or Alaska Native	3	2	5
Native Hawaiian or Pacific Islander	3	2	5
Ethnicity			
Units: Subjects			
Hispanic or Latino	32	52	84
Not Hispanic or Latino	469	388	857
IL28b Status			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	166	136	302
CT	253	245	498
TT	82	59	141
HCV RNA Category			
Units: Subjects			
< 800,000 IU/mL	155	138	293
≥ 800,000 IU/mL	346	302	648

HCV RNA			
Units: log10 IU/mL			
arithmetic mean	6.1	6.2	
standard deviation	± 0.75	± 0.66	-

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 with or without 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)
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	

End point values	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	501	440		
Units: percentage of participants				
number (confidence interval 95%)	95.2 (93.0 to 96.9)	98.2 (96.4 to 99.2)		

Statistical analyses

Statistical analysis title	SVR12 – SOF/VEL/VOX 8 Weeks vs SOF/VEL 12 Weeks
Comparison groups	SOF/VEL 12 Weeks v SOF/VEL/VOX 8 Weeks
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Difference in proportions
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	-0.4

Notes:

[1] - Noninferiority was demonstrated if the lower bound of the 2-sided 95% confidence interval (CI) for the difference in SVR12 was greater than -5%. If the lower bound of the CI was greater than -5% (ie, the noninferiority null hypothesis was rejected), a 2-sided stratified Cochran-Mantel-Haenszel test was to be used to test for the superiority of SOF/VEL/VOX for 8 weeks over SOF/VEL for 12 weeks at a significance level of 0.05.

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]
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End point description:

Safety Analysis Set

End point type	Primary
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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	501	440		
Units: percentage of participants				
number (not applicable)	0	0.5		

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)
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End point description:

1) SVR4 and SVR 24 were defined as HCV RNA < LLOQ at 4 and 24 weeks after stopping study treatment, respectively.

2) Full Analysis Set

End point type	Secondary
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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	501	440		
Units: percentage of participants				
number (confidence interval 95%)				
SVR4	96.4 (94.4 to 97.9)	98.9 (97.4 to 99.6)		
SVR24	95.0 (92.7 to 96.7)	98.0 (96.2 to 99.1)		

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:	
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	501	440		
Units: percentage of participants				
number (confidence interval 95%)				
Week 1 (SOF/VEL/VOX: N = 501; SOF/VEL: N= 440)	24.8 (21.0 to 28.8)	22.7 (18.9 to 26.9)		
Week 2 (SOF/VEL/VOX: N = 501; SOF/VEL: N= 439)	65.9 (61.5 to 70.0)	61.3 (56.5 to 65.9)		
Week 4 (SOF/VEL/VOX: N = 501; SOF/VEL:N= 439)	92.4 (89.7 to 94.6)	92.0 (89.1 to 94.4)		
Week 8 (SOF/VEL/VOX: N = 500; SOF/VEL: N= 439)	99.2 (98.0 to 99.8)	99.8 (98.7 to 100.0)		
Week 12 (SOF/VEL/VOX: N =NA; SOF/VEL: N= 439)	999 (999 to 999)	99.8 (98.7 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:	
Up to 12 weeks	

End point values	SOF/VEL/VOX 8 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	501	440		
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Week 1 (SOF/VEL/VOX: N = 491; SOF/VEL: N= 433)	-4.23 (± 0.689)	-4.24 (± 0.679)		
Week 2 (SOF/VEL/VOX: N = 496; SOF/VEL: N= 436)	-4.75 (± 0.747)	-4.77 (± 0.646)		
Week 4 (SOF/VEL/VOX: N = 501; SOF/VEL: N= 437)	-4.95 (± 0.75)	-4.99 (± 0.656)		
Week 8 (SOF/VEL/VOX: N = 496; SOF/VEL: N= 439)	-4.99 (± 0.754)	-5.03 (± 0.655)		
Week 12 (SOF/VEL/VOX: N = NA; SOF/VEL: N= 438)	999 (± 999)	-5.03 (± 0.656)		

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 is defined as:	
1) On-treatment virologic failure:	
a) Breakthrough (confirmed HCV RNA \geq LLOQ after having previously had HCV RNA < LLOQ while on treatment), or	
b) Rebound (confirmed > 1 log10 IU/mL increase in HCV RNA from nadir while on treatment), or	
c) Non-response (HCV RNA persistently \geq LLOQ through 8 weeks of treatment)	
2) Virologic relapse:	
a) Confirmed HCV RNA \geq 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 8 Weeks	SOF/VEL 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	501	440		
Units: percentage of participants				
number (not applicable)	4.2	0.7		

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	SOF/VEL/VOX 8 Weeks
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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
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Reporting group description:

SOF/VEL (400/100 mg) FDC tablet orally once daily with or without 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	15 / 501 (2.99%)	7 / 440 (1.59%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma metastatic			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral artery occlusion			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 501 (0.00%)	1 / 440 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 501 (0.00%)	1 / 440 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 501 (0.00%)	1 / 440 (0.23%)	
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			
Multiple fractures			
subjects affected / exposed	0 / 501 (0.00%)	1 / 440 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 501 (0.00%)	1 / 440 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 501 (0.00%)	1 / 440 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (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			
Cerebral haemorrhage			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (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			
Back pain			

subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 501 (0.00%)	1 / 440 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 501 (0.00%)	1 / 440 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	1 / 501 (0.20%)	0 / 440 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 501 (0.00%)	1 / 440 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 501 (0.20%)	1 / 440 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Myositis			
subjects affected / exposed	0 / 501 (0.00%)	1 / 440 (0.23%)	
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	280 / 501 (55.89%)	213 / 440 (48.41%)	
Nervous system disorders			
Headache			
subjects affected / exposed	134 / 501 (26.75%)	99 / 440 (22.50%)	
occurrences (all)	150	112	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	32 / 501 (6.39%)	27 / 440 (6.14%)	
occurrences (all)	35	27	
Fatigue			
subjects affected / exposed	106 / 501 (21.16%)	91 / 440 (20.68%)	
occurrences (all)	114	93	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	88 / 501 (17.56%)	32 / 440 (7.27%)	
occurrences (all)	98	36	
Nausea			
subjects affected / exposed	80 / 501 (15.97%)	40 / 440 (9.09%)	
occurrences (all)	83	45	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	26 / 501 (5.19%)	21 / 440 (4.77%)	
occurrences (all)	28	21	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 501 (3.79%)	24 / 440 (5.45%)	
occurrences (all)	19	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 October 2015	<ol style="list-style-type: none">1. Removed all references to genotype 3 cirrhotic subjects and clarified that these subjects will not be enrolled in this study, but rather will be included in GS-US-367-11732. The total number of study centers participating were increased from 100 to 120.3. Revisions were made to the approximate number of subjects by genotype to be randomized or enrolled into each group.4. Updates were made to Rationale for This Study, Rationale for the Study Design, and Risk/Benefit Assessment for the Study to account for study changes and provide clarification.5. Additional formatting, minor grammatical corrections, and updates were made.

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/28390869>