

**Clinical trial results:****A Phase 2, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination (FDC) and Sofosbuvir/Velpatasvir FDC and Ribavirin in Subjects with Chronic Genotype 3 HCV Infection and Cirrhosis****Summary**

EudraCT number	2016-000417-73
Trial protocol	ES
Global end of trial date	27 October 2017

Results information

Result version number	v1 (current)
This version publication date	26 October 2018
First version publication date	26 October 2018

Trial information**Trial identification**

Sponsor protocol code	GS-US-342-2097
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02781558
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	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	27 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 October 2017
Global end of trial reached?	Yes
Global end of trial date	27 October 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 evaluate the efficacy, safety, and tolerability of sofosbuvir velpatasvir (SOF/VEL) fixed-dose combination (FDC) and SOF/VEL FDC and ribavirin (RBV) for 12 weeks in participants with chronic genotype 3 hepatitis C virus (HCV) infection and compensated 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	29 July 2016
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	Spain: 204
Worldwide total number of subjects	204
EEA total number of subjects	204

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)	199
From 65 to 84 years	4
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Spain. The first participant was screened on 29 July 2016. The last study visit occurred on 27 October 2017.

Pre-assignment

Screening details:

269 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
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Arm title	SOF/VEL
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Arm description:

SOF/VEL for 12 weeks

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

Dosage and administration details:

400/100 FDC administered once daily

Arm title	SOF/VEL + RBV
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Arm description:

SOF/VEL + RBV for 12 weeks

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

Dosage and administration details:

1000 or 1200 mg daily based on weight (< 75 kg = 1000 mg and ≥ 75 kg = 1200 mg)

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

Dosage and administration details:

400/100 FDC administered once daily

Number of subjects in period 1	SOF/VEL	SOF/VEL + RBV
Started	101	103
Completed	98	101
Not completed	3	2
Adverse event, non-fatal	1	-
Lost to follow-up	2	2

Baseline characteristics

Reporting groups

Reporting group title	SOF/VEL
Reporting group description: SOF/VEL for 12 weeks	
Reporting group title	SOF/VEL + RBV
Reporting group description: SOF/VEL + RBV for 12 weeks	

Reporting group values	SOF/VEL	SOF/VEL + RBV	Total
Number of subjects	101	103	204
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	51 ± 7.3	51 ± 7.6	-
Gender categorical Units: Subjects			
Female	26	16	42
Male	75	87	162
Race Units: Subjects			
White	84	95	179
Asian	17	8	25
Ethnicity Units: Subjects			
Hispanic or Latino	9	10	19
Not Hispanic or Latino	92	93	185
IL28B			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	64	53	117
Non-CC	36	50	86
Missing	1	0	1
HCV RNA Category Units: Subjects			
< 800,000 IU/mL	32	24	56
≥ 800,000 IU/mL	69	79	148
HCV RNA Units: log ₁₀ IU/mL arithmetic mean standard deviation	6.2 ± 0.64	6.3 ± 0.56	-

End points

End points reporting groups

Reporting group title	SOF/VEL
Reporting group description:	SOF/VEL for 12 weeks
Reporting group title	SOF/VEL + RBV
Reporting group description:	SOF/VEL + RBV for 12 weeks

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

End point title	Percentage of Participants With Sustained Virologic Response (SVR) 12 Weeks After Cessation of Therapy (SVR12) ^[1]
End point description:	SVR12 was defined as HCV RNA < the lower limit of quantitation (LLOQ; ie, 15 IU/mL) at 12 weeks after stopping study treatment. Participants in the Full Analysis Set (all randomized participants who took at least 1 dose of any 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: No statistical comparison was planned or performed.

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	103		
Units: percentage of participants				
number (confidence interval 95%)	91.1 (83.8 to 95.8)	96.1 (90.4 to 98.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Permanently Discontinued Any Study Drug (Which Included SOF/VEL and RBV) Due to Any Adverse Event

End point title	Percentage of Participants Who Permanently Discontinued Any Study Drug (Which Included SOF/VEL and RBV) Due to Any Adverse Event
End point description:	Participants in the Safety Analysis Set (participants who took at least 1 dose of any study drug (which included SOF/VEL and RBV)) were analyzed.
End point type	Secondary

End point timeframe:
Posttreatment Week 12

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	103		
Units: percentage of participants				
number (not applicable)	1.0	1.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Attain Sustained Virologic Response at 4 Weeks After Cessation of the Study Treatment Regimen (SVR4)

End point title	Percentage of Participants Who Attain Sustained Virologic Response at 4 Weeks After Cessation of the Study Treatment Regimen (SVR4)
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End point description:

SVR4 was defined as HCV RNA < the lower limit of quantitation (LLOQ; ie, 15 IU/mL) at 4 weeks after stopping study treatment.
Participants on the Full Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:
Posttreatment Week 4

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	103		
Units: percentage of participants				
number (confidence interval 95%)	93.1 (86.2 to 97.2)	97.1 (91.7 to 99.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Have HCV RNA < LLOQ at Week 2

End point title	Percentage of Participants Who Have HCV RNA < LLOQ at Week 2
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End point description:

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

End point type	Secondary
End point timeframe:	
Week 2	

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	103		
Units: percentage of participants				
number (confidence interval 95%)	51.0 (40.8 to 61.1)	44.7 (34.9 to 54.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Have HCV RNA < LLOQ at Week 4

End point title	Percentage of Participants Who Have HCV RNA < LLOQ at Week 4
End point description:	Participants in the Full Analysis Set with available data were analyzed.
End point type	Secondary
End point timeframe:	
Week 4	

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	103		
Units: percentage of participants				
number (confidence interval 95%)	85.0 (76.5 to 91.4)	90.3 (82.9 to 95.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Have HCV RNA < LLOQ at Week 8

End point title	Percentage of Participants Who Have HCV RNA < LLOQ at Week 8
End point description:	Participants in the Full Analysis Set with available data were analyzed.
End point type	Secondary

End point timeframe:

Week 8

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Percentage of participants				
number (confidence interval 95%)	99.0 (94.6 to 100.0)	100.0 (96.4 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Have HCV RNA < LLOQ at Week 12

End point title | Percentage of Participants Who Have HCV RNA < LLOQ at Week 12

End point description:

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

End point type | Secondary

End point timeframe:

Week 12

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: percentage of participants				
number (confidence interval 95%)	99.0 (94.6 to 100.0)	100.0 (96.4 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: HCV RNA at Week 2

End point title | HCV RNA at Week 2

End point description:

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

End point type | Secondary

End point timeframe:

Week 2

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	102		
Units: log ₁₀ IU/mL				
arithmetic mean (standard deviation)	1.52 (± 0.513)	1.47 (± 0.413)		

Statistical analyses

No statistical analyses for this end point

Secondary: HCV RNA at Week 4

End point title	HCV RNA at Week 4
End point description:	Participants in the Full Analysis Set with available data were analyzed.
End point type	Secondary
End point timeframe:	Week 4

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	103		
Units: log ₁₀ IU/mL				
arithmetic mean (standard deviation)	1.22 (± 0.257)	1.19 (± 0.152)		

Statistical analyses

No statistical analyses for this end point

Secondary: HCV RNA at Week 8

End point title	HCV RNA at Week 8
End point description:	Participants in the Full Analysis Set with available data were analyzed.
End point type	Secondary
End point timeframe:	Week 8

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: log ₁₀ IU/mL				
arithmetic mean (standard deviation)	1.15 (± 0.040)	1.15 (± 0.000)		

Statistical analyses

No statistical analyses for this end point

Secondary: HCV RNA at Week 12

End point title	HCV RNA at Week 12
End point description:	Participants in the Full Analysis Set with available data were analyzed.
End point type	Secondary
End point timeframe:	Week 12

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: log ₁₀ IU/mL				
arithmetic mean (standard deviation)	1.15 (± 0.018)	1.15 (± 0.000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HCV RNA at Week 2

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

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	102		
Units: log ₁₀ IU/mL				
arithmetic mean (standard deviation)	-4.67 (± 0.627)	-4.80 (± 0.580)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HCV RNA at Week 4

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

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	103		
Units: log ₁₀ IU/mL				
arithmetic mean (standard deviation)	-4.96 (± 0.641)	-5.09 (± 0.559)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HCV RNA at Week 8

End point title	Change From Baseline in HCV RNA at Week 8
End point description:	Participants in the Full Analysis Set with available data were analyzed.
End point type	Secondary
End point timeframe:	Baseline; Week 8

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: log ₁₀ IU/mL				
arithmetic mean (standard deviation)	-5.04 (± 0.638)	-5.13 (± 0.565)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HCV RNA at Week 12

End point title	Change From Baseline in HCV RNA at Week 12
End point description:	Participants in the Full Analysis Set with available data were analyzed.
End point type	Secondary
End point timeframe:	Baseline; Week 12

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: log ₁₀ IU/mL				
arithmetic mean (standard deviation)	-5.04 (± 0.640)	-5.13 (± 0.568)		

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: 1) On-treatment virologic failure: a) Breakthrough (confirmed HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while on treatment), or b) Rebound (confirmed > 1 log ₁₀ IU/mL increase in HCV RNA from nadir while on treatment), or c) Non-response (HCV RNA persistently ≥ LLOQ through 8 weeks of treatment), or 2) 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 12

End point values	SOF/VEL	SOF/VEL + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	103		
Units: percentage of participants ²				
number (not applicable)	5.9	1.9		

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	SOF/VEL
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Reporting group description:

SOF/VEL for 12 weeks

Reporting group title	SOF/VEL + RBV
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Reporting group description:

SOF/VEL + RBV for 12 weeks

Serious adverse events	SOF/VEL	SOF/VEL + RBV	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 101 (3.96%)	2 / 103 (1.94%)	
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)			
Hepatic cancer			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
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			

Accident at work			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (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			
Pharyngotonsillitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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	SOF/VEL + RBV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 101 (23.76%)	55 / 103 (53.40%)	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 101 (7.92%)	25 / 103 (24.27%)	
occurrences (all)	12	29	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 101 (11.88%)	28 / 103 (27.18%)	
occurrences (all)	13	30	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 101 (1.98%)	6 / 103 (5.83%)	
occurrences (all)	2	6	
Skin and subcutaneous tissue disorders			

Pruritus subjects affected / exposed occurrences (all)	2 / 101 (1.98%) 2	9 / 103 (8.74%) 9	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1	12 / 103 (11.65%) 12	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	7 / 101 (6.93%) 7	4 / 103 (3.88%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2016	<ul style="list-style-type: none">• Clarified that subjects who did not have definitive genotype 3 HCV at screening were not eligible for study participation• The calculation of Child-Pugh-Turcotte (CPT) score was removed from the posttreatment assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported