



Clinical trial results:

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks in Subjects with Chronic HCV

Summary

EudraCT number	2014-001683-35
Trial protocol	DE GB IT BE FR
Global end of trial date	23 September 2015

Results information

Result version number	v1 (current)
This version publication date	07 October 2016
First version publication date	07 October 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-342-1138
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02201940
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 Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial 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	23 September 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 September 2015
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) for 12 weeks in adults with chronic genotype 1, 2, 4, 5, or 6 hepatitis C virus (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	18 July 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 104
Country: Number of subjects enrolled	Belgium: 45
Country: Number of subjects enrolled	France: 158
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Canada: 62
Country: Number of subjects enrolled	United States: 279
Country: Number of subjects enrolled	China: 23
Worldwide total number of subjects	741
EEA total number of subjects	377

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)	641
From 65 to 84 years	100
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States, Canada, Europe, and Asia. The first participant was screened on 18 July 2014. The last study visit occurred on 23 September 2015.

Pre-assignment

Screening details:

847 participants were screened.

Period 1

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

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	Epclusa®, GS-7977/GS-5816
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400/100 mg FDC tablet administered once daily

Arm title	Placebo
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Arm description:

SOF/VEL placebo for 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:

Placebo tablet administered once daily

Number of subjects in period 1^[1]	SOF/VEL	Placebo
Started	624	116
Completed	613	0
Not completed	11	116
Withdrew Consent	2	1
Adverse event, non-fatal	-	1
Death	1	-
Investigator's Discretion	1	1
Lost to follow-up	5	-
Lack of efficacy	2	113

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 who was enrolled but not treated is not included in the subject disposition table.

Baseline characteristics

Reporting groups

Reporting group title	SOF/VEL
Reporting group description: SOF/VEL for 12 weeks	
Reporting group title	Placebo
Reporting group description: SOF/VEL placebo for 12 weeks	

Reporting group values	SOF/VEL	Placebo	Total
Number of subjects	624	116	740
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	54 ± 10.9	53 ± 10.4	-
Gender categorical Units: Subjects			
Female	250	48	298
Male	374	68	442
Ethnicity Units: Subjects			
Hispanic or Latino	31	5	36
Not Hispanic or Latino	589	111	700
Not Disclosed	4	0	4
Race Units: Subjects			
Black or African American	52	12	64
White	493	89	582
Asian	62	11	73
American Indian/ Alaska Native	7	0	7
Hawaiian or Pacific Islander	1	1	2
Other	6	3	9
Not Disclosed	3	0	3
HCV Genotype Units: Subjects			
Genotype 1	328	65	393
Genotype 2	104	21	125
Genotype 4	116	22	138
Genotype 5	35	0	35
Genotype 6	41	8	49
IL28b Status			
CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	186	36	222

CT	339	53	392
TT	94	26	120
Missing	5	1	6
HCV RNA Category			
Units: Subjects			
< 800,000 IU/mL	163	29	192
≥ 800,000 IU/mL	461	87	548
Cirrhosis Status			
Units: Subjects			
Present	121	21	142
Absent	501	95	596
Missing	2	0	2
HCV RNA			
Units: log10 IU/mL			
arithmetic mean	6.3	6.3	
standard deviation	± 0.66	± 0.58	-

End points

End points reporting groups

Reporting group title	SOF/VEL
Reporting group description: SOF/VEL for 12 weeks	
Reporting group title	Placebo
Reporting group description: SOF/VEL placebo 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 was defined as HCV RNA < the lower limit of quantitation (LLOQ; ie, 15 IU/mL) at 12 weeks after stopping study treatment. Full Analysis Set: participants randomized or enrolled into the study and received 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: Statistical analysis was performed against a performance goal of 85% and not between the treatment groups.

End point values	SOF/VEL	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	624	116		
Units: percentage of participants				
number (confidence interval 95%)	99 (97.9 to 99.6)	0 (0 to 3.1)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants Who Permanently Discontinued Any Study Drug Due to an Adverse Event ^[2]
End point description: Safety Analysis Set: participants who received 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 comparison was planned or performed.

End point values	SOF/VEL	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	624	116		
Units: percentage of participants				
number (not applicable)	0.2	1.7		

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)
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End point description:

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

Full Analysis Set

End point type	Secondary
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End point timeframe:

Posttreatment Weeks 4 and 24

End point values	SOF/VEL	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	624	116		
Units: percentage of participants				
number (confidence interval 95%)				
SVR4	99.2 (98.1 to 99.7)	0 (0 to 3.1)		
SVR24	99 (97.9 to 99.6)	0 (0 to 3.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HCV RNA < LLOQ at Weeks 1, 2, 4, 6, 8, 10, and 12

End point title	Percentage of Participants With HCV RNA < LLOQ at Weeks 1, 2, 4, 6, 8, 10, and 12
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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:	
Weeks 1, 2, 4, 6, 8, 10, and 12	

End point values	SOF/VEL	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	624	116		
Units: percentage of participants				
number (confidence interval 95%)				
Week 1 (SOF/VEL: N = 624; Placebo: N = 116)	18.8 (15.8 to 22)	0 (0 to 3.1)		
Week 2 (SOF/VEL: N = 624; Placebo: N = 116)	56.9 (52.9 to 60.8)	0 (0 to 3.1)		
Week 4 (SOF/VEL: N = 623; Placebo: N = 116)	90.5 (88 to 92.7)	0 (0 to 3.1)		
Week 6 (SOF/VEL: N = 623; Placebo: N = 115)	98.9 (97.7 to 99.5)	0 (0 to 3.2)		
Week 8 (SOF/VEL: N = 622; Placebo: N = 114)	99.7 (98.8 to 100)	0 (0 to 3.2)		
Week 10 (SOF/VEL: N = 622; Placebo: N = 114)	100 (99.4 to 100)	0 (0 to 3.2)		
Week 12 (SOF/VEL: N = 622; Placebo: N = 113)	100 (99.4 to 100)	0 (0 to 3.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HCV RNA at Weeks 1, 2, 4, 6, 8, 10, and 12

End point title	Change From Baseline in HCV RNA at Weeks 1, 2, 4, 6, 8, 10, and 12
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, 6, 8, 10, and 12	

End point values	SOF/VEL	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	624	116		
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Change at Wk 1 (SOF/VEL: N= 617; Placebo: N= 114)	-4.29 (± 0.647)	-0.05 (± 0.561)		

Change at Wk 2 (SOF/VEL: N= 622; Placebo: N= 116)	-4.82 (± 0.685)	0.01 (± 0.28)		
Change at Wk 4 (SOF/VEL: N= 617; Placebo: N= 114)	-5.08 (± 0.656)	-0.01 (± 0.297)		
Change at Wk 6 (SOF/VEL: N= 623; Placebo: N= 115)	-5.11 (± 0.664)	0.07 (± 0.298)		
Change at Wk 8 (SOF/VEL: N= 622; Placebo: N= 113)	-5.11 (± 0.664)	0.05 (± 0.281)		
Change at Wk 10 (SOF/VEL: N= 622; Placebo: N= 112)	-5.12 (± 0.662)	0.05 (± 0.337)		
Change at Wk 12 (SOF/VEL: N= 622; Placebo: N= 111)	-5.12 (± 0.662)	-0.06 (± 0.58)		

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
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End point description:

Virologic failure was defined as:

1) On-treatment virologic failure:

- Breakthrough (confirmed HCV RNA $\geq$ 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 $\geq$ LLOQ through 8 weeks of treatment), OR

2) Virologic relapse:

- Confirmed HCV RNA $\geq$ LLOQ during the posttreatment period having achieved HCV RNA $<$ LLOQ at last on-treatment visit.

Full Analysis Set

End point type	Secondary
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End point timeframe:

Up to Posttreatment Week 24

End point values	SOF/VEL	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	624	116		
Units: percentage of participants				
number (not applicable)	0.3	100		

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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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	Placebo
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Reporting group description:

SOF/VEL placebo for 12 weeks

Serious adverse events	SOF/VEL	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 624 (2.40%)	0 / 116 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Extremity necrosis			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (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			
Epilepsy			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (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			
Sudden death			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Mania			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (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			
Rotator cuff syndrome			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (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			
Abscess limb			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vestibular neuronitis			
subjects affected / exposed	1 / 624 (0.16%)	0 / 116 (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	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	393 / 624 (62.98%)	77 / 116 (66.38%)	
Nervous system disorders			
Headache			
subjects affected / exposed	182 / 624 (29.17%)	33 / 116 (28.45%)	
occurrences (all)	236	39	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	127 / 624 (20.35%)	24 / 116 (20.69%)	
occurrences (all)	132	26	
Asthenia			
subjects affected / exposed	42 / 624 (6.73%)	9 / 116 (7.76%)	
occurrences (all)	46	9	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	75 / 624 (12.02%)	13 / 116 (11.21%)	
occurrences (all)	80	14	
Diarrhoea			
subjects affected / exposed	48 / 624 (7.69%)	8 / 116 (6.90%)	
occurrences (all)	53	8	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	39 / 624 (6.25%)	4 / 116 (3.45%)	
occurrences (all)	41	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	50 / 624 (8.01%)	11 / 116 (9.48%)	
occurrences (all)	51	12	

Musculoskeletal and connective tissue disorders			
	Arthralgia		
	subjects affected / exposed	40 / 624 (6.41%)	9 / 116 (7.76%)
	occurrences (all)	41	11
	Back pain		
	subjects affected / exposed	29 / 624 (4.65%)	11 / 116 (9.48%)
	occurrences (all)	29	12
	Myalgia		
	subjects affected / exposed	25 / 624 (4.01%)	6 / 116 (5.17%)
	occurrences (all)	27	6
Infections and infestations			
	Nasopharyngitis		
	subjects affected / exposed	80 / 624 (12.82%)	12 / 116 (10.34%)
	occurrences (all)	87	14

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There were no limitations affecting the analysis or results.
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Notes: