Clinical trial results:
A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination (FDC) +/- Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection.

Summary

EudraCT number	2012-003387-43
Trial protocol	GB DE ES FR
Global end of trial date	30 April 2014

Results information

Result version number	v1 (current)
This version publication date	22 March 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	GS-US-337-0102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01701401
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences, Inc.
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	30 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety, tolerability, and antiviral efficacy of ledipasvir (LDV)/sofosbuvir (SOF) fixed-dose combination (FDC) tablets with or without ribavirin (RBV) administered for 12 and 24 weeks in treatment-naive subjects with chronic genotype 1 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	26 September 2012
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: 55
Country: Number of subjects enrolled	United Kingdom: 55
Country: Number of subjects enrolled	Germany: 84
Country: Number of subjects enrolled	Italy: 96
Country: Number of subjects enrolled	France: 63
Country: Number of subjects enrolled	United States: 512
Worldwide total number of subjects	865
EEA total number of subjects	353

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	793
From 65 to 84 years	72
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at a total of 100 study sites in the United States and Europe. The first participant was screened on 26 September 2012. The last study visit occurred on 30 April 2014.

Pre-assignment

Screening details:

1015 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	LDV/SOF 12 weeks

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	LDV/SOF, Harvoni®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LDV/SOF 90/400 mg fixed-dose combination (FDC) tablet administered orally once daily

Arm title	LDV/SOF+RBV 12 weeks

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	LDV/SOF, Harvoni®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LDV/SOF 90/400 mg fixed-dose combination (FDC) tablet administered orally once daily

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

Dosage and administration details:

Ribavirin (RBV) tablets administered orally in a divided daily dose according to package insert weight-based dosing recommendations (< 75 kg= 1000 mg and 75 kg= 1200 mg)

Arm title	LDV/SOF 24 weeks

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	LDV/SOF, Harvoni®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LDV/SOF 90/400 mg fixed-dose combination (FDC) tablet administered orally once daily

Arm title	LDV/SOF+RBV 24 weeks

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	LDV/SOF, Harvoni®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LDV/SOF 90/400 mg fixed-dose combination (FDC) tablet administered orally once daily

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

Dosage and administration details:

Ribavirin (RBV) tablets administered orally in a divided daily dose according to package insert weight-based dosing recommendations (< 75 kg= 1000 mg and 75 kg= 1200 mg)

Number of subjects in period 1	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks
Started	214	217	217
Completed	207	209	212
Not completed	7	8	5
Protocol violation	-	-	1
Non-treatment emergent death	1	-	-
Lost to follow-up	5	5	1
Withdrew consent	-	3	1
Lack of efficacy	1	-	2

Number of subjects in period 1	LDV/SOF+RBV 24 weeks
Started	217
Completed	212
Not completed	5
Protocol violation	-
Non-treatment emergent death	-
Lost to follow-up	3
Withdrew consent	2

Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	LDV/SOF 12 weeks
Reporting group description: -	
Reporting group title	LDV/SOF+RBV 12 weeks
Reporting group description: -	
Reporting group title	LDV/SOF 24 weeks
Reporting group description: -	
Reporting group title	LDV/SOF+RBV 24 weeks
Reporting group description: -	

Reporting group values	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks
Number of subjects	214	217	217
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	52	52	53
standard deviation	± 10.7	± 11.5	± 10.3
Gender, Male/Female Units: participants			
Female	87	89	78
Male	127	128	139
Race Units: Subjects			
Black or African American	24	26	32
White	187	188	177
Asian	1	0	5
American Indian/Alaska Native	0	1	0
Hawaiian or Pacific Islander	0	0	1
Other	2	1	2
Not Disclosed	0	1	0
Ethnicity Units: Subjects			
Hispanic or Latino	26	20	29
Not Hispanic or Latino	187	197	188
Not Disclosed	1	0	0
HCV RNA Category Units: Subjects			
< 800,000 IU/mL	45	44	49
≥ 800,000 IU/mL	169	173	168
HCV Genotype			
There are variations of HCV which are all similar enough to be called HCV, but are distinct enough to be referred to as HCV genotypes.			
Units: Subjects			
Genotype 1a	144	148	146

Genotype 1b	66	68	68
Genotype 1 (no confirmed subtype)	1	1	1
Genotype 4	1	0	0
Missing	2	0	2
IL28b Status			
CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	55	76	52
CT	113	107	119
TT	46	34	46
Hepatitis C Virus (HCV) RNA Units: log10 IU/mL			
arithmetic mean	6.4	6.4	6.3
standard deviation	± 0.69	± 0.64	± 0.68

Reporting group values	LDV/SOF+RBV 24 weeks	Total	
Number of subjects	217	865	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	53		
standard deviation	± 9.9	-	
Gender, Male/Female Units: participants			
Female	98	352	
Male	119	513	
Race Units: Subjects			
Black or African American	26	108	
White	183	735	
Asian	5	11	
American Indian/Alaska Native	1	2	
Hawaiian or Pacific Islander	0	1	
Other	1	6	
Not Disclosed	1	2	
Ethnicity Units: Subjects			
Hispanic or Latino	26	101	
Not Hispanic or Latino	190	762	
Not Disclosed	1	2	
HCV RNA Category Units: Subjects			
< 800,000 IU/mL	44	182	
≥ 800,000 IU/mL	173	683	
HCV Genotype			
There are variations of HCV which are all similar enough to be called HCV, but are distinct enough to be referred to as HCV genotypes.			
Units: Subjects			
Genotype 1a	143	581	

Genotype 1b	71	273	
Genotype 1 (no confirmed subtype)	1	4	
Genotype 4	1	2	
Missing	1	5	
IL28b Status			
CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	73	256	
CT	112	451	
TT	32	158	
Hepatitis C Virus (HCV) RNA Units: log10 IU/mL			
arithmetic mean	6.3		
standard deviation	± 0.65	-	

End points

End points reporting groups

Reporting group title	LDV/SOF 12 weeks
Reporting group description: -	
Reporting group title	LDV/SOF+RBV 12 weeks
Reporting group description: -	
Reporting group title	LDV/SOF 24 weeks
Reporting group description: -	
Reporting group title	LDV/SOF+RBV 24 weeks
Reporting group description: -	

Primary: Percentage of participants with sustained virologic response (SVR) 12 weeks after discontinuation of study drug (SVR12)

End point title	Percentage of participants with sustained virologic response (SVR) 12 weeks after discontinuation of study drug (SVR12)[1]
End point description:	
SVR12 was defined as HCV RNA level < the lower limit of quantification (LLOQ, ie, < 25 copies/mL) 12 weeks after last 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: No intergroup analysis was planned or performed.

End point values	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	214	217	217	217
Units: percentage of participants				
number (not applicable)	98.6	97.2	98.2	99.1

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Adverse Events Leading to Permanent Discontinuation From Any Study Drug

End point title	Incidence of Adverse Events Leading to Permanent Discontinuation From Any Study Drug[2]
End point description:	
The percentage of participants who experienced an adverse event leading to permanent discontinuation from any study drug was summarized.	
End point type	Primary
End point timeframe:	
Up to 24 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 intergroup analysis was planned or performed.

End point values	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	214	217	217	217
Units: percentage of participants				
number (not applicable)	0	0.5	1.8	3.7

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with SVR at 4 and 24 weeks after discontinuation of study drug

End point title	Percentage of participants with SVR at 4 and 24 weeks after discontinuation of study drug

End point description:

SVR4 and SVR24 were defined as HCV RNA level < LLOQ at 4 and 24 weeks after discontinuation of study drug, respectively.

End point type	Secondary

End point timeframe:

Posttreatment Weeks 4 and 24

End point values	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	214	217	217	217
Units: percentage of participants				
number (not applicable)				
SVR4	98.6	98.2	99.1	99.1
SVR24	98.6	97.2	98.2	99.1

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with HCV RNA < LLOQ at Week 2

End point title	Percentage of participants with HCV RNA < LLOQ at Week 2

End point description:

End point type	Secondary

End point timeframe:
Week 2

End point values	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	213	217	216	217
Units: percentage of participants				
number (not applicable)	82.2	83.4	82.9	82.9

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with HCV RNA < LLOQ at Week 4

End point title	Percentage of participants with HCV RNA < LLOQ at Week 4

End point description:

End point type	Secondary

End point timeframe:
Week 4

End point values	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	213	217	216	217
Units: percentage of participants				
number (not applicable)	100	99.1	100	100

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with HCV RNA < LLOQ at Week 8

End point title	Percentage of participants with HCV RNA < LLOQ at Week 8

End point description:

End point type	Secondary

End point timeframe:
Week 8

End point values	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	213	215	215	217
Units: percentage of participants				
number (not applicable)	99.5	100	99.5	100

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:

End point type	Secondary

End point timeframe:

Baseline; Week 2

End point values	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	213	217	216	216
Units: log10 IU/mL				
arithmetic mean (standard deviation)	-4.9 (± 0.657)	-4.94 (± 0.633)	-4.86 (± 0.67)	-4.89 (± 0.648)

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:

End point type	Secondary

End point timeframe:

Baseline; Week 4

End point values	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	213	216	216	217
Units: log10 IU/mL				
arithmetic mean (standard deviation)	-4.99 (± 0.697)	-5.02 (± 0.623)	-4.93 (± 0.678)	-4.96 (± 0.651)

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:

End point type	Secondary

End point timeframe:

Baseline; Week 8

End point values	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	213	215	216	217
Units: log10 IU/mL				
arithmetic mean (standard deviation)	-4.99 (± 0.696)	-5.02 (± 0.625)	-4.91 (± 0.702)	-4.96 (± 0.651)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with virologic failure

End point title	Percentage of participants with virologic failure

End point description:

On-treatment virologic failure was defined as:
- Breakthrough: HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ, while on treatment, confirmed with 2 consecutive values (second confirmation value could have been posttreatment), or last available on-treatment measurement with no subsequent follow- up values, OR
- Rebound: > 1 log10 IU/mL increase in HCV RNA from nadir while on treatment, confirmed with 2 consecutive values (second confirmation value could have been posttreatment), or last available on-treatment measurement with no subsequent follow-up values, OR
- Nonresponse: HCV RNA persistently ≥ LLOQ through 8 weeks of treatment

Virologic relapse was defined as HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at end of treatment, confirmed with 2 consecutive values or last available posttreatment measurement

End point type	Secondary

End point timeframe:

Baseline to posttreatment Week 24

End point values	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks	LDV/SOF+RBV 24 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	214	217	217	217
Units: percentage of participants				
number (not applicable)				
On-treatment virologic failure	0	0	0.5	0
Virologic relapse	0.5	0	0.5	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 24 weeks plus 30 days	
Adverse event reporting additional description:	
Safety Analysis Set: participants were randomized and received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	LDV/SOF 12 weeks
Reporting group description:	
LDV/SOF 90/400 mg FDC tablet once daily for 12 weeks	
Reporting group title	LDV/SOF+RBV 12 weeks
Reporting group description:	
LDV/SOF 90/400 mg FDC tablet once daily plus RBV tablets (1000 to 1200 mg daily based on weight) in a divided daily dose for 12 weeks	
Reporting group title	LDV/SOF 24 weeks
Reporting group description:	
LDV/SOF 90/400 mg FDC tablet once daily for 24 weeks	
Reporting group title	LDV/SOF+RBV 24 weeks
Reporting group description:	
LDV/SOF 90/400 mg FDC tablet once daily plus RBV tablets (1000 to 1200 mg daily based on weight) in a divided daily dose for 24 weeks	

Serious adverse events	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 214 (0.47%)	7 / 217 (3.23%)	18 / 217 (8.29%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	0 / 217 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hand fracture			

subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	2 / 217 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol poisoning			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	0 / 217 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	0 / 217 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	0 / 217 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	0 / 217 (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
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	0 / 217 (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			
Carotid artery stenosis			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	0 / 217 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	0 / 217 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	0 / 217 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Factor VIII inhibition			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	0 / 217 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 214 (0.47%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Non-cardiac chest pain			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	0 / 217 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	0 / 217 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance abuse			

subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	0 / 217 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	0 / 217 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	0 / 217 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
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			
Cellulitis			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	2 / 217 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 214 (0.00%)	1 / 217 (0.46%)	0 / 217 (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
Progressive multifocal leukoencephalopathy			

subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 214 (0.00%)	0 / 217 (0.00%)	1 / 217 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LDV/SOF+RBV 24 weeks		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 217 (3.23%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alcohol poisoning			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			

subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 217 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	0 / 217 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 217 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 217 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertension				
subjects affected / exposed	0 / 217 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carotid artery stenosis				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				

subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Factor VIII inhibition			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Colitis			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Substance abuse			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			

subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Salpingitis			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	LDV/SOF 12 weeks	LDV/SOF+RBV 12 weeks	LDV/SOF 24 weeks
Total subjects affected by non-serious adverse events			
subjects affected / exposed	140 / 214 (65.42%)	168 / 217 (77.42%)	149 / 217 (68.66%)
Nervous system disorders			
Headache			
subjects affected / exposed	54 / 214 (25.23%)	50 / 217 (23.04%)	54 / 217 (24.88%)
occurrences (all)	65	58	66
Dizziness			
subjects affected / exposed	11 / 214 (5.14%)	10 / 217 (4.61%)	14 / 217 (6.45%)
occurrences (all)	12	11	15
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 214 (0.00%)	25 / 217 (11.52%)	0 / 217 (0.00%)
occurrences (all)	0	25	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	46 / 214 (21.50%)	79 / 217 (36.41%)	53 / 217 (24.42%)
occurrences (all)	52	80	63
Asthenia			
subjects affected / exposed	14 / 214 (6.54%)	23 / 217 (10.60%)	20 / 217 (9.22%)
occurrences (all)	14	24	23
Irritability			
subjects affected / exposed	11 / 214 (5.14%)	17 / 217 (7.83%)	17 / 217 (7.83%)
occurrences (all)	11	17	17
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	24 / 214 (11.21%)	37 / 217 (17.05%)	29 / 217 (13.36%)
occurrences (all)	25	41	36
Diarrhoea			
subjects affected / exposed	24 / 214 (11.21%)	18 / 217 (8.29%)	24 / 217 (11.06%)
occurrences (all)	28	18	27
Constipation			
subjects affected / exposed	13 / 214 (6.07%)	12 / 217 (5.53%)	15 / 217 (6.91%)
occurrences (all)	13	12	16

Dyspepsia			
subjects affected / exposed	7 / 214 (3.27%)	11 / 217 (5.07%)	14 / 217 (6.45%)
occurrences (all)	7	14	15
Abdominal pain			
subjects affected / exposed	12 / 214 (5.61%)	9 / 217 (4.15%)	7 / 217 (3.23%)
occurrences (all)	13	11	7
Vomiting			
subjects affected / exposed	7 / 214 (3.27%)	9 / 217 (4.15%)	6 / 217 (2.76%)
occurrences (all)	7	9	8
Abdominal pain upper			
subjects affected / exposed	5 / 214 (2.34%)	11 / 217 (5.07%)	7 / 217 (3.23%)
occurrences (all)	5	11	8
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 214 (1.87%)	7 / 217 (3.23%)	3 / 217 (1.38%)
occurrences (all)	4	7	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 214 (2.80%)	22 / 217 (10.14%)	16 / 217 (7.37%)
occurrences (all)	6	22	17
Dyspnoea			
subjects affected / exposed	3 / 214 (1.40%)	18 / 217 (8.29%)	5 / 217 (2.30%)
occurrences (all)	3	18	5
Dyspnoea exertional			
subjects affected / exposed	3 / 214 (1.40%)	9 / 217 (4.15%)	2 / 217 (0.92%)
occurrences (all)	3	9	2
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	16 / 214 (7.48%)	21 / 217 (9.68%)	16 / 217 (7.37%)
occurrences (all)	18	24	17
Pruritus			
subjects affected / exposed	11 / 214 (5.14%)	22 / 217 (10.14%)	8 / 217 (3.69%)
occurrences (all)	11	22	8
Dry skin			
subjects affected / exposed	2 / 214 (0.93%)	14 / 217 (6.45%)	3 / 217 (1.38%)
occurrences (all)	2	14	3
Psychiatric disorders			

Insomnia			
subjects affected / exposed	17 / 214 (7.94%)	45 / 217 (20.74%)	26 / 217 (11.98%)
occurrences (all)	17	45	27
Anxiety			
subjects affected / exposed	7 / 214 (3.27%)	9 / 217 (4.15%)	12 / 217 (5.53%)
occurrences (all)	7	9	12
Depression			
subjects affected / exposed	5 / 214 (2.34%)	6 / 217 (2.76%)	5 / 217 (2.30%)
occurrences (all)	5	6	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 214 (4.21%)	14 / 217 (6.45%)	21 / 217 (9.68%)
occurrences (all)	9	14	23
Myalgia			
subjects affected / exposed	9 / 214 (4.21%)	13 / 217 (5.99%)	12 / 217 (5.53%)
occurrences (all)	10	13	12
Back pain			
subjects affected / exposed	12 / 214 (5.61%)	5 / 217 (2.30%)	12 / 217 (5.53%)
occurrences (all)	12	5	12
Muscle spasms			
subjects affected / exposed	7 / 214 (3.27%)	14 / 217 (6.45%)	9 / 217 (4.15%)
occurrences (all)	7	15	10
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 214 (6.54%)	9 / 217 (4.15%)	13 / 217 (5.99%)
occurrences (all)	15	9	13
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 214 (4.67%)	12 / 217 (5.53%)	8 / 217 (3.69%)
occurrences (all)	10	12	8

Non-serious adverse events	LDV/SOF+RBV 24 weeks		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	189 / 217 (87.10%)		
Nervous system disorders			
Headache			

subjects affected / exposed	66 / 217 (30.41%)		
occurrences (all)	75		
Dizziness			
subjects affected / exposed	18 / 217 (8.29%)		
occurrences (all)	18		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	22 / 217 (10.14%)		
occurrences (all)	22		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	84 / 217 (38.71%)		
occurrences (all)	88		
Asthenia			
subjects affected / exposed	26 / 217 (11.98%)		
occurrences (all)	35		
Irritability			
subjects affected / exposed	24 / 217 (11.06%)		
occurrences (all)	25		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	32 / 217 (14.75%)		
occurrences (all)	35		
Diarrhoea			
subjects affected / exposed	14 / 217 (6.45%)		
occurrences (all)	16		
Constipation			
subjects affected / exposed	10 / 217 (4.61%)		
occurrences (all)	11		
Dyspepsia			
subjects affected / exposed	12 / 217 (5.53%)		
occurrences (all)	14		
Abdominal pain			
subjects affected / exposed	8 / 217 (3.69%)		
occurrences (all)	10		
Vomiting			

subjects affected / exposed	12 / 217 (5.53%)		
occurrences (all)	13		
Abdominal pain upper			
subjects affected / exposed	9 / 217 (4.15%)		
occurrences (all)	10		
Gastrooesophageal reflux disease			
subjects affected / exposed	11 / 217 (5.07%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	25 / 217 (11.52%)		
occurrences (all)	25		
Dyspnoea			
subjects affected / exposed	15 / 217 (6.91%)		
occurrences (all)	16		
Dyspnoea exertional			
subjects affected / exposed	11 / 217 (5.07%)		
occurrences (all)	11		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	26 / 217 (11.98%)		
occurrences (all)	29		
Pruritus			
subjects affected / exposed	20 / 217 (9.22%)		
occurrences (all)	22		
Dry skin			
subjects affected / exposed	13 / 217 (5.99%)		
occurrences (all)	14		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	46 / 217 (21.20%)		
occurrences (all)	49		
Anxiety			
subjects affected / exposed	19 / 217 (8.76%)		
occurrences (all)	21		
Depression			

subjects affected / exposed occurrences (all)	11 / 217 (5.07%) 11		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all)	 13 / 217 (5.99%) 14 12 / 217 (5.53%) 12 14 / 217 (6.45%) 14 12 / 217 (5.53%) 16		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 19 / 217 (8.76%) 21		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 9 / 217 (4.15%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24725239