



Clinical trial results:

An open-Label, multicenter study to evaluate the efficacy and safety of sofosbuvir/ledipasvir fixed-dose combination ± ribavirin for 12 or 24 weeks in chronic genotype 1 HCV infected subjects who participated in a prior gilead-sponsored HCV treatment study

Summary

EudraCT number	2014-001245-24
Trial protocol	ES
Global end of trial date	12 November 2015

Results information

Result version number	v1 (current)
This version publication date	28 November 2016
First version publication date	28 November 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-337-1118
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01987453
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	12 November 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are to evaluate the efficacy, safety, and tolerability of ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) with or without ribavirin (RBV) in participants with chronic genotype 1 hepatitis C virus (HCV) infection who have participated in a prior Gilead-sponsored HCV treatment study, and who did not achieve sustained virologic response (SVR24), defined as HCV RNA < lower limit of quantification (LLOQ) 24 weeks after last dose of study drug (SVR24).

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	30 July 2014
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: 3
Country: Number of subjects enrolled	United States: 96
Country: Number of subjects enrolled	Australia: 1
Worldwide total number of subjects	100
EEA total number of subjects	3

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)	85
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the US, Australia, and Spain. The first participant was screened on 30 July 2014. The last study visit occurred on 12 November 2015.

Pre-assignment

Screening details:

101 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	LDV/SOF + RBV 12 weeks (Group 1)
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Arm description:

Participants who failed a prior sofosbuvir (SOF) + ribavirin (RBV) ± pegylated interferon (Peg-IFN) regimen received LDV/SOF + RBV for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	Harvoni®; GS-5885/GS-7977
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

90/400 mg FDC administered once daily

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

Dosage and administration details:

1000 or 1200 mg daily based on weight for 12 weeks

Arm title	LDV/SOF 24 weeks (Group 2)
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Arm description:

Participants who failed a prior LDV/SOF±RBV regimen received LDV/SOF for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	Harvoni®; GS-5885/GS-7977
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

90/400 mg FDC administered once daily

Arm title	LDV/SOF + RBV 24 weeks (Group 3)
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Arm description:

Participants with advanced compensated or decompensated cirrhosis who failed a prior SOF+RBV

regimen received LDV/SOF + RBV for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	Harvoni®; GS-5885/GS-7977
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

90/400 mg FDC administered once daily

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

Dosage and administration details:

Ribavirin (dose adjusted according to hemoglobin and renal status) administered for 24 weeks

Number of subjects in period 1	LDV/SOF + RBV 12 weeks (Group 1)	LDV/SOF 24 weeks (Group 2)	LDV/SOF + RBV 24 weeks (Group 3)
Started	51	41	8
Completed	50	29	7
Not completed	1	12	1
Death	-	-	1
Lack of efficacy	1	12	-

Baseline characteristics

Reporting groups

Reporting group title	LDV/SOF + RBV 12 weeks (Group 1)
Reporting group description: Participants who failed a prior sofosbuvir (SOF) + ribavirin (RBV) ± pegylated interferon (Peg-IFN) regimen received LDV/SOF + RBV for 12 weeks.	
Reporting group title	LDV/SOF 24 weeks (Group 2)
Reporting group description: Participants who failed a prior LDV/SOF±RBV regimen received LDV/SOF for 24 weeks.	
Reporting group title	LDV/SOF + RBV 24 weeks (Group 3)
Reporting group description: Participants with advanced compensated or decompensated cirrhosis who failed a prior SOF+RBV regimen received LDV/SOF + RBV for 24 weeks.	

Reporting group values	LDV/SOF + RBV 12 weeks (Group 1)	LDV/SOF 24 weeks (Group 2)	LDV/SOF + RBV 24 weeks (Group 3)
Number of subjects	51	41	8
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	54	58	61
standard deviation	± 8.7	± 6.9	± 6.7
Gender categorical			
Units: Subjects			
Female	20	7	1
Male	31	34	7
Ethnicity			
Units: Subjects			
Hispanic or Latino	4	5	0
Not Hispanic or Latino	47	36	8
Race			
Units: Subjects			
Black or African American	8	10	1
White	43	31	7
Prior HCV Treatment Experience			
Units: Subjects			
SOF+PEG+RBV	25	0	0
SOF+RBV	20	0	8

LDV/SOF	0	18	0
LDV/SOF+RBV	0	15	0
LDV/SOF+GS-9669	0	8	0
Without SOF	6	0	0
IL28B			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	4	3	0
CT	33	27	7
TT	14	11	1
HCV RNA Category			
Units: Subjects			
< 800,000 IU/mL	13	11	6
>= 800,000 IU/mL	38	30	2
HCV RNA			
Units: log10 IU/mL			
arithmetic mean	6.2	6.2	5.6
standard deviation	± 0.58	± 0.62	± 0.44

Reporting group values	Total		
Number of subjects	100		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	28		
Male	72		
Ethnicity			
Units: Subjects			
Hispanic or Latino	9		
Not Hispanic or Latino	91		
Race			
Units: Subjects			
Black or African American	19		
White	81		
Prior HCV Treatment Experience			
Units: Subjects			

SOF+PEG+RBV	25		
SOF+RBV	28		
LDV/SOF	18		
LDV/SOF+RBV	15		
LDV/SOF+GS-9669	8		
Without SOF	6		
IL28B			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	7		
CT	67		
TT	26		
HCV RNA Category			
Units: Subjects			
< 800,000 IU/mL	30		
>= 800,000 IU/mL	70		
HCV RNA			
Units: log ₁₀ IU/mL			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	LDV/SOF + RBV 12 weeks (Group 1)
Reporting group description:	Participants who failed a prior sofosbuvir (SOF) + ribavirin (RBV) ± pegylated interferon (Peg-IFN) regimen received LDV/SOF + RBV for 12 weeks.
Reporting group title	LDV/SOF 24 weeks (Group 2)
Reporting group description:	Participants who failed a prior LDV/SOF±RBV regimen received LDV/SOF for 24 weeks.
Reporting group title	LDV/SOF + RBV 24 weeks (Group 3)
Reporting group description:	Participants with advanced compensated or decompensated cirrhosis who failed a prior SOF+RBV regimen received LDV/SOF + RBV for 24 weeks.

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

End point title	Percentage of Participants With Sustained Virologic Response 12 Weeks After Discontinuation of Therapy (SVR12) ^[1]
End point description:	SVR12 was defined as HCV RNA < the lower limit of quantitation (LLOQ) 12 weeks following the last dose of study treatment. Full Analysis Set: participants enrolled into the study and received at least 1 dose of study drug
End point type	Primary
End point timeframe:	Post-treatment 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	LDV/SOF + RBV 12 weeks (Group 1)	LDV/SOF 24 weeks (Group 2)	LDV/SOF + RBV 24 weeks (Group 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	41	8	
Units: percentage of participants				
number (not applicable)	98	70.7	100	

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]
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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 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 statistical comparison was planned or performed.

End point values	LDV/SOF + RBV 12 weeks (Group 1)	LDV/SOF 24 weeks (Group 2)	LDV/SOF + RBV 24 weeks (Group 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	41	8	
Units: percentage of participants				
number (not applicable)	5.9	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Sustained Virologic Response (SVR) at 4 and 24 Weeks After Discontinuation of Therapy (SVR4 and SVR24)

End point title Percentage of Participants With Sustained Virologic Response (SVR) at 4 and 24 Weeks After Discontinuation of Therapy (SVR4 and SVR24)

End point description:

SVR4 and SVR24 were defined as HCV RNA < LLOQ at 4 and 24 weeks following the last dose of study treatment, respectively. Full Analysis set

End point type Secondary

End point timeframe:

Posttreatment Weeks 4 and 24

End point values	LDV/SOF + RBV 12 weeks (Group 1)	LDV/SOF 24 weeks (Group 2)	LDV/SOF + RBV 24 weeks (Group 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	41	8	
Units: percentage of participants				
number (not applicable)				
SVR4	98	73.2	100	
SVR24	98	70.7	100	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HCV RNA < LLOQ While on Treatment

End point title	Percentage of Participants With HCV RNA < LLOQ While on Treatment
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End point description:

Full Analysis Set

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	LDV/SOF + RBV 12 weeks (Group 1)	LDV/SOF 24 weeks (Group 2)	LDV/SOF + RBV 24 weeks (Group 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	41	8	
Units: percentage of participants				
number (not applicable)				
Week 1	23.5	31.7	0	
Week 4	98	95.1	100	
Week 8	100	100	100	
Week 12	100	100	100	
Week 16	999	97.6	100	
Week 20	999	97.6	100	
Week 24	999	100	100	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HCV RNA From Baseline

End point title	Change in HCV RNA From Baseline
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End point description:

Full Analysis Set

End point type	Secondary
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End point timeframe:

Baseline to Week 8

End point values	LDV/SOF + RBV 12 weeks (Group 1)	LDV/SOF 24 weeks (Group 2)	LDV/SOF + RBV 24 weeks (Group 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	41	8	
Units: log ₁₀ IU/mL				
arithmetic mean (standard deviation)				
Change at Week 1	-4.47 (± 0.5)	-4.4 (± 0.535)	-3.75 (± 0.878)	
Change at Week 4	-5.07 (± 0.565)	-5.06 (± 0.6)	-4.47 (± 0.441)	
Change at Week 8	-5.09 (± 0.583)	-5.08 (± 0.617)	-4.47 (± 0.441)	

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:	
<ul style="list-style-type: none"> • On-treatment virologic failure: • Breakthrough (confirmed HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while on treatment), or • Rebound (confirmed > 1 log₁₀ IU/mL increase in HCV RNA from nadir while on treatment), or • Non-response (HCV RNA persistently ≥ LLOQ through 8 weeks of treatment) • Virologic relapse: • Confirmed HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at last ontreatment visit confirmed with 2 consecutive values or last available posttreatment measurement 	
Full Analysis Set	
End point type	Secondary
End point timeframe:	
Up to posttreatment Week 24	

End point values	LDV/SOF + RBV 12 weeks (Group 1)	LDV/SOF 24 weeks (Group 2)	LDV/SOF + RBV 24 weeks (Group 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	41	8	
Units: percentage of participants				
number (not applicable)				
On treatment Virologic Failure	0	2.4	0	
Relapse	2	27.5	0	

Statistical analyses

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 who received at least 1 dose of study drug

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	LDV/SOF + RBV 12 (Group 1)
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Reporting group description:

Participants who failed a prior sofosbuvir (SOF) + ribavirin (RBV) ± pegylated interferon (Peg-IFN) regimen received LDV/SOF + RBV for 12 weeks.

Reporting group title	LDV/SOF 24 Week (Group 2)
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Reporting group description:

Participants who failed a prior LDV/SOF±RBV regimen received LDV/SOF for 24 weeks.

Reporting group title	LDV/SOF + RBV (Group 2)
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Reporting group description:

Participants with advanced compensated or decompensated cirrhosis who failed a prior SOF+RBV regimen received LDV/SOF + RBV for 24 weeks.

Serious adverse events	LDV/SOF + RBV 12 (Group 1)	LDV/SOF 24 Week (Group 2)	LDV/SOF + RBV (Group 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 51 (3.92%)	2 / 41 (4.88%)	2 / 8 (25.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 51 (0.00%)	1 / 41 (2.44%)	0 / 8 (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	1 / 51 (1.96%)	0 / 41 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	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 / 51 (1.96%)	0 / 41 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	0 / 51 (0.00%)	0 / 41 (0.00%)	1 / 8 (12.50%)
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			
Bipolar disorder			
subjects affected / exposed	1 / 51 (1.96%)	0 / 41 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 51 (0.00%)	0 / 41 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 51 (0.00%)	1 / 41 (2.44%)	0 / 8 (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
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 51 (0.00%)	0 / 41 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	1 / 51 (1.96%)	0 / 41 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	LDV/SOF + RBV 12 (Group 1)	LDV/SOF 24 Week (Group 2)	LDV/SOF + RBV (Group 2)
Total subjects affected by non-serious adverse events subjects affected / exposed	37 / 51 (72.55%)	16 / 41 (39.02%)	7 / 8 (87.50%)
Investigations Haemoglobin decreased subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	0 / 41 (0.00%) 0	1 / 8 (12.50%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all) Encephalopathy subjects affected / exposed occurrences (all)	11 / 51 (21.57%) 11 0 / 51 (0.00%) 0	6 / 41 (14.63%) 6 0 / 41 (0.00%) 0	0 / 8 (0.00%) 0 2 / 8 (25.00%) 2
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Oedema subjects affected / exposed occurrences (all) Oedema Peripheral subjects affected / exposed occurrences (all)	13 / 51 (25.49%) 13 1 / 51 (1.96%) 1 0 / 51 (0.00%) 0 0 / 51 (0.00%) 0	4 / 41 (9.76%) 4 0 / 41 (0.00%) 0 0 / 41 (0.00%) 0	3 / 8 (37.50%) 3 2 / 8 (25.00%) 2 2 / 8 (25.00%) 2 1 / 8 (12.50%) 1
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	7 / 51 (13.73%) 8 5 / 51 (9.80%) 6	2 / 41 (4.88%) 2 1 / 41 (2.44%) 1	2 / 8 (25.00%) 2 2 / 8 (25.00%) 3

Constipation subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 4	1 / 41 (2.44%) 1	0 / 8 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	0 / 41 (0.00%) 0	0 / 8 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 41 (0.00%) 0	2 / 8 (25.00%) 2
Abdominal pain subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 41 (0.00%) 0	1 / 8 (12.50%) 1
Ascites subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 41 (0.00%) 0	1 / 8 (12.50%) 1
Oesophagitis subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 41 (0.00%) 0	1 / 8 (12.50%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	2 / 41 (4.88%) 2	1 / 8 (12.50%) 1
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 7	1 / 41 (2.44%) 1	0 / 8 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	0 / 41 (0.00%) 0	1 / 8 (12.50%) 2
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 41 (0.00%) 0	1 / 8 (12.50%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 6	3 / 41 (7.32%) 3	2 / 8 (25.00%) 2

Depression subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	1 / 41 (2.44%) 1	0 / 8 (0.00%) 0
Irritability subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	0 / 41 (0.00%) 0	0 / 8 (0.00%) 0
Infections and infestations			
Influenza subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	0 / 41 (0.00%) 0	1 / 8 (12.50%) 1
Sinusitis subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	1 / 41 (2.44%) 1	0 / 8 (0.00%) 0
Upper respiratory tract infection' subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	1 / 41 (2.44%) 1	1 / 8 (12.50%) 1
Anal abscess subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 41 (0.00%) 0	1 / 8 (12.50%) 2
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 41 (0.00%) 0	1 / 8 (12.50%) 1
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 41 (0.00%) 0	1 / 8 (12.50%) 1
Viral infection subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 41 (0.00%) 0	1 / 8 (12.50%) 1
Metabolism and nutrition disorders			
Arthralgia subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 1	2 / 41 (4.88%) 2	0 / 8 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2014	Protocol title was updated to reflect additional treatment arm. Duration of treatment was extended as a result of Group 2 treatment length. Objectives were updated to reflect Group 2 Arm which didn't include ribavirin. Study design was revised to detail about stratification of subjects into different treatment groups. Study procedure and frequency sections were updated to account for additional visits for Group 2 subjects on 24 week regimen. Statistical methods were updated as a result of additional group. Updated rationale of the current study and risk/benefit assessment to account for inclusion of Group 2 subjects.
09 April 2014	Duration of treatment was updated to include Group 3 treatment arm of 24 weeks. Study design was updated to detail about stratification of subjects into different treatment groups. Updated eligibility criteria for inclusion of Group 3 subjects. Revised study procedures/frequency to include additional assessments required by Group 3 subjects. Updated test product, dose and mode of administration specific to inclusion of Group 3 subjects

Notes:

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.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25846014>