Clinical trial results:
A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of GS-5885, GS-9451, Tegobuvir and Ribavirin (RBV) Compared with GS-5885, GS-9451 with Tegobuvir or RBV in Treatment-Experienced Subjects with Chronic Genotype 1a or 1b Hepatitis C Virus (HCV) Infection

Summary

EudraCT number	2011-002748-28
Trial protocol	DE
Global end of trial date	29 July 2013

Results information

Result version number	v1 (current)
This version publication date	22 March 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	GS-US-248-0131

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01435226
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	29 July 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was to evaluate the antiviral efficacy, safety, and tolerability of combination therapy with ledispasvir (LDV; formerly GS-5885), vedroprevir (VDV; formerly GS-9451), tegobuvir (TGV), and ribavirin (RBV) compared with LDV+VDV+TGV or LDV+VDV+RBV in treatment-experienced participants with chronic genotype 1a or 1b hepatitis C virus (HCV) infection. The treatment duration for all arms was 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2), had ontreatment virologic breakthrough, or relapse following completion of initial treatment were eligible for treatment with LDV+VDV+pegylated interferon (PEG)+RBV for an additional 24 to 48 weeks in the Rescue Therapy Substudy.

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	12 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 107
Country: Number of subjects enrolled	Germany: 62
Worldwide total number of subjects	169
EEA total number of subjects	62

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)	153
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States and Germany. The first participant was screened on 21 September 2011. The last study visit occurred on 29 July 2013.

Pre-assignment

Screening details:

266 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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LDV+VDV+TGV+RBV

Arm description:

Initial treatment: ledipasvir (LDV)+vedroprevir (VDV)+tegobuvir (TGV)+ribavirin (RBV) for 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2), had ontreatment virologic breakthrough, or relapse following initial treatment were eligible for treatment with LDV+VDV+PEG+RBV for an additional 24 to 48 weeks in the Rescue Therapy Substudy.

Arm type	Experimental
Investigational medicinal product name	Ledipasvir
Investigational medicinal product code	
Other name	GS-5885
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ledipasvir (LDV) 90 mg (3 x 30 mg tablets) administered orally once daily with food in the morning

Investigational medicinal product name	Vedroprevir
Investigational medicinal product code	
Other name	GS-9451
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vedroprevir (VDV) 200 mg (2 x 100 mg tablets) administered orally once daily with food in the morning

Investigational medicinal product name	Tegobuvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tegobuvir (TGV) 60 mg (2 x 30 mg capsules) administered orally with food once in the morning and once in the evening

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus®
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)

Investigational medicinal product name	Pegylated interferon
Investigational medicinal product code	
Other name	PEG
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Pegylated interferon alfa-2a (PEG) 180 µg was administered once weekly by subcutaneous injection for participants receiving treatment in the Rescue Therapy Substudy.

Arm title	LDV+VDV+TGV

Arm description:

Initial treatment: LDV+VDV+TGV+RBV placebo for 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2), had ontreatment virologic breakthrough, or relapse following initial treatment were eligible for treatment with LDV+VDV+PEG+RBV for an additional 24 to 48 weeks in the Rescue Therapy Substudy.

Arm type	Experimental
Investigational medicinal product name	Ledipasvir
Investigational medicinal product code	
Other name	GS-5885
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ledipasvir (LDV) 90 mg (3 x 30 mg tablets) administered orally once daily with food in the morning

Investigational medicinal product name	Vedroprevir
Investigational medicinal product code	
Other name	GS-9451
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vedroprevir (VDV) 200 mg (2 x 100 mg tablets) administered orally once daily with food in the morning

Investigational medicinal product name	Tegobuvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tegobuvir (TGV) 60 mg (2 x 30 mg capsules) administered orally with food once in the morning and once in the evening

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

Dosage and administration details:

Placebo to match ribavirin tablets administered orally in a divided daily dose

Investigational medicinal product name	Pegylated interferon
Investigational medicinal product code	
Other name	PEG
Pharmaceutical forms	Solution for injection

Routes of administration	Intravenous use

Dosage and administration details:

Pegylated interferon alfa-2a (PEG) 180 µg was administered once weekly by subcutaneous injection for participants receiving treatment in the Rescue Therapy Substudy.

Arm title	LDV+VDV+RBV

Arm description:

Initial Treatment: LDV+VDV+TGV placebo+RBV for 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2), had ontreatment virologic breakthrough, or relapse following initial treatment were eligible for treatment with LDV+VDV+PEG+RBV for an additional 24 to 48 weeks in the Rescue Therapy Substudy.

Arm type	Experimental
Investigational medicinal product name	Ledipasvir
Investigational medicinal product code	
Other name	GS-5885
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ledipasvir (LDV) 90 mg (3 x 30 mg tablets) administered orally once daily with food in the morning

Investigational medicinal product name	Vedroprevir
Investigational medicinal product code	
Other name	GS-9451
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vedroprevir (VDV) 200 mg (2 x 100 mg tablets) administered orally once daily with food in the morning

Investigational medicinal product name	Tegobuvir placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to match tegobuvir capsules administered orally with food once in the morning and once in the evening

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus®
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)

Investigational medicinal product name	Pegylated interferon
Investigational medicinal product code	
Other name	PEG
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Pegylated interferon alfa-2a (PEG) 180 µg was administered once weekly by subcutaneous injection for participants receiving treatment in the Rescue Therapy Substudy.

Number of subjects in period 1	LDV+VDV+TGV+RBV	LDV+VDV+TGV	LDV+VDV+RBV
Started	57	56	56
Entered Rescue Therapy Substudy	30 [1]	36	42
Completed	31	25	19
Not completed	26	31	37
Physician decision	2	-	3
Adverse event, non-fatal	2	5	5
Protocol violation	1	-	1
Study terminated by sponsor	-	-	2
Lost to follow-up	1	1	1
Lack of efficacy	19	22	19
Withdrawal by subject	1	3	6

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The overall number completed includes participants who completed the initial treatment and did not continue in the Rescue Therapy Substudy, and those who continued after initial treatment and completed the Rescue Therapy Substudy.

Baseline characteristics

Reporting groups	
Reporting group title	LDV+VDV+TGV+RBV

Reporting group description:

Initial treatment: ledipasvir (LDV)+vedroprevir (VDV)+tegobuvir (TGV)+ribavirin (RBV) for 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2), had ontreatment virologic breakthrough, or relapse following initial treatment were eligible for treatment with LDV+VDV+PEG+RBV for an additional 24 to 48 weeks in the Rescue Therapy Substudy.

Reporting group title	LDV+VDV+TGV

Reporting group description:

Initial treatment: LDV+VDV+TGV+RBV placebo for 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2), had ontreatment virologic breakthrough, or relapse following initial treatment were eligible for treatment with LDV+VDV+PEG+RBV for an additional 24 to 48 weeks in the Rescue Therapy Substudy.

Reporting group title	LDV+VDV+RBV

Reporting group description:

Initial Treatment: LDV+VDV+TGV placebo+RBV for 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2), had ontreatment virologic breakthrough, or relapse following initial treatment were eligible for treatment with LDV+VDV+PEG+RBV for an additional 24 to 48 weeks in the Rescue Therapy Substudy.

Reporting group values	LDV+VDV+TGV+RBV	LDV+VDV+TGV	LDV+VDV+RBV
Number of subjects	57	56	56
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	53	54	56
standard deviation	± 8.8	± 7.6	± 8.5
Gender categorical Units: Subjects			
Female	16	19	24
Male	41	37	32
Race Units: Subjects			
White	46	45	51
Black or African American	9	9	4
Asian	0	1	1

American Indian or Alaska Native	0	1	0
Not Permitted	1	0	0
Other	1	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	4	5	5
Not Hispanic or Latino	53	51	51
HCV Genotype Units: Subjects			
1a	35	34	35
1b	22	22	21
IL28B Status			
CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	5	1	6
CT	38	40	39
TT	14	15	11
HCV RNA Units: log10 IU/mL			
arithmetic mean	6.7	6.5	6.5
standard deviation	± 0.45	± 0.57	± 0.51

Reporting group values	Total		
Number of subjects	169		
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	59		
Male	110		
Race Units: Subjects			
White	142		
Black or African American	22		
Asian	2		
American Indian or Alaska Native	1		
Not Permitted	1		

Other	1		
Ethnicity Units: Subjects			
Hispanic or Latino	14		
Not Hispanic or Latino	155		
HCV Genotype Units: Subjects			
1a	104		
1b	65		
IL28B Status			
CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	12		
CT	117		
TT	40		
HCV RNA Units: log10 IU/mL arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	LDV+VDV+TGV+RBV

Reporting group description:

Initial treatment: ledipasvir (LDV)+vedroprevir (VDV)+tegobuvir (TGV)+ribavirin (RBV) for 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2), had ontreatment virologic breakthrough, or relapse following initial treatment were eligible for treatment with LDV+VDV+PEG+RBV for an additional 24 to 48 weeks in the Rescue Therapy Substudy.

Reporting group title	LDV+VDV+TGV

Reporting group description:

Initial treatment: LDV+VDV+TGV+RBV placebo for 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2), had ontreatment virologic breakthrough, or relapse following initial treatment were eligible for treatment with LDV+VDV+PEG+RBV for an additional 24 to 48 weeks in the Rescue Therapy Substudy.

Reporting group title	LDV+VDV+RBV

Reporting group description:

Initial Treatment: LDV+VDV+TGV placebo+RBV for 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2), had ontreatment virologic breakthrough, or relapse following initial treatment were eligible for treatment with LDV+VDV+PEG+RBV for an additional 24 to 48 weeks in the Rescue Therapy Substudy.

Subject analysis set title	LDV+VDV+TGV+RBV - Main Study
Subject analysis set type	Sub-group analysis

Subject analysis set description:

LDV+VDV+TGV+RBV for 24 weeks

Subject analysis set title	LDV+VDV+TGV - Main Study
Subject analysis set type	Sub-group analysis

Subject analysis set description:

LDV+VDV+TGV+RBV placebo for 24 weeks

Subject analysis set title	LDV+VDV+RBV - Main Study
Subject analysis set type	Sub-group analysis

Subject analysis set description:

LDV+VDV+TGV placebo+RBV for 24 weeks

Subject analysis set title	LDV+VDV+TGV+RBV - Rescue Therapy Substudy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Initial treatment: LDV+VDV+TGV+RBV for 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at
Week 2), had ontreatment virologic breakthrough, or relapse following initial treatment were eligible for treatment with LDV+VDV+PEG+RBV for an additional 24 to 48 weeks in the Rescue Therapy Substudy.

Subject analysis set title	LDV+VDV+TGV - Rescue Therapy Substudy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Initial treatment: LDV+VDV+TGV+RBV placebo for 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2), had ontreatment virologic breakthrough, or relapse following initial treatment were eligible for treatment with LDV+VDV+PEG+RBV for an additional 24 to 48 weeks in the Rescue Therapy Substudy.

Subject analysis set title	LDV+VDV+RBV - Rescue Therapy Substudy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Initial treatment: LDV+VDV+TGV placebo+RBV for 24 weeks. Participants who did not achieve a very rapid virologic response (vRVR, defined as HCV RNA < LLOQ at Week 2), had ontreatment virologic breakthrough, or relapse following initial treatment were eligible for treatment with

Primary: Percentage of participants with sustained virologic response (SVR) 24 weeks after discontinuation of therapy (SVR24)

End point title	Percentage of participants with sustained virologic response (SVR) 24 weeks after discontinuation of therapy (SVR24)[1]

End point description:

SVR24 was defined as HCV RNA < the lower limit of quantitation (LLOQ; ie, 25 IU/mL) 24 weeks following the last dose of study drug.

End point type	Primary

End point timeframe:

Posttreatment Week 24

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 hypothesis testing was planned or performed.

End point values	LDV+VDV+TGV +RBV - Main Study	LDV+VDV+TGV - Main Study	LDV+VDV+RBV - Main Study	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	54	55	
Units: percentage of participants				
number (not applicable)	33.3	22.2	9.1	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants who experienced an adverse event leading to permanent discontinuation from any study drug

End point title	Percentage of participants who experienced an adverse event leading to permanent discontinuation from any study drug[2]

End point description:

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 hypothesis testing was planned or performed.

End point values	LDV+VDV+TGV +RBV - Main Study	LDV+VDV+TGV - Main Study	LDV+VDV+RBV - Main Study	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	56	56	
Units: percentage of participants				
number (not applicable)	0	7.1	3.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with SVR4 and SVR12

End point title	Percentage of participants with SVR4 and SVR12

End point description:

SVR4 and SVR12 were defined as HCV RNA < LLOQ at 4 and 12 weeks following the last dose of study drug, respectively.

End point type	Secondary

End point timeframe:

Posttreatment Weeks 4 and 12

End point values	LDV+VDV+TGV +RBV - Main Study	LDV+VDV+TGV - Main Study	LDV+VDV+RBV - Main Study	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	54	55	
Units: percentage of participants				
number (not applicable)				
SVR4	35.1	24.1	10.9	
SVR12	33.3	22.2	9.1	

Statistical analyses

No statistical analyses for this end point

Secondary: In the rescue therapy substudy, percentage of participants with SVR4, SVR12, and SVR24

End point title	In the rescue therapy substudy, percentage of participants with SVR4, SVR12, and SVR24

End point description:

SVR4, SVR12, and SVR24 were defined as HCV RNA < LLOQ at 4, 12, and 24 weeks following the last dose of study drug during the rescue therapy substudy, respectively. This endpoint only includes data from the Rescue Therapy Substudy Analysis Set.

End point type	Secondary

End point timeframe:

Posttreatment Weeks 4, 12, and 24

End point values	LDV+VDV+TGV +RBV - Rescue Therapy Substudy	LDV+VDV+TGV - Rescue Therapy Substudy	LDV+VDV+RBV - Rescue Therapy Substudy	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	30	36	42	
Units: percentage of participants				
number (not applicable)				
SVR4	40	44.4	40.5	
SVR12	30	36.1	31	
SVR24	30	33.3	31	

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	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16
Reporting groups	
Reporting group title	LDV+VDV+TGV+RBV
Reporting group description: Ledipasvir (LDV) + vedroprevir (VDV) + tegobuvir (TGV) + ribavirin (RBV) for 24 weeks	
Reporting group title	LDV+VDV+TGV
Reporting group description: LDV+VDV+TGV+RBV placebo for 24 weeks	
Reporting group title	LDV+VDV+RBV
Reporting group description: LDV+VDV+TGV placebo+RBV for 24 weeks	

Serious adverse events	LDV+VDV+TGV+RBV	LDV+VDV+TGV	LDV+VDV+RBV
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 57 (1.75%)	1 / 56 (1.79%)	1 / 56 (1.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 56 (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
Duodenitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 56 (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

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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+VDV+TGV+RBV	LDV+VDV+TGV	LDV+VDV+RBV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 57 (75.44%)	38 / 56 (67.86%)	41 / 56 (73.21%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 57 (5.26%)	0 / 56 (0.00%)	0 / 56 (0.00%)
occurrences (all)	3	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 57 (26.32%)	12 / 56 (21.43%)	13 / 56 (23.21%)
occurrences (all)	19	15	15
Dizziness			
subjects affected / exposed	4 / 57 (7.02%)	7 / 56 (12.50%)	0 / 56 (0.00%)
occurrences (all)	5	7	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 57 (3.51%)	0 / 56 (0.00%)	4 / 56 (7.14%)
occurrences (all)	2	0	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	20 / 57 (35.09%)	13 / 56 (23.21%)	15 / 56 (26.79%)
occurrences (all)	20	13	15
Irritability			
subjects affected / exposed	2 / 57 (3.51%)	3 / 56 (5.36%)	4 / 56 (7.14%)
occurrences (all)	2	3	4
Asthenia			

subjects affected / exposed	5 / 57 (8.77%)	1 / 56 (1.79%)	2 / 56 (3.57%)
occurrences (all)	5	1	2
Chills			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	3 / 56 (5.36%)
occurrences (all)	1	0	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 57 (15.79%)	8 / 56 (14.29%)	9 / 56 (16.07%)
occurrences (all)	13	8	11
Diarrhoea			
subjects affected / exposed	8 / 57 (14.04%)	3 / 56 (5.36%)	3 / 56 (5.36%)
occurrences (all)	9	3	3
Dyspepsia			
subjects affected / exposed	10 / 57 (17.54%)	2 / 56 (3.57%)	2 / 56 (3.57%)
occurrences (all)	16	2	2
Vomiting			
subjects affected / exposed	4 / 57 (7.02%)	0 / 56 (0.00%)	3 / 56 (5.36%)
occurrences (all)	5	0	3
Constipation			
subjects affected / exposed	1 / 57 (1.75%)	2 / 56 (3.57%)	3 / 56 (5.36%)
occurrences (all)	1	2	3
Dry mouth			
subjects affected / exposed	2 / 57 (3.51%)	0 / 56 (0.00%)	3 / 56 (5.36%)
occurrences (all)	2	0	3
Flatulence			
subjects affected / exposed	1 / 57 (1.75%)	3 / 56 (5.36%)	1 / 56 (1.79%)
occurrences (all)	2	3	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 57 (12.28%)	2 / 56 (3.57%)	11 / 56 (19.64%)
occurrences (all)	8	2	11
Dyspnoea			
subjects affected / exposed	3 / 57 (5.26%)	1 / 56 (1.79%)	5 / 56 (8.93%)
occurrences (all)	3	1	5
Dyspnoea exertional			

subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	7 / 56 (12.50%)
occurrences (all)	0	1	7
Oropharyngeal pain			
subjects affected / exposed	3 / 57 (5.26%)	1 / 56 (1.79%)	1 / 56 (1.79%)
occurrences (all)	3	1	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	10 / 57 (17.54%)	7 / 56 (12.50%)	7 / 56 (12.50%)
occurrences (all)	13	7	8
Rash			
subjects affected / exposed	5 / 57 (8.77%)	3 / 56 (5.36%)	4 / 56 (7.14%)
occurrences (all)	6	3	4
Dry skin			
subjects affected / exposed	4 / 57 (7.02%)	0 / 56 (0.00%)	4 / 56 (7.14%)
occurrences (all)	4	0	4
Photosensitivity reaction			
subjects affected / exposed	3 / 57 (5.26%)	2 / 56 (3.57%)	0 / 56 (0.00%)
occurrences (all)	3	2	0
Alopecia			
subjects affected / exposed	3 / 57 (5.26%)	0 / 56 (0.00%)	0 / 56 (0.00%)
occurrences (all)	3	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 57 (7.02%)	3 / 56 (5.36%)	2 / 56 (3.57%)
occurrences (all)	4	3	2
Anxiety			
subjects affected / exposed	5 / 57 (8.77%)	0 / 56 (0.00%)	1 / 56 (1.79%)
occurrences (all)	5	0	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 57 (3.51%)	4 / 56 (7.14%)	2 / 56 (3.57%)
occurrences (all)	2	4	2
Arthralgia			
subjects affected / exposed	4 / 57 (7.02%)	3 / 56 (5.36%)	0 / 56 (0.00%)
occurrences (all)	4	3	0
Back pain			

subjects affected / exposed	4 / 57 (7.02%)	0 / 56 (0.00%)	1 / 56 (1.79%)
occurrences (all)	5	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 57 (0.00%)	4 / 56 (7.14%)	0 / 56 (0.00%)
occurrences (all)	0	4	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 57 (12.28%)	4 / 56 (7.14%)	0 / 56 (0.00%)
occurrences (all)	8	5	0
Oral herpes			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	3 / 56 (5.36%)
occurrences (all)	2	0	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 57 (3.51%)	2 / 56 (3.57%)	4 / 56 (7.14%)
occurrences (all)	2	2	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2011	The virologic breakthrough futility rule was revised based on FDA recommendation.
15 September 2011	Due to two cases of pancytopenia/aplastic anemia observed in subjects receiving tegobuvir plus a protease inhibitor plus PEG/RBV (in different studies), the decision was made to discontinue dosing of tegobuvir when given in combination with PEG/RBV and another oral antiviral. Therefore, tegobuvir was removed from the Rescue Therapy Substudy.
11 April 2012	On 26 March 2012, the Data Monitoring Committee (DMC) determined that the protocol-specified virologic breakthrough futility rule had been met for subjects with genotype 1a HCV infection in Arm 2 and Arm 3. Based on the DMC's recommendations, the following changes were made: - study was unblinded and the treatment assignment for every subject was provided to the treating investigator - all genotype 1a subjects in Arms 2 and 3 was offered enrollment in the Rescue Therapy Substudy (GS-5885+GS-9451+PEG+RBV for 24-48 weeks). This instruction superseded any other references to eligibility for the Rescue Therapy Substudy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 March 2012	On 26 March 2012, the DMC determined that the protocol-specified virologic breakthrough futility rule had been met for subjects with genotype 1a HCV infection in Arm 2 and Arm 3. As the study completed enrollment in February 2012, the DMC's recommendations was implemented as follows: - the study was unblinded and the treatment assignment for every subject was provided to the treating investigator - all genotype 1a subjects in Arms 2 and 3 was offered enrollment in the Rescue Therapy Substudy (LDV+VDV+PEG+RBV for 24-48 weeks). This instruction superseded any other references to eligibility for the Rescue Therapy Substudy.	11 April 2012

Notes:

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: