Clinical trial results:
A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating 16 and 24 Weeks of Response Guided Therapy With GS-9190, GS-9256, Ribavirin (Copegus®) and Peginterferon Alfa 2a (Pegasys®) in Treatment Naïve Subjects with Chronic Genotype 1 Hepatitis C Virus Infection

Summary

EudraCT number	2010-020911-35
Trial protocol	CZ DE GB BE AT PL IT
Global end of trial date	19 September 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-196-0123

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01225380
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	19 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the antiviral efficacy (sustained virologic response [SVR]; defined as undetectable HCV RNA 24 weeks following treatment cessation) of 16 and 24 weeks of response guided duration of therapy with tegobuvir (TGV, GS-9190), GS-9256, ribavirin (RBV), and peginterferon alfa 2a (PEG).

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	11 October 2010
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	Poland: 45
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Czech Republic: 32
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Canada: 46
Country: Number of subjects enrolled	United States: 142
Worldwide total number of subjects	323
EEA total number of subjects	135

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)	312
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America and Europe. The first participant was screened on 11 October 2010. The last study visit occurred on 19 September 2013.

Pre-assignment

Screening details:

323 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	GS-9190+GS-9256

Arm description:

GS-9190+GS-9256+PEG+RBV for 16 or 24 weeks; PEG+RBV may have been continued for up to 48 weeks total duration depending on individual response to therapy.

Arm type	Experimental
Investigational medicinal product name	Tegobuvir
Investigational medicinal product code	
Other name	TGV, GS-9190
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tegobuvir (TGV) 20 mg capsule administered orally twice daily

Investigational medicinal product name	GS-9256
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

GS-9256 150 mg (1 × 100-mg capsule/1 × 50-mg capsule) twice daily

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

Dosage and administration details:

Pegylated interferon alfa-2a (PEG) 180 µg administered once weekly by subcutaneous injection

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

Dosage and administration details:

Ribavirin (RBV) 1000 mg administered orally in a divided daily dose (3 × 200 tablets in the morning, 2 × 200 tablets in the evening)

Arm title	GS-9256

Arm description:

GS-9256+placebo to match TGV+PEG+RBV for 24 weeks; PEG+RBV may have been continued for up to 48 weeks total duration depending on individual response to therapy.

Arm type	Experimental
Investigational medicinal product name	GS-9256
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

GS-9256 150 mg (1 × 100-mg capsule/1 × 50-mg capsule) twice daily

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 administered orally twice daily

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

Dosage and administration details:

Pegylated interferon alfa-2a (PEG) 180 µg administered once weekly by subcutaneous injection

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

Dosage and administration details:

Ribavirin (RBV) 1000 mg administered orally in a divided daily dose (3 × 200 tablets in the morning, 2 × 200 tablets in the evening)

Arm title	Placebo

Arm description:

Placebo to match GS-9190+placebo to match GS-9256+PEG+RBV for 24 weeks; PEG+RBV may have been continued for up to 48 weeks total duration.

Arm type	Experimental
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 administered orally twice daily

Investigational medicinal product name	GS-9256 Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to match GS-9256 administered orally twice daily

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

Dosage and administration details:

Pegylated interferon alfa-2a (PEG) 180 µg administered once weekly by subcutaneous injection

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

Dosage and administration details:

Ribavirin (RBV) 1000 mg administered orally in a divided daily dose (3 × 200 tablets in the morning, 2 × 200 tablets in the evening)

Number of subjects in period 1	GS-9190+GS-9256	GS-9256	Placebo
Started	163	78	82
Completed	124	55	49
Not completed	39	23	33
Efficacy failure	15	15	19
Consent withdrawn by subject	7	3	2
Adverse event, non-fatal	7	-	4
Protocol violation	3	-	-
Death	-	-	1
Discontinued by sponsor	-	-	5
Lost to follow-up	7	5	2

Baseline characteristics

Reporting groups	
Reporting group title	GS-9190+GS-9256
Reporting group description:	
GS-9190+GS-9256+PEG+RBV for 16 or 24 weeks; PEG+RBV may have been continued for up to 48 weeks total duration depending on individual response to therapy.	
Reporting group title	GS-9256
Reporting group description:	
GS-9256+placebo to match TGV+PEG+RBV for 24 weeks; PEG+RBV may have been continued for up to 48 weeks total duration depending on individual response to therapy.	
Reporting group title	Placebo
Reporting group description:	
Placebo to match GS-9190+placebo to match GS-9256+PEG+RBV for 24 weeks; PEG+RBV may have been continued for up to 48 weeks total duration.	

Reporting group values	GS-9190+GS-9256	GS-9256	Placebo
Number of subjects	163	78	82
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	48	47	46
standard deviation	± 11.3	± 12.3	± 12.4
Gender categorical			
Units: Subjects			
Female	65	31	31
Male	98	47	51
Race			
Units: Subjects			
White	150	69	76
Black or African Heritage	6	6	2
Asian	4	1	2
American Indian or Alaska Native	1	1	1
Native Hawaiian or Pacific Islander	1	0	0
Other	1	1	1
Ethnicity			
Units: Subjects			
Hispanic/Latino	5	3	8
Not Hispanic/Latino	158	75	74
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			
1a	90	42	37
1b	73	36	45
IL28b status			
CC and non-CC alleles are different forms of the IL28b gene.			
Units: Subjects			

CC	53	25	28
Non-CC	110	53	54

Hepatitis C Virus (HCV) RNA			
Units: log10 IU/mL			
arithmetic mean	6.36	6.33	6.42
standard deviation	± 0.772	± 0.672	± 0.694

Reporting group values	Total		
Number of subjects	323		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	127		
Male	196		
Race			
Units: Subjects			
White	295		
Black or African Heritage	14		
Asian	7		
American Indian or Alaska Native	3		
Native Hawaiian or Pacific Islander	1		
Other	3		
Ethnicity			
Units: Subjects			
Hispanic/Latino	16		
Not Hispanic/Latino	307		
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			
1a	169		
1b	154		
IL28b status			
CC and non-CC alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	106		
Non-CC	217		
Hepatitis C Virus (HCV) RNA			
Units: log10 IU/mL			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	GS-9190+GS-9256
Reporting group description:	
GS-9190+GS-9256+PEG+RBV for 16 or 24 weeks; PEG+RBV may have been continued for up to 48 weeks total duration depending on individual response to therapy.	
Reporting group title	GS-9256
Reporting group description:	
GS-9256+placebo to match TGV+PEG+RBV for 24 weeks; PEG+RBV may have been continued for up to 48 weeks total duration depending on individual response to therapy.	
Reporting group title	Placebo
Reporting group description:	
Placebo to match GS-9190+placebo to match GS-9256+PEG+RBV for 24 weeks; PEG+RBV may have been continued for up to 48 weeks total duration.	

Primary: Percentage of Participants With Sustained Virologic Response 24 Weeks After Discontinuation of Therapy (SVR24)

End point title	Percentage of Participants With Sustained Virologic Response 24 Weeks After Discontinuation of Therapy (SVR24)
End point description:	
End point type	Primary
End point timeframe:	
Posttreatment Week 24	

End point values	GS-9190+GS-9256	GS-9256	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163	78	82	
Units: percentage of participants				
number (not applicable)	79.1	70.5	54.9	

Statistical analyses

Statistical analysis title	Difference in rates
Statistical analysis description:	
The total sample size of 160 subjects in Arm 2 and 3 will have 80% power to evaluate superiority of Arm 2 over Arm 3, assuming a 50% response rate in Arm 3 and a 20% treatment effect delta associated with the co-administration of GS-9256, PEG, and RBV.	
Comparison groups	GS-9256 v Placebo

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031 [1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - The p-value comparing achievement of SVR between the GS-9256 and placebo groups is based on the Cochran-Mantel-Haenszel (CMH) test for stratified proportions.

Secondary: Percentage of Participants With Very Rapid Virologic Response (vRVR)

End point title	Percentage of Participants With Very Rapid Virologic Response (vRVR)

End point description:

vRVR was defined as HCV RNA < 25 IU/mL at Week 2 and Week 4 and HCV RNA < 10 IU/mL at Week 8 maintained through Week 16.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	GS-9190+GS-9256	GS-9256	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163	78	82	
Units: percentage of participants				
number (not applicable)	72.4	60.3	13.4	

Statistical analyses

Statistical analysis title	Difference in percentage
Comparison groups	Placebo v GS-9256
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.001 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[2] - Comparative analysis

[3] - P-value between the GS-9256 and placebo groups is based on the Cochran-Mantel-Haenszel (CMH) test for stratified proportions.

Secondary: Percentage of Participants With Extended Rapid Virologic Response (eRVR)

End point title	Percentage of Participants With Extended Rapid Virologic Response (eRVR)

End point description:

eRVR was defined as HCV RNA < 25 IU/mL at Week 4 and HCV RNA < 10 IU/mL at Week 8 maintained through Week 24.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	GS-9190+GS-9256	GS-9256	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163	78	82	
Units: percentage of participants				
number (not applicable)	82.8	70.5	22	

Statistical analyses

Statistical analysis title	Difference in percentage
Comparison groups	GS-9256 v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.001 [5]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - Comparative analysis

[5] - P-value between the GS-9256 and placebo groups is based on the Cochran-Mantel-Haenszel (CMH) test for stratified proportions.

Secondary: Percentage of Participants With Partial Early Virologic Response (pEVR)

End point title	Percentage of Participants With Partial Early Virologic Response (pEVR)

End point description:

pEVR was defined as at least a 2 log10 IU/mL reduction from baseline in HCV RNA at Week 12.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	GS-9190+GS-9256	GS-9256	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163	78	82	
Units: percentage of participants				
number (not applicable)	93.9	96.2	84.1	

Statistical analyses

Statistical analysis title	Difference in percentage
Comparison groups	GS-9256 v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.11 [7]
Method	Cochran-Mantel-Haenszel

Notes:

[6] - Comparative analysis

[7] - P-value between the GS-9256 and placebo groups is based on the Cochran-Mantel-Haenszel (CMH) test for stratified proportions.

Secondary: Percentage of participants with Virologic Breakthrough and Relapse

End point title	Percentage of participants with Virologic Breakthrough and Relapse

End point description:

Breakthrough was defined as 2 consecutive values that were undetectable followed (at a later point in time) by 2 consecutive detectable HCV RNA values while on treatment. Relapse was defined as undetectable HCV RNA at end of treatment followed by two consecutive detectable HCV RNA values during off-treatment follow-up.

End point type	Secondary

End point timeframe:

Up to 48 weeks

End point values	GS-9190+GS-9256	GS-9256	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163	78	82	
Units: percentage of participants				
number (not applicable)				
Breakthrough	1.2	2.6	0	
Relapse	9.2	11.5	18.3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 48 weeks plus 30 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16..1

Reporting groups	
Reporting group title	GS-9190+GS-9256
Reporting group description:	
GS-9190+GS-9256+PEG+RBV for 16 or 24 weeks; PEG+RBV may have been continued for up to 48 weeks total duration depending on individual response to therapy.	
Reporting group title	GS-9256
Reporting group description:	
GS-9256+placebo to match TGV+PEG+RBV for 24 weeks; PEG+RBV may have been continued for up to 48 weeks total duration depending on individual response to therapy.	
Reporting group title	Placebo
Reporting group description:	
Placebo to match GS-9190+placebo to match GS-9256+PEG+RBV for 24 weeks; PEG+RBV may have been continued for up to 48 weeks total duration.	

Serious adverse events	GS-9190+GS-9256	GS-9256	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 163 (6.75%)	0 / 78 (0.00%)	5 / 82 (6.10%)
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)			
Prostate cancer			
subjects affected / exposed	0 / 163 (0.00%)	0 / 78 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 163 (0.00%)	0 / 78 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			

subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Chest pain			
subjects affected / exposed	0 / 163 (0.00%)	0 / 78 (0.00%)	1 / 82 (1.22%)
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			
Balanitis			
subjects affected / exposed	0 / 163 (0.00%)	0 / 78 (0.00%)	1 / 82 (1.22%)
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			
Suicidal ideation			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 163 (0.00%)	0 / 78 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 163 (1.23%)	0 / 78 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Febrile neutropenia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Neutropenia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Pruritus			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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

Rash			
subjects affected / exposed	2 / 163 (1.23%)	0 / 78 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Arthritis bacterial			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Cellulitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Abscess			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Staphylococcal bacteraemia			

subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Staphylococcal infection			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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
Urinary tract infection			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 163 (0.61%)	0 / 78 (0.00%)	0 / 82 (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	GS-9190+GS-9256	GS-9256	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	155 / 163 (95.09%)	76 / 78 (97.44%)	79 / 82 (96.34%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	83 / 163 (50.92%)	34 / 78 (43.59%)	44 / 82 (53.66%)
occurrences (all)	85	35	45
Pyrexia			
subjects affected / exposed	43 / 163 (26.38%)	22 / 78 (28.21%)	20 / 82 (24.39%)
occurrences (all)	52	28	40
Chills			
subjects affected / exposed	35 / 163 (21.47%)	12 / 78 (15.38%)	10 / 82 (12.20%)
occurrences (all)	39	13	12
Irritability			
subjects affected / exposed	26 / 163 (15.95%)	13 / 78 (16.67%)	15 / 82 (18.29%)
occurrences (all)	26	13	15

Influenza like illness			
subjects affected / exposed	14 / 163 (8.59%)	15 / 78 (19.23%)	14 / 82 (17.07%)
occurrences (all)	14	15	14
Asthenia			
subjects affected / exposed	21 / 163 (12.88%)	10 / 78 (12.82%)	10 / 82 (12.20%)
occurrences (all)	21	12	11
Injection site erythema			
subjects affected / exposed	21 / 163 (12.88%)	6 / 78 (7.69%)	10 / 82 (12.20%)
occurrences (all)	21	6	10
Injection site reaction			
subjects affected / exposed	10 / 163 (6.13%)	4 / 78 (5.13%)	5 / 82 (6.10%)
occurrences (all)	10	4	6
Pain			
subjects affected / exposed	7 / 163 (4.29%)	5 / 78 (6.41%)	2 / 82 (2.44%)
occurrences (all)	8	5	2
Chest pain			
subjects affected / exposed	3 / 163 (1.84%)	0 / 78 (0.00%)	6 / 82 (7.32%)
occurrences (all)	3	0	7
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	35 / 163 (21.47%)	11 / 78 (14.10%)	12 / 82 (14.63%)
occurrences (all)	36	12	14
Dyspnoea			
subjects affected / exposed	22 / 163 (13.50%)	10 / 78 (12.82%)	8 / 82 (9.76%)
occurrences (all)	22	10	8
Oropharyngeal pain			
subjects affected / exposed	9 / 163 (5.52%)	4 / 78 (5.13%)	8 / 82 (9.76%)
occurrences (all)	10	4	10
Dyspnoea exertional			
subjects affected / exposed	10 / 163 (6.13%)	5 / 78 (6.41%)	3 / 82 (3.66%)
occurrences (all)	10	5	3
Sinus congestion			
subjects affected / exposed	4 / 163 (2.45%)	4 / 78 (5.13%)	1 / 82 (1.22%)
occurrences (all)	4	4	1
Psychiatric disorders			

Insomnia			
subjects affected / exposed	33 / 163 (20.25%)	15 / 78 (19.23%)	15 / 82 (18.29%)
occurrences (all)	33	15	15
Depression			
subjects affected / exposed	25 / 163 (15.34%)	9 / 78 (11.54%)	10 / 82 (12.20%)
occurrences (all)	25	10	11
Anxiety			
subjects affected / exposed	10 / 163 (6.13%)	6 / 78 (7.69%)	6 / 82 (7.32%)
occurrences (all)	10	7	6
Mood swings			
subjects affected / exposed	6 / 163 (3.68%)	4 / 78 (5.13%)	4 / 82 (4.88%)
occurrences (all)	6	4	4
Investigations			
Blood bilirubin increased			
subjects affected / exposed	20 / 163 (12.27%)	11 / 78 (14.10%)	1 / 82 (1.22%)
occurrences (all)	20	14	1
Weight decreased			
subjects affected / exposed	8 / 163 (4.91%)	6 / 78 (7.69%)	3 / 82 (3.66%)
occurrences (all)	8	6	3
Nervous system disorders			
Headache			
subjects affected / exposed	66 / 163 (40.49%)	26 / 78 (33.33%)	25 / 82 (30.49%)
occurrences (all)	77	27	33
Dizziness			
subjects affected / exposed	19 / 163 (11.66%)	14 / 78 (17.95%)	12 / 82 (14.63%)
occurrences (all)	22	15	14
Dysgeusia			
subjects affected / exposed	17 / 163 (10.43%)	3 / 78 (3.85%)	6 / 82 (7.32%)
occurrences (all)	17	3	6
Disturbance in attention			
subjects affected / exposed	5 / 163 (3.07%)	4 / 78 (5.13%)	2 / 82 (2.44%)
occurrences (all)	5	4	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	39 / 163 (23.93%)	20 / 78 (25.64%)	12 / 82 (14.63%)
occurrences (all)	40	21	12
Neutropenia			

subjects affected / exposed	29 / 163 (17.79%)	17 / 78 (21.79%)	15 / 82 (18.29%)
occurrences (all)	33	25	23
Leukopenia			
subjects affected / exposed	6 / 163 (3.68%)	5 / 78 (6.41%)	1 / 82 (1.22%)
occurrences (all)	7	6	1
Lymphopenia			
subjects affected / exposed	4 / 163 (2.45%)	4 / 78 (5.13%)	0 / 82 (0.00%)
occurrences (all)	4	5	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	15 / 163 (9.20%)	2 / 78 (2.56%)	2 / 82 (2.44%)
occurrences (all)	15	2	2
Eye disorders			
Vision blurred			
subjects affected / exposed	7 / 163 (4.29%)	3 / 78 (3.85%)	5 / 82 (6.10%)
occurrences (all)	7	3	6
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	63 / 163 (38.65%)	27 / 78 (34.62%)	20 / 82 (24.39%)
occurrences (all)	71	32	23
Diarrhoea			
subjects affected / exposed	34 / 163 (20.86%)	18 / 78 (23.08%)	12 / 82 (14.63%)
occurrences (all)	41	20	16
Vomiting			
subjects affected / exposed	25 / 163 (15.34%)	9 / 78 (11.54%)	5 / 82 (6.10%)
occurrences (all)	31	9	6
Dyspepsia			
subjects affected / exposed	16 / 163 (9.82%)	5 / 78 (6.41%)	7 / 82 (8.54%)
occurrences (all)	16	5	9
Abdominal pain			
subjects affected / exposed	15 / 163 (9.20%)	8 / 78 (10.26%)	4 / 82 (4.88%)
occurrences (all)	16	9	5
Abdominal pain upper			
subjects affected / exposed	7 / 163 (4.29%)	4 / 78 (5.13%)	6 / 82 (7.32%)
occurrences (all)	7	4	7
Dry mouth			

subjects affected / exposed	7 / 163 (4.29%)	6 / 78 (7.69%)	4 / 82 (4.88%)
occurrences (all)	7	6	4
Constipation			
subjects affected / exposed	9 / 163 (5.52%)	3 / 78 (3.85%)	1 / 82 (1.22%)
occurrences (all)	9	3	1
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	20 / 163 (12.27%)	9 / 78 (11.54%)	0 / 82 (0.00%)
occurrences (all)	23	9	0
Jaundice			
subjects affected / exposed	13 / 163 (7.98%)	3 / 78 (3.85%)	0 / 82 (0.00%)
occurrences (all)	13	3	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	60 / 163 (36.81%)	15 / 78 (19.23%)	15 / 82 (18.29%)
occurrences (all)	67	15	17
Alopecia			
subjects affected / exposed	48 / 163 (29.45%)	22 / 78 (28.21%)	16 / 82 (19.51%)
occurrences (all)	49	22	16
Rash			
subjects affected / exposed	39 / 163 (23.93%)	19 / 78 (24.36%)	19 / 82 (23.17%)
occurrences (all)	47	20	19
Dry skin			
subjects affected / exposed	35 / 163 (21.47%)	12 / 78 (15.38%)	6 / 82 (7.32%)
occurrences (all)	36	12	6
Erythema			
subjects affected / exposed	11 / 163 (6.75%)	4 / 78 (5.13%)	2 / 82 (2.44%)
occurrences (all)	12	4	2
Pruritus generalised			
subjects affected / exposed	9 / 163 (5.52%)	6 / 78 (7.69%)	2 / 82 (2.44%)
occurrences (all)	10	6	2
Eczema			
subjects affected / exposed	8 / 163 (4.91%)	5 / 78 (6.41%)	0 / 82 (0.00%)
occurrences (all)	8	5	0
Rash papular			

subjects affected / exposed	5 / 163 (3.07%)	2 / 78 (2.56%)	6 / 82 (7.32%)
occurrences (all)	5	2	7
Rash pruritic			
subjects affected / exposed	3 / 163 (1.84%)	0 / 78 (0.00%)	6 / 82 (7.32%)
occurrences (all)	3	0	7
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	11 / 163 (6.75%)	4 / 78 (5.13%)	2 / 82 (2.44%)
occurrences (all)	12	4	2
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	37 / 163 (22.70%)	8 / 78 (10.26%)	11 / 82 (13.41%)
occurrences (all)	39	9	18
Arthralgia			
subjects affected / exposed	25 / 163 (15.34%)	9 / 78 (11.54%)	12 / 82 (14.63%)
occurrences (all)	26	12	15
Back pain			
subjects affected / exposed	11 / 163 (6.75%)	7 / 78 (8.97%)	13 / 82 (15.85%)
occurrences (all)	12	7	14
Muscle spasms			
subjects affected / exposed	14 / 163 (8.59%)	4 / 78 (5.13%)	5 / 82 (6.10%)
occurrences (all)	15	4	5
Infections and infestations			
Oral herpes			
subjects affected / exposed	2 / 163 (1.23%)	2 / 78 (2.56%)	6 / 82 (7.32%)
occurrences (all)	2	2	7
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	40 / 163 (24.54%)	15 / 78 (19.23%)	14 / 82 (17.07%)
occurrences (all)	41	15	14

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 August 2010	A genotypic resistance analysis was included for the viral population in Arm 1 vRVR subjects who relapsed and, in combination with unblinded IL28B genotype data, investigators were allowed to use this information in the decision-making process for retreatment. The following virologic stopping rules were included: (1) confirmed ≥ 1 log10 IU/mL HCV RNA increase from nadir between Weeks 4 and 24 with an absolute value > 1000 IU/mL and (2) confirmed detectable HCV RNA after 2 consecutive visits in which HCV RNA level was undetectable.
10 November 2010	Based on FDA advice, a confirmatory assessment of plasma HCV RNA within approximately 2 weeks was added for subjects with evidence of possible virologic breakthrough but not yet meeting a protocol-defined treatment stopping rule. The initial Data Monitoring Committee (DMC) review of data was planned to occur after the first 40 subjects enrolled completed through Week 12. To allow for an earlier DMC assessment of subject safety and study integrity, the protocol was amended to conduct this initial DMC review after the first 40 subjects enrolled had completed through Week 4.
15 September 2011	In consultation with the FDA, the decision was made to discontinue dosing of TGV when given in combination with Peg-IFN+RBV and another DAA across all active Gilead studies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported