Clinical trial results:
A phase 3 randomised, partially double-blind and placebo-controlled study of BI 207127 in combination with faldaprevir and ribavirin in treatment naïve patients with chronic genotype 1 HCV infection.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-003533-41
Trial protocol	DE PT GB ES IE IT NL HU AT
Global end of trial date	22 January 2015

Results information

Result version number	v1 (current)
This version publication date	05 May 2016
First version publication date	05 May 2016

Trial information

Trial identification

Sponsor protocol code	1241.20

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01732796
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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	03 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 February 2014
Global end of trial reached?	Yes
Global end of trial date	22 January 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of the study was to confirm efficacy and safety of treatment with 600 milligram (mg) of BID (twice daily) Deleobuvir (DBV) in combination with 120 mg QD (once daily) Faldaprevir (FDV) and Ribavirin (RBV) for 16 or 24 weeks in chronically infected hepatitis C virus (HCV) genotype (GT)1b treatment-naïve patients, including a separate group of patients with compensated cirrhosis who were treated open-label for 24 weeks.
The primary objective was to determine if minimum historical target sustained virologic response at week 12 (SVR12) rates of 71% could be achieved by the combination treatments of DBV, FDV and RBV in GT1b patients, including patients with compensated cirrhosis. The comparison with historical control was framed as a statistical superiority test.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 December 2012
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	Austria: 1
Country: Number of subjects enrolled	Canada: 65
Country: Number of subjects enrolled	France: 68
Country: Number of subjects enrolled	Germany: 109
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Ireland: 13
Country: Number of subjects enrolled	Italy: 104
Country: Number of subjects enrolled	Netherlands: 20
Country: Number of subjects enrolled	Portugal: 20
Country: Number of subjects enrolled	Romania: 38
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Spain: 84
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	United States: 125

Worldwide total number of subjects	691
EEA total number of subjects	493

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)	607
From 65 to 84 years	84
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

It was planned that approximately 800 patients would be screened in order to randomize and treat approximately 460 patients (195 in treatment Groups 1 and 2 each, 40-70 in group 3). Treatment-naïve patients with chronic hepatitis C infection of GT1b were included in the trial. Patients with compensated liver cirrhosis were assigned to Group 3.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that the subject met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Treatment period (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	16 wk NC FDV+DBV+RBV

Arm description:

600 milligram (mg) of Deleobuvir (DBV) twice daily (BID) combined with 240 mg on the first day followed by 120mg of Faldaprevir (FDV) once daily (QD) and 1000-1200mg Ribavirin BID (RBV) for 16 weeks (wk) followed by DBV placebo, FDV placebo and RBV placebo for 8 weeks. All were administered per os (orally). This group included non-cirrhotic patients (NC).

Arm type	Experimental
Investigational medicinal product name	Faldaprevir
Investigational medicinal product code	BI 201335
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

starting dose of 240 milligram (mg) Faldaprevir (FDV), thereafter 120mg FDV once daily for 16 weeks followed by 8 weeks FDV placebo

Investigational medicinal product name	Deleobuvir
Investigational medicinal product code	BI 207127
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

total daily dose of 1200mg Deleobuvir (DBV), administered twice daily (BID) 600mg for 16 weeks followed by 8 weeks of DBV placebo

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	Copegus (R)
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

total daily dose of 1000-1200mg Ribavirin (RBV), administered BID 500-600mg for 16 weeks followed

by 8 weeks RBV placebo

Investigational medicinal product name	Placebo FDV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Placebo FDV once daily for 8 weeks after 16 weeks FDV treatment

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

Dosage and administration details:

BID for 8 weeks after 16 weeks DBV treatment

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

Dosage and administration details:

BID for 8 weeks after 16 weeks RBV treatment

Arm title	24 wk NC FDV+DBV+RBV

Arm description:

600 milligram (mg) of Deleobuvir (DBV) twice daily (BID) combined with 240 mg on the first day followed by 120mg of Faldaprevir (FDV) once daily (QD) and 1000-1200mg Ribavirin (RBV) BID for 24 weeks (wk). All were administered per os (orally). This group included non-cirrhotic patients (NC).

Arm type	Experimental
Investigational medicinal product name	Faldaprevir
Investigational medicinal product code	BI 201335
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

starting dose of 240 milligram (mg) Faldaprevir (FDV), thereafter 120mg FDV once daily for 16 weeks followed by 8 weeks FDV placebo

Investigational medicinal product name	Deleobuvir
Investigational medicinal product code	BI 207127
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

total daily dose of 1200mg Deleobuvir (DBV), administered twice daily (BID) 600mg for 16 weeks followed by 8 weeks of DBV placebo

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	Copegus (R)
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

total daily dose of 1000-1200mg Ribavirin (RBV), administered BID 500-600mg for 16 weeks followed by 8 weeks RBV placebo

Arm title	24 wk CR FDV+DBV+RBV

Arm description:

600 milligram (mg) of Deleobuvir (DBV) twice daily (BID) combined with 240 mg on the first day followed by 120mg of Faldaprevir (FDV) once daily (QD) and 1000-1200mg Ribavirin (RBV) BID for 24 weeks (wk). All were administered per os (orally). This group comprised patients with compensated cirrhosis (CR) who received open label treatment.

Arm type	Experimental
Investigational medicinal product name	Faldaprevir
Investigational medicinal product code	BI 201335
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

starting dose of 240 milligram (mg) Faldaprevir (FDV), thereafter 120mg FDV once daily for 16 weeks followed by 8 weeks FDV placebo

Investigational medicinal product name	Deleobuvir
Investigational medicinal product code	BI 207127
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

total daily dose of 1200mg Deleobuvir (DBV), administered twice daily (BID) 600mg for 16 weeks followed by 8 weeks of DBV placebo

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	Copegus (R)
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

total daily dose of 1000-1200mg Ribavirin (RBV), administered BID 500-600mg for 16 weeks followed by 8 weeks RBV placebo

Number of subjects in period 1[1]	16 wk NC FDV+DBV+RBV	24 wk NC FDV+DBV+RBV	24 wk CR FDV+DBV+RBV
Started	208	211	51
Completed	162	169	38
Not completed	46	42	13
Consent withdrawn by subject	6	8	2
Adverse event, non-fatal	16	16	4
other reason, not defined above	1	-	2
Lost to follow-up	2	-	-
Lack of efficacy	21	18	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	16 wk NC FDV+DBV+RBV
Reporting group description:	
600 milligram (mg) of Deleobuvir (DBV) twice daily (BID) combined with 240 mg on the first day followed by 120mg of Faldaprevir (FDV) once daily (QD) and 1000-1200mg Ribavirin BID (RBV) for 16 weeks (wk) followed by DBV placebo, FDV placebo and RBV placebo for 8 weeks. All were administered per os (orally). This group included non-cirrhotic patients (NC).	
Reporting group title	24 wk NC FDV+DBV+RBV
Reporting group description:	
600 milligram (mg) of Deleobuvir (DBV) twice daily (BID) combined with 240 mg on the first day followed by 120mg of Faldaprevir (FDV) once daily (QD) and 1000-1200mg Ribavirin (RBV) BID for 24 weeks (wk). All were administered per os (orally). This group included non-cirrhotic patients (NC).	
Reporting group title	24 wk CR FDV+DBV+RBV
Reporting group description:	
600 milligram (mg) of Deleobuvir (DBV) twice daily (BID) combined with 240 mg on the first day followed by 120mg of Faldaprevir (FDV) once daily (QD) and 1000-1200mg Ribavirin (RBV) BID for 24 weeks (wk). All were administered per os (orally). This group comprised patients with compensated cirrhosis (CR) who received open label treatment.	

Reporting group values	16 wk NC FDV+DBV+RBV	24 wk NC FDV+DBV+RBV	24 wk CR FDV+DBV+RBV
Number of subjects	208	211	51
Age categorical			
The baseline characteristics were carried out on an intent-to-treat basis including all randomized patients who were dispensed study medication and were documented to havetaken at least one dose of study medication (FAS).			
Units: Subjects			
Age Continuous |			
Units: years			
arithmetic mean	50.1	51.1	57.9
standard deviation	± 12.7	± 12.9	± 8.8
Gender, Male/Female			
FAS			
Units: Participants			
Female	122	114	18
Male	86	97	33

Reporting group values	Total		
Number of subjects	470		
Age categorical			
The baseline characteristics were carried out on an intent-to-treat basis including all randomized patients who were dispensed study medication and were documented to havetaken at least one dose of study medication (FAS).			
Units: Subjects			
Age Continuous |			
Units: years			
arithmetic mean			
standard deviation	-		

Gender, Male/Female			
FAS			
Units: Participants			
Female	254		
Male	216		

End points

End points reporting groups

Reporting group title	16 wk NC FDV+DBV+RBV

Reporting group description:

600 milligram (mg) of Deleobuvir (DBV) twice daily (BID) combined with 240 mg on the first day followed by 120mg of Faldaprevir (FDV) once daily (QD) and 1000-1200mg Ribavirin BID (RBV) for 16 weeks (wk) followed by DBV placebo, FDV placebo and RBV placebo for 8 weeks. All were administered per os (orally). This group included non-cirrhotic patients (NC).

Reporting group title	24 wk NC FDV+DBV+RBV

Reporting group description:

600 milligram (mg) of Deleobuvir (DBV) twice daily (BID) combined with 240 mg on the first day followed by 120mg of Faldaprevir (FDV) once daily (QD) and 1000-1200mg Ribavirin (RBV) BID for 24 weeks (wk). All were administered per os (orally). This group included non-cirrhotic patients (NC).

Reporting group title	24 wk CR FDV+DBV+RBV

Reporting group description:

600 milligram (mg) of Deleobuvir (DBV) twice daily (BID) combined with 240 mg on the first day followed by 120mg of Faldaprevir (FDV) once daily (QD) and 1000-1200mg Ribavirin (RBV) BID for 24 weeks (wk). All were administered per os (orally). This group comprised patients with compensated cirrhosis (CR) who received open label treatment.

Subject analysis set title	24 wk FDV+DBV+RBV
Subject analysis set type	Full analysis

Subject analysis set description:

600 mg DBV (BID) + 120mg FDV (QD) + 1000-1200mg RBV (BID) for 24wk (orally) in cirrhotic and non-cirrhotic patients.

Subject analysis set title	16 wk FDV+DBV+RBV
Subject analysis set type	Full analysis

Subject analysis set description:

600 mg DBV (BID) + 120mg FDV (QD) + 1000-1200mg RBV (BID), orally. This is the combination of non-cirrhotic patients in the 16 week treatment group and cirrhosis patients in the 24-week treatment group.

Primary: SVR12 rates with historical control

End point title	SVR12 rates with historical control[1]

End point description:

Sustained Virologic Response at Week 12 post-treatment (SVR12): Plasma Hepatitis C Virus ribonucleic acid (HCV RNA) level <25 international units/millilitre (IU/mL) at 12 weeks after End of Treatment (EoT). SVR12, was assessed based on the observed HCV RNA result taken at least 10 weeks after treatment discontinuation. This definition was also applied to patients who discontinued treatment early: if the patient had HCV RNA undetected at least 10 weeks after stopping all treatment, they were considered a responder in the primary analysis. This is the primary analyses of the primary endpoint.The primary analyses of efficacy were carried out on an intent-to-treat basis including all randomized patients who were dispensed study medication and were documented to have taken at least one dose of study medication (FAS).

End point type	Primary

End point timeframe:

12 Week (post-treatment)

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: This Primary outcome measure reporting statistical analysis for one group are defined and analysed for trial 1241.20, however due to the platform limitations those could not be provided. Results can be found on CT.gov study number: NCT01732796.

End point values	24 wk FDV+DBV+RBV	16 wk FDV+DBV+RBV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	262[2]	259[3]		
Units: Percentage of participants				
number (not applicable)				
non-cirrhotic	82.5	71.6		
cirrhotic	72.5	72.5		

Notes:

[2] - FAS

[3] - FAS

Statistical analyses

No statistical analyses for this end point

Primary: Comparisons of SVR12 rates across treatment arms

End point title	Comparisons of SVR12 rates across treatment arms

End point description:

Sustained Virologic Response rates across treatment arms at Week 12 post-treatment (SVR12). This is the secondary analyses of the primary endpoint.

End point type	Primary

End point timeframe:

12 Week (post-treatment)

End point values	16 wk NC FDV+DBV+RBV	24 wk NC FDV+DBV+RBV	24 wk CR FDV+DBV+RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	208[4]	211[5]	51[6]	
Units: Percentage of participants				
number (not applicable)	71.6	82.5	72.5	

Notes:

[4] - FAS

[5] - FAS

[6] - FAS

Statistical analyses

Statistical analysis title	16 wk NC FDV+DBV+RBV vs. 24 wk NC FDV+DBV+RBV

Statistical analysis description:

Koch’s stratum-adjusted Mantel Haenszel methods were used to compare durations, adjusting for stratification factors.

Comparison groups	16 wk NC FDV+DBV+RBV v 24 wk NC FDV+DBV+RBV
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [7]
Method	z-test
Parameter estimate	Koch's method with continuity correction
Point estimate	10.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	18.8

Notes:

[7] - based on two sample z-test with continuity correction for variance.

Secondary: SVR4

End point title	SVR4

End point description:

Sustained Virologic Response rates across treatment arms at Week 4 post-treatment (SVR4).
The prognostic value of SVR12 predicting SVR4 are the patients with an SVR4 (=YES) and the SVR12 was assessed.

End point type	Secondary

End point timeframe:

4 Week (post-treatment)

End point values	16 wk NC FDV+DBV+RBV	24 wk NC FDV+DBV+RBV	24 wk CR FDV+DBV+RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	208[8]	211[9]	51[10]	
Units: Percentage of participants				
number (not applicable)				
Percentage of patients with response	78.4	84.4	76.5	
Positive predictive Value	94	98	95	

Notes:

[8] - FAS

[9] - FAS

[10] - FAS

Statistical analyses

Statistical analysis title	16 wk NC FDV+DBV+RBV vs. 24 wk NC FDV+DBV+RBV

Statistical analysis description:

Koch’s stratum-adjusted Mantel Haenszel methods were used to compare durations, adjusting for stratification factors.
Category: Percentage of patient with response

Comparison groups	16 wk NC FDV+DBV+RBV v 24 wk NC FDV+DBV+RBV
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0575 [11]
Method	z-test
Parameter estimate	Koch's method with continuity correction
Point estimate	6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	13.5

Notes:

[11] - based on two sample z-test with continuity correction for variance.

Secondary: SVR24

End point title	SVR24

End point description:

Sustained Virologic Response rates across treatment arms at Week 24 post-treatment (SVR24).
The prognostic value of SVR12 predicting SVR24 are the patients with an SVR12 (=YES) and the SVR24 was assessed.

End point type	Secondary

End point timeframe:

24 Week (post-treatment)

End point values	16 wk NC FDV+DBV+RBV	24 wk NC FDV+DBV+RBV	24 wk CR FDV+DBV+RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	208[12]	211[13]	51[14]	
Units: Percentage of participants				
number (not applicable)				
Percentage of patients with response	70.7	80.6	72.5	
Positive predicted value	97	99	100	

Notes:

[12] - FAS

[13] - FAS

[14] - FAS

Statistical analyses

Statistical analysis title	16 wk NC FDV+DBV+RBV vs. 24 wk NC FDV+DBV+RBV

Statistical analysis description:

Koch’s stratum-adjusted Mantel Haenszel methods were used to compare durations, adjusting for stratification factors.

Comparison groups	16 wk NC FDV+DBV+RBV v 24 wk NC FDV+DBV+RBV
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0089 [15]
Method	z-test
Parameter estimate	Koch's method with continuity correction
Point estimate	9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	18.1

Notes:
[15] - based on two sample z-test with continuity correction for variance.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of study medication to 4 weeks after last intake (up to 200 days). Adverse events with an onset date thereafter were to be reported only if serious up to 24 or 48 weeks after last study treatment (up to 340 or 508 days).

Adverse event reporting additional description:

Safety analyses were based on the safety set that included all patients who were dispensed study medication and were documented to have taken at least 1 dose of investigational treatment, regardless of randomization.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	16 wk NC FDV+DBV+RBV

Reporting group description:

600 mg DBV (BID) + 120mg FDV (QD) + 1000-1200mg RBV (BID) for 16wk followed by DBV placebo, FDV placebo and RBV placebo for 8wk. All were administered per os (orally). This group included non-cirrhotic patients (NC).

Reporting group title	24 wk NC FDV+DBV+RBV

Reporting group description:

600 mg DBV (BID) + 120mg FDV (QD) + 1000-1200mg RBV (BID) for 24wk. All were administered per os (orally). This group included non-cirrhotic patients (NC).

Reporting group title	24 wk CR FDV+DBV+RBV

Reporting group description:

600 mg DBV (BID) + 120mg FDV (QD) + 1000-1200mg RBV (BID) for 24wk. All were administered per os (orally). This group comprised patients with compensated cirrhosis (CR) who received open label treatment.

Serious adverse events	16 wk NC FDV+DBV+RBV	24 wk NC FDV+DBV+RBV	24 wk CR FDV+DBV+RBV
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 208 (3.37%)	11 / 211 (5.21%)	4 / 51 (7.84%)
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)			
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 208 (0.48%)	0 / 211 (0.00%)	0 / 51 (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
Pancreatic carcinoma			

subjects affected / exposed	1 / 208 (0.48%)	0 / 211 (0.00%)	0 / 51 (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
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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
Thrombosis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 208 (0.48%)	0 / 211 (0.00%)	0 / 51 (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
Pyrexia			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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
Drug abuse			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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
Psychotic disorder			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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

Injury, poisoning and procedural complications			
Dumping syndrome			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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
Fall			
subjects affected / exposed	1 / 208 (0.48%)	1 / 211 (0.47%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	1 / 208 (0.48%)	0 / 211 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Pericarditis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 211 (0.00%)	0 / 51 (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
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 208 (0.48%)	0 / 211 (0.00%)	0 / 51 (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
Loss of consciousness			
subjects affected / exposed	1 / 208 (0.48%)	0 / 211 (0.00%)	0 / 51 (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
Syncope			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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			
Agranulocytosis			

subjects affected / exposed	1 / 208 (0.48%)	1 / 211 (0.47%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 208 (0.48%)	2 / 211 (0.95%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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			
Diarrhoea			
subjects affected / exposed	0 / 208 (0.00%)	0 / 211 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 208 (0.00%)	0 / 211 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 208 (0.00%)	0 / 211 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			

subjects affected / exposed	0 / 208 (0.00%)	0 / 211 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Prerenal failure			
subjects affected / exposed	0 / 208 (0.00%)	0 / 211 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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
Urethral stenosis			
subjects affected / exposed	0 / 208 (0.00%)	0 / 211 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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			
Escherichia urinary tract infection			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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
Gastritis bacterial			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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
Gingivitis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 211 (0.47%)	0 / 51 (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

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 208 (0.48%)	0 / 211 (0.00%)	0 / 51 (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

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

Non-serious adverse events	16 wk NC FDV+DBV+RBV	24 wk NC FDV+DBV+RBV	24 wk CR FDV+DBV+RBV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	192 / 208 (92.31%)	198 / 211 (93.84%)	49 / 51 (96.08%)
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	5 / 208 (2.40%)	3 / 211 (1.42%)	3 / 51 (5.88%)
occurrences (all)	5	4	3
Asthenia			
subjects affected / exposed	40 / 208 (19.23%)	58 / 211 (27.49%)	7 / 51 (13.73%)
occurrences (all)	43	59	7
Chills			
subjects affected / exposed	5 / 208 (2.40%)	3 / 211 (1.42%)	3 / 51 (5.88%)
occurrences (all)	5	3	3
Fatigue			
subjects affected / exposed	53 / 208 (25.48%)	50 / 211 (23.70%)	13 / 51 (25.49%)
occurrences (all)	57	50	14
Pyrexia			
subjects affected / exposed	6 / 208 (2.88%)	6 / 211 (2.84%)	4 / 51 (7.84%)
occurrences (all)	7	7	4
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	14 / 208 (6.73%)	18 / 211 (8.53%)	4 / 51 (7.84%)
occurrences (all)	15	19	4
Cough			
subjects affected / exposed	13 / 208 (6.25%)	17 / 211 (8.06%)	7 / 51 (13.73%)
occurrences (all)	13	18	8
Psychiatric disorders			

Depression			
subjects affected / exposed	11 / 208 (5.29%)	18 / 211 (8.53%)	1 / 51 (1.96%)
occurrences (all)	11	18	1
Irritability			
subjects affected / exposed	6 / 208 (2.88%)	14 / 211 (6.64%)	2 / 51 (3.92%)
occurrences (all)	6	14	2
Insomnia			
subjects affected / exposed	17 / 208 (8.17%)	29 / 211 (13.74%)	10 / 51 (19.61%)
occurrences (all)	17	30	10
Investigations			
Blood bilirubin increased			
subjects affected / exposed	8 / 208 (3.85%)	10 / 211 (4.74%)	5 / 51 (9.80%)
occurrences (all)	8	11	5
Weight decreased			
subjects affected / exposed	13 / 208 (6.25%)	19 / 211 (9.00%)	5 / 51 (9.80%)
occurrences (all)	13	21	5
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	9 / 208 (4.33%)	17 / 211 (8.06%)	4 / 51 (7.84%)
occurrences (all)	11	19	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 208 (6.25%)	18 / 211 (8.53%)	5 / 51 (9.80%)
occurrences (all)	14	19	5
Dysgeusia			
subjects affected / exposed	11 / 208 (5.29%)	8 / 211 (3.79%)	4 / 51 (7.84%)
occurrences (all)	11	9	4
Headache			
subjects affected / exposed	33 / 208 (15.87%)	30 / 211 (14.22%)	4 / 51 (7.84%)
occurrences (all)	36	41	4
Syncope			
subjects affected / exposed	0 / 208 (0.00%)	8 / 211 (3.79%)	3 / 51 (5.88%)
occurrences (all)	0	9	4
Paraesthesia			
subjects affected / exposed	11 / 208 (5.29%)	17 / 211 (8.06%)	2 / 51 (3.92%)
occurrences (all)	11	18	2

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	40 / 208 (19.23%)	53 / 211 (25.12%)	19 / 51 (37.25%)
occurrences (all)	43	56	20
Eye disorders			
Ocular icterus			
subjects affected / exposed	20 / 208 (9.62%)	15 / 211 (7.11%)	3 / 51 (5.88%)
occurrences (all)	20	17	3
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	14 / 208 (6.73%)	10 / 211 (4.74%)	3 / 51 (5.88%)
occurrences (all)	14	10	3
Abdominal pain			
subjects affected / exposed	14 / 208 (6.73%)	16 / 211 (7.58%)	4 / 51 (7.84%)
occurrences (all)	15	19	4
Abdominal pain upper			
subjects affected / exposed	25 / 208 (12.02%)	27 / 211 (12.80%)	2 / 51 (3.92%)
occurrences (all)	26	33	2
Diarrhoea			
subjects affected / exposed	50 / 208 (24.04%)	66 / 211 (31.28%)	17 / 51 (33.33%)
occurrences (all)	58	88	24
Constipation			
subjects affected / exposed	12 / 208 (5.77%)	14 / 211 (6.64%)	3 / 51 (5.88%)
occurrences (all)	13	16	3
Dyspepsia			
subjects affected / exposed	24 / 208 (11.54%)	25 / 211 (11.85%)	5 / 51 (9.80%)
occurrences (all)	25	26	5
Nausea			
subjects affected / exposed	96 / 208 (46.15%)	112 / 211 (53.08%)	27 / 51 (52.94%)
occurrences (all)	111	141	33
Vomiting			
subjects affected / exposed	64 / 208 (30.77%)	62 / 211 (29.38%)	18 / 51 (35.29%)
occurrences (all)	87	88	30
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	17 / 208 (8.17%)	17 / 211 (8.06%)	5 / 51 (9.80%)
occurrences (all)	18	19	6

Jaundice			
subjects affected / exposed	28 / 208 (13.46%)	35 / 211 (16.59%)	10 / 51 (19.61%)
occurrences (all)	28	36	10
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	18 / 208 (8.65%)	9 / 211 (4.27%)	2 / 51 (3.92%)
occurrences (all)	18	9	2
Dry skin			
subjects affected / exposed	18 / 208 (8.65%)	13 / 211 (6.16%)	2 / 51 (3.92%)
occurrences (all)	19	13	2
Erythema			
subjects affected / exposed	23 / 208 (11.06%)	28 / 211 (13.27%)	8 / 51 (15.69%)
occurrences (all)	25	31	10
Photosensitivity reaction			
subjects affected / exposed	29 / 208 (13.94%)	30 / 211 (14.22%)	10 / 51 (19.61%)
occurrences (all)	33	33	11
Pruritus			
subjects affected / exposed	38 / 208 (18.27%)	53 / 211 (25.12%)	20 / 51 (39.22%)
occurrences (all)	43	65	23
Rash			
subjects affected / exposed	35 / 208 (16.83%)	37 / 211 (17.54%)	11 / 51 (21.57%)
occurrences (all)	43	40	15
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 208 (6.25%)	11 / 211 (5.21%)	1 / 51 (1.96%)
occurrences (all)	15	11	1
Back pain			
subjects affected / exposed	13 / 208 (6.25%)	6 / 211 (2.84%)	1 / 51 (1.96%)
occurrences (all)	13	6	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 208 (5.77%)	13 / 211 (6.16%)	4 / 51 (7.84%)
occurrences (all)	15	14	5
Metabolism and nutrition disorders			
Vitamin D deficiency			

subjects affected / exposed	14 / 208 (6.73%)	21 / 211 (9.95%)	1 / 51 (1.96%)
occurrences (all)	14	21	1
Decreased appetite			
subjects affected / exposed	20 / 208 (9.62%)	33 / 211 (15.64%)	6 / 51 (11.76%)
occurrences (all)	20	33	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2012	Excluded patients with GT1a IL28b CC; Removed stratification by sub-GT and IL-28b; Extended safety data collection at rescue to 4 weeks after the end of rescue therapy; Removed protein electrophoresis at screening; Revised sample size to 195 patients for Group 1, 195 patients for Group 2 and 40-70 patients for Group 3, based on exclusion of GT1a patients.
04 July 2013	Redefined the minimum historical target SVR12 rates from a point estimate of 71% for the lower bound of the CI (original protocol) to a weighted average of 66% (PegIFN-eligible) where 1/2 CI is approximately 6%; Added power calculations for comparison to the historical control; Added increased ECG monitoring based on preliminary results from 1241.25; Added monitoring for appearance of systemic symptoms of DRESS and criteria for treatment discontinuation in case of potentially lifethreatening skin reactions; Added PK trough samples for all patients in the trial; Added second confirmation in case of virologic breakthrough; clarified the confirmation process; Clarified procedures related to rescue medication; Added details on the assessment of liver progression assessment; Revised SAE reporting processes based on updated sponsor SOP; Added IgE assessment for mild rash events.
30 October 2013	Changed the order of primary and secondary objectives; Re-defined the minimum historical target SVR12 rates. Specified a hierarchical order for primary and secondary objective testing; Updated power calculation for the primaryanalysis based on the proposed sample size; Specified collection of all SAEs with onset date after 28 days post-EOT until EOO. Defined residual effect period. Extended safety reporting during follow-up period; Added potential risk of agranulocytosis/neutropenia; Added discontinuation of patients with ANC≤500 cells/mm3; Clarified SAE reporting requirements.
03 April 2014	Due to termination of the DBV program, the FU period was reduced to 24 weeks for patients who achieved SVR12, and to 48 weeks for SVR12 nonresponders provided they had not started an alternative HCV treatment; Follow-up of rescue treatment was reduced to RFU1 at REOT+12 weeks; FU3 snapshot was removed.

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.

BI stopped further development of DBV, the Follow-up period was reduced.
First outcome measure: statistical analysis for one group are defined and analysed, due to the platform limitations those could not be provided (results in ct.gov NCT01732796)

Notes: