Clinical trial results:
A Phase 3, Safety and Efficacy Study of Boceprevir/Peginterferon Alfa-2a/ribavirin in Chronic HCV Genotype 1 IL28B CC Subjects (P07755)

Summary

EudraCT number	2011-001345-32
Trial protocol	PT ES CZ SE AT BE DE GB PL LT EE HU
Global end of trial date	19 May 2015

Results information

Result version number	v1 (current)
This version publication date	20 May 2016
First version publication date	20 May 2016

Trial information

Trial identification

Sponsor protocol code	P07755

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01544920
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol No.: MK-3034-040

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2015
Global end of trial reached?	Yes
Global end of trial date	19 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study is to compare the efficacy of two boceprevir (BOC)-containing therapeutic regimens in the treatment of naïve participants with chronic hepatitis C virus (HCV) genotype 1 who have the IL28B CC allele.

The regimens differ in the treatment for participants who achieve undetectable HCV ribonucleic acid (RNA) at the end of the peginterferon alfa-2a (peg-IFN) plus ribavirin (RBV) 4 week lead-in. Participants receive either peg-IFN + RBV (Arm 1) or BOC + peg-IFN + RBV (Arm 2). The hypothesis is that Arm 2 is noninferior to Arm 1 in the proportion of participants with undetectable HCV RNA at Follow-Up (FU) Week 24.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 21
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	Brazil: 10
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Chile: 7
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Czech Republic: 26
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Guatemala: 1
Country: Number of subjects enrolled	Hong Kong: 9
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Korea, Republic of: 34
Country: Number of subjects enrolled	Malaysia: 40

Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Peru: 2
Country: Number of subjects enrolled	Philippines: 31
Country: Number of subjects enrolled	Poland: 103
Country: Number of subjects enrolled	Portugal: 11
Country: Number of subjects enrolled	Russian Federation: 149
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	Thailand: 20
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	United States: 106
Worldwide total number of subjects	737
EEA total number of subjects	212

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)	711
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult male and female participants infected with the HCV genotype (GT) 1 with IL-28B CC gene allele and no evidence of liver cirrhosis or hepatocellular carcinoma were recruited.

Pre-assignment

Screening details:

The screening period lasted 8 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1: peg-IFN + RBV

Arm description:

Participants received an initial 4 week lead-in of peg-IFN + RBV. Following HCV RNA analysis at Week 4, participants with undetectable HCV RNA received open label peg-IFN + RBV for an additional 18 weeks (total of 24 weeks of peg-IFN/RBV therapy) [Arm 1a]. Participants with detectable HCV RNA at Week 4 had BOC added to the peg-IFN + RBV regimen at Week 6 and then followed the Response Guided Therapy (RGT) regimen for BOC + peg-IFN + RBV [Arm 1b].

Arm type	Active comparator
Investigational medicinal product name	peg-Interferon alfa-2a (peg-IFN)
Investigational medicinal product code	
Other name	Pegasys™; SCH 054031
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

peg-IFN (180 µg) was taken once weekly via subcutaneous injection.

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

Dosage and administration details:

RBV 200 mg tablets were taken by mouth at a total daily dose of 1,000 mg (body weight <75 kg) or 1,200 mg (body weight ≥75 kg) with total daily dose divided into 2 separate dosings.

Arm title	Arm 2: BOC + Peg-IFN + RBV

Arm description:

Participants received an initial 4-week lead-in of peg-IFN + RBV. Following HCV RNA analysis at Week 4, all participants had BOC added to the peg-IFN + RBV regimen at Week 6 regardless of HCV RNA levels. Participants who had undetectable HCV RNA at Week 4 continued on the BOC + peg-IFN + RBV regimen for an additional 20 weeks (total of 24 weeks of BOC + peg-IFN + RBV therapy) [Arm 2a]. Participants with detectable HCV RNA at Week 4 followed the RGT regimen for BOC + peg-IFN + RBV [Arm 2b].

Arm type	Experimental

Investigational medicinal product name	peg-Interferon alfa-2a (peg-IFN)
Investigational medicinal product code	
Other name	Pegasys™; SCH 054031
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

peg-IFN (180 µg) was taken once weekly via subcutaneous injection.

Investigational medicinal product name	Boceprevir (BOC)
Investigational medicinal product code	
Other name	Victrelis™; SCH 503034
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

BOC was taken as four 200 mg capsules taken three times daily at a total daily dose of 2,400 mg.

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

Dosage and administration details:

RBV 200 mg tablets were taken by mouth at a total daily dose of 1,000 mg (body weight <75 kg) or 1,200 mg (body weight ≥75 kg) with total daily dose divided into 2 separate dosings.

Number of subjects in period 1	Arm 1: peg-IFN + RBV	Arm 2: BOC + Peg-IFN + RBV
Started	368	369
Completed	349	346
Not completed	19	23
Adverse event, serious fatal	-	1
Physician decision	4	1
Consent withdrawn by subject	4	4
Adverse event, non-fatal	-	3
Lost to follow-up	11	12
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1: peg-IFN + RBV

Reporting group description:

Participants received an initial 4 week lead-in of peg-IFN + RBV. Following HCV RNA analysis at Week 4, participants with undetectable HCV RNA received open label peg-IFN + RBV for an additional 18 weeks (total of 24 weeks of peg-IFN/RBV therapy) [Arm 1a]. Participants with detectable HCV RNA at Week 4 had BOC added to the peg-IFN + RBV regimen at Week 6 and then followed the Response Guided Therapy (RGT) regimen for BOC + peg-IFN + RBV [Arm 1b].

Reporting group title	Arm 2: BOC + Peg-IFN + RBV

Reporting group description:

Participants received an initial 4-week lead-in of peg-IFN + RBV. Following HCV RNA analysis at Week 4, all participants had BOC added to the peg-IFN + RBV regimen at Week 6 regardless of HCV RNA levels. Participants who had undetectable HCV RNA at Week 4 continued on the BOC + peg-IFN + RBV regimen for an additional 20 weeks (total of 24 weeks of BOC + peg-IFN + RBV therapy) [Arm 2a]. Participants with detectable HCV RNA at Week 4 followed the RGT regimen for BOC + peg-IFN + RBV [Arm 2b].

Reporting group values	Arm 1: peg-IFN + RBV	Arm 2: BOC + Peg-IFN + RBV	Total
Number of subjects	368	369	737
Age categorical Units: Subjects			
Adults (18-64 years)	352	359	711
From 65-84 years	16	10	26
Age Continuous | Units: Years			
arithmetic mean	43.9	42.4	
standard deviation	± 12	± 12.4	-
Gender, Male/Female Units: Participants			
Female	167	148	315
Male	201	221	422

End points

End points reporting groups

Reporting group title	Arm 1: peg-IFN + RBV

Reporting group description:

Participants received an initial 4 week lead-in of peg-IFN + RBV. Following HCV RNA analysis at Week 4, participants with undetectable HCV RNA received open label peg-IFN + RBV for an additional 18 weeks (total of 24 weeks of peg-IFN/RBV therapy) [Arm 1a]. Participants with detectable HCV RNA at Week 4 had BOC added to the peg-IFN + RBV regimen at Week 6 and then followed the Response Guided Therapy (RGT) regimen for BOC + peg-IFN + RBV [Arm 1b].

Reporting group title	Arm 2: BOC + Peg-IFN + RBV

Reporting group description:

Participants received an initial 4-week lead-in of peg-IFN + RBV. Following HCV RNA analysis at Week 4, all participants had BOC added to the peg-IFN + RBV regimen at Week 6 regardless of HCV RNA levels. Participants who had undetectable HCV RNA at Week 4 continued on the BOC + peg-IFN + RBV regimen for an additional 20 weeks (total of 24 weeks of BOC + peg-IFN + RBV therapy) [Arm 2a]. Participants with detectable HCV RNA at Week 4 followed the RGT regimen for BOC + peg-IFN + RBV [Arm 2b].

Subject analysis set title	Arm 1a: peg-IFN + RBV 24 weeks
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received an initial 4 week lead-in of peg-IFN + RBV. The subset of participants with undetectable HCV RNA at Week 4 received an additional 20 weeks of peg-IFN + RBV for a total of 24 weeks of peg-IFN + RBV therapy.

Subject analysis set title	Arm 2a: BOC + peg-IFN + RBV 24 weeks
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received an initial 4 week lead-in of peg-IFN + RBV. The subset of participants with undetectable HCV RNA at Week 4 received an additional 20 weeks of BOC + peg-IFN + RBV for a total of 24 weeks of BOC (added at Week 4) + peg-IFN + RBV therapy.

Primary: Percentage of participants with undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) 24 weeks after completing study treatment (SVR24)

End point title	Percentage of participants with undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) 24 weeks after completing study treatment (SVR24)

End point description:

SVR24 rates were determined for all participants in Arm 1 and Arm 2. HCV RNA viral load was determined using the Roche COBAS® AmpliPrep/COBAS® TaqMan HCV Test v1.0, which has a lower limit of quantification of 43 IU/mL. The Full Analysis Set (FAS) consisted of all participants who completed the 4-week peg-IFN + RBV lead-in and who were randomized at Week 4.

End point type	Primary

End point timeframe:

Up to Week 74

End point values	Arm 1: peg-IFN + RBV	Arm 2: BOC + Peg-IFN + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	368	369		
Units: Percentage of participants				
number (not applicable)	86.7	88.3		

Statistical analyses

Statistical analysis title	Difference in SVR24 Percentage

Statistical analysis description:

This SVR24 analysis includes all participants.

Comparison groups	Arm 1: peg-IFN + RBV v Arm 2: BOC + Peg-IFN + RBV
Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in SVR24% in Arm 2 vs. Arm 1
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	6.5

Notes:

[1] - Non-inferiority was declared if the lower bound of the 95% CI of the difference in SVR24 % exceeded -10%.

Secondary: Percentage of participants who had undetectable HCV RNA at Week 4 achieving SVR24

End point title	Percentage of participants who had undetectable HCV RNA at Week 4 achieving SVR24

End point description:

SVR24 rates were determined for only participants that had undetectable HCV RNA at Week 4 of treatment (Arm 1a and Arm 2a). HCV RNA viral load was determined using the Roche COBAS® AmpliPrep/COBAS® TaqMan HCV Test v1.0, which has a lower limit of quantification of 43 IU/mL. The analysis set consisted of all participants who completed the 4-week peg-IFN + RBV lead-in, were randomized at Week 4, and had undetectable HCV RNA at Week 4.

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	Arm 1a: peg-IFN + RBV 24 weeks	Arm 2a: BOC + peg-IFN + RBV 24 weeks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	107		
Units: Percentage of participants				
number (not applicable)	87	97.2		

Statistical analyses

Statistical analysis title	Difference in SVR24 percentage
Statistical analysis description:	
This SVR24 analysis includes only the participants with undetectable HCV RNA at Week 4.	
Comparison groups	Arm 1a: peg-IFN + RBV 24 weeks v Arm 2a: BOC + peg-IFN + RBV 24 weeks
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference in SVR24%
Point estimate	10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	18.1

Notes:

[2] - The observed lower bound of the 95% CI for the difference was 2.5% (which exceeds 0) for BOC added to peg-IFN + RBV in contrast to peg-IFN + RBV alone.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 78 weeks

Adverse event reporting additional description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. The All Participants as Treated (APaT) population includes all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	.18.0

Reporting groups

Reporting group title	Arm 2: BOC + peg-IFN + RBV

Reporting group description:

Participants received an initial 4-week lead-in of peg-IFN + RBV. Following HCV RNA analysis at Week 4, all participants had BOC added to the peg-IFN + RBV regimen at Week 6 regardless of HCV RNA levels. Participants who had undetectable HCV RNA at Week 4 continued on the BOC + peg-IFN + RBV regimen for an additional 20 weeks (total of 24 weeks of BOC + peg-IFN + RBV therapy) [Arm 2a]. Participants with detectable HCV RNA at Week 4 followed the RGT regimen for BOC + peg-IFN + RBV [Arm 2b].

Reporting group title	Arm 1: peg-IFN + RBV

Reporting group description:

Participants received an initial 4 week lead-in of peg-IFN + RBV. Following HCV RNA analysis at Week 4, participants with undetectable HCV RNA received open label peg-IFN + RBV for an additional 18 weeks (total of 24 weeks of peg-IFN/RBV therapy) [Arm 1a]. Participants with detectable HCV RNA at Week 4 had BOC added to the peg-IFN + RBV regimen at Week 6 and then followed the Response Guided Therapy (RGT) regimen for BOC + peg-IFN + RBV [Arm 1b].

Serious adverse events	Arm 2: BOC + peg-IFN + RBV	Arm 1: peg-IFN + RBV	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 369 (10.03%)	27 / 368 (7.34%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Conjunctival melanoma			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Malaise			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 369 (0.54%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Miscarriage of partner			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine haemorrhage			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			

alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Adjustment disorder			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Activated partial thromboplastin time prolonged			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prothrombin time prolonged			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block first degree			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 369 (0.54%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory bowel disease			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal cyst			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Autoimmune thyroiditis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hyperthyroidism			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis viral			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 369 (0.54%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes pharyngitis			

alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 369 (0.81%)	4 / 368 (1.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 369 (0.54%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 369 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 369 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm 2: BOC + peg-IFN + RBV	Arm 1: peg-IFN + RBV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	351 / 369 (95.12%)	348 / 368 (94.57%)	
Investigations			
Haemoglobin decreased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	31 / 369 (8.40%)	24 / 368 (6.52%)	
occurrences (all)	33	29	
Neutrophil count decreased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	29 / 369 (7.86%)	24 / 368 (6.52%)	
occurrences (all)	41	30	
Nervous system disorders			
Dizziness			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	42 / 369 (11.38%)	46 / 368 (12.50%)	
occurrences (all)	48	51	
Dysgeusia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	94 / 369 (25.47%)	65 / 368 (17.66%)	
occurrences (all)	95	69	
Headache			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	100 / 369 (27.10%)	118 / 368 (32.07%)	
occurrences (all)	148	152	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	168 / 369 (45.53%)	169 / 368 (45.92%)	
occurrences (all)	210	219	
Leukopenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	33 / 369 (8.94%)	39 / 368 (10.60%)	
occurrences (all)	46	66	
Neutropenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	108 / 369 (29.27%)	109 / 368 (29.62%)	
occurrences (all)	161	194	
Thrombocytopenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	24 / 369 (6.50%)	19 / 368 (5.16%)	
occurrences (all)	28	24	
General disorders and administration site conditions			
Asthenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	74 / 369 (20.05%)	82 / 368 (22.28%)	
occurrences (all)	90	108	
Chills			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	26 / 369 (7.05%)	36 / 368 (9.78%)	
occurrences (all)	32	39	
Fatigue			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	117 / 369 (31.71%)	118 / 368 (32.07%)	
occurrences (all)	154	135	
Influenza like illness			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	35 / 369 (9.49%)	34 / 368 (9.24%)	
occurrences (all)	48	39	
Pyrexia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	148 / 369 (40.11%)	101 / 368 (27.45%)	
occurrences (all)	243	148	
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	22 / 369 (5.96%)	18 / 368 (4.89%)	
occurrences (all)	26	18	
Abdominal pain upper			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	14 / 369 (3.79%)	22 / 368 (5.98%)	
occurrences (all)	18	26	
Diarrhoea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	49 / 369 (13.28%)	62 / 368 (16.85%)	
occurrences (all)	55	77	
Dry mouth			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	26 / 369 (7.05%)	25 / 368 (6.79%)	
occurrences (all)	28	26	
Dyspepsia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	35 / 369 (9.49%)	23 / 368 (6.25%)	
occurrences (all)	39	25	
Nausea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	94 / 369 (25.47%)	100 / 368 (27.17%)	
occurrences (all)	112	117	
Vomiting			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	53 / 369 (14.36%)	46 / 368 (12.50%)	
occurrences (all)	78	68	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	52 / 369 (14.09%)	66 / 368 (17.93%)	
occurrences (all)	56	83	
Dyspnoea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	34 / 369 (9.21%)	34 / 368 (9.24%)	
occurrences (all)	38	36	
Oropharyngeal pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	20 / 369 (5.42%)	11 / 368 (2.99%)	
occurrences (all)	22	13	
Skin and subcutaneous tissue disorders			
Alopecia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	70 / 369 (18.97%)	72 / 368 (19.57%)	
occurrences (all)	74	76	
Dry skin			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	41 / 369 (11.11%)	44 / 368 (11.96%)	
occurrences (all)	41	45	
Pruritus			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	77 / 369 (20.87%)	75 / 368 (20.38%)	
occurrences (all)	84	85	
Rash			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	67 / 369 (18.16%)	69 / 368 (18.75%)	
occurrences (all)	85	82	
Psychiatric disorders			

Anxiety			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	14 / 369 (3.79%)	26 / 368 (7.07%)	
occurrences (all)	14	29	
Depression			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	20 / 369 (5.42%)	29 / 368 (7.88%)	
occurrences (all)	22	38	
Insomnia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	53 / 369 (14.36%)	70 / 368 (19.02%)	
occurrences (all)	57	73	
Irritability			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	28 / 369 (7.59%)	38 / 368 (10.33%)	
occurrences (all)	28	43	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	45 / 369 (12.20%)	44 / 368 (11.96%)	
occurrences (all)	52	49	
Myalgia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	58 / 369 (15.72%)	61 / 368 (16.58%)	
occurrences (all)	74	79	
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	53 / 369 (14.36%)	54 / 368 (14.67%)	
occurrences (all)	55	60	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2012	AM1: The primary purpose of was to clarify the language on birth control, modify the previously documented CHC -1 genotype Inclusion Criterion #5, and to update the study flow charts to include visit windows and to remove Chest X-Ray and inosine triphosphate pyrophosphohydrolase (ITPA) sample collection.
21 May 2013	AM2: The primary purpose was to allow retesting of platelet count at Screening Visit, add an interim analysis of SVR12 and SVR when all participants in Arm 1a and Arm 2a have completed FW 12 and 24.
16 July 2013	AM3: The primary purpose was to re-insert text that restricts participants from entering the study if they were planning to donate sperm or eggs while participating in the study.
10 February 2014	AM4: The primary purpose was to add results and conclusion from a review of pooled data (blinded to treatment), the interim analysis, that was conducted after 40% (first 500 IL28B CC subjects) of participants overall have completed 4 weeks of PEG2a/RBV lead-in and have been randomized in order to assess the assumed estimates of the proportion of screened participants with IL28B CC and the proportion with undetectable HCV RNA at Week 4.
16 June 2014	AM5: The primary purpose was to provide more details on the statistical power for the primary analysis and describe the key secondary analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported