Clinical trial results:
A Phase 3 Evaluation of BMS-790052 (Daclatasvir) Compared with Telaprevir in Combination with Peg-Interferon Alfa-2a and Ribavirin in Treatment-Naive Patients with Chronic Hepatitis-C

Summary

EudraCT number	2011-004237-14
Trial protocol	DE AT ES GB IT DK
Global end of trial date	20 March 2014

Results information

Result version number	v1 (current)
This version publication date	09 June 2016
First version publication date	09 June 2016

Trial information

Trial identification

Sponsor protocol code	AI444-052

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01492426
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, clinical.trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, clinical.trials@bms.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	20 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to compare rates of sustained virologic response, defined as Hepatitis C virus RNA < LOQ (target detected [TD] or target not detected [TND]) at follow-up Week 12, for genotype-1b subjects treated with either BMS-790052 (daclatasvir) or telaprevir in combination with peginterferon (PegINF)-alfa 2a/ribavirin.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 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	Poland: 94
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Austria: 41
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 82
Country: Number of subjects enrolled	Germany: 84
Country: Number of subjects enrolled	Italy: 54
Country: Number of subjects enrolled	Argentina: 28
Country: Number of subjects enrolled	Australia: 29
Country: Number of subjects enrolled	Canada: 52
Country: Number of subjects enrolled	Israel: 55
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United States: 183
Worldwide total number of subjects	793
EEA total number of subjects	409

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)	751
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 90 sites in 15 countries.

Pre-assignment

Screening details:

A total of 793 subjects were enrolled, of which 605 subjects were randomised into the study. A total of 602 subjects were treated.

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

As this was an open-label study, blinding was not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Daclatasvir + PegIFNalfa-2a+ Ribavirin

Arm description:

Subjects received daclatasvir 60-mg tablet orally once daily for 24 weeks in combination with pegIFNalfa-2a 180 µg administered subcutaneously once a week and ribavirin administered in a body weight stratified dose range of 1000 – 1200 mg per day (for subjects weighing less than 75 kg, the total dose was 1000 mg per day and for those weighing greater than or equal to 75 kg, the dose was 1200 mg per day) for 24 or 48 weeks depending on response.

Arm type	Experimental
Investigational medicinal product name	Daclatasvir
Investigational medicinal product code	BMS-790052
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Daclatasvir 60-mg tablet was administered orally once daily for 24 weeks.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ribavirin body-weight stratified dose ranging between 1000-1200 mg per day was administered with food for 24 or 48 weeks depending on response.

Investigational medicinal product name	Peginterferon alfa-2a
Investigational medicinal product code	
Other name	Pegasys
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PegIFNalfa-2a 180-µg was administered subcutaneously once a week for 24 or 48 weeks depending on response.

Arm title	Telaprevir + PegIFNalfa-2a + Ribavirin

Arm description:

Subjects received 2 telaprevir 375-mg tablets orally 3 times a day for 12 weeks. PegIFNalfa-2a 180 µg was co-administered subcutaneously once a week and ribavirin in a body weight stratified dose range of 1000–1200 mg per day was administered twice daily with food for 24 or 48 weeks depending on response.

Arm type	Active comparator
Investigational medicinal product name	Telaprevir
Investigational medicinal product code	
Other name	Incivek
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Telaprevir 750-mg was administered orally (2*375-mg tablet 3 times daily approximately 7-9 hours apart) for 12 weeks.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ribavirin body-weight stratified dose ranging between 1000-1200-mg per day was administered with food for 24 or 48 weeks depending on response.

Investigational medicinal product name	Peginterferon alfa-2a
Investigational medicinal product code	
Other name	Pegasys
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PegIFNalfa-2a 180-µg was administered subcutaneously once a week for 24 or 48 weeks depending on response.

Number of subjects in period 1[1]	Daclatasvir + PegIFNalfa-2a+ Ribavirin	Telaprevir + PegIFNalfa-2a + Ribavirin
Started	402	200
Completed	319	160
Not completed	83	40
Subject withdrew consent	1	2
Subject request to discontinue study treatment	7	3
Other	1	-
Poor compliance/noncompliance	1	-
Death	-	1
Adverse event	25	25
Lost to follow-up	9	4
Subject no longer meets study criteria	1	-
Lack of efficacy	38	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: Of the 793 subjects enrolled, 605 were randomised. A total of 191 enrolled subjects did not enter the treatment period: no longer met study entry criteria during the screening period - 139, Withdrew consent to participate - 28, administrative reason by sponsor - 5, lost to follow up - 3, pre-treatment adverse event - 2, other reasons - 11. 3 subjects who were randomised did not receive study therapy.

Period 2

Period 2 title	Follow-up Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Daclatasvir + PegIFNalfa-2a+ Ribavirin

Arm description:

Subjects were followed up to 48 weeks after treatment with daclatasvir 60-mg tablet orally once daily for 24 weeks in combination with pegIFNalfa-2a 180 µg administered subcutaneously once a week and ribavirin administered in a body weight stratified dose range of 1000 – 1200 mg per day (for subjects weighing less than 75 kg, the total dose was 1000 mg per day and for those weighing greater than or equal to 75 kg, the dose was 1200 mg per day) for 24 or 48 weeks depending on response.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Telaprevir + PegIFNalfa-2a + Ribavirin

Arm description:

Subjects were followed up to 48 weeks after treatment with 2 telaprevir 375-mg tablets orally 3 times a day for 12 weeks in combination with PegIFNalfa-2a 180 µg administered subcutaneously once a week and ribavirin administered in a body weight stratified dose range of 1000–1200 mg per day for 24 or 48 weeks depending on response.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Daclatasvir + PegIFNalfa-2a+ Ribavirin	Telaprevir + PegIFNalfa-2a + Ribavirin
Started	319	160
Completed	359	181
Not completed	25	10
Consent withdrawn by subject	6	1
Death	1	-
Other	4	2
Follow-up no longer required per protocol	2	1
Lost to follow-up	12	6
Joined	65	31
Re-joined for follow-up	65	31

Baseline characteristics

Reporting groups	
Reporting group title	Daclatasvir + PegIFNalfa-2a+ Ribavirin
Reporting group description:	
Subjects received daclatasvir 60-mg tablet orally once daily for 24 weeks in combination with pegIFNalfa-2a 180 µg administered subcutaneously once a week and ribavirin administered in a body weight stratified dose range of 1000 – 1200 mg per day (for subjects weighing less than 75 kg, the total dose was 1000 mg per day and for those weighing greater than or equal to 75 kg, the dose was 1200 mg per day) for 24 or 48 weeks depending on response.	
Reporting group title	Telaprevir + PegIFNalfa-2a + Ribavirin
Reporting group description:	
Subjects received 2 telaprevir 375-mg tablets orally 3 times a day for 12 weeks. PegIFNalfa-2a 180 µg was co-administered subcutaneously once a week and ribavirin in a body weight stratified dose range of 1000–1200 mg per day was administered twice daily with food for 24 or 48 weeks depending on response.	

Reporting group values	Daclatasvir + PegIFNalfa-2a+ Ribavirin	Telaprevir + PegIFNalfa-2a + Ribavirin	Total
Number of subjects	402	200	602
Age categorical Units: Subjects			
< 65 years	387	188	575
>= 65 years	15	12	27
Age continuous Units: years			
arithmetic mean	46.5	47.6	
standard deviation	± 12.12	± 12.29	-
Gender categorical Units: Subjects			
Female	145	81	226
Male	257	119	376

End points

End points reporting groups

Reporting group title	Daclatasvir + PegIFNalfa-2a+ Ribavirin

Reporting group description:

Subjects received daclatasvir 60-mg tablet orally once daily for 24 weeks in combination with pegIFNalfa-2a 180 µg administered subcutaneously once a week and ribavirin administered in a body weight stratified dose range of 1000 – 1200 mg per day (for subjects weighing less than 75 kg, the total dose was 1000 mg per day and for those weighing greater than or equal to 75 kg, the dose was 1200 mg per day) for 24 or 48 weeks depending on response.

Reporting group title	Telaprevir + PegIFNalfa-2a + Ribavirin

Reporting group description:

Subjects received 2 telaprevir 375-mg tablets orally 3 times a day for 12 weeks. PegIFNalfa-2a 180 µg was co-administered subcutaneously once a week and ribavirin in a body weight stratified dose range of 1000–1200 mg per day was administered twice daily with food for 24 or 48 weeks depending on response.

Reporting group title	Daclatasvir + PegIFNalfa-2a+ Ribavirin

Reporting group description:

Subjects were followed up to 48 weeks after treatment with daclatasvir 60-mg tablet orally once daily for 24 weeks in combination with pegIFNalfa-2a 180 µg administered subcutaneously once a week and ribavirin administered in a body weight stratified dose range of 1000 – 1200 mg per day (for subjects weighing less than 75 kg, the total dose was 1000 mg per day and for those weighing greater than or equal to 75 kg, the dose was 1200 mg per day) for 24 or 48 weeks depending on response.

Reporting group title	Telaprevir + PegIFNalfa-2a + Ribavirin

Reporting group description:

Subjects were followed up to 48 weeks after treatment with 2 telaprevir 375-mg tablets orally 3 times a day for 12 weeks in combination with PegIFNalfa-2a 180 µg administered subcutaneously once a week and ribavirin administered in a body weight stratified dose range of 1000–1200 mg per day for 24 or 48 weeks depending on response.

Primary: Percentage of Genotype 1b Subjects With Sustained Virologic Response at follow-up Week 12 (SVR12)

End point title	Percentage of Genotype 1b Subjects With Sustained Virologic Response at follow-up Week 12 (SVR12)

End point description:

SVR12 was defined as hepatitis C virus RNA levels lower than the lower limit of quantitation, target detected or target not detected at follow-up Week 12. The analysis was performed in all treated subjects who received at least 1 dose of active study therapy. Here, 'Number of Subjects analysed' signifies Genotype 1b subjects assessed for SVR12 response.

End point type	Primary

End point timeframe:

Week 12 (Follow-up period)

End point values	Daclatasvir + PegIFNalfa-2a+ Ribavirin	Telaprevir + PegIFNalfa-2a + Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	134		
Units: Percentage of Subjects				
number (confidence interval 95%)	85.1 (80.2 to 89.1)	81.3 (73.7 to 87.5)		

Statistical analyses

Statistical analysis title	Percentage difference of treatments with SVR12

Statistical analysis description:

Percentage difference between SVR12 rate in the experimental and control arms was computed using a stratum-adjusted Mantel-Haenszel confidence interval (95% level) for the difference in rates. The stratification factors were IL28B rs1297860 single nucleotide polymorphism and baseline cirrhosis status (absent or present), unless otherwise indicated.

Comparison groups	Daclatasvir + PegIFNalfa-2a+ Ribavirin v Telaprevir + PegIFNalfa-2a + Ribavirin
Number of subjects included in analysis	402
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	Stratum-adjusted Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	11.9
Variability estimate	Standard error of the mean
Dispersion value	3.885

Notes:

[1] - Test of noninferiority was based on non-inferiority margin of -12% and 2-sided alpha level of 5%. That is, if the lower bound of the 95% CI > -12%, the daclatasvir arm would be considered non-inferior to the telaprevir arm.

Secondary: Percentage of Genotype 1b Subjects With Rapid Virologic Response (RVR) at Week 4

End point title	Percentage of Genotype 1b Subjects With Rapid Virologic Response (RVR) at Week 4

End point description:

RVR was defined as hepatitis C virus RNA levels lower than lower limit of quantitation, target not detected at Week 4 of treatment. The analysis was performed in all treated subjects who received at least 1 dose of active study therapy. Here, 'Number of Subjects analysed' signifies Genotype 1b subjects assessed for RVR response.

End point type	Secondary

End point timeframe:

Week 4

End point values	Daclatasvir + PegIFNalfa-2a+ Ribavirin	Telaprevir + PegIFNalfa-2a + Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	134		
Units: Percentage of Subjects				
number (confidence interval 95%)	77.2 (71.7 to 82.1)	79.1 (71.2 to 85.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Genotype 1b Subjects With Extended Rapid Virologic Response (eRVR) at both Week 4 and Week 12

End point title	Percentage of Genotype 1b Subjects With Extended Rapid Virologic Response (eRVR) at both Week 4 and Week 12

End point description:

eRVR was defined as hepatitis C virus RNA levels lower than the lower limit of quantitation, target not detected at both Weeks 4 and 12 of treatment. The analysis was performed in all treated subjects who received at least 1 dose of active study therapy. Here, 'Number of Subjects analysed' signifies Genotype 1b subjects assessed for eRVR response.

End point type	Secondary

End point timeframe:

Week 4, Week 12

End point values	Daclatasvir + PegIFNalfa-2a+ Ribavirin	Telaprevir + PegIFNalfa-2a + Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	134		
Units: Percentage of Subjects				
number (confidence interval 95%)	75 (69.4 to 80.1)	73.1 (64.8 to 80.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Genotype 1b Subjects With Complete Early Virologic Response (cEVR)

End point title	Percentage of Genotype 1b Subjects With Complete Early Virologic Response (cEVR)

End point description:

cEVR was defined as hepatitis C virus RNA levels lower than the lower limit of quantitation, target not detected at Week 12 of treatment. The analysis was performed in all treated subjects who received at least 1 dose of active study therapy. Here, 'Number of Subjects analysed' signifies Genotype 1b subjects assessed for cEVR response.

End point type	Secondary

End point timeframe:

Week 12

End point values	Daclatasvir + PegIFNalfa-2a+ Ribavirin	Telaprevir + PegIFNalfa-2a + Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	134		
Units: Percentage of Subjects				
number (confidence interval 95%)	90.7 (86.5 to 93.9)	90.3 (84 to 94.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Genotype 1b Subjects With Sustained Virologic Response at Follow-up Week 24 (SVR24)

End point title	Percentage of Genotype 1b Subjects With Sustained Virologic Response at Follow-up Week 24 (SVR24)

End point description:

SVR24 was defined as hepatitis C virus RNA levels lower than the lower limit of quantitation, target detected or target not detected at follow-up week 24 of treatment. The analysis was performed in all treated subjects who received at least 1 dose of active study therapy. Here, 'Number of Subjects analysed' signifies Genotype 1b subjects assessed for SVR24 response.

End point type	Secondary

End point timeframe:

Week 24 (Follow-up period)

End point values	Daclatasvir + PegIFNalfa-2a+ Ribavirin	Telaprevir + PegIFNalfa-2a + Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	134		
Units: Percentage of Subjects				
number (confidence interval 95%)	84.3 (79.4 to 88.5)	80.6 (72.9 to 86.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Genotype 1a Subjects With Sustained Virologic Response

at Follow-up Week 12 (SVR12)

End point title	Percentage of Genotype 1a Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12)

End point description:

SVR12 was defined as hepatitis C virus RNA levels lower than the lower limit of quantitation, target detected or target not detected at follow-up week 12 of treatment. The analysis was performed in all treated subjects who received at least 1 dose of active study therapy. Here, 'Number of Subjects analysed' signifies Genotype 1a subjects assessed for SVR12 response.

End point type	Secondary

End point timeframe:

Week 12 (Follow-up period)

End point values	Daclatasvir + PegIFNalfa-2a+ Ribavirin	Telaprevir + PegIFNalfa-2a + Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	66		
Units: Percentage of Subjects				
number (confidence interval 95%)	64.9 (56.2 to 73)	69.7 (57.1 to 80.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment to last dose of study treatment plus 7 days (On-Treatment period)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Telaprevir + PegIFNalfa-2a + Ribavirin

Reporting group description:

Subjects received two telaprevir 375-mg tablets orally 3 times a day for 12 weeks. PegIFNalfa-2a 180 µg was co-administered subcutaneously once a week, and ribavirin in a body weight stratified dose range of 1000–1200 mg per day was administered twice daily with food for 24 or 48 weeks depending on response.

Reporting group title	Daclatasvir + PegIFNalfa-2a+ Ribavirin

Reporting group description:

Subjects received daclatasvir 60-mg tablet orally once daily for 24 weeks in combination with pegIFNalfa-2a 180 µg administered subcutaneously once a week and ribavirin administered in a body weight stratified dose range of 1000–1200 mg per day (for Subjects weighing less than 75 kg, the total dose was 1000 mg per day and for those weighing greater than or equal to 75 kg, the dose was 1200 mg per day) for 24 or 48 weeks depending on response.

Serious adverse events	Telaprevir + PegIFNalfa-2a + Ribavirin	Daclatasvir + PegIFNalfa-2a+ Ribavirin	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 200 (10.00%)	26 / 402 (6.47%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemothorax			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	2 / 200 (1.00%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mental status changes			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic disorder			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 200 (0.50%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	5 / 200 (2.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenitis			

subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 200 (0.50%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 200 (0.50%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry skin			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	2 / 200 (1.00%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 200 (0.00%)	3 / 402 (0.75%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 200 (0.00%)	2 / 402 (0.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis infectious			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 200 (0.50%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Telaprevir + PegIFNalfa-2a + Ribavirin	Daclatasvir + PegIFNalfa-2a+ Ribavirin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	194 / 200 (97.00%)	390 / 402 (97.01%)	
Nervous system disorders			
Headache			
subjects affected / exposed	57 / 200 (28.50%)	137 / 402 (34.08%)	
occurrences (all)	73	175	
Dizziness			
subjects affected / exposed	18 / 200 (9.00%)	32 / 402 (7.96%)	
occurrences (all)	18	35	
Dysgeusia			

subjects affected / exposed	21 / 200 (10.50%)	23 / 402 (5.72%)	
occurrences (all)	21	24	
Disturbance in attention			
subjects affected / exposed	10 / 200 (5.00%)	22 / 402 (5.47%)	
occurrences (all)	10	22	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	98 / 200 (49.00%)	96 / 402 (23.88%)	
occurrences (all)	105	116	
Neutropenia			
subjects affected / exposed	27 / 200 (13.50%)	87 / 402 (21.64%)	
occurrences (all)	30	128	
Thrombocytopenia			
subjects affected / exposed	14 / 200 (7.00%)	19 / 402 (4.73%)	
occurrences (all)	18	22	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	81 / 200 (40.50%)	140 / 402 (34.83%)	
occurrences (all)	83	148	
Asthenia			
subjects affected / exposed	53 / 200 (26.50%)	109 / 402 (27.11%)	
occurrences (all)	59	116	
Influenza like illness			
subjects affected / exposed	38 / 200 (19.00%)	85 / 402 (21.14%)	
occurrences (all)	43	99	
Pyrexia			
subjects affected / exposed	42 / 200 (21.00%)	80 / 402 (19.90%)	
occurrences (all)	56	102	
Chills			
subjects affected / exposed	18 / 200 (9.00%)	31 / 402 (7.71%)	
occurrences (all)	19	34	
Injection site erythema			
subjects affected / exposed	7 / 200 (3.50%)	21 / 402 (5.22%)	
occurrences (all)	7	21	
Injection site reaction			

subjects affected / exposed	5 / 200 (2.50%)	22 / 402 (5.47%)	
occurrences (all)	6	22	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	12 / 200 (6.00%)	18 / 402 (4.48%)	
occurrences (all)	12	19	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	74 / 200 (37.00%)	88 / 402 (21.89%)	
occurrences (all)	80	94	
Diarrhoea			
subjects affected / exposed	35 / 200 (17.50%)	63 / 402 (15.67%)	
occurrences (all)	43	67	
Vomiting			
subjects affected / exposed	23 / 200 (11.50%)	26 / 402 (6.47%)	
occurrences (all)	23	29	
Abdominal pain upper			
subjects affected / exposed	15 / 200 (7.50%)	24 / 402 (5.97%)	
occurrences (all)	17	26	
Dyspepsia			
subjects affected / exposed	16 / 200 (8.00%)	17 / 402 (4.23%)	
occurrences (all)	16	17	
Anal pruritus			
subjects affected / exposed	25 / 200 (12.50%)	3 / 402 (0.75%)	
occurrences (all)	27	3	
Anorectal discomfort			
subjects affected / exposed	19 / 200 (9.50%)	3 / 402 (0.75%)	
occurrences (all)	19	3	
Haemorrhoids			
subjects affected / exposed	11 / 200 (5.50%)	7 / 402 (1.74%)	
occurrences (all)	11	7	
Proctalgia			
subjects affected / exposed	11 / 200 (5.50%)	2 / 402 (0.50%)	
occurrences (all)	11	2	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	31 / 200 (15.50%)	76 / 402 (18.91%)	
occurrences (all)	32	82	
Dyspnoea			
subjects affected / exposed	25 / 200 (12.50%)	48 / 402 (11.94%)	
occurrences (all)	26	51	
Oropharyngeal pain			
subjects affected / exposed	11 / 200 (5.50%)	22 / 402 (5.47%)	
occurrences (all)	12	26	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	75 / 200 (37.50%)	107 / 402 (26.62%)	
occurrences (all)	81	119	
Rash			
subjects affected / exposed	69 / 200 (34.50%)	93 / 402 (23.13%)	
occurrences (all)	78	105	
Alopecia			
subjects affected / exposed	32 / 200 (16.00%)	86 / 402 (21.39%)	
occurrences (all)	33	86	
Dry skin			
subjects affected / exposed	34 / 200 (17.00%)	84 / 402 (20.90%)	
occurrences (all)	34	90	
Erythema			
subjects affected / exposed	10 / 200 (5.00%)	16 / 402 (3.98%)	
occurrences (all)	10	16	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	35 / 200 (17.50%)	71 / 402 (17.66%)	
occurrences (all)	36	76	
Irritability			
subjects affected / exposed	27 / 200 (13.50%)	43 / 402 (10.70%)	
occurrences (all)	27	45	
Depression			
subjects affected / exposed	12 / 200 (6.00%)	29 / 402 (7.21%)	
occurrences (all)	12	30	
Anxiety			

subjects affected / exposed	16 / 200 (8.00%)	10 / 402 (2.49%)	
occurrences (all)	16	10	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	23 / 200 (11.50%)	61 / 402 (15.17%)	
occurrences (all)	25	63	
Arthralgia			
subjects affected / exposed	14 / 200 (7.00%)	55 / 402 (13.68%)	
occurrences (all)	14	57	
Back pain			
subjects affected / exposed	14 / 200 (7.00%)	27 / 402 (6.72%)	
occurrences (all)	14	28	
Muscle spasms			
subjects affected / exposed	11 / 200 (5.50%)	7 / 402 (1.74%)	
occurrences (all)	11	8	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	10 / 200 (5.00%)	7 / 402 (1.74%)	
occurrences (all)	10	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	39 / 200 (19.50%)	61 / 402 (15.17%)	
occurrences (all)	40	65	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2011	• The primary and secondary objectives and endpoints were modified to reflect analysis of GT-1b and GT-1a populations. • The overall risk/benefit section was updated. • Fibroscan as a method of confirming a diagnosis of chronic hepatitis-C was removed. • Subjects with history of coagulopathy were excluded. • Specified washout for investigational drug/placebo and washout period for exclusions prior therapy. • Confirmed length of follow-up period for subjects who discontinued study drug early. • Updated dosing information to allow for missed doses and for country-specific food preference with telaprevir dosing. • Added Grade 4 rash description and management. • Clarified single nucleotide polymorphism sample at screening used for stratification.
22 January 2013	• Added pertinent telaprevir safety information with regards to fatalities. • Clarified use of prednisone/prednisilone with daclatasvir and clarified that prohibited concomitant medications during daclatasvir dosing refer to systemic dosing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported