Clinical trial results:
A Phase 3 Evaluation of BMS-790052 in Combination With Peg-Interferon Alfa-2a and Ribavirin in Treatment Naive Subjects With Chronic Hepatitis C Genotype 4

Summary

EudraCT number	2011-002793-23
Trial protocol	GB ES IT GR
Global end of trial date	23 January 2014

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	01 April 2016

Trial information

Trial identification

Sponsor protocol code	AI444-042

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01448044
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	23 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare rates of sustained virologic response at post-treatment Week 12 (SVR12) for hepatitis c virus (HCV) genotype 4 (GT-4) infected subjects treated with either BMS-790052 (daclatasvir) or placebo in combination with peginterferon-alfa plus ribavirin (pegIFNalfa/RBV).

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	12 December 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	France: 80
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	Puerto Rico: 2
Worldwide total number of subjects	152
EEA total number of subjects	135

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	148
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 26 sites in 6 countries.

Pre-assignment

Screening details:

A total of 152 subjects were enrolled in the study, of which 125 were randomized and 27 subjects were not randomized due to 23 no longer met criteria, 1 withdrew consent, 1 due to administrative reason, and 2 other reasons. Of 125 randomized, 124 were treated and 1 was not treated due to withdrawal of consent.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

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

Arm description:

Daclatasvir 60 mg tablets were administered orally once daily for 24 weeks, PegIFNalfa-2a 180 µg was administered subcutaneously once in a week for 24 or 48 weeks depending on response and ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening 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 tablets was administered orally once daily for 24 weeks.

Investigational medicinal product name	Pegylated-interferon 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 in a week for 24 or 48 weeks depending on response.

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

Dosage and administration details:

Ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 24 or 48 weeks depending on response.

Arm title	Placebo + PegIFNα-2a + Ribavirin

Arm description:

Placebo matching daclatasvir tablets was administered orally once daily for 48 weeks. PegIFNalfa-2a 180 µg was administered subcutaneously once in a week for 48 weeks and ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 48 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching BMS-790052 tablets was administered orally once daily for 48 weeks.

Investigational medicinal product name	Pegylated-interferon 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 in a week for 48 weeks.

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

Dosage and administration details:

Ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 48 weeks.

Number of subjects in period 1[1]	Daclatasvir+ PegIFNα-2a + Ribavirin	Placebo + PegIFNα-2a + Ribavirin
Started	82	42
Completed	59	26
Not completed	23	16
Others	2	-
Adverse event	4	3
Completed 24 weeks treatment period only	8	-
Subjects no longer meets study criteria	1	-
Subject requested discontinue study drug	1	-
Lost to follow-up	2	1
Lack of efficacy	5	12

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: A total of 125 subjects were randomized and 124 subjects received treatment during the study.

Period 2

Period 2 title	Follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

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

Arm description:

Subjects were followed up till 72 weeks. During treatment period Daclatasvir 60 mg tablets were administered orally once daily for 24 weeks, PegIFNalfa-2a 180 µg was administered subcutaneously once in a week for 24 or 48 weeks depending on response and ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening 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 tablets was administered orally once daily for 24 weeks.

Investigational medicinal product name	Pegylated-interferon 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 in a week for 24 or 48 weeks depending on response.

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

Dosage and administration details:

Ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 24 or 48 weeks depending on response.

Arm title	Placebo + PegIFNα-2a + Ribavirin

Arm description:

Subjects were followed up till 72 weeks. During treatment period Placebo matching daclatasvir tablets was administered orally once daily for 48 weeks. PegIFNalfa-2a 180 µg was administered subcutaneously once in a week for 48 weeks and ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 48 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:	
Placebo matching BMS-790052 tablets was administered orally once daily for 48 weeks.	
Investigational medicinal product name	Pegylated-interferon 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 in a week for 48 weeks.	
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 48 weeks.	

Number of subjects in period 2	Daclatasvir+ PegIFNα-2a + Ribavirin	Placebo + PegIFNα-2a + Ribavirin
Started	59	26
Completed	65	26
Not completed	12	14
Consent withdrawn by subject	1	1
Other reasons	5	11
Lost to follow-up	6	2
Joined	18	14
Subjects rejoined in Follow-up period	18	14

Baseline characteristics

Reporting groups	
Reporting group title	Daclatasvir+ PegIFNα-2a + Ribavirin

Reporting group description:

Daclatasvir 60 mg tablets were administered orally once daily for 24 weeks, PegIFNalfa-2a 180 µg was administered subcutaneously once in a week for 24 or 48 weeks depending on response and ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 24 or 48 weeks depending on response.

Reporting group title	Placebo + PegIFNα-2a + Ribavirin

Reporting group description:

Placebo matching daclatasvir tablets was administered orally once daily for 48 weeks. PegIFNalfa-2a 180 µg was administered subcutaneously once in a week for 48 weeks and ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 48 weeks.

Reporting group values	Daclatasvir+ PegIFNα-2a + Ribavirin	Placebo + PegIFNα-2a + Ribavirin	Total
Number of subjects	82	42	124
Age categorical Units: Subjects			
Adults (18-64 years)	79	42	121
From 65 to 84 years	3	0	3
Age continuous Units: years			
arithmetic mean	47.7	48.4	
standard deviation	± 10.23	± 8.09	-
Gender categorical Units: Subjects			
Female	21	13	34
Male	61	29	90

End points

End points reporting groups

Reporting group title	Daclatasvir+ PegIFNα-2a + Ribavirin

Reporting group description:

Daclatasvir 60 mg tablets were administered orally once daily for 24 weeks, PegIFNalfa-2a 180 µg was administered subcutaneously once in a week for 24 or 48 weeks depending on response and ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 24 or 48 weeks depending on response.

Reporting group title	Placebo + PegIFNα-2a + Ribavirin

Reporting group description:

Placebo matching daclatasvir tablets was administered orally once daily for 48 weeks. PegIFNalfa-2a 180 µg was administered subcutaneously once in a week for 48 weeks and ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 48 weeks.

Reporting group title	Daclatasvir+ PegIFNα-2a + Ribavirin

Reporting group description:

Subjects were followed up till 72 weeks. During treatment period Daclatasvir 60 mg tablets were administered orally once daily for 24 weeks, PegIFNalfa-2a 180 µg was administered subcutaneously once in a week for 24 or 48 weeks depending on response and ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 24 or 48 weeks depending on response.

Reporting group title	Placebo + PegIFNα-2a + Ribavirin

Reporting group description:

Subjects were followed up till 72 weeks. During treatment period Placebo matching daclatasvir tablets was administered orally once daily for 48 weeks. PegIFNalfa-2a 180 µg was administered subcutaneously once in a week for 48 weeks and ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 48 weeks.

Primary: Percentage of Subjects With 12 Week Sustained Virologic Response (SVR12)

End point title	Percentage of Subjects With 12 Week Sustained Virologic Response (SVR12)

End point description:

Subjects were assessed for sustained virologic response 12 weeks post treatment (SVR12) defined as hepatitis C virus (HCV) RNA levels <lower limit of quantitation (LLOQ was 25 IU/mL), target detected (TD) or target not detected (TND) at post-treatment Week 12. The analysis was performed in modified Intent to treat population (ITT), defined as the proportions of subjects meeting the response criteria in numerator and denominator based on all treated subjects. Missing values were imputed using backward imputation technique.

End point type	Primary

End point timeframe:

Week 12 (Follow-up period)

End point values	Daclatasvir+ PegIFNα-2a + Ribavirin	Placebo + PegIFNα-2a + Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	42		
Units: Percentage of Subjects				
number (confidence interval 95%)				

Backward Imputation	81.7 (73.3 to 90.1)	42.9 (27.9 to 57.8)		

Statistical analyses

Statistical analysis title	Percentage difference of treatments in SVR12
Comparison groups	Daclatasvir+ PegIFNα-2a + Ribavirin v Placebo + PegIFNα-2a + Ribavirin
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	38.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.703
upper limit	55.997

Notes:

[1] - The p-value is based on the Cochran-Mantel-Haenszel (CMH) test, stratified by IL28B host genotype, geography, and baseline cirrhosis status.

Secondary: Percentage of Subjects Who Achieved HCV Ribonucleic Acid (RNA) < Limit of Quantification (LLOQ)

End point title	Percentage of Subjects Who Achieved HCV Ribonucleic Acid (RNA) < Limit of Quantification (LLOQ)

End point description:

Subjects who achieved HCV RNA levels below LLOQ ie, 25 international unit per milliliter (IU/mL). Subjects in the placebo arm did not have visits beyond post treatment Week 24. The analysis was performed in modified ITT population. Here ‘99999’represents not estimable data for specified category in respective treatment arm.

End point type	Secondary

End point timeframe:

Treatment Weeks 1, 2, 4, 6, 8 and 12; Weeks 4 and 12; End of treatment (EOT); Post treatment Week 24; Post treatment Week 48

End point values	Daclatasvir+ PegIFNα-2a + Ribavirin	Placebo + PegIFNα-2a + Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	42[2]		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Week 1	53.7 (42.9 to 64.5)	4.8 (0 to 11.2)		
Week 2	89 (82.3 to 95.8)	11.9 (2.1 to 21.7)		

Week 4	91.5 (85.4 to 97.5)	19 (7.2 to 30.9)		
Week 6	84.1 (76.2 to 92.1)	40.5 (25.6 to 55.3)		
Week 8	87.8 (80.7 to 94.9)	47.6 (32.5 to 62.7)		
Week 12	85.4 (77.7 to 93)	59.5 (44.7 to 74.4)		
Weeks 4 and 12	84.1 (76.2 to 92.1)	19 (7.2 to 30.9)		
EOT	92.7 (87 to 98.3)	64.3 (49.8 to 78.8)		
Post treatment Week 24	80.5 (71.9 to 89.1)	40.5 (25.6 to 55.3)		
Post treatment Week 48	83.6 (73.9 to 93.4)	99999 (99999 to 99999)		

Notes:

[2] - As there was no visit at post treatment Week 48, SVR is depicted as 0%.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Undetectable Hepatitis C Virus (HCV) RNA Levels

End point title	Percentage of Subjects With Undetectable Hepatitis C Virus (HCV) RNA Levels

End point description:

Subjects who achieved HCV RNA undetectable ie, 10 international unit per milliliter (IU/mL). Subjects in the placebo arm did not have visits beyond post treatment Week 24. The analysis was performed in modified ITT population. Here '99999' represents not estimable data for specified category in respective treatment arm.

End point type	Secondary

End point timeframe:

Treatment Weeks 1, 2, 4, 6, 8 and 12; Weeks 4 and 12, End of treatment (EOT), Post treatment Week 24, Post treatment Week 48

End point values	Daclatasvir+ PegIFNα-2a + Ribavirin	Placebo + PegIFNα-2a + Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	42[3]		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Week 1	14.6 (7 to 22.3)	0 (0 to 0)		
Week 2	45.1 (34.4 to 55.9)	9.5 (0.6 to 18.4)		
Week 4	85.4 (77.7 to 93)	11.9 (2.1 to 21.7)		
Week 6	80.5 (71.9 to 89.1)	16.7 (5.4 to 27.9)		
Week 8	87.8 (80.7 to 94.9)	38.1 (23.4 to 52.8)		

Week 12	84.1 (76.2 to 92.1)	47.6 (32.5 to 62.7)		
Weeks 4 and 12 (VR 4& 12)	79.3 (70.5 to 88)	11.9 (2.1 to 21.7)		
EOT	90.2 (83.8 to 96.7)	64.3 (49.8 to 78.8)		
Post treatment Week 24	78 (69.1 to 87)	40.5 (25.6 to 55.3)		
Post treatment Week 48	81.8 (71.6 to 92)	99999 (99999 to 99999)		

Notes:

[3] - As there was no visit at post treatment Week 48, SVR is depicted as 0%.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Serious Adverse Events (SAEs), Discontinuations Due to Adverse Events (AEs) and Who Died

End point title	Number of Subjects With Serious Adverse Events (SAEs), Discontinuations Due to Adverse Events (AEs) and Who Died

End point description:

AE was defined as any new unfavorable symptom, sign, or disease or worsening of a pre-existing condition that does not necessarily have a causal relationship with treatment. SAE was defined as a medical event that at any dose resulted in death, persistent or significant disability/incapacity, was life-threatening, an important medical event, or a congenital anomaly/birth defect; or required or prolonged hospitalisation. Analysis was performed on all treated subjects.

End point type	Secondary

End point timeframe:

From Day 1 (start of study treatment) up to Follow-up Week 4

End point values	Daclatasvir+ PegIFNα-2a + Ribavirin	Placebo + PegIFNα-2a + Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	42		
Units: Subjects				
AEs leading to discontinuation of study drug	4	3		
SAEs	8	2		
Death	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12) or Sustained Virologic Response at Follow-up Week 24 (SVR24) by rs12979860 Single Nucleotide Polymorphism (SNP) in the IL28B Gene

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

	Follow-up Week 24 (SVR24) by rs12979860 Single Nucleotide Polymorphism (SNP) in the IL28B Gene

End point description:

Subjects categorized into three genotypes based on SNPs in the IL28B gene were assessed for SVR12 and SVR24, defined as response in which HCV RNA levels below LLOQ or below TD or TND at follow-up Week 12 and Week 24 respectively. For SVR12: analysis was performed by backward imputation method, For SVR24: analysis was performed in Modified ITT population.

End point type	Secondary

End point timeframe:

Post Treatment Weeks 12, 24

End point values	Daclatasvir+ PegIFNα-2a + Ribavirin	Placebo + PegIFNα-2a + Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	42		
Units: Percentage of Subjects				
number (not applicable)				
IL28B Genotype CC (SVR12) (n=22,9)	95.5	100		
IL28B Genotype CT (SVR12) (n=40,27)	75	33.3		
IL28B Genotype TT (SVR12) (n=20,6)	80	0		
IL28B Genotype CC (SVR24) (n=22,9)	95.5	88.9		
IL28B Genotype CT (SVR24) (n=40,27)	72.5	33.3		
IL28B Genotype TT (SVR24) (n=20,6)	80	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose to last dose plus 7 days (up to Week 49)

Adverse event reporting additional description:

On-treatment period

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Daclatasvir+ PegIFNα-2a + Ribavirin

Reporting group description:

Daclatasvir 60 mg tablets were administered orally once daily for 24 weeks, PegIFNalfa-2a 180 µg was administered subcutaneously once in a week for 24 or 48 weeks depending on response and ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 24 or 48 weeks depending on response.

Reporting group title	Placebo + PegIFNα-2a + Ribavirin

Reporting group description:

Placebo matching daclatasvir tablets was administered orally once daily for 48 weeks. PegIFNalfa-2a 180 µg was administered subcutaneously once in a week for 48 weeks and ribavirin 400 mg (2 tablets for subjects <75 kg) or 600 mg (3 tablets for subjects >=75 kg) was administered orally in the morning and 600 mg (3 tablets) in the evening for 48 weeks.

Serious adverse events	Daclatasvir+ PegIFNα-2a + Ribavirin	Placebo + PegIFNα-2a + Ribavirin	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 82 (9.76%)	2 / 42 (4.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid cancer metastatic			
subjects affected / exposed	1 / 82 (1.22%)	0 / 42 (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			
Cerebrovascular accident			
subjects affected / exposed	1 / 82 (1.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cluster headache			

subjects affected / exposed	1 / 82 (1.22%)	0 / 42 (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			
subjects affected / exposed	2 / 82 (2.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 82 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 82 (1.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 82 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	1 / 82 (1.22%)	0 / 42 (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	Daclatasvir+ PegIFNα-2a + Ribavirin	Placebo + PegIFNα-2a + Ribavirin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 82 (97.56%)	39 / 42 (92.86%)	
Nervous system disorders			
Headache			
subjects affected / exposed	28 / 82 (34.15%)	11 / 42 (26.19%)	
occurrences (all)	30	12	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 82 (24.39%)	12 / 42 (28.57%)	
occurrences (all)	23	15	
Neutropenia			
subjects affected / exposed	12 / 82 (14.63%)	11 / 42 (26.19%)	
occurrences (all)	14	14	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	47 / 82 (57.32%)	25 / 42 (59.52%)	
occurrences (all)	48	26	
Fatigue			
subjects affected / exposed	6 / 82 (7.32%)	7 / 42 (16.67%)	
occurrences (all)	6	8	
Influenza like illness			
subjects affected / exposed	23 / 82 (28.05%)	13 / 42 (30.95%)	
occurrences (all)	25	15	
Irritability			
subjects affected / exposed	11 / 82 (13.41%)	9 / 42 (21.43%)	
occurrences (all)	11	9	
Pyrexia			

subjects affected / exposed	13 / 82 (15.85%)	8 / 42 (19.05%)	
occurrences (all)	13	10	
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 82 (3.66%)	4 / 42 (9.52%)	
occurrences (all)	3	4	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	7 / 82 (8.54%)	5 / 42 (11.90%)	
occurrences (all)	7	7	
Constipation			
subjects affected / exposed	2 / 82 (2.44%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	3 / 82 (3.66%)	4 / 42 (9.52%)	
occurrences (all)	8	4	
Dry mouth			
subjects affected / exposed	3 / 82 (3.66%)	3 / 42 (7.14%)	
occurrences (all)	3	3	
Dyspepsia			
subjects affected / exposed	3 / 82 (3.66%)	3 / 42 (7.14%)	
occurrences (all)	3	3	
Nausea			
subjects affected / exposed	10 / 82 (12.20%)	5 / 42 (11.90%)	
occurrences (all)	10	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 82 (12.20%)	8 / 42 (19.05%)	
occurrences (all)	11	10	
Dyspnoea			
subjects affected / exposed	5 / 82 (6.10%)	8 / 42 (19.05%)	
occurrences (all)	5	8	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 82 (8.54%)	2 / 42 (4.76%)	
occurrences (all)	7	2	

Dry skin			
subjects affected / exposed	12 / 82 (14.63%)	7 / 42 (16.67%)	
occurrences (all)	12	7	
Eczema			
subjects affected / exposed	3 / 82 (3.66%)	4 / 42 (9.52%)	
occurrences (all)	3	4	
Erythema			
subjects affected / exposed	2 / 82 (2.44%)	5 / 42 (11.90%)	
occurrences (all)	2	6	
Pruritus			
subjects affected / exposed	25 / 82 (30.49%)	13 / 42 (30.95%)	
occurrences (all)	30	18	
Rash			
subjects affected / exposed	15 / 82 (18.29%)	8 / 42 (19.05%)	
occurrences (all)	17	10	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 82 (3.66%)	4 / 42 (9.52%)	
occurrences (all)	3	4	
Depression			
subjects affected / exposed	3 / 82 (3.66%)	3 / 42 (7.14%)	
occurrences (all)	3	3	
Insomnia			
subjects affected / exposed	18 / 82 (21.95%)	6 / 42 (14.29%)	
occurrences (all)	19	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 82 (10.98%)	6 / 42 (14.29%)	
occurrences (all)	9	8	
Back pain			
subjects affected / exposed	11 / 82 (13.41%)	6 / 42 (14.29%)	
occurrences (all)	12	6	
Myalgia			
subjects affected / exposed	15 / 82 (18.29%)	11 / 42 (26.19%)	
occurrences (all)	16	14	
Metabolism and nutrition disorders			

Abnormal loss of weight			
subjects affected / exposed	5 / 82 (6.10%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
Decreased appetite			
subjects affected / exposed	20 / 82 (24.39%)	5 / 42 (11.90%)	
occurrences (all)	21	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2011	1) Restricted enrollment to subjects chronically infected with HCV GT-4, rather than HCV GT-1 and GT-4, across all study sites. The population sample size and statistical analysis were adjusted to accommodate this change. 2) Changed primary objective to compare rates of SVR12 for HCV GT-4 infected subjects treated with either DCV or placebo in combination with pegIFNalfa-2a/RBV, not GT-1 subjects. 3) Added OATP1B3, atorvastatin, methotrexate, thryoxine, mitoxantrone, imatinib, irinotecan, lapatinib, sulfasalazine, and topotecan as prohibited or restricted treatments during DCV dosing. 4) Corrected the exceptions for unblinding to include subjects who reach virologic failure, not treatment futility. 5) Updated the sample size determination to reflect the change of enrolling GT-4 subjects, not GT-1 subjects.
19 July 2013	1) Clarified that that enrollment into a 3-year observational study may be offered to subjects following the completion of the follow-up phase of this study to assess long-term SVR, resistance, and HCV-related complications. 2) Added QTcB >500 msec to the exclusion criteria. 3) Clarified co-administration of prednisone and prednisolone were to be avoided, but used with caution if deemed necessary. 4) Reduced requirement for monitoring of blood pressure when erythropoiesis-stimulating agents (ESA) initiated. 5) Added instructions for missed doses of DCV and RBV. 6) Clarified that the pharmacokinetic (PK) assessments of DCV and RBV would be based on plasma and concentrations and PK assessments of pegIFNalfa-2a would be based on serum concentrations. 7) Table for Grading the Severity of Adult and Pediatric Adverse Events was to be used for grading laboratory abnormalities reported as AEs or SAEs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported