Clinical trial results:
A Phase 3 Evaluation of Daclatasvir in Combination with Peginterferon Lambda-1a and Ribavirin (RBV) or Telaprevir in Combination with Peginterferon Alfa-2a and RBV in Patients with Chronic Hepatitis C Genotype 1b who are Treatment Naïve or Prior Relapsers to Alfa/RBV Therapy.

Summary

EudraCT number	2011-005409-65
Trial protocol	ES IT DE PL GB
Global end of trial date	09 October 2014

Results information

Result version number	v1 (current)
This version publication date	22 April 2016
First version publication date	22 April 2016

Trial information

Trial identification

Sponsor protocol code	AI452-021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01718158
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Bristol-Myers Squibb International Corporation, Chaussée 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	09 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 October 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to compare the efficacy of pegylated interferon lambda-1a/ ribavirin/ daclatasvir (Lambda/RBV/DCV) to pegylated interferon alfa-2a/ ribavirin/ telaprevir (alfa-2a/RBV/TVR) in subjects with chronic hepatitis C virus (HCV) genotype-1b (GT-1b) infection, measured as the proportion of subjects in each treatment group.

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:

Telaprevir (TVR), a directly acting antiviral (DAA) along with a backbone of alfa/RBV, is approved for treatment of chronic HCV GT-1 infection. The safety profile of TVR in subjects with chronic HCV GT-1 infection has been well characterized in both treatment-naive subjects and those with prior treatment failure to alfa-2a/RBV.

Actual start date of recruitment	29 January 2013
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: 65
Country: Number of subjects enrolled	Spain: 38
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Italy: 35
Country: Number of subjects enrolled	Argentina: 70
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Israel: 54
Country: Number of subjects enrolled	Japan: 120
Country: Number of subjects enrolled	Korea, Republic of: 45
Country: Number of subjects enrolled	Russian Federation: 72
Country: Number of subjects enrolled	Taiwan: 70
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	641
EEA total number of subjects	192

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)	568
From 65 to 84 years	73
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 85 sites in 13 countries.

Pre-assignment

Screening details:

A total of 641 subjects were enrolled, out of which 444 subjects were randomized and 440 were treated; Reasons for not being randomized: subject withdrew consent (17), poor/non-compliance (1), subject no longer met study criteria (167) and other reasons (12).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lambda/RBV/DCV

Arm description:

Subjects (treatment-naive or prior relapsers to alfa-2a/RBV) received daclatasvir (DCV) tablets 60 mg orally, once daily for 12 weeks, pegIFNlambda-1a injection 180 µg subcutaneously, once weekly and RBV tablets for a total daily dose of 1000-1200 mg orally twice daily for 24 weeks. Subjects were originally required to be followed-up for a minimum total period of 24 weeks post-treatment and subjects with any futility criteria or lack of efficacy [HCV RNA >=lower limit of quantitation (LLOQ) at Week 48] were required to be followed-up for a period of 48 weeks post-treatment. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment .

Arm type	Experimental
Investigational medicinal product name	Pegylated interferon lambda-1a
Investigational medicinal product code	BMS-914143
Other name	Lambda
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received pegIFNlambda-1a solution for injection 180 µg subcutaneously, once weekly for 24 weeks.

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

Dosage and administration details:

Subjects received ribavirin tablets for a total daily dose of 1000-1200 mg orally, twice daily for up to 24 weeks.

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 12 weeks.

Arm title	Alfa-2a/RBV/TVR

Arm description:

Subjects (treatment-naive or prior relapsers to alfa-2a/RBV) received telaprevir tablets 375 mg orally, thrice daily for 12 weeks, pegIFNlalfa-2a injection 180 µg subcutaneously, once weekly and ribavirin tablets for a total daily dose of 1000-1200 mg orally twice daily for up to 48 weeks [duration of treatment based on eRVR response (HCV RNA < LLOQ at Weeks 4 and 12)]. At Week 24, subjects who achieved eRVR were discontinued from therapy versus subjects who failed to achieve eRVR yet continued to demonstrate benefit from therapy received an additional 24 weeks of pegIFNalfa-2a/RBV for a total treatment course of 48 weeks. Following discontinuation of study therapy, all subjects were originally planned to complete 24 weeks of post-treatment follow-up. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

Arm type	Experimental
Investigational medicinal product name	Pegylated interferon alfa-2a
Investigational medicinal product code	
Other name	Pegasys
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received pegIFNalfa-2a solution for injection 180 µg subcutaneously, once weekly for 48 weeks.

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

Dosage and administration details:

Subjects received ribavirin tablets for a total daily dose of 1000-1200 mg orally, twice daily for up to 48 weeks.

Investigational medicinal product name	Telaprevir
Investigational medicinal product code	
Other name	Incivek
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 2 telaprevir 375-mg tablets orally, three times daily for 12 weeks.

Number of subjects in period 1[1]	Lambda/RBV/DCV	Alfa-2a/RBV/TVR
Started	294	146
Completed	271	99
Not completed	23	47
Consent withdrawn by subject	1	3
Adverse event, non-fatal	16	28
Other reason	-	1
subject no longer meets study criteria	-	3
Lost to follow-up	-	2
Lack of efficacy	4	3

Subject request to discontinue study therapy	2	7

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: Out of 641 subjects who were enrolled in the study, 444 subjects were randomized and 440 subjects got the study treatment.

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	Lambda/RBV/DCV

Arm description:

Subjects (treatment-naive or prior relapsers to alfa-2a/RBV) received daclatasvir (DCV) tablets 60 mg orally, once daily for 12 weeks, pegIFNlambda-1a injection 180 µg subcutaneously, once weekly and RBV tablets for a total daily dose of 1000-1200 mg orally twice daily for 24 weeks. Subjects were originally required to be followed-up for a minimum total period of 24 weeks post-treatment and subjects with any futility criteria or lack of efficacy [HCV RNA >=lower limit of quantitation (LLOQ) at Week 48] were required to be followed-up for a period of 48 weeks post-treatment. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

Arm type	Experimental
Investigational medicinal product name	Pegylated interferon lambda-1a
Investigational medicinal product code	BMS-914143
Other name	Lambda
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received pegIFNlambda-1a solution for injection 180 µg subcutaneously, once weekly for 24 weeks.

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

Dosage and administration details:

Subjects received ribavirin tablets for a total daily dose of 1000-1200 mg orally, twice daily for up to 24 weeks.

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 12 weeks.

Arm title	Alfa-2a/RBV/TVR

Arm description:

Subjects (treatment-naive or prior relapsers to alfa-2a/RBV) received telaprevir tablets 375 mg orally, thrice daily for 12 weeks, pegIFNlalfa-2a injection 180 µg subcutaneously, once weekly and ribavirin tablets for a total daily dose of 1000-1200 mg orally twice daily for up to 48 weeks [duration of treatment based on eRVR response (HCV RNA < LLOQ at Weeks 4 and 12)]. At Week 24, subjects who achieved eRVR were discontinued from therapy versus subjects who failed to achieve eRVR yet continued to demonstrate benefit from therapy received an additional 24 weeks of pegIFNalfa-2a/RBV for a total treatment course of 48 weeks. Following discontinuation of study therapy, all subjects were originally planned to complete 24 weeks of post-treatment follow-up. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

Arm type	Experimental
Investigational medicinal product name	Pegylated interferon alfa-2a
Investigational medicinal product code	
Other name	Pegasys
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received pegIFNalfa-2a solution for injection 180 µg subcutaneously, once weekly for 48 weeks.

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

Dosage and administration details:

Subjects received ribavirin tablets for a total daily dose of 1000-1200 mg orally, twice daily for up to 48 weeks.

Investigational medicinal product name	Telaprevir
Investigational medicinal product code	
Other name	Incivek
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 2 telaprevir 375-mg tablets orally, three times daily for 12 weeks.

Number of subjects in period 2	Lambda/RBV/DCV	Alfa-2a/RBV/TVR
Started	271	99
Completed	284	130
Not completed	7	8
Consent withdrawn by subject	-	3
Death	-	1
Follow up no longer required per protocol	3	1
Other reason	1	2
Lost to follow-up	3	1
Joined	20	39
Rejoined for follow-up	20	39

Baseline characteristics

Reporting groups	
Reporting group title	Lambda/RBV/DCV

Reporting group description:

Subjects (treatment-naive or prior relapsers to alfa-2a/RBV) received daclatasvir (DCV) tablets 60 mg orally, once daily for 12 weeks, pegIFNlambda-1a injection 180 µg subcutaneously, once weekly and RBV tablets for a total daily dose of 1000-1200 mg orally twice daily for 24 weeks. Subjects were originally required to be followed-up for a minimum total period of 24 weeks post-treatment and subjects with any futility criteria or lack of efficacy [HCV RNA >=lower limit of quantitation (LLOQ) at Week 48] were required to be followed-up for a period of 48 weeks post-treatment. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment .

Reporting group title	Alfa-2a/RBV/TVR

Reporting group description:

Subjects (treatment-naive or prior relapsers to alfa-2a/RBV) received telaprevir tablets 375 mg orally, thrice daily for 12 weeks, pegIFNlalfa-2a injection 180 µg subcutaneously, once weekly and ribavirin tablets for a total daily dose of 1000-1200 mg orally twice daily for up to 48 weeks [duration of treatment based on eRVR response (HCV RNA < LLOQ at Weeks 4 and 12)]. At Week 24, subjects who achieved eRVR were discontinued from therapy versus subjects who failed to achieve eRVR yet continued to demonstrate benefit from therapy received an additional 24 weeks of pegIFNalfa-2a/RBV for a total treatment course of 48 weeks. Following discontinuation of study therapy, all subjects were originally planned to complete 24 weeks of post-treatment follow-up. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

Reporting group values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR	Total
Number of subjects	294	146	440
Age categorical Units: Subjects			
< 65 years	256	131	387
>= 65 years	38	15	53
Age continuous Units: years			
arithmetic mean	50	48	
standard deviation	± 12.1	± 13.2	-
Gender categorical Units: Subjects			
Female	137	76	213
Male	157	70	227

End points

End points reporting groups

Reporting group title	Lambda/RBV/DCV

Reporting group description:

Subjects (treatment-naive or prior relapsers to alfa-2a/RBV) received daclatasvir (DCV) tablets 60 mg orally, once daily for 12 weeks, pegIFNlambda-1a injection 180 µg subcutaneously, once weekly and RBV tablets for a total daily dose of 1000-1200 mg orally twice daily for 24 weeks. Subjects were originally required to be followed-up for a minimum total period of 24 weeks post-treatment and subjects with any futility criteria or lack of efficacy [HCV RNA >=lower limit of quantitation (LLOQ) at Week 48] were required to be followed-up for a period of 48 weeks post-treatment. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment .

Reporting group title	Alfa-2a/RBV/TVR

Reporting group description:

Subjects (treatment-naive or prior relapsers to alfa-2a/RBV) received telaprevir tablets 375 mg orally, thrice daily for 12 weeks, pegIFNlalfa-2a injection 180 µg subcutaneously, once weekly and ribavirin tablets for a total daily dose of 1000-1200 mg orally twice daily for up to 48 weeks [duration of treatment based on eRVR response (HCV RNA < LLOQ at Weeks 4 and 12)]. At Week 24, subjects who achieved eRVR were discontinued from therapy versus subjects who failed to achieve eRVR yet continued to demonstrate benefit from therapy received an additional 24 weeks of pegIFNalfa-2a/RBV for a total treatment course of 48 weeks. Following discontinuation of study therapy, all subjects were originally planned to complete 24 weeks of post-treatment follow-up. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

Reporting group title	Lambda/RBV/DCV

Reporting group description:

Subjects (treatment-naive or prior relapsers to alfa-2a/RBV) received daclatasvir (DCV) tablets 60 mg orally, once daily for 12 weeks, pegIFNlambda-1a injection 180 µg subcutaneously, once weekly and RBV tablets for a total daily dose of 1000-1200 mg orally twice daily for 24 weeks. Subjects were originally required to be followed-up for a minimum total period of 24 weeks post-treatment and subjects with any futility criteria or lack of efficacy [HCV RNA >=lower limit of quantitation (LLOQ) at Week 48] were required to be followed-up for a period of 48 weeks post-treatment. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

Reporting group title	Alfa-2a/RBV/TVR

Reporting group description:

Subjects (treatment-naive or prior relapsers to alfa-2a/RBV) received telaprevir tablets 375 mg orally, thrice daily for 12 weeks, pegIFNlalfa-2a injection 180 µg subcutaneously, once weekly and ribavirin tablets for a total daily dose of 1000-1200 mg orally twice daily for up to 48 weeks [duration of treatment based on eRVR response (HCV RNA < LLOQ at Weeks 4 and 12)]. At Week 24, subjects who achieved eRVR were discontinued from therapy versus subjects who failed to achieve eRVR yet continued to demonstrate benefit from therapy received an additional 24 weeks of pegIFNalfa-2a/RBV for a total treatment course of 48 weeks. Following discontinuation of study therapy, all subjects were originally planned to complete 24 weeks of post-treatment follow-up. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

Primary: Percentage of Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12)

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

End point description:

SVR12 was defined as Hepatitis C virus (HCV) RNA <LLOQ, target detected (TD) or target not detected (TND) at post-treatment follow-up Week 12. The LLOQ was 25 IU/mL. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed in Modified intent-to-treat (modified ITT) population, the numerator was based on subjects

meeting the response criteria and denominator based on all treated subjects.

End point type	Primary

End point timeframe:

Follow-up Week 12

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	146		
Units: Percentage of subjects				
number (confidence interval 95%)	88.8 (85.2 to 92.4)	70.5 (63.2 to 77.9)		

Statistical analyses

Statistical analysis title	Treatment difference in SVR12

Statistical analysis description:

The treatment difference and its two-sided 95% confidence interval (CI) were estimated using stratum-adjusted Mantel-Haenszel approach stratified by IL28B rs12979860 host genotype (CC, non-CC), treatment naive or relapse status, and region (Japan vs rest of world), using modified ITT.

Comparison groups	Lambda/RBV/DCV v Alfa-2a/RBV/TVR
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001
Method	Stratum-adjusted Mantel-Haenszel
Parameter estimate	Percentage difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.9
upper limit	25.7

Notes:

[1] - Non-inferiority and superiority of Lambda/RBV/DCV to Alfa-2a/RBV/TVR were established because the P-value was < 0.05.

Secondary: Percentage of Treatment-Naive Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12)

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

End point description:

SVR12 was defined as HCV RNA <LLOQ, TD or TND at follow-up Week 12. The LLOQ was 25 IU/mL. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed in modified ITT population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects. Here, number of subjects analysed signifies number of treatment-naïve subjects in each reporting arm.

End point type	Secondary

End point timeframe:

Follow-up week 12

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235	115		
Units: Percentage of subjects				
number (confidence interval 95%)	89.8 (85.9 to 93.7)	72.2 (64 to 80.4)		

Statistical analyses

Statistical analysis title	Treatment difference in SVR12

Statistical analysis description:

The treatment difference and its two-sided 95% CI were estimated using stratum-adjusted Mantel-Haenszel approach stratified by IL28B rs12979860 host genotype (CC, non-CC), treatment naive or relapse status, and region (Japan vs rest of world) using modified ITT.

Comparison groups	Lambda/RBV/DCV v Alfa-2a/RBV/TVR
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.0001
Method	Stratum-adjusted Mantel-Haenszel
Parameter estimate	Percentage difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.8
upper limit	26.3

Notes:

[2] - Non-inferiority and superiority of Lambda/RBV/DCV to Alfa-2a/RBV/TVR were established because the P-value was < 0.05.

Secondary: Percentage of subjects With Sustained Virologic Response at Follow-up Week 24 (SVR24)

End point title	Percentage of subjects With Sustained Virologic Response at Follow-up Week 24 (SVR24)

End point description:

SVR24 was defined as HCV RNA levels <LLOQ, TD or TND at follow-up Week 24. The LLOQ was 25 IU/mL. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed in observed population, the numerator was based on subjects meeting the response criteria and denominator based on treated subjects with HCV RNA at follow-up Week 24. Here, number of subjects analysed signifies number of treated subjects with HCV RNA at follow-up Week 24 in each reporting arm. The modified ITT analysis was not performed because not all subjects had the opportunity to reach follow-up Week 24 due to early study termination.

End point type	Secondary

End point timeframe:

Follow-up Week 24

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	112		
Units: Percentage of subjects				
number (confidence interval 95%)	82.7 (78.3 to 87)	60.3 (52.3 to 68.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Rash Related Dermatologic Events

End point title	Percentage of Subjects With Rash Related Dermatologic Events

End point description:

Rash related dermatological events were graded as grade 1- mild, grade 2-moderate and grade 3-severe. The analysis was performed in modified ITT population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects.

End point type	Secondary

End point timeframe:

From Day 1 of study treatment up to Week 12

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	146		
Units: Percentage of Subjects				
number (confidence interval 95%)	26.5 (21.5 to 31.6)	37 (29.2 to 44.8)		

Statistical analyses

Statistical analysis title	Treatment difference for rash events

Statistical analysis description:

The treatment difference and its two-sided 95% CI were estimated using stratum-adjusted Mantel-Haenszel approach stratified by IL28B rs12979860 host genotype (CC, non-CC), treatment naive or relapse status, and region (Japan vs rest of world).

Comparison groups	Lambda/RBV/DCV v Alfa-2a/RBV/TVR

Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0177
Method	Stratum-adjusted Mantel-Haenszel
Parameter estimate	Percentage difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.1
upper limit	-1.9

Notes:

[3] - Superiority of Lambda/RBV/DCV to Alfa-2a/RBV/TVR was established because the P-value was < 0.05.

Secondary: Percentage of Subjects With Treatment Emergent Cytopenic Abnormalities

End point title	Percentage of Subjects With Treatment Emergent Cytopenic Abnormalities

End point description:

Treatment emergent cytopenic abnormalities included anemia, defined as hemoglobin <10 grams/deciliters, neutropenia, defined as absolute neutrophil count <750/mm^3 and thrombocytopenia, defined as platelets <50,000/mm^3. The analysis was performed in modified ITT population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects.

End point type	Secondary

End point timeframe:

From Day 1 of study treatment up to Week 48

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	146		
Units: Percentage of Subjects				
number (confidence interval 95%)	10.2 (6.7 to 13.7)	56.2 (48.1 to 64.2)		

Statistical analyses

Statistical analysis title	Treatment difference in cytopenic abnormalities

Statistical analysis description:

The treatment difference and its two-sided 95% CI were estimated using stratum-adjusted Mantel-Haenszel approach stratified by IL28B rs12979860 host genotype (CC, non-CC), treatment naive or relapse status, and region (Japan vs rest of world).

Comparison groups	Lambda/RBV/DCV v Alfa-2a/RBV/TVR

Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001
Method	Stratum-adjusted Mantel-Haenszel
Parameter estimate	Percentage difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.4
upper limit	-37.5

Notes:

[4] - Superiority of Lambda/RBV/DCV to Alfa-2a/RBV/TVR was established because the P-value was <0.05.

Secondary: Percentage of Subjects With On-treatment Interferon (IFN)-Associated flu Like Symptoms

End point title	Percentage of Subjects With On-treatment Interferon (IFN)-Associated flu Like Symptoms

End point description:

Subjects were assessed for flu-like symptoms like pyrexia, chills or pain. The analysis was performed in modified ITT population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects.

End point type	Secondary

End point timeframe:

From Day 1 of study treatment up to Week 48

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	146		
Units: Percentage of subjects				
number (confidence interval 95%)	9.9 (6.5 to 13.3)	27.4 (20.2 to 34.6)		

Statistical analyses

Statistical analysis title	Treatment difference for flu like symptoms

Statistical analysis description:

The treatment difference and its two-sided 95% CI were estimated using stratum-adjusted Mantel-Haenszel approach stratified by IL28B rs12979860 host genotype (CC, non-CC), treatment-naive or prior relapse to alfa-2a/RBV, and region (Japan vs rest of world).

Comparison groups	Lambda/RBV/DCV v Alfa-2a/RBV/TVR

Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001
Method	Stratum-adjusted Mantel-Haenszel
Parameter estimate	Percentage difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.9
upper limit	-9.2

Notes:

[5] - Superiority of Lambda/RBV/DCV to Alfa-2a/RBV/TVR was established because the P-value was <0.05.

Secondary: Percentage of Subjects With On-treatment Interferon (IFN) Associated Musculoskeletal Symptoms

End point title	Percentage of Subjects With On-treatment Interferon (IFN) Associated Musculoskeletal Symptoms

End point description:

Subjects were assessed for musculoskeletal symptoms which includes arthralgia, myalgia or back pain. The analysis was performed in modified ITT population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects.

End point type	Secondary

End point timeframe:

From Day 1 of study treatment up to Week 48

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	146		
Units: Percentage of subjects				
number (confidence interval 95%)	17.7 (13.3 to 22)	19.9 (13.4 to 26.3)		

Statistical analyses

Statistical analysis title	Treatment difference for musculoskeletal symptoms

Statistical analysis description:

The treatment difference and its two-sided 95% CI were estimated using stratum-adjusted Mantel-Haenszel approach stratified by IL28B rs12979860 host genotype (CC, non-CC), treatment naive or relapse status, and region (Japan vs rest of world).

Comparison groups	Lambda/RBV/DCV v Alfa-2a/RBV/TVR

Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.584
Method	Stratum-adjusted Mantel-Haenszel
Parameter estimate	Percentage difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	5.5

Notes:

[6] - Superiority of Lambda/RBV/DCV to Alfa-2a/RBV/TVR was not established because the P-value was >=0.05. No further hierachical testing of secondary endpoints (eg, SVR14) was conducted.

Secondary: Number of Subjects With Adverse events (AEs), Serious Adverse Events (SAEs), Dose Reductions, and Discontinuations due to AEs during treatment period

End point title	Number of Subjects With Adverse events (AEs), Serious Adverse Events (SAEs), Dose Reductions, and Discontinuations due to AEs during treatment period

End point description:

An AE was defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product. An SAE was defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening , required inpatient hospitalization or caused prolongation of existing hospitalization. The analysis was performed on all subjects who received at least 1 dose of study therapy.

End point type	Secondary

End point timeframe:

From Day 1 of study treatment up to Week 48

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	146		
Units: Subjects				
AEs	254	138		
SAEs	11	16		
Dose reduction	26	33		
Discontinuations due to AEs	16	41		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

eRVR was defined as HCV RNA <LLOQ TND at Weeks 4 and 12 of treatment. The LLOQ was 25 IU/mL. HCV RNA levels were measured by the Roche COBAS® TaqMan ® HCV Test version 2.0 from the central laboratory. The analysis was performed in modified ITT population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects. Missing values were imputed using backward imputation technique.

End point type	Secondary

End point timeframe:

Weeks 4, 12

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	146		
Units: Percentage of subjects				
number (confidence interval 95%)	76.9 (72.1 to 81.7)	67.1 (59.5 to 74.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Rapid Virologic Response (RVR)

End point title	Percentage of Subjects With Rapid Virologic Response (RVR)

End point description:

RVR was defined as HCV RNA <LLOQ TND at Week 4 of treatment. The LLOQ was 25 IU/mL. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed in modified ITT population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects.

End point type	Secondary

End point timeframe:

Week 4

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	146		
Units: Percentage of subjects				
number (confidence interval 95%)	79.3 (74.6 to 83.9)	75.3 (68.4 to 82.3)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

cEVR was defined as HCV RNA <LLOQ TND at Week 12 of treatment. The LLOQ was 25 IU/mL. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed in modified ITT population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects.

End point type	Secondary

End point timeframe:

Week 12

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	146		
Units: Percentage of subjects				
number (confidence interval 95%)	93.5 (90.7 to 96.3)	80.1 (73.7 to 86.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With End of Treatment Response (EOTR)

End point title	Percentage of Subjects With End of Treatment Response (EOTR)

End point description:

EOTR was defined as HCV RNA <LLOQ TND at end of treatment. The LLOQ was 25 IU/mL. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed in modified ITT population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects.

End point type	Secondary

End point timeframe:

End of treatment (up to Week 48)

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	146		
Units: Percentage of subjects				
number (confidence interval 95%)	95.6 (93.2 to 97.9)	89 (84 to 94.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Grade 3 to 4 Laboratory Abnormalities

End point title	Number of Subjects with Treatment Emergent Grade 3 to 4 Laboratory Abnormalities

End point description:

On-treatment emergent abnormalities were those with a higher toxicity grade than the baseline toxicity grade. Laboratory abnormalities were determined and graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 1.0. Hemoglobin: <7.5 g/dL; Platelet count: <50,000/mm^3; International Normalized Ratio (INR) : >2.0*Upper limit of normal (ULN); Leukocytes: <1,500/mm^3; Lymphocytes (Absolute) : <500/mm^3; Neutrophils + bands (absolute): <750/mm^3; Alanine aminotransferase (ALT) : >5*ULN; Aspartate aminotransferase (AST): >5*ULN; Bilirubin (Total) : >2.5*ULN; G-Glutamyl transferase (GGT): >5*ULN; Amylase: >2.0*ULN; Lipase: >3*ULN; Creatinine: >1.8*ULN. The analysis was performed on all subjects who received at least 1 dose of study therapy.

End point type	Secondary

End point timeframe:

From Day 1 of study treatment up to Week 48

End point values	Lambda/RBV/DCV	Alfa-2a/RBV/TVR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	146		
Units: Subjects				
Hemoglobin	6	30		
INR	2	1		
Leukocytes	2	19		
Lymphocytes	10	30		
Neutrophils + bands	3	36		
ALT	13	2		
AST	26	4		
Bilirubin (Total)	28	3		
Bilirubin (Direct)	18	1		
GGT	40	7		
Amylase	5	5		
Lipase	1	3		
Creatinine	0	2		
Platelet count	1	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 of study treatment up to Week 48

Adverse event reporting additional description:

On-treatment period (1 death reported at follow-up week 12).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Lambda/RBV/DCV

Reporting group description:

Subjects (treatment-naive or prior relapsers to alfa-2a/RBV) received daclatasvir (DCV) tablets 60 mg orally, once daily for 12 weeks, pegIFNlambda-1a injection 180 µg subcutaneously, once weekly and RBV tablets for a total daily dose of 1000-1200 mg orally twice daily for 24 weeks. Subjects were originally required to be followed-up for a minimum total period of 24 weeks post-treatment and subjects with any futility criteria or lack of efficacy [HCV RNA >=lower limit of quantitation (LLOQ) at Week 48] were required to be followed-up for a period of 48 weeks post-treatment. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment .

Reporting group title	Alfa-2a/RBV/TVR

Reporting group description:

Subjects (treatment-naive or prior relapsers to alfa-2a/RBV) received telaprevir tablets 375 mg orally, thrice daily for 12 weeks, pegIFNlalfa-2a injection 180 µg subcutaneously, once weekly and ribavirin tablets for a total daily dose of 1000-1200 mg orally twice daily for up to 48 weeks [duration of treatment based on eRVR response (HCV RNA < LLOQ at Weeks 4 and 12)]. At Week 24, subjects who achieved eRVR were discontinued from therapy versus subjects who failed to achieve eRVR yet continued to demonstrate benefit from therapy received an additional 24 weeks of pegIFNalfa-2a/RBV for a total treatment course of 48 weeks. Following discontinuation of study therapy, all subjects were originally planned to complete 24 weeks of post-treatment follow-up. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

Serious adverse events	Lambda/RBV/DCV	Alfa-2a/RBV/TVR	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 294 (3.74%)	16 / 146 (10.96%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 294 (0.34%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Hepatocellular carcinoma			
subjects affected / exposed	0 / 294 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 294 (0.34%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 294 (0.00%)	2 / 146 (1.37%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 294 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 294 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 294 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice			

subjects affected / exposed	3 / 294 (1.02%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 294 (0.34%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 294 (0.34%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 294 (0.34%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	1 / 294 (0.34%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	0 / 294 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 294 (0.00%)	1 / 146 (0.68%)	
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			
Rash			
subjects affected / exposed	0 / 294 (0.00%)	5 / 146 (3.42%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 294 (0.00%)	1 / 146 (0.68%)	
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 / 294 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 294 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 294 (0.00%)	2 / 146 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acinetobacter bacteraemia			
subjects affected / exposed	1 / 294 (0.34%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 294 (0.34%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 294 (0.34%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	0 / 294 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 294 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lambda/RBV/DCV	Alfa-2a/RBV/TVR	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	235 / 294 (79.93%)	136 / 146 (93.15%)	
Investigations			
Blood uric acid increased			
subjects affected / exposed	8 / 294 (2.72%)	11 / 146 (7.53%)	
occurrences (all)	8	11	
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 294 (0.34%)	9 / 146 (6.16%)	
occurrences (all)	1	9	
Alanine aminotransferase increased			
subjects affected / exposed	20 / 294 (6.80%)	4 / 146 (2.74%)	
occurrences (all)	21	4	
Aspartate aminotransferase increased			
subjects affected / exposed	24 / 294 (8.16%)	3 / 146 (2.05%)	
occurrences (all)	26	3	
Blood bilirubin increased			
subjects affected / exposed	20 / 294 (6.80%)	3 / 146 (2.05%)	
occurrences (all)	22	3	
Nervous system disorders			
Headache			
subjects affected / exposed	38 / 294 (12.93%)	27 / 146 (18.49%)	
occurrences (all)	69	41	
Dizziness			

subjects affected / exposed	23 / 294 (7.82%)	22 / 146 (15.07%)	
occurrences (all)	39	24	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	55 / 294 (18.71%)	44 / 146 (30.14%)	
occurrences (all)	65	48	
Pyrexia			
subjects affected / exposed	23 / 294 (7.82%)	31 / 146 (21.23%)	
occurrences (all)	29	50	
Asthenia			
subjects affected / exposed	58 / 294 (19.73%)	27 / 146 (18.49%)	
occurrences (all)	66	34	
Malaise			
subjects affected / exposed	13 / 294 (4.42%)	17 / 146 (11.64%)	
occurrences (all)	13	17	
Chills			
subjects affected / exposed	9 / 294 (3.06%)	14 / 146 (9.59%)	
occurrences (all)	18	27	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	31 / 294 (10.54%)	75 / 146 (51.37%)	
occurrences (all)	35	79	
Neutropenia			
subjects affected / exposed	3 / 294 (1.02%)	35 / 146 (23.97%)	
occurrences (all)	3	40	
Leukopenia			
subjects affected / exposed	0 / 294 (0.00%)	13 / 146 (8.90%)	
occurrences (all)	0	19	
Thrombocytopenia			
subjects affected / exposed	1 / 294 (0.34%)	9 / 146 (6.16%)	
occurrences (all)	1	10	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	43 / 294 (14.63%)	41 / 146 (28.08%)	
occurrences (all)	56	50	
Anal pruritus			

subjects affected / exposed	2 / 294 (0.68%)	14 / 146 (9.59%)	
occurrences (all)	2	16	
Diarrhoea			
subjects affected / exposed	32 / 294 (10.88%)	14 / 146 (9.59%)	
occurrences (all)	35	14	
Vomiting			
subjects affected / exposed	14 / 294 (4.76%)	11 / 146 (7.53%)	
occurrences (all)	17	16	
Epigastric discomfort			
subjects affected / exposed	1 / 294 (0.34%)	9 / 146 (6.16%)	
occurrences (all)	1	9	
Dry mouth			
subjects affected / exposed	2 / 294 (0.68%)	8 / 146 (5.48%)	
occurrences (all)	2	10	
Dyspepsia			
subjects affected / exposed	16 / 294 (5.44%)	8 / 146 (5.48%)	
occurrences (all)	16	8	
Abdominal pain upper			
subjects affected / exposed	16 / 294 (5.44%)	5 / 146 (3.42%)	
occurrences (all)	19	6	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	19 / 294 (6.46%)	25 / 146 (17.12%)	
occurrences (all)	22	31	
Cough			
subjects affected / exposed	18 / 294 (6.12%)	19 / 146 (13.01%)	
occurrences (all)	19	20	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	106 / 294 (36.05%)	59 / 146 (40.41%)	
occurrences (all)	120	69	
Rash			
subjects affected / exposed	49 / 294 (16.67%)	58 / 146 (39.73%)	
occurrences (all)	54	64	
Alopecia			

subjects affected / exposed	13 / 294 (4.42%)	17 / 146 (11.64%)	
occurrences (all)	13	18	
Dry skin			
subjects affected / exposed	22 / 294 (7.48%)	17 / 146 (11.64%)	
occurrences (all)	22	17	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	60 / 294 (20.41%)	33 / 146 (22.60%)	
occurrences (all)	64	36	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	37 / 294 (12.59%)	23 / 146 (15.75%)	
occurrences (all)	47	35	
Arthralgia			
subjects affected / exposed	34 / 294 (11.56%)	15 / 146 (10.27%)	
occurrences (all)	43	22	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 294 (5.44%)	3 / 146 (2.05%)	
occurrences (all)	23	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	32 / 294 (10.88%)	37 / 146 (25.34%)	
occurrences (all)	34	41	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2012	The recommendations from the Food and Drug Administration following their review of the protocol at the end of phase-2 meeting on 15-Oct-2012, to clarify some inclusion/exclusion criteria and study procedures and to incorporate some administrative changes.
20 February 2013	New safety information on telaprevir was added in to the protocol along with the clarifications on the list of prohibited medications during dosing with daclatasvir, new cardiac safety monitoring procedures and guidelines for subjects who develop clinically significant symptoms suggestive of cardiac pathology and clarify some study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated after all subjects completed the post-dosing Week 12 follow-up visit.

Notes: