



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Controlled Study Evaluating the Efficacy and Safety of Peginterferon Lambda-1a, with and without Daclatasvir, Compared to Peginterferon Alfa-2a, Each in Combination with Ribavirin, in the Treatment of Naïve Genotype 2 and 3 Chronic Hepatitis C Subjects.

Summary

EudraCT number	2011-004885-14
Trial protocol	GB BE FI NL IT GR
Global end of trial date	24 September 2014

Results information

Result version number	v1 (current)
This version publication date	28 April 2016
First version publication date	28 April 2016

Trial information

Trial identification

Sponsor protocol code	AI452-017
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01616524
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	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com
Scientific contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, 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	24 September 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate in treatment naive subjects with chronic hepatitis c virus (HCV) genotype (GT)-2 or -3 infection:

1) Sustained virologic response rate at post-treatment week 12 (SVR12) following 24 weeks of treatment with pegylated interferon lambda-1a/ribavirin and the SVR12 following 24 weeks of treatment with pegylated interferon alfa-2a/ribavirin (alfa-2a/RBV).

2) SVR12 following 12 weeks of treatment with pegylated interferon lambda-1a/ribavirin/daclatasvir and the SVR12 following 24 weeks of treatment with alfa-2a/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	20 July 2012
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	Argentina: 79
Country: Number of subjects enrolled	Australia: 143
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Finland: 16
Country: Number of subjects enrolled	France: 55
Country: Number of subjects enrolled	United Kingdom: 38
Country: Number of subjects enrolled	Greece: 17
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	Italy: 62
Country: Number of subjects enrolled	Japan: 103
Country: Number of subjects enrolled	Korea, Republic of: 169
Country: Number of subjects enrolled	Mexico: 59
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Russian Federation: 191

Country: Number of subjects enrolled	Singapore: 17
Country: Number of subjects enrolled	Taiwan: 59
Country: Number of subjects enrolled	United States: 190
Worldwide total number of subjects	1243
EEA total number of subjects	217

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)	1148
From 65 to 84 years	95
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 124 centers in 18 countries.

Pre-assignment

Screening details:

1243 subjects were enrolled, of which 880 subjects were randomized and 874 received study treatment (353: peginterferon lambda-1a+ribavirin+placebo, 349: peginterferon lambda-1a+ribavirin+daclatasvir, 172: peginterferon alfa-2a+ribavirin+placebo, remaining 6 subjects either no longer met study criteria, or withdrew consent or lost to follow-up).

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	PegIFN Lambda-1a+Ribavirin+Placebo

Arm description:

Subjects received pegIFN lambda-1a solution for injection 180 µg subcutaneously, once weekly, with placebo matched with daclatasvir tablets orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks. Subjects continued to receive pegIFN lambda-1a with ribavirin for an additional 12 weeks and followed-up for 24 weeks.

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

Dosage and administration details:

Self-administration of peginterferon lambda -1a 180 µg subcutaneous injection once in a week.

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

Dosage and administration details:

Ribavirin 400 mg was administered twice daily (2 tablets of 200 mg in the morning with food and 2 tablets of 200 mg in the evening with food).

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 matched to daclatasvir was administered once daily with or without a meal.

Arm title	PegIFNλ-1a+Ribavirin+Daclatasvir
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Arm description:

Subjects received pegIFN lambda-1a solution for injection 180 µg subcutaneously, once weekly, with

daclatasvir tablets 60 mg orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks and followed-up for 48 weeks.

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

Dosage and administration details:

Self-administration of peginterferon lamda-1a 180 µg subcutaneous injection once in a week.

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 was administered orally once daily with or without a meal.

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

Dosage and administration details:

Ribavirin 400 mg was administered twice daily (2 tablets of 200 mg in the morning with food and 2 tablets of 200 mg in the evening with food).

Arm title	PegIFN alfa-2a+Ribavirin+Placebo
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Arm description:

Subjects received pegIFN alfa-2a solution for injection 180 µg subcutaneously, once weekly, with placebo matched with daclatasvir tablets orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks. Subjects continued to receive pegIFN alfa-2a with ribavirin for an additional 12 weeks and followed-up for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Peginterferon Alfa-2a
Investigational medicinal product code	
Other name	Pegasys
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Self-administration of peginterferon Alfa-2a 180 µg subcutaneous injection once in a week.

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 matched to daclatasvir was administered once daily with or without a meal.

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

Dosage and administration details:

Ribavirin 400 mg was administered twice daily (2 tablets of 200 mg in the morning with food and 2

tablets of 200 mg in the evening with food).

Number of subjects in period 1^[1]	PegIFN Lambda-1a+Ribavirin+Placebo	PegIFNλ-1a+Ribavirin+Daclatasvir	PegIFN alfa-2a+Ribavirin+Placebo
Started	353	349	172
Completed	311	331	153
Not completed	42	18	19
Consent withdrawn by subject	2	2	2
Adverse event, non-fatal	26	10	15
Subject request	3	-	-
No longer meets study criteria	3	1	-
Unspecified	1	-	-
Lost to follow-up	2	-	-
Poor/non-compliance	1	1	-
Lack of efficacy	4	4	2

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 1243 subjects enrolled, 880 subjects were randomised and 874 received study treatment.

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	PegIFN Lambda-1a+Ribavirin+Placebo

Arm description:

Subjects received pegIFN lambda-1a solution for injection 180 µg subcutaneously, once weekly, with placebo matched with daclatasvir tablets orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks. Subjects continued to receive pegIFN lambda-1a with ribavirin for an additional 12 weeks and followed-up for 24 weeks.

Arm type	Experimental
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Investigational medicinal product name	Peginterferon Lambda-1a
Investigational medicinal product code	BMS-914143
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details:	
Self-administration of peginterferon lambda -1a 180 µg subcutaneous injection once in a week.	
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Ribasphere
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Ribavirin 400 mg was administered twice daily (2 tablets of 200 mg in the morning with food and 2 tablets of 200 mg in the evening with food).	
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 matched to daclatasvir was administered once daily with or without a meal.	
Arm title	PegIFNλ-1a+Ribavirin+Daclatasvir
Arm description:	
Subjects received pegIFN lambda-1a solution for injection 180 µg subcutaneously, once weekly, with daclatasvir tablets 60 mg orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks and followed-up for 48 weeks.	
Arm type	Experimental
Investigational medicinal product name	Peginterferon Lambda -1a
Investigational medicinal product code	BMS-914143
Other name	Lambda
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details:	
Self-administration of peginterferon lamda-1a 180 µg subcutaneous injection once in a week.	
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 was administered orally once daily with or without a meal.	
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Ribasphere
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Ribavirin 400 mg was administered twice daily (2 tablets of 200 mg in the morning with food and 2 tablets of 200 mg in the evening with food).	
Arm title	PegIFN alfa-2a+Ribavirin+Placebo

Arm description:

Subjects received pegIFN alfa-2a solution for injection 180 µg subcutaneously, once weekly, with placebo matched with daclatasvir tablets orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks. Subjects continued to receive pegIFN alfa-2a with ribavirin for an additional 12 weeks and followed-up for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Peginterferon Alfa-2a
Investigational medicinal product code	
Other name	Pegasys
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Self-administration of peginterferon Alfa-2a 180 µg subcutaneous injection once in a week.

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 matched to daclatasvir was administered once daily with or without a meal.

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

Dosage and administration details:

Ribavirin 400 mg was administered twice daily (2 tablets of 200 mg in the morning with food and 2 tablets of 200 mg in the evening with food).

Number of subjects in period 2	PegIFN Lambda-1a+Ribavirin+Placebo	PegIFNλ-1a+Ribavirin+Daclatasvir	PegIFN alfa-2a+Ribavirin+Placebo
Started	311	331	153
Completed	313	324	159
Not completed	30	18	9
Consent withdrawn by subject	6	1	2
Death	-	1	-
Follow-up no longer required per protocol	6	7	1
Unspecified	6	4	1
Lost to follow-up	12	5	5
Joined	32	11	15
Rejoined for follow-up	32	11	15

Baseline characteristics

Reporting groups

Reporting group title	PegIFN Lambda-1a+Ribavirin+Placebo
Reporting group description: Subjects received pegIFN lambda-1a solution for injection 180 µg subcutaneously, once weekly, with placebo matched with daclatasvir tablets orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks. Subjects continued to receive pegIFN lambda-1a with ribavirin for an additional 12 weeks and followed-up for 24 weeks.	
Reporting group title	PegIFNλ-1a+Ribavirin+Daclatasvir
Reporting group description: Subjects received pegIFN lambda-1a solution for injection 180 µg subcutaneously, once weekly, with daclatasvir tablets 60 mg orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks and followed-up for 48 weeks.	
Reporting group title	PegIFN alfa-2a+Ribavirin+Placebo
Reporting group description: Subjects received pegIFN alfa-2a solution for injection 180 µg subcutaneously, once weekly, with placebo matched with daclatasvir tablets orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks. Subjects continued to receive pegIFN alfa-2a with ribavirin for an additional 12 weeks and followed-up for 24 weeks.	

Reporting group values	PegIFN Lambda-1a+Ribavirin+Placebo	PegIFNλ-1a+Ribavirin+Daclatasvir	PegIFN alfa-2a+Ribavirin+Placebo
Number of subjects	353	349	172
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	331	321	166
From 65-84 years	22	28	6
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	47.8	47.4	46.2
standard deviation	± 11.28	± 11.96	± 11.45
Gender categorical Units: Subjects			
Female	143	154	79
Male	210	195	93

Reporting group values	Total		
Number of subjects	874		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	818		
From 65-84 years	56		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	376		
Male	498		

End points

End points reporting groups

Reporting group title	PegIFN Lambda-1a+Ribavirin+Placebo
Reporting group description: Subjects received pegIFN lambda-1a solution for injection 180 µg subcutaneously, once weekly, with placebo matched with daclatasvir tablets orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks. Subjects continued to receive pegIFN lambda-1a with ribavirin for an additional 12 weeks and followed-up for 24 weeks.	
Reporting group title	PegIFNλ-1a+Ribavirin+Daclatasvir
Reporting group description: Subjects received pegIFN lambda-1a solution for injection 180 µg subcutaneously, once weekly, with daclatasvir tablets 60 mg orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks and followed-up for 48 weeks.	
Reporting group title	PegIFN alfa-2a+Ribavirin+Placebo
Reporting group description: Subjects received pegIFN alfa-2a solution for injection 180 µg subcutaneously, once weekly, with placebo matched with daclatasvir tablets orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks. Subjects continued to receive pegIFN alfa-2a with ribavirin for an additional 12 weeks and followed-up for 24 weeks.	
Reporting group title	PegIFN Lambda-1a+Ribavirin+Placebo
Reporting group description: Subjects received pegIFN lambda-1a solution for injection 180 µg subcutaneously, once weekly, with placebo matched with daclatasvir tablets orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks. Subjects continued to receive pegIFN lambda-1a with ribavirin for an additional 12 weeks and followed-up for 24 weeks.	
Reporting group title	PegIFNλ-1a+Ribavirin+Daclatasvir
Reporting group description: Subjects received pegIFN lambda-1a solution for injection 180 µg subcutaneously, once weekly, with daclatasvir tablets 60 mg orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks and followed-up for 48 weeks.	
Reporting group title	PegIFN alfa-2a+Ribavirin+Placebo
Reporting group description: Subjects received pegIFN alfa-2a solution for injection 180 µg subcutaneously, once weekly, with placebo matched with daclatasvir tablets orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks. Subjects continued to receive pegIFN alfa-2a with ribavirin for an additional 12 weeks and followed-up for 24 weeks.	

Primary: Percentage of Chronically Infected Genotype 2 and 3 Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12)

End point title	Percentage of Chronically Infected Genotype 2 and 3 Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12)
End point description: SVR12 was defined as Hepatitis C virus (HCV) RNA <lower limit of quantitation (LLOQ), target detected (TD) or target not detected (TND) at follow-up Week 12. The LLOQ was 25 international units per milliliter (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 (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	PegIFN Lambda-1a+Ribavirin+Placebo	PegIFNλ-1a+Ribavirin+Daclatasvir	PegIFN alfa-2a+Ribavirin+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	353	349	172	
Units: Percentage of subjects				
number (confidence interval 95%)	68 (63.1 to 72.9)	82.5 (78.5 to 86.5)	73.3 (66.6 to 79.9)	

Statistical analyses

Statistical analysis title	Treatment difference in SVR12
Statistical analysis description:	
The treatment difference in SVR12 response rates and its two-sided 97.5% CI were estimated using a stratum-adjusted Mantel-Haenszel (MH) approach stratified by HCV GT-2 or -3, baseline HCV RNA (< 800,000 or ≥ 800,000 IU/mL), cirrhosis status and region (Japan/ROW) using modified ITT.	
Comparison groups	PegIFN Lambda-1a+Ribavirin+Placebo v PegIFN alfa-2a+Ribavirin+Placebo
Number of subjects included in analysis	525
Analysis specification	Pre-specified
Analysis type	other ^[1]
Method	Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	-5.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-14.9
upper limit	3.4

Notes:

[1] - Non-inferiority of PegIFN Lambda-1a+Ribavirin+Placebo to PegIFN alfa-2a+Ribavirin+Placebo was not demonstrated because the 97.5% CI lower limit was ≤10%. Therefore, the second stage test for superiority was not conducted. No further hierarchical testing of secondary endpoints was conducted.

Statistical analysis title	Treatment difference in SVR12
Statistical analysis description:	
The treatment difference in SVR12 response rates and its two-sided 97.5% CI were estimated using a stratum-adjusted MH approach stratified by HCV GT-2 or -3, baseline HCV RNA, cirrhosis status and region using modified ITT.	
Comparison groups	PegIFNλ-1a+Ribavirin+Daclatasvir v PegIFN alfa-2a+Ribavirin+Placebo
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	other ^[2]
Method	Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	9

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.3
upper limit	17.6

Notes:

[2] - Both non-inferiority and superiority of PegIFNλ-1a+Ribavirin+Daclatasvir to PegIFN alfa-2a+Ribavirin+Placebo were demonstrated because the 97.5% CI lower limit was >0.

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

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

RVR was defined as undetectable HCV RNA <LLOQ, TND at Week 4. 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
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End point timeframe:

Week 4

End point values	PegIFN Lambda-1a+Ribavirin+Placebo	PegIFNλ-1a+Ribavirin+Daclatasvir	PegIFN alfa-2a+Ribavirin+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	353	349	172	
Units: Percentage of subjects				
number (confidence interval 95%)	64.3 (59.3 to 69.3)	85.7 (82 to 89.3)	57.6 (50.2 to 64.9)	

Statistical analyses

Statistical analysis title	Treatment difference in RVR
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Statistical analysis description:

The treatment difference in RVR response rates and its two-sided 97.5% CI were estimated using a stratum-adjusted MH approach stratified by HCV GT-2 or -3, baseline HCV RNA, cirrhosis status and region using modified ITT.

Comparison groups	PegIFN alfa-2a+Ribavirin+Placebo v PegIFNλ-1a+Ribavirin+Daclatasvir
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	other ^[3]
Method	Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	27.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	18.7
upper limit	37.1

Notes:

[3] - Both non-inferiority and superiority of PegIFNλ-1a+Ribavirin+Daclatasvir to PegIFN alfa-2a+Ribavirin+Placebo were demonstrated because the 97.5% CI lower limit was >0.

Secondary: Percentage of Subjects With Treatment Emergent Cytopenic Abnormalities

End point title	Percentage of Subjects With Treatment Emergent Cytopenic Abnormalities
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End point description:

Cytopenic abnormalities included anemia as defined by haemoglobin (Hb) <10 g/dL, neutropenia as defined by absolute neutrophil count (ANC) <750 mm³ or thrombocytopenia as defined by platelets <50,000 mm³. The analysis was performed in modified ITT population, the numerator was based on subjects having cytopenic abnormalities and denominator based on all treated subjects.

End point type	Secondary
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End point timeframe:

Up to End of Treatment (Week 12 or 24)

End point values	PegIFN Lambda-1a+Ribavirin+Placebo	PegIFNλ-1a+Ribavirin+Daclatasvir	PegIFN alfa-2a+Ribavirin+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	353	349	172	
Units: Percentage of subjects				
number (confidence interval 95%)	2.8 (1.1 to 4.6)	2 (0.5 to 3.5)	36.6 (29.4 to 43.8)	

Statistical analyses

Statistical analysis title	Treatment difference in cytopenic abnormalities
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Statistical analysis description:

The treatment difference in cytopenic abnormality rates and its two-sided 97.5% CI were estimated using a stratum-adjusted Mantel-Haenszel (MH) approach stratified by HCV GT-2 or -3, baseline HCV RNA, cirrhosis status and region using modified ITT.

Comparison groups	PegIFNλ-1a+Ribavirin+Daclatasvir v PegIFN alfa-2a+Ribavirin+Placebo
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	other ^[4]
Method	Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	-34.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-42.4
upper limit	-26.4

Notes:

[4] - Superiority of PegIFNλ-1a+Ribavirin+Daclatasvir to PegIFN alfa-2a+Ribavirin+Placebo was demonstrated because the 97.5% CI upper limit was <0.

Secondary: Percentage of Subjects With Sustained Virologic Response Rate at Follow-up Week 12 (SVR12) For Genotype 3 Chronic Hepatitis C Virus (HCV) Infection

End point title	Percentage of Subjects With Sustained Virologic Response Rate at Follow-up Week 12 (SVR12) For Genotype 3 Chronic Hepatitis C Virus (HCV) Infection
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End point description:

SVR12 rate was defined 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 with HCV genotype 3. Missing values were imputed using backward imputation technique

End point type	Secondary
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End point timeframe:

Follow-up Week 12

End point values	PegIFN Lambda-1a+Ribavirin+Placebo	PegIFNλ-1a+Ribavirin+Daclatasvir	PegIFN alfa-2a+Ribavirin+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	165	81	
Units: Percentage of subjects				
number (confidence interval 95%)	64.1 (56.9 to 71.3)	74.5 (67.9 to 81.2)	72.8 (63.2 to 82.5)	

Statistical analyses

Statistical analysis title	Treatment difference in SVR12
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Statistical analysis description:

The treatment difference in SVR12 response rates and its two-sided 97.5% CI were estimated using a stratum-adjusted Mantel-Haenszel (MH) approach stratified by HCV GT-2 or -3, baseline HCV RNA, cirrhosis status and region using modified ITT.

Comparison groups	PegIFNλ-1a+Ribavirin+Daclatasvir v PegIFN alfa-2a+Ribavirin+Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	other ^[5]
Method	Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	1.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-11.5
upper limit	14.3

Notes:

[5] - Non-inferiority of PegIFN Lambda-1a+Ribavirin+Daclatasvir to PegIFN alfa-2a+Ribavirin+Placebo was not demonstrated because the 97.5% CI lower limit was ≤10%. Therefore, the second stage test for superiority was not conducted. No further hierarchical testing of secondary endpoints was conducted.

Secondary: Percentage of Subjects With On-treatment Interferon-Associated Flu-Like Symptoms

End point title	Percentage of Subjects With On-treatment Interferon-Associated Flu-Like Symptoms
End point description: Interferon-associated flu-like symptoms were defined by pyrexia or chills or pain. The analysis was performed on modified intent-to-treat (ITT) population, the numerator was based on subjects having interferon-associated flu-like symptoms and denominator based on all treated subjects.	
End point type	Secondary
End point timeframe: Baseline up to End of Treatment (Week 12 or 24)	

End point values	PegIFN Lambda-1a+Ribavirin+P lacebo	PegIFNλ-1a+Ribavirin+ Daclatasvir	PegIFN alfa-2a+Ribavirin+P lacebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	353	349	172	
Units: Percentage of subjects				
number (confidence interval 95%)	11.6 (8.3 to 15)	9.2 (6.1 to 12.2)	36.6 (29.4 to 43.8)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Subjects With On-treatment Interferon-Associated Musculoskeletal Symptoms
End point description: Musculoskeletal symptoms was defined by arthralgia or myalgia or back pain. The analysis was performed in modified intent-to-treat (ITT) population, the numerator was based on subjects having interferon-associated musculoskeletal symptoms and denominator based on all treated subjects.	
End point type	Secondary
End point timeframe: Baseline up to End of Treatment (Week 12 or 24)	

End point values	PegIFN Lambda-1a+Ribavirin+P lacebo	PegIFNλ-1a+Ribavirin+ Daclatasvir	PegIFN alfa-2a+Ribavirin+P lacebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	353	349	172	
Units: Percentage of subjects				
number (confidence interval 95%)	25.5 (20.9 to 30)	20.6 (16.4 to 24.9)	49.4 (41.9 to 56.9)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Subjects With Sustained Virologic Response at Post-treatment Follow-up Week 24 (SVR24)
End point description: SVR24 rate was defined HCV RNA <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 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: Follow-up Week 24	

End point values	PegIFN Lambda-1a+Ribavirin+P lacebo	PegIFNλ-1a+Ribavirin+ Daclatasvir	PegIFN alfa-2a+Ribavirin+P lacebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	353	349	172	
Units: Percentage of subjects				
number (confidence interval 95%)	65.7 (60.8 to 70.7)	81.7 (77.6 to 85.7)	71.5 (64.8 to 78.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With On-Treatment Serious Adverse Events (SAEs) and Discontinuations Due to Adverse Events (AEs)

End point title	Percentage of Subjects With On-Treatment Serious Adverse Events (SAEs) and Discontinuations Due to Adverse Events (AEs)
End point description: AE was defined as any new unfavorable symptom, sign, or disease or worsening of a pre-existing condition that does not has a causal relationship with treatment. SAE was defined as a medical event that at any dose resulted in death, persistent or significant disability/incapacity, or drug dependency/abuse; was life-threatening, an important medical event, or a congenital anomaly/birth defect; or required or prolonged hospitalization. The analysis was performed on all treated subjects who received at least 1 dose of study therapy.	
End point type	Secondary

End point timeframe:

Baseline up to end of treatment (Week 12 or 24)

End point values	PegIFN Lambda- 1a+Ribavirin+P lacebo	PegIFNλ- 1a+Ribavirin+ Daclatasvir	PegIFN alfa- 2a+Ribavirin+P lacebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	353	349	172	
Units: Percentage of subjects				
number (not applicable)				
SAEs	6.2	2.9	2.3	
AEs leading to discontinuation	7.4	2.9	8.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With On-treatment Interferon- Associated Constitutional Symptoms

End point title	Percentage of Subjects With On-treatment Interferon- Associated Constitutional Symptoms
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End point description:

Constitutional symptoms include fatigue and asthenia. The analysis was performed on all treated subjects who received at least 1 dose of study therapy.

End point type	Secondary
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End point timeframe:

Baseline up to End of Treatment (Week 12 or 24)

End point values	PegIFN Lambda- 1a+Ribavirin+P lacebo	PegIFNλ- 1a+Ribavirin+ Daclatasvir	PegIFN alfa- 2a+Ribavirin+P lacebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	353	349	172	
Units: Percentage of subjects				
number (not applicable)				
Fatigue	31.2	24.9	43	
Asthenia	12.2	10	13.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Dose Reductions

End point title	Percentage of Subjects With Dose Reductions
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End point description:

Dose reductions were mainly due to adverse events or elevated liver function tests. The analysis was performed on all treated subjects who received at least 1 dose of study therapy.

End point type	Secondary
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End point timeframe:

Baseline up to End of Treatment (Week 12 or 24)

End point values	PegIFN Lambda-1a+Ribavirin+P lacebo	PegIFNλ-1a+Ribavirin+ Daclatasvir	PegIFN alfa-2a+Ribavirin+P lacebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	353	349	172	
Units: Percentage of subjects				
number (not applicable)				
pegIFNλ dose reduction	7.08	2.87	0	
Ribavirin dose reduction	5.95	3.44	19.19	
pegIFNalfa-2a dose reduction	0	0	29.07	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to end of treatment (Week 12 or 24) (On-treatment Period)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	PegIFN Lambda-1a+Ribavirin+Placebo
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Reporting group description:

Subjects received pegIFN lambda-1a solution for injection 180 µg subcutaneously, once weekly, with placebo matched with daclatasvir tablets orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks. Subjects continued to receive pegIFN lambda-1a with ribavirin for an additional 12 weeks and followed-up for 24 weeks.

Reporting group title	PegIFNλ-1a+Ribavirin+Daclatasvir
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Reporting group description:

Subjects received pegIFN lambda-1a solution for injection 180 µg subcutaneously, once weekly, with daclatasvir tablets 60 mg orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks and followed-up for 48 weeks.

Reporting group title	PegIFN alfa-2a+Ribavirin+Placebo
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Reporting group description:

Subjects received pegIFN alfa-2a solution for injection 180 µg subcutaneously, once weekly, with placebo matched with daclatasvir tablets orally, once daily and ribavirin tablets 400 mg orally, twice daily, for up to 12 weeks. Subjects continued to receive pegIFN alfa-2a with ribavirin for an additional 12 weeks and followed-up for 24 weeks.

Serious adverse events	PegIFN Lambda-1a+Ribavirin+Placebo	PegIFNλ-1a+Ribavirin+Daclatasvir	PegIFN alfa-2a+Ribavirin+Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 353 (6.23%)	10 / 349 (2.87%)	4 / 172 (2.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 353 (0.28%)	1 / 349 (0.29%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood potassium decreased			

subjects affected / exposed	0 / 353 (0.00%)	0 / 349 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 353 (0.28%)	1 / 349 (0.29%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 353 (0.28%)	1 / 349 (0.29%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Anosmia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar Syndrome			
subjects affected / exposed	0 / 353 (0.00%)	0 / 349 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 353 (0.00%)	0 / 349 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 353 (0.00%)	0 / 349 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	7 / 353 (1.98%)	1 / 349 (0.29%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	7 / 7	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinemia			
subjects affected / exposed	1 / 353 (0.28%)	1 / 349 (0.29%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			

subjects affected / exposed	0 / 353 (0.00%)	2 / 349 (0.57%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance abuse			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal tubular necrosis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc generation			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations Stoma site abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 353 (0.28%) 0 / 1 0 / 0	 0 / 349 (0.00%) 0 / 0 0 / 0	 0 / 172 (0.00%) 0 / 0 0 / 0
Urosepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 353 (0.28%) 1 / 1 0 / 0	 0 / 349 (0.00%) 0 / 0 0 / 0	 0 / 172 (0.00%) 0 / 0 0 / 0
Abscess limb subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 353 (0.00%) 0 / 0 0 / 0	 0 / 349 (0.00%) 0 / 0 0 / 0	 1 / 172 (0.58%) 0 / 2 0 / 0
Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 353 (0.00%) 0 / 0 0 / 0	 0 / 349 (0.00%) 0 / 0 0 / 0	 1 / 172 (0.58%) 0 / 1 0 / 0
Pyelonephritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 353 (0.00%) 0 / 0 0 / 0	 0 / 349 (0.00%) 0 / 0 0 / 0	 1 / 172 (0.58%) 0 / 1 0 / 0

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

Non-serious adverse events	PegIFN Lambda-1a+Ribavirin+Placebo	PegIFNλ-1a+Ribavirin+Daclatasvir	PegIFN alfa-2a+Ribavirin+Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	295 / 353 (83.57%)	279 / 349 (79.94%)	163 / 172 (94.77%)
Investigations			
Alanine Aminotransferase increased			
subjects affected / exposed	32 / 353 (9.07%)	24 / 349 (6.88%)	7 / 172 (4.07%)
occurrences (all)	35	28	7
Aspartate Aminotransferase increased			
subjects affected / exposed	27 / 353 (7.65%)	19 / 349 (5.44%)	6 / 172 (3.49%)
occurrences (all)	28	22	6

Weight decreased subjects affected / exposed occurrences (all)	9 / 353 (2.55%) 9	4 / 349 (1.15%) 4	12 / 172 (6.98%) 12
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	64 / 353 (18.13%) 87	47 / 349 (13.47%) 56	44 / 172 (25.58%) 57
Dizziness subjects affected / exposed occurrences (all)	34 / 353 (9.63%) 39	46 / 349 (13.18%) 51	38 / 172 (22.09%) 43
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	110 / 353 (31.16%) 122	87 / 349 (24.93%) 100	74 / 172 (43.02%) 79
Asthenia subjects affected / exposed occurrences (all)	43 / 353 (12.18%) 48	35 / 349 (10.03%) 35	23 / 172 (13.37%) 25
Influenza like illness subjects affected / exposed occurrences (all)	26 / 353 (7.37%) 26	18 / 349 (5.16%) 18	36 / 172 (20.93%) 39
Chills subjects affected / exposed occurrences (all)	26 / 353 (7.37%) 31	16 / 349 (4.58%) 19	25 / 172 (14.53%) 27
Pyrexia subjects affected / exposed occurrences (all)	20 / 353 (5.67%) 24	23 / 349 (6.59%) 27	41 / 172 (23.84%) 48
Injection site erythema subjects affected / exposed occurrences (all)	13 / 353 (3.68%) 14	17 / 349 (4.87%) 18	10 / 172 (5.81%) 11
Malaise subjects affected / exposed occurrences (all)	11 / 353 (3.12%) 11	9 / 349 (2.58%) 9	12 / 172 (6.98%) 14
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	14 / 353 (3.97%) 15	14 / 349 (4.01%) 14	35 / 172 (20.35%) 37

Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 353 (0.57%) 3	2 / 349 (0.57%) 2	21 / 172 (12.21%) 24
Neutropenia subjects affected / exposed occurrences (all)	1 / 353 (0.28%) 1	1 / 349 (0.29%) 1	53 / 172 (30.81%) 74
Leukopenia subjects affected / exposed occurrences (all)	1 / 353 (0.28%) 1	1 / 349 (0.29%) 1	16 / 172 (9.30%) 18
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	88 / 353 (24.93%) 119	71 / 349 (20.34%) 88	51 / 172 (29.65%) 52
Diarrhoea subjects affected / exposed occurrences (all)	44 / 353 (12.46%) 47	25 / 349 (7.16%) 33	18 / 172 (10.47%) 20
Vomiting subjects affected / exposed occurrences (all)	36 / 353 (10.20%) 45	26 / 349 (7.45%) 33	17 / 172 (9.88%) 24
Dyspepsia subjects affected / exposed occurrences (all)	21 / 353 (5.95%) 24	19 / 349 (5.44%) 19	11 / 172 (6.40%) 12
Abdominal pain upper subjects affected / exposed occurrences (all)	21 / 353 (5.95%) 27	16 / 349 (4.58%) 22	13 / 172 (7.56%) 15
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	32 / 353 (9.07%) 36	15 / 349 (4.30%) 16	24 / 172 (13.95%) 26
Cough subjects affected / exposed occurrences (all)	15 / 353 (4.25%) 17	9 / 349 (2.58%) 9	10 / 172 (5.81%) 12
Oropharyngeal pain subjects affected / exposed occurrences (all)	12 / 353 (3.40%) 12	9 / 349 (2.58%) 9	9 / 172 (5.23%) 9
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	109 / 353 (30.88%)	82 / 349 (23.50%)	50 / 172 (29.07%)
occurrences (all)	120	92	58
Rash			
subjects affected / exposed	46 / 353 (13.03%)	45 / 349 (12.89%)	33 / 172 (19.19%)
occurrences (all)	53	54	34
Dry skin			
subjects affected / exposed	44 / 353 (12.46%)	37 / 349 (10.60%)	27 / 172 (15.70%)
occurrences (all)	47	41	28
Alopecia			
subjects affected / exposed	12 / 353 (3.40%)	4 / 349 (1.15%)	30 / 172 (17.44%)
occurrences (all)	13	4	30
Psychiatric disorders			
Insomnia			
subjects affected / exposed	110 / 353 (31.16%)	74 / 349 (21.20%)	50 / 172 (29.07%)
occurrences (all)	121	79	54
Irritability			
subjects affected / exposed	41 / 353 (11.61%)	30 / 349 (8.60%)	20 / 172 (11.63%)
occurrences (all)	46	30	20
Depression			
subjects affected / exposed	29 / 353 (8.22%)	16 / 349 (4.58%)	14 / 172 (8.14%)
occurrences (all)	29	16	14
Sleep Disorder			
subjects affected / exposed	23 / 353 (6.52%)	18 / 349 (5.16%)	10 / 172 (5.81%)
occurrences (all)	25	21	11
Anxiety			
subjects affected / exposed	20 / 353 (5.67%)	17 / 349 (4.87%)	14 / 172 (8.14%)
occurrences (all)	21	17	14
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	49 / 353 (13.88%)	45 / 349 (12.89%)	60 / 172 (34.88%)
occurrences (all)	55	57	69
Arthralgia			
subjects affected / exposed	48 / 353 (13.60%)	44 / 349 (12.61%)	49 / 172 (28.49%)
occurrences (all)	56	51	54
Back pain			

subjects affected / exposed	20 / 353 (5.67%)	11 / 349 (3.15%)	15 / 172 (8.72%)
occurrences (all)	21	11	16
Muscle spasms			
subjects affected / exposed	11 / 353 (3.12%)	18 / 349 (5.16%)	4 / 172 (2.33%)
occurrences (all)	14	19	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 353 (3.68%)	9 / 349 (2.58%)	9 / 172 (5.23%)
occurrences (all)	16	9	12
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	68 / 353 (19.26%)	51 / 349 (14.61%)	55 / 172 (31.98%)
occurrences (all)	78	64	57

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2012	Incorporated recommendations from the food and drug administration (daclatasvir dosing and prohibited medications clarified), added clarification text for dosing, inclusion/exclusion criteria and study procedures.
19 March 2013	Incorporated cardiac safety monitoring laboratory tests, updated and clarified text for dose modifications and study procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported