

**Clinical trial results:**

A phase III, randomised, double-blind and placebo-controlled study of once daily BI 201335 120 mg for 12 or 24 weeks or BI 201335 240 mg for 12 weeks in combination with pegylated interferon- and ribavirin in treatment-naïve patients with genotype 1 chronic hepatitis C infection.

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2010-021716-42
Trial protocol	PT BE GB DE ES AT
Global end of trial date	12 March 2014

Results information

Result version number	v2 (current)
This version publication date	02 July 2016
First version publication date	26 July 2015
Version creation reason	• Correction of full data set Data correction due to system error in EudraCT- Results

Trial information**Trial identification**

Sponsor protocol code	1220.30
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01343888
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173 , Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 243 0127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 243 0127 , clintriage.rdg@boehringer-ingelheim.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	15 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 January 2014
Global end of trial reached?	Yes
Global end of trial date	12 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial is to show superior efficacy of treatment with BI 201335 combined with PegIFN/RBV as compared to PegIFN/RBV alone (SOC) in patients with genotype 1 (GT-1) chronic hepatitis C infection

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	11 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 41
Country: Number of subjects enrolled	Belgium: 43
Country: Number of subjects enrolled	France: 92
Country: Number of subjects enrolled	Germany: 94
Country: Number of subjects enrolled	Japan: 151
Country: Number of subjects enrolled	Portugal: 51
Country: Number of subjects enrolled	Romania: 61
Country: Number of subjects enrolled	Russian Federation: 77
Country: Number of subjects enrolled	Spain: 62
Country: Number of subjects enrolled	Switzerland: 37
Country: Number of subjects enrolled	United Kingdom: 69
Worldwide total number of subjects	778
EEA total number of subjects	513

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)	719
From 65 to 84 years	59
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subject) met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Faldaprevir 120mg and PegIFN/RBV

Arm description:

Faldaprevir (BI 201335) 120 mg once daily (oral) plus Pegylated Interferon-alpha (PegIFN)/ Ribavirin (RBV) (subcutaneous injection/oral) for 12 or 24 weeks, depending on achievement of early treatment success (ETS). Patients with ETS received this treatment for 12 weeks and subsequently PegIFN/RBV alone up to Week 24; patients without ETS received this treatment for 24 weeks and subsequently PegIFN/RBV alone up to Week 48. Two subject screened/randomised to Faldaprevir 120mg and PegIFN/RBV was not treated. Although actual number of subjects started is 261, 259 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Arm type	Experimental
Investigational medicinal product name	Faldaprevir 120mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Faldaprevir 120mg administered orally in a form of soft gelatine capsule once daily

Investigational medicinal product name	Pegylated Interferon-alpha
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

180 µg Pegylated Interferon-alpha in 0.5 mL solution administered via subcutaneous injection once weekly.

For Japan: 180 µg Pegylated Interferon-alpha in 1 mL solution administered via subcutaneous injection once weekly.

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

Dosage and administration details:

1000 mg (<75 kg body weight) or 1200 mg (≥75 kg body weight) of Ribavirin administered orally in 2 divided doses in a form of a tablet.

For Japan: 600 mg (≤60 kg body weight), 800 mg (>60 kg and ≤80 kg body weight), or 1000 mg (>80 kg body weight) of Ribavirin administered orally in 2 divided doses in a form of a tablet.

Arm title	Faldaprevir 240mg and PegIFN/RBV
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Arm description:

Faldaprevir 240 mg once daily (oral) plus PegIFN/RBV (subcutaneous injection/oral) for 12 weeks, followed by PegIFN/RBV up to Week 24. Patients with ETS stopped all study medication at Week 24; patients without ETS subsequently received PegIFN/RBV alone up to Week 48. One subject screened/randomised to Faldaprevir 240mg and PegIFN/RBV was not treated. Although actual number of subjects started is 262, 261 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Arm type	Experimental
Investigational medicinal product name	Faldaprevir 240mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Faldaprevir 240mg administered orally in a form of soft gelatine capsule once daily

Investigational medicinal product name	Pegylated Interferon-alpha
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

180 µg Pegylated Interferon-alpha in 0.5 mL solution administered via subcutaneous injection once weekly.

For Japan: 180 µg Pegylated Interferon-alpha in 1 mL solution administered via subcutaneous injection once weekly.

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

Dosage and administration details:

1000 mg (<75 kg body weight) or 1200 mg (≥75 kg body weight) of Ribavirin administered orally in 2 divided doses in a form of a tablet.

For Japan: 600 mg (≤60 kg body weight), 800 mg (>60 kg and ≤80 kg body weight), or 1000 mg (>80 kg body weight) of Ribavirin administered orally in 2 divided doses in a form of a tablet.

Arm title	Placebo and PegIFN/RBV
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Arm description:

Placebo (oral) once daily plus PegIFN/RBV (subcutaneous injection/oral) for 24 weeks, followed by PegIFN/RBV alone up to Week 48. One subject screened/randomised to Placebo and PegIFN/RBV was not treated. Although actual number of subjects started is 133, 132 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Placebo matching Faldaprevir soft gelatine capsule administered orally, once daily.

Investigational medicinal product name	Pegylated Interferon-alpha
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

180 µg Pegylated Interferon-alpha in 0.5 mL solution administered via subcutaneous injection once weekly.

For Japan: 180 µg Pegylated Interferon-alpha in 1 mL solution administered via subcutaneous injection once weekly.

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

Dosage and administration details:

1000 mg (<75 kg body weight) or 1200 mg (≥75 kg body weight) of Ribavirin administered orally in 2 divided doses in a form of a tablet.

For Japan: 600 mg (≤60 kg body weight), 800 mg (>60 kg and ≤80 kg body weight), or 1000 mg (>80 kg body weight) of Ribavirin administered orally in 2 divided doses in a form of a tablet.

Number of subjects in period 1^[1]	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV
Started	259	261	132
Completed	234	222	110
Not completed	25	39	22
Consent withdrawn by subject	4	4	2
Adverse event, non-fatal	12	22	5
Lost to follow-up	-	2	1
Lack of efficacy	9	9	13
Protocol deviation	-	2	-
Reasons other than stated above	-	-	1

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: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups

Reporting group title	Faldaprevir 120mg and PegIFN/RBV
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Reporting group description:

Faldaprevir (BI 201335) 120 mg once daily (oral) plus Pegylated Interferon-alpha (PegIFN)/ Ribavirin (RBV) (subcutaneous injection/oral) for 12 or 24 weeks, depending on achievement of early treatment success (ETS). Patients with ETS received this treatment for 12 weeks and subsequently PegIFN/RBV alone up to Week 24; patients without ETS received this treatment for 24 weeks and subsequently PegIFN/RBV alone up to Week 48. Two subject screened/randomised to Faldaprevir 120mg and PegIFN/RBV was not treated. Although actual number of subjects started is 261, 259 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Reporting group title	Faldaprevir 240mg and PegIFN/RBV
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Reporting group description:

Faldaprevir 240 mg once daily (oral) plus PegIFN/RBV (subcutaneous injection/oral) for 12 weeks, followed by PegIFN/RBV up to Week 24. Patients with ETS stopped all study medication at Week 24; patients without ETS subsequently received PegIFN/RBV alone up to Week 48. One subject screened/randomised to Faldaprevir 240mg and PegIFN/RBV was not treated. Although actual number of subjects started is 262, 261 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Reporting group title	Placebo and PegIFN/RBV
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Reporting group description:

Placebo (oral) once daily plus PegIFN/RBV (subcutaneous injection/oral) for 24 weeks, followed by PegIFN/RBV alone up to Week 48. One subject screened/randomised to Placebo and PegIFN/RBV was not treated. Although actual number of subjects started is 133, 132 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Reporting group values	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV
Number of subjects	259	261	132
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	47.9 ± 11.44	48.3 ± 11.89	46.6 ± 12.53
Gender, Male/Female Units: participants			
Female	138	115	57
Male	121	146	75

Reporting group values	Total		
Number of subjects	652		
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	-		
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Gender, Male/Female			
Units: participants			
Female	310		
Male	342		

End points

End points reporting groups

Reporting group title	Faldaprevir 120mg and PegIFN/RBV
Reporting group description: Faldaprevir (BI 201335) 120 mg once daily (oral) plus Pegylated Interferon-alpha (PegIFN)/ Ribavirin (RBV) (subcutaneous injection/oral) for 12 or 24 weeks, depending on achievement of early treatment success (ETS). Patients with ETS received this treatment for 12 weeks and subsequently PegIFN/RBV alone up to Week 24; patients without ETS received this treatment for 24 weeks and subsequently PegIFN/RBV alone up to Week 48. Two subject screened/randomised to Faldaprevir 120mg and PegIFN/RBV was not treated. Although actual number of subjects started is 261, 259 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.	
Reporting group title	Faldaprevir 240mg and PegIFN/RBV
Reporting group description: Faldaprevir 240 mg once daily (oral) plus PegIFN/RBV (subcutaneous injection/oral) for 12 weeks, followed by PegIFN/RBV up to Week 24. Patients with ETS stopped all study medication at Week 24; patients without ETS subsequently received PegIFN/RBV alone up to Week 48. One subject screened/randomised to Faldaprevir 240mg and PegIFN/RBV was not treated. Although actual number of subjects started is 262, 261 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.	
Reporting group title	Placebo and PegIFN/RBV
Reporting group description: Placebo (oral) once daily plus PegIFN/RBV (subcutaneous injection/oral) for 24 weeks, followed by PegIFN/RBV alone up to Week 48. One subject screened/randomised to Placebo and PegIFN/RBV was not treated. Although actual number of subjects started is 133, 132 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.	

Primary: Sustained Virological Response 12 weeks post-treatment (SVR12)

End point title	Sustained Virological Response 12 weeks post-treatment (SVR12)
End point description: Sustained Virological Response 12 weeks post-treatment (SVR12), defined as plasma Hepatitis C virus (HCV) Ribonucleic acid (RNA) level < 25 IU/mL (undetected) 12 weeks after the originally planned treatment duration. Full analysis set (FAS) included all randomised patients who were dispensed study medication and were documented to have taken at least one dose of study medication.	
End point type	Primary
End point timeframe: 12 weeks post treatment, up to 60 weeks	

End point values	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259 ^[1]	261 ^[2]	132 ^[3]	
Units: percentage of participants				
number (confidence interval 95%)	79.5 (74.6 to 84.4)	80.5 (75.6 to 85.3)	52.3 (43.8 to 60.8)	

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

The Cochran-Mantel-Haenszel method stratified by genotype subtype (1a, 1b, and non-1a/1b) and race (Black, Asian, other) was used, where Faldaprevir 120 mg was compared to placebo. The proportions of responders were calculated per group and 95% confidence intervals (CI) reported, adjusted for stratification factors.

Comparison groups	Faldaprevir 120mg and PegIFN/RBV v Placebo and PegIFN/RBV
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Koch's method
Point estimate	27.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.9
upper limit	37

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

The Cochran-Mantel-Haenszel method stratified by genotype subtype (1a, 1b, and non-1a/1b) and race (Black, Asian, other) was used, where Faldaprevir 240 mg was compared to placebo. The proportions of responders were calculated per group and 95% confidence intervals (CI) reported, adjusted for stratification factors.

Comparison groups	Faldaprevir 240mg and PegIFN/RBV v Placebo and PegIFN/RBV
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Koch's method
Point estimate	28.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	19
upper limit	38.2

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: The Cochran-Mantel-Haenszel method stratified by genotype subtype (1a, 1b, and non-1a/1b) and race (Black, Asian, other) was used, where Faldaprevir 120 mg was compared to Faldaprevir 240 mg The proportions of responders were calculated per group and 95% confidence intervals (CI) reported, adjusted for stratification factors.	
Comparison groups	Faldaprevir 120mg and PegIFN/RBV v Faldaprevir 240mg and PegIFN/RBV
Number of subjects included in analysis	520
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cochran-Mantel-Haenszel
Parameter estimate	Koch's methond
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	5.8

Secondary: Sustained Virological Response 24 weeks post-treatment (SVR24)

End point title	Sustained Virological Response 24 weeks post-treatment (SVR24)
End point description: Sustained Virological Response 24 weeks post-treatment (SVR24), defined as plasma HCV RNA level < 25 IU/mL (undetected) 24 weeks after the originally planned treatment duration.	
End point type	Secondary
End point timeframe: 24 weeks post treatment, up to 72 weeks	

End point values	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259 ^[4]	261 ^[5]	132 ^[6]	
Units: percentage of participants				
number (confidence interval 95%)	79.2 (74.2 to 84.1)	79.7 (74.8 to 84.6)	52.3 (43.8 to 60.8)	

Notes:

[4] - FAS

[5] - FAS

[6] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: The Cochran-Mantel-Haenszel method stratified by genotype subtype (1a, 1b, and non-1a/1b) and race (Black, Asian, other) was used, where Faldaprevir 120 mg was compared to placebo. The proportions of responders were calculated per group and 95% confidence intervals (CI) reported,	

adjusted for stratification factors.

Comparison groups	Faldaprevir 120mg and PegIFN/RBV v Placebo and PegIFN/RBV
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Koch's method
Point estimate	27.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.5
upper limit	36.7

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

The Cochran-Mantel-Haenszel method stratified by genotype subtype (1a, 1b, and non-1a/1b) and race (Black, Asian, other) was used, where Faldaprevir 240 mg was compared to placebo. The proportions of responders were calculated per group and 95% confidence intervals (CI) reported, adjusted for stratification factors.

Comparison groups	Faldaprevir 240mg and PegIFN/RBV v Placebo and PegIFN/RBV
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Koch's method
Point estimate	27.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.2
upper limit	37.4

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

The Cochran-Mantel-Haenszel method stratified by genotype subtype (1a, 1b, and non-1a/1b) and race (Black, Asian, other) was used, where Faldaprevir 120 mg was compared to Faldaprevir 240 mg. The proportions of responders were calculated per group and 95% confidence intervals (CI) reported, adjusted for stratification factors.

Comparison groups	Faldaprevir 120mg and PegIFN/RBV v Faldaprevir 240mg and PegIFN/RBV
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Number of subjects included in analysis	520
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Koch's method
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	6.3

Secondary: Early treatment success (ETS)

End point title	Early treatment success (ETS)
End point description:	Early treatment success (ETS), defined as a plasma HCV RNA level <25 IU/mL (detected or undetected) at week 4 and HCV RNA <25 IU/mL (undetected) at week 8.
End point type	Secondary
End point timeframe:	week 4 and week 8

End point values	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259 ^[7]	261 ^[8]	132 ^[9]	
Units: percentage of participants				
number (not applicable)	87.3	89.3	22	

Notes:

[7] - FAS

[8] - FAS

[9] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Alanine Aminotransferase (ALT) Normalisation: ALT in Normal Range at End of Treatment (EoT) When SVR12=YES

End point title	Alanine Aminotransferase (ALT) Normalisation: ALT in Normal Range at End of Treatment (EoT) When SVR12=YES
End point description:	This will be presented as the number of patients. SVR12 means Sustained virological response 12 weeks post-treatment. BL = Baseline
End point type	Secondary
End point timeframe:	12 weeks post treatment, up to 60 weeks

End point values	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259 ^[10]	261 ^[11]	132 ^[12]	
Units: participants				
SVR12 = Yes	206	210	69	
SVR12 = Yes, BL normal to EOT normal	66	68	27	
SVR12 = Yes, BL elevated to EOT normal	97	115	31	
SVR12 = Yes, No ALT data available at EoT	0	0	0	

Notes:

[10] - FAS

[11] - FAS

[12] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Alanine Aminotransferase (ALT) Normalisation: ALT in Normal Range at End of Treatment (EoT) When SVR12= NO

End point title	Alanine Aminotransferase (ALT) Normalisation: ALT in Normal Range at End of Treatment (EoT) When SVR12= NO
End point description:	
This will be presented as the number of patients. SVR12 means Sustained virological response 12 weeks post-treatment. BL = Baseline	
End point type	Secondary
End point timeframe:	
12 weeks post treatment, up to 60 weeks	

End point values	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259 ^[13]	261 ^[14]	132 ^[15]	
Units: participants				
SVR12 = No	53	51	63	
SVR12 = No, BL normal to EOT normal	15	10	15	
SVR12 = No, BL elevated to EOT normal	16	22	20	
SVR12 = No, No ALT data available at EoT	0	0	1	

Notes:

[13] - FAS

[14] - FAS

[15] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Alanine Aminotransferase (ALT) Normalisation: ALT in Normal Range at Sustained Virological Response 12 Weeks Post-treatment (SVR12) Visit, When SVR12=YES

End point title	Alanine Aminotransferase (ALT) Normalisation: ALT in Normal Range at Sustained Virological Response 12 Weeks Post-treatment (SVR12) Visit, When SVR12=YES
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End point description:

This will be presented as the number of patients. BL = Baseline

End point type	Secondary
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End point timeframe:

12 weeks post treatment, up to 60 weeks

End point values	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259 ^[16]	261 ^[17]	132 ^[18]	
Units: participants				
SVR12 = Yes	206	210	69	
SVR12 = Yes, BL normal to SVR12 normal	72	73	27	
SVR12 = Yes, BL elevated to SVR12 normal	125	126	39	
SVR12 = Yes, No ALT data available post treatment	4	5	1	

Notes:

[16] - FAS

[17] - FAS

[18] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Alanine Aminotransferase (ALT) Normalisation: ALT in Normal Range at Sustained Virological Response 12 Weeks Post-treatment (SVR12) Visit, When SVR12=NO

End point title	Alanine Aminotransferase (ALT) Normalisation: ALT in Normal Range at Sustained Virological Response 12 Weeks Post-treatment (SVR12) Visit, When SVR12=NO
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End point description:

This will be presented as the number of patients. BL = Baseline

End point type	Secondary
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End point timeframe:

12 weeks post treatment, up to 60 weeks

End point values	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259 ^[19]	261 ^[20]	132 ^[21]	
Units: participants				
SVR12 = No	53	51	63	
SVR12 = No, BL normal to SVR12 normal	9	5	5	
SVR12 = No, BL elevated to SVR12 normal	6	6	1	
SVR12 = No, No ALT data available post treatment	8	14	45	

Notes:

[19] - FAS

[20] - FAS

[21] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Aspartate Aminotransferase (AST) Normalisation: AST in Normal Range at End of Treatment (EoT) When SVR12=YES

End point title	Aspartate Aminotransferase (AST) Normalisation: AST in Normal Range at End of Treatment (EoT) When SVR12=YES
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End point description:

This will be presented as the number of patients. SVR12 means Sustained virological response 12 weeks post-treatment. BL = Baseline

End point type	Secondary
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End point timeframe:

12 weeks post treatment, up to 60 weeks

End point values	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259 ^[22]	261 ^[23]	132 ^[24]	
Units: participants				
SVR12 = Yes	206	210	69	
SVR12 = Yes, BL normal to EOT normal	95	99	34	
SVR12 = Yes, BL elevated to EOT normal	74	76	25	
SVR12 = Yes, No AST data available at EoT	0	0	0	

Notes:

[22] - FAS

[23] - FAS

[24] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Aspartate Aminotransferase (AST) Normalisation: AST in Normal Range at End of Treatment (EoT) When SVR12=NO

End point title	Aspartate Aminotransferase (AST) Normalisation: AST in Normal Range at End of Treatment (EoT) When SVR12=NO
End point description: This will be presented as the number of patients. SVR12 means Sustained virological response 12 weeks post-treatment. BL = Baseline	
End point type	Secondary
End point timeframe: 12 weeks post treatment, up to 60 weeks	

End point values	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259 ^[25]	261 ^[26]	132 ^[27]	
Units: participants				
SVR12 = No	53	51	63	
SVR12 = No, BL normal to EOT normal	17	16	21	
SVR12 = No, BL elevated to EOT normal	14	16	13	
SVR12 = No, No AST data available at EoT	0	0	1	

Notes:

[25] - FAS

[26] - FAS

[27] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Aspartate Aminotransferase (AST) Normalisation: AST in Normal Range at Sustained Virological Response 12 Weeks Post-treatment (SVR12) Visit, When SVR12=YES

End point title	Aspartate Aminotransferase (AST) Normalisation: AST in Normal Range at Sustained Virological Response 12 Weeks Post-treatment (SVR12) Visit, When SVR12=YES
End point description: This will be presented as the number of patients. BL = Baseline	
End point type	Secondary
End point timeframe: 12 weeks post treatment, up to 60 weeks	

End point values	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259 ^[28]	261 ^[29]	132 ^[30]	
Units: participants				
SVR12 = Yes	206	210	69	
SVR12 = Yes, BL normal to SVR12 normal	102	109	39	
SVR12 = Yes, BL elevated to SVR12 normal	90	88	27	
SVR12 = Yes, No AST data available post-treatment	5	5	1	

Notes:

[28] - FAS

[29] - FAS

[30] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Aspartate Aminotransferase (AST) Normalisation: AST in Normal Range at Sustained Virological Response 12 Weeks Post-treatment (SVR12) Visit, When SVR12=NO

End point title	Aspartate Aminotransferase (AST) Normalisation: AST in Normal Range at Sustained Virological Response 12 Weeks Post-treatment (SVR12) Visit, When SVR12=NO
End point description:	
This will be presented as the number of patients. BL = Baseline	
End point type	Secondary
End point timeframe:	
12 weeks post treatment, up to 60 weeks	

End point values	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259 ^[31]	261 ^[32]	132 ^[33]	
Units: participants				
SVR12 = No	53	51	63	
SVR12 = No, BL normal to SVR12 normal	10	10	5	
SVR12 = No, BL elevated to SVR12 normal	10	5	1	
SVR12 = No, No AST data available post-treatment	8	14	45	

Notes:

[31] - FAS

[32] - FAS

[33] - FAS

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The double-blind treatment phase of the trial was from the randomization visit when the patient received the first dose of study drug to 30 days after the last dose of blinded trial medication up to 206 (176 +30) days.

Adverse event reporting additional description:

AEs that pre-existed prior to randomization but worsened during treatment were also considered treatment emergent. All patients who received at least 1 dose of study drug after randomization [safety set (SAF)] were included in the presentation of AE data.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Faldaprevir 120mg and PegIFN/RBV
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Reporting group description:

Faldaprevir 120 mg once daily (oral) plus Pegylated Interferon-alpha (PegIFN)/ Ribavirin (RBV) (subcutaneous injection/oral) for 12 or 24 weeks, depending on achievement of early treatment success (ETS). Patients with ETS received this treatment for 12 weeks and subsequently PegIFN/RBV alone up to Week 24; patients without ETS received this treatment for 24 weeks and subsequently PegIFN/RBV alone up to Week 48. Two subject screened/randomised to Faldaprevir 120mg and PegIFN/RBV was not treated. Although actual number of subjects started is 261, 259 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Reporting group title	Faldaprevir 240mg and PegIFN/RBV
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Reporting group description:

Faldaprevir 240 mg once daily (oral) plus PegIFN/RBV (subcutaneous injection/oral) for 12 weeks, followed by PegIFN/RBV up to Week 24. Patients with ETS stopped all study medication at Week 24; patients without ETS subsequently received PegIFN/RBV alone up to Week 48. One subject screened/randomised to Faldaprevir 240mg and PegIFN/RBV was not treated. Although actual number of subjects started is 262, 261 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Reporting group title	Placebo and PegIFN/RBV
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Reporting group description:

Placebo (oral) once daily plus PegIFN/RBV (subcutaneous injection/oral) for 24 weeks, followed by PegIFN/RBV alone up to Week 48. One subject screened/randomised to Placebo and PegIFN/RBV was not treated. Although actual number of subjects started is 133, 132 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Serious adverse events	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 259 (6.56%)	17 / 261 (6.51%)	8 / 132 (6.06%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			

subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Chest pain			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Pyrexia			
subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Sarcoidosis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Respiratory, thoracic and mediastinal disorders			
Epistaxis			

subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Dyspnoea exertional			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Injury, poisoning and procedural complications			
Gun shot wound			
subjects affected / exposed	0 / 259 (0.00%)	0 / 261 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Subdural haematoma			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Myocardial infarction			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Cubital tunnel syndrome			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Dizziness			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Headache			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Sciatica			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 259 (0.39%)	2 / 261 (0.77%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Leukopenia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Histiocytosis haematophagic			

subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Pancytopenia			
subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Thrombocytopenia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Eye disorders			
Optic ischaemic neuropathy			
subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Retinopathy			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 259 (0.00%)	0 / 261 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Pancreatitis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Vomiting			

subjects affected / exposed	0 / 259 (0.00%)	2 / 261 (0.77%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 259 (0.00%)	0 / 261 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic lesion			
subjects affected / exposed	0 / 259 (0.00%)	0 / 261 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 259 (0.00%)	0 / 261 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug eruption			
subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Psoriasis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Rash			
subjects affected / exposed	1 / 259 (0.39%)	1 / 261 (0.38%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 259 (0.00%)	0 / 261 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Hypoparathyroidism			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Polymyositis			
subjects affected / exposed	0 / 259 (0.00%)	0 / 261 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Urinary tract infection			
subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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
Pneumonia			
subjects affected / exposed	0 / 259 (0.00%)	1 / 261 (0.38%)	0 / 132 (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
Diverticulitis			
subjects affected / exposed	0 / 259 (0.00%)	0 / 261 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	1 / 259 (0.39%)	0 / 261 (0.00%)	0 / 132 (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

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

Non-serious adverse events	Faldaprevir 120mg and PegIFN/RBV	Faldaprevir 240mg and PegIFN/RBV	Placebo and PegIFN/RBV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	246 / 259 (94.98%)	250 / 261 (95.79%)	120 / 132 (90.91%)
Investigations			
Weight decreased			
subjects affected / exposed	13 / 259 (5.02%)	15 / 261 (5.75%)	10 / 132 (7.58%)
occurrences (all)	13	15	10
Haemoglobin decreased			
subjects affected / exposed	15 / 259 (5.79%)	5 / 261 (1.92%)	7 / 132 (5.30%)
occurrences (all)	16	5	8
Nervous system disorders			
Dizziness			
subjects affected / exposed	17 / 259 (6.56%)	21 / 261 (8.05%)	13 / 132 (9.85%)
occurrences (all)	20	22	14
Dysgeusia			
subjects affected / exposed	13 / 259 (5.02%)	10 / 261 (3.83%)	5 / 132 (3.79%)
occurrences (all)	13	10	5
Headache			
subjects affected / exposed	76 / 259 (29.34%)	70 / 261 (26.82%)	40 / 132 (30.30%)
occurrences (all)	102	81	54
Disturbance in attention			
subjects affected / exposed	10 / 259 (3.86%)	8 / 261 (3.07%)	7 / 132 (5.30%)
occurrences (all)	10	8	7
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	32 / 259 (12.36%)	25 / 261 (9.58%)	18 / 132 (13.64%)
occurrences (all)	45	34	21
Anaemia			
subjects affected / exposed	46 / 259 (17.76%)	43 / 261 (16.48%)	23 / 132 (17.42%)
occurrences (all)	49	45	30

General disorders and administration site conditions			
Malaise			
subjects affected / exposed	20 / 259 (7.72%)	16 / 261 (6.13%)	12 / 132 (9.09%)
occurrences (all)	20	18	12
Irritability			
subjects affected / exposed	19 / 259 (7.34%)	18 / 261 (6.90%)	9 / 132 (6.82%)
occurrences (all)	19	18	9
Influenza like illness			
subjects affected / exposed	40 / 259 (15.44%)	52 / 261 (19.92%)	21 / 132 (15.91%)
occurrences (all)	40	52	21
Pyrexia			
subjects affected / exposed	57 / 259 (22.01%)	53 / 261 (20.31%)	32 / 132 (24.24%)
occurrences (all)	71	65	44
Asthenia			
subjects affected / exposed	53 / 259 (20.46%)	43 / 261 (16.48%)	27 / 132 (20.45%)
occurrences (all)	56	44	28
Fatigue			
subjects affected / exposed	66 / 259 (25.48%)	77 / 261 (29.50%)	35 / 132 (26.52%)
occurrences (all)	71	77	37
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 259 (4.25%)	15 / 261 (5.75%)	10 / 132 (7.58%)
occurrences (all)	13	17	10
Abdominal pain upper			
subjects affected / exposed	18 / 259 (6.95%)	24 / 261 (9.20%)	14 / 132 (10.61%)
occurrences (all)	20	26	15
Constipation			
subjects affected / exposed	11 / 259 (4.25%)	16 / 261 (6.13%)	5 / 132 (3.79%)
occurrences (all)	11	17	5
Stomatitis			
subjects affected / exposed	12 / 259 (4.63%)	11 / 261 (4.21%)	7 / 132 (5.30%)
occurrences (all)	13	13	13
Diarrhoea			
subjects affected / exposed	53 / 259 (20.46%)	68 / 261 (26.05%)	17 / 132 (12.88%)
occurrences (all)	60	78	18
Dry mouth			

subjects affected / exposed occurrences (all)	8 / 259 (3.09%) 8	6 / 261 (2.30%) 6	9 / 132 (6.82%) 9
Dyspepsia subjects affected / exposed occurrences (all)	12 / 259 (4.63%) 12	14 / 261 (5.36%) 14	9 / 132 (6.82%) 10
Nausea subjects affected / exposed occurrences (all)	73 / 259 (28.19%) 79	95 / 261 (36.40%) 100	19 / 132 (14.39%) 19
Vomiting subjects affected / exposed occurrences (all)	28 / 259 (10.81%) 34	52 / 261 (19.92%) 66	6 / 132 (4.55%) 6
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	4 / 259 (1.54%) 4	14 / 261 (5.36%) 14	1 / 132 (0.76%) 1
Jaundice subjects affected / exposed occurrences (all)	17 / 259 (6.56%) 17	48 / 261 (18.39%) 49	1 / 132 (0.76%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	30 / 259 (11.58%) 31	28 / 261 (10.73%) 28	20 / 132 (15.15%) 22
Dyspnoea subjects affected / exposed occurrences (all)	17 / 259 (6.56%) 17	19 / 261 (7.28%) 20	16 / 132 (12.12%) 16
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	42 / 259 (16.22%) 42	47 / 261 (18.01%) 47	15 / 132 (11.36%) 15
Dry skin subjects affected / exposed occurrences (all)	35 / 259 (13.51%) 35	45 / 261 (17.24%) 47	17 / 132 (12.88%) 17
Pruritus subjects affected / exposed occurrences (all)	82 / 259 (31.66%) 87	78 / 261 (29.89%) 84	41 / 132 (31.06%) 49
Erythema			

subjects affected / exposed occurrences (all)	9 / 259 (3.47%) 10	18 / 261 (6.90%) 23	6 / 132 (4.55%) 7
Rash subjects affected / exposed occurrences (all)	69 / 259 (26.64%) 80	70 / 261 (26.82%) 83	25 / 132 (18.94%) 31
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	20 / 259 (7.72%) 20	12 / 261 (4.60%) 12	8 / 132 (6.06%) 8
Insomnia subjects affected / exposed occurrences (all)	38 / 259 (14.67%) 38	32 / 261 (12.26%) 33	22 / 132 (16.67%) 24
Sleep disorder subjects affected / exposed occurrences (all)	12 / 259 (4.63%) 12	14 / 261 (5.36%) 15	5 / 132 (3.79%) 5
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	19 / 259 (7.34%) 24	20 / 261 (7.66%) 22	14 / 132 (10.61%) 15
Back pain subjects affected / exposed occurrences (all)	14 / 259 (5.41%) 17	8 / 261 (3.07%) 8	10 / 132 (7.58%) 10
Myalgia subjects affected / exposed occurrences (all)	22 / 259 (8.49%) 22	19 / 261 (7.28%) 22	20 / 132 (15.15%) 22
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	14 / 259 (5.41%) 18	16 / 261 (6.13%) 19	10 / 132 (7.58%) 11
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	35 / 259 (13.51%) 36	52 / 261 (19.92%) 54	22 / 132 (16.67%) 24

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2011	<ol style="list-style-type: none">1. Implementation of a grading system for AEs to harmonize AE reporting across HCV projects2. Change of procedures and tests at various visits to improve data collection and procedural feasibility at each visit, e.g., HCV RNA test and virology sample were added to FU1 visit, additional laboratory tests were moved from EoT to extended FU. In addition, the time window for the screening visit could be extended to afford more flexibility for centers and subjects3. Clarification of inclusion criteria: subjects at risk were no longer excluded if they did not have a liver biopsy4. Clarification of exclusion criteria: incidental steatosis diagnosed by biopsy was no longer an exclusion criterion; decompensated liver disease was based on Child-Turcotte-Pugh classification. In addition, psychiatric conditions and 'creatinine clearance ≤ 50 mL/min' were added as exclusion criteria to comply with the updated Summary of Product Characteristics for RBV (Copegus)5. Clarification of definition of SVR: HCV RNA <25 IU/mL (undetected) after the planned end of treatment (based on assigned treatment group and achievement of ETS)6. Adjustments of the rash management plan to make it consistent across all trials in the program7. Clarification of details of genotypic and phenotypic viral resistance analysis8. Modification of procedures for subjects discontinuing treatment prematurely: they were to follow the 48-week visit schedule9. Modification of safety endpoints: rash and photosensitivity are AEs that are captured in Endpoints 1, 2, 3, and 410. Clarification that not every severe or serious AE should prompt treatment discontinuation11. Clarification on appropriate management of missed PegIFN and RBV doses

09 March 2012	<ol style="list-style-type: none"> 1. Change of primary endpoint from SVR24 to SVR12: this change was based on FDA public comments and BI retrospective analysis of Phase II data indicating a 98% positive predictive value of SVR12 for SVR24 2. Addition of post-treatment ALT and AST normalization as efficacy endpoint to correlate this with SVR12 3. Addition of SVR24 to better define the post-EoO visit 4. Clarifications were added to the inclusion and exclusion criteria to make them consistent across the FDV program 5. Clarifications of stopping rule criteria 6. Clarification of the blinding process 7. Clarifications of the process for the discontinuation and modification of FDV and PegIFN 8. Modification of compliance assessment: planned interruptions and dose reductions were not automatically to be counted as noncompliance 9. Clarification of the definitions of AEs: worsening of underlying disease or pre-existing conditions and changes in vital signs, ECG, physical examination and laboratory test results (if clinically relevant) were to be recorded as (S)AE, 10. Clarification of definition and reporting of 'always serious adverse events' to comply with a new corporate SOP 11. Clarifications were added for the laboratory test schedule 12. Clarification of grading of the intensity of rash when photo documentation is required 13. Clarification of the process for rash management 14. Statistical analysis of primary and secondary endpoints was adjusted to comply with the changes made in these endpoints 15. An interim analysis was conducted, with SVR12 as the primary endpoint 16. Handling of missing data was changed to include rules for imputing missing SVR12 values 17. The determination of sample size was adjusted for SVR12 as the primary endpoint
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported