

**Clinical trial results:**

**A phase III, open-label study of once daily BI 201335 240 mg for 24 weeks in combination with pegylated interferon-a (PegIFN) and ribavirin (RBV) in patients with genotype 1 chronic hepatitis C infection who failed a prior PegIFN / RBV treatment**

**Summary**

EudraCT number	2011-000141-20
Trial protocol	GB PT DE AT BE ES
Global end of trial date	24 June 2014

**Results information**

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	26 July 2015

**Trial information****Trial identification**

Sponsor protocol code	1220.48
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01330316
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 Pharma GmbH & Co. KG, +1 8002430127, clintrriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG, +1 8002430127, clintrriage.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	08 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 June 2014
Global end of trial reached?	Yes
Global end of trial date	24 June 2014
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The objective of this trial is to collect evidence for the safety and efficacy of 24 weeks of treatment with BI 201335 240mg given once daily in combination with 24 or 48 weeks of PegIFN and RBV in HCV GT-1 infected treatment-experienced patients who have been withdrawn from PegIFN and RBV treatment due to lack of efficacy in the 1220.7, 1220.30 and 1220.47 trials of the BI 201335 Phase III program.

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. Rescue medication was allowed for all patients as required.

An independent data monitoring committee (DMC) was established to ensure the welfare of patients participating in this trial.

Background therapy:

Pegylated interferon  $\alpha$ -2a (PegIFN) and Ribavirin (RBV)

Evidence for comparator: -

Actual start date of recruitment	07 October 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Japan: 14
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Switzerland: 1

Country: Number of subjects enrolled	United States: 24
Country: Number of subjects enrolled	Taiwan: 1
Worldwide total number of subjects	121
EEA total number of subjects	58

Notes:

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### 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)	110
From 65 to 84 years	11
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This was a multi-national, open-label trial enrolling 2 cohorts of patients with chronic Hepatitis C Virus (HCV) infection of genotype 1 (GT-1) who were randomized to the placebo arm (+ Pegylated interferon  $\alpha$ -2a/Ribavirin) and experienced virologic failure in one of the 1220.7(2010-021715-17), 1220.30(2010-021716-42), 1220.47(2010-021716-42) trials

### Pre-assignment

Screening details:

Eligible patients who entered the rollover trial within 14 weeks of their last study visit in one of the predecessor trials were not required to do a screening visit (treatment start: Day 1). Eligible patients who were outside of this 14-week window were required to do a screening visit (Visit 1) and started treatment at Visit 2 (Day 1).

### Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
Arm title	Relapse

Arm description:

Faldaprevir (FDV) 240 mg once daily combined with Pegylated interferon  $\alpha$ -2a (PegIFN)/ Ribavirin (RBV) for 24 weeks was administered for relapser patients.

At week 24, patients who did not achieve early treatment success (ETS) continue with an additional 24 weeks of PegIFN/RBV.

ETS is defined as Hepatitis C virus (HCV) Ribonucleic Acid (RNA) <25 International Units (IU)/millilitre (ml) (detected or undetected) at week 4 and <25 IU/ml (undetected) at week 8.

Patients who had undetectable Hepatitis C Virus (HCV) Ribonucleic Acid (RNA) levels at the end of treatment in one of the previous studies (see recruitment details) but had detectable levels in subsequent assessments are called relapser.

Arm type	Experimental
Investigational medicinal product name	Faldaprevir (FDV)
Investigational medicinal product code	BI 201335
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

240 mg Faldaprevir once daily for 24 weeks.

Investigational medicinal product name	Pegasys (R)
Investigational medicinal product code	
Other name	Pegylated interferon- $\alpha$ 2a
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Up to 180 Microgram (mcg) once weekly for 24 weeks. All relapsed patients who do not achieve ETS at week 8 will extend treatment for additional 24 weeks.

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

Dosage and administration details:

The daily dose is 1000 milligram (mg) (<75 kilogram (kg) body weight) or 1200mg (≥ 75 kg body weight), administered twice daily. All relapsed patients who do not achieve ETS at week 8 will extend treatment for additional 24 weeks.

<b>Arm title</b>	Non-relapse
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Arm description:

Faldaprevir (FDV) 240mg once daily combined with Pegylated interferon α-2a (PegIFN)/ Ribavirin (RBV) for 24 weeks, followed by an additional 24 weeks of PegIFN/RBV for non-relapser patients.

Non-relapser are non-responder (null and partial) and breakthrough patients.

Null responders are patients who did not achieve > 2 log<sub>10</sub> decrease in HCV RNA from baseline during the treatment period.

Partial non-responders are patients who achieved > 2 log<sub>10</sub> decrease in HCV RNA from baseline but who never achieved an undetectable level of HCV RNA.

Breakthrough are patients who achieved an undetectable HCV RNA during the treatment period but had detectable HCV RNA at the end of treatment.

Arm type	Experimental
Investigational medicinal product name	Faldaprevir (FDV)
Investigational medicinal product code	BI 201335
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

240mg Faldaprevir once daily combined with PegIFN/RBV for 24 weeks.

Investigational medicinal product name	Pegasys (R)
Investigational medicinal product code	
Other name	Pegylated interferon-α 2a
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Up to 180 Microgram (mcg) once weekly for 24 weeks. All relapsed patients who do not achieve ETS at week 8 will extend treatment for additional 24 weeks.

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

Dosage and administration details:

The daily dose is 1000 milligram (mg) (<75 kilogram (kg) body weight) or 1200mg (≥ 75 kg body weight), administered twice daily. All relapsed patients who do not achieve ETS at week 8 will extend treatment for additional 24 weeks.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Relapse	Non-relapse
Started	43	75
Completed	41	60
Not completed	2	15
Adverse event, non-fatal	2	2
Withdrawal by Subject	-	1

Other than specified	-	1
Lost to follow-up	-	1
Lack of efficacy	-	10

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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 of the study medication.

## Baseline characteristics

### Reporting groups

Reporting group title	Relapse
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Reporting group description:

Faldaprevir (FDV) 240 mg once daily combined with Pegylated interferon  $\alpha$ -2a (PegIFN)/ Ribavirin (RBV) for 24 weeks was administered for relapser patients.

At week 24, patients who did not achieve early treatment success (ETS) continue with an additional 24 weeks of PegIFN/RBV.

ETS is defined as Hepatitis C virus (HCV) Ribonucleic Acid (RNA) <25 International Units (IU)/millilitre (ml) (detected or undetected) at week 4 and <25 IU/ml (undetected) at week 8.

Patients who had undetectable Hepatitis C Virus (HCV) Ribonucleic Acid (RNA) levels at the end of treatment in one of the previous studies (see recruitment details) but had detectable levels in subsequent assessments are called relapser.

Reporting group title	Non-relapse
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Reporting group description:

Faldaprevir (FDV) 240mg once daily combined with Pegylated interferon  $\alpha$ -2a (PegIFN)/ Ribavirin (RBV) for 24 weeks, followed by an additional 24 weeks of PegIFN/RBV for non-relapser patients.

Non-relapser are non-responder (null and partial) and breakthrough patients.

Null responders are patients who did not achieve > 2 log<sub>10</sub> decrease in HCV RNA from baseline during the treatment period.

Partial non-responders are patients who achieved > 2 log<sub>10</sub> decrease in HCV RNA from baseline but who never achieved an undetectable level of HCV RNA.

Breakthrough are patients who achieved an undetectable HCV RNA during the treatment period but had detectable HCV RNA at the end of treatment.

Reporting group values	Relapse	Non-relapse	Total
Number of subjects	43	75	118
Age categorical			
Units: Subjects			

Age Continuous			
Full analysis set (FAS): This set included all patients who entered the trial, were dispensed study medication, and were documented to have taken at least one dose of study medication.			
Units: years			
arithmetic mean	55.4	53.4	
standard deviation	± 7.38	± 9.46	-
Gender, Male/Female			
Full analysis set (FAS): This set included all patients who entered the trial, were dispensed study medication, and were documented to have taken at least one dose of study medication.			
Units: participants			
Female	16	25	41
Male	27	50	77

## End points

### End points reporting groups

Reporting group title	Relapse
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Reporting group description:

Faldaprevir (FDV) 240 mg once daily combined with Pegylated interferon  $\alpha$ -2a (PegIFN)/ Ribavirin (RBV) for 24 weeks was administered for relapser patients.

At week 24, patients who did not achieve early treatment success (ETS) continue with an additional 24 weeks of PegIFN/RBV.

ETS is defined as Hepatitis C virus (HCV) Ribonucleic Acid (RNA) <25 International Units (IU)/millilitre (ml) (detected or undetected) at week 4 and <25 IU/ml (undetected) at week 8.

Patients who had undetectable Hepatitis C Virus (HCV) Ribonucleic Acid (RNA) levels at the end of treatment in one of the previous studies (see recruitment details) but had detectable levels in subsequent assessments are called relapser.

Reporting group title	Non-relapse
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Reporting group description:

Faldaprevir (FDV) 240mg once daily combined with Pegylated interferon  $\alpha$ -2a (PegIFN)/ Ribavirin (RBV) for 24 weeks, followed by an additional 24 weeks of PegIFN/RBV for non-relapser patients.

Non-relapser are non-responder (null and partial) and breakthrough patients.

Null responders are patients who did not achieve > 2 log<sub>10</sub> decrease in HCV RNA from baseline during the treatment period.

Partial non-responders are patients who achieved > 2 log<sub>10</sub> decrease in HCV RNA from baseline but who never achieved an undetectable level of HCV RNA.

Breakthrough are patients who achieved an undetectable HCV RNA during the treatment period but had detectable HCV RNA at the end of treatment.

### Primary: Sustained Virological Response (SVR): Plasma HCV RNA level < 25 IU/mL

End point title	Sustained Virological Response (SVR): Plasma HCV RNA level < 25 IU/mL <sup>[1]</sup>
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End point description:

The primary endpoint was SVR12, defined as a plasma Hepatitis C virus (HCV) Ribonucleic acid (RNA) level <25 IU/mL (undetected) 12 weeks after the originally planned treatment duration.

End point type	Primary
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End point timeframe:

12 weeks post treatment, up to 60 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: All the analyses are descriptive in nature and no hypothesis will be tested.

End point values	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[2]</sup>	75 <sup>[3]</sup>		
Units: percentage of participants				
number (confidence interval 95%)	95.3 (89.1 to 100)	54.7 (43.4 to 65.9)		

Notes:

[2] - FAS

[3] - FAS

### Statistical analyses

No statistical analyses for this end point

## Secondary: Sustained virological response after 24 weeks of treatment discontinuation (SVR24)

End point title	Sustained virological response after 24 weeks of treatment discontinuation (SVR24)
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End point description:

Sustained virologic response 24 weeks, defined as a plasma HCV RNA level < 25 IU/mL (undetected) 24 weeks after the originally planned treatment duration.

End point type	Secondary
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End point timeframe:

24 weeks post treatment, up to 72 weeks

End point values	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[4]</sup>	75 <sup>[5]</sup>		
Units: percentage of participants				
number (confidence interval 95%)	95.3 (89.1 to 100)	54.7 (43.4 to 65.9)		

Notes:

[4] - FAS

[5] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Early Treatment Success (ETS)

End point title	Early Treatment Success (ETS)
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End point description:

ETS is 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
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End point timeframe:

Week 4 and Week 8

End point values	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[6]</sup>	75 <sup>[7]</sup>		
Units: percentage of participants				
number (not applicable)	97.7	65.3		

Notes:

[6] - FAS

[7] - FAS

## Statistical analyses

No statistical analyses for this end point

**Secondary: Alanine Aminotransferase (ALT) normalisation: ALT in normal range at end of treatment (EoT)**

End point title	Alanine Aminotransferase (ALT) normalisation: ALT in normal range at end of treatment (EoT)
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End point description:

This will be presented as the number of patients in/not in normal range from baseline EoT. SVR12 is sustained virological response 12 weeks post-treatment.

End point type	Secondary
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End point timeframe:

Week 24 for relapsers with ETS; Week 48 for relapsers without ETS, and non-relapsers

End point values	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[8]</sup>	75 <sup>[9]</sup>		
Units: participants				
number (not applicable)				
SVR12 = Yes	41	41		
SVR12 = Yes, Baseline Normal to EOT Normal	12	10		
SVR12 = Yes, Baseline Elevated to EOT Normal	16	15		
SVR12 = No	2	34		
SVR12 = No, Baseline Normal to EOT Normal	0	11		
SVR12 = No, Baseline Elevated to EOT Normal	2	9		

Notes:

[8] - FAS

[9] - FAS

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Alanine Aminotransferase (ALT) normalisation: ALT in normal range at 12 weeks post-treatment.**

End point title	Alanine Aminotransferase (ALT) normalisation: ALT in normal range at 12 weeks post-treatment.
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End point description:

This will be presented as the number of patients in/not in normal range from baseline to 12 weeks post treatment. SVR12 is sustained virological response 12 weeks post-treatment.

End point type	Secondary
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End point timeframe:

48 weeks for relapsers with ETS; 60 weeks for non-relapsers and relapsers without ETS

<b>End point values</b>	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[10]</sup>	75 <sup>[11]</sup>		
Units: participants				
number (not applicable)				
SVR12 = Yes	41	41		
SVR12 = Yes, Baseline Normal to SVR12 Normal	12	11		
SVR12 = Yes, Baseline Elevated to SVR12 Normal	27	27		
SVR12 = No	2	34		
SVR12 = No, Baseline Normal to SVR12 Normal	0	8		
SVR12 = No, Baseline Elevated to SVR12 Normal	1	2		

Notes:

[10] - FAS

[11] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: Aspartate Aminotransferase (AST) normalisation: AST in normal range at end of treatment (EoT)

End point title	Aspartate Aminotransferase (AST) normalisation: AST in normal range at end of treatment (EoT)
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End point description:

This will be presented as the number of patients in/not in normal range from baseline to EoT. SVR12 is sustained virological response 12 weeks post-treatment.

End point type	Secondary
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End point timeframe:

Week 24 for relapsers with ETS; Week 48 for relapsers without ETS, and non-relapsers.

<b>End point values</b>	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[12]</sup>	75 <sup>[13]</sup>		
Units: participants				
number (not applicable)				
SVR12 = Yes	41	41		
SVR12 = Yes, Baseline Normal to EOT Normal	15	13		
SVR12 = Yes, Baseline Elevated to EOT Normal	14	11		
SVR12 = No	2	34		
SVR12 = No, Baseline Normal to EOT Normal	1	12		
SVR12 = No, Baseline Elevated to EOT Normal	1	7		

Notes:

[12] - FAS

[13] - FAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Aspartate Aminotransferase (AST) normalisation: AST in normal range at 12 weeks post-treatment.

End point title	Aspartate Aminotransferase (AST) normalisation: AST in normal range at 12 weeks post-treatment.
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End point description:

This will be presented as the number of patients in/not in normal range from baseline to 12 weeks post treatment. SVR12 is sustained virological response 12 weeks post-treatment.

End point type	Secondary
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End point timeframe:

Week 48 for relapsers with ETS; Week 48 for relapsers without ETS, and non-relapsers

End point values	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[14]</sup>	75 <sup>[15]</sup>		
Units: participants				
number (not applicable)				
SVR12 = Yes	41	41		
SVR12 = Yes, Baseline Normal to SVR12 Normal	15	14		
SVR12 = Yes, Baseline Elevated to SVR12 Normal	22	24		
SVR12 = No	2	34		
SVR12 = No, Baseline Normal to SVR12 Normal	1	10		
SVR12 = No, Baseline Elevated to SVR12 Normal	0	3		

Notes:

[14] - FAS

[15] - FAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Occurrence of adverse events (overall and by DAIDS grade)

End point title	Occurrence of adverse events (overall and by DAIDS grade)
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End point description:

This outcome measure will be presented as the percentage of subjects with any adverse event (AE). Percentages are calculated using total number of subjects per treatment cohort as the denominator. The intensity of all AEs was evaluated according to the DAIDS (Division of Acquired Immunodeficiency Syndrome) grading scale with AEs of mild, moderate, or severe intensity receiving Grades 1, 2, or 3,

respectively. Adverse events judged potentially life threatening received a Grade 4 assessment.

End point type	Secondary
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End point timeframe:

from first intake of study medication until 30 days after discontinuing faldaprevir, up to a maximum of 213 days

End point values	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[16]</sup>	75 <sup>[17]</sup>		
Units: percentage of participants				
number (not applicable)				
Overall	90.7	93.3		
Subjects with DAIDS Grade 2, 3 or 4 AEs	65.1	56		
Subjects with DAIDS Grade 3 or 4 AEs	27.9	17.3		
Subjects with DAIDS Grade 4 AEs	7	1.3		

Notes:

[16] - FAS

[17] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: Occurrence of adverse events leading to treatment discontinuation

End point title	Occurrence of adverse events leading to treatment discontinuation
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End point description:

This outcome measure will be presented as the percentage of subjects with adverse events leading to discontinuation of Faldaprevir and all study medication. Percentages are calculated using total number of subjects per treatment cohort as the denominator.

End point type	Secondary
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End point timeframe:

from first intake of study medication until 30 days after discontinuing faldaprevir, up to a maximum of 213 days

End point values	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[18]</sup>	75 <sup>[19]</sup>		
Units: percentage of participants				
number (not applicable)				
discontinuation of faldaprevir	4.3	2.7		
discontinuation of all study medication	2.3	0		

Notes:

[18] - FAS

[19] - FAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Occurrence of serious adverse events

End point title Occurrence of serious adverse events

End point description:

This outcome measure will be presented as the percentage of subjects with any serious adverse event (SAE). Percentages are calculated using total number of subjects per treatment cohort as the denominator.

End point type Secondary

End point timeframe:

from first intake of study medication until 30 days after discontinuing faldaprevir, up to a maximum of 213 days

End point values	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[20]</sup>	75 <sup>[21]</sup>		
Units: percentage of participants				
number (not applicable)	2.3	8		

Notes:

[20] - FAS

[21] - FAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Occurrence of drug-related AEs as assessed by the investigator

End point title Occurrence of drug-related AEs as assessed by the investigator

End point description:

This outcome measure will be presented as the percentage of subjects with any drug-related AEs as assessed by the investigator. Percentages are calculated using total number of subjects per treatment cohort as the denominator.

End point type Secondary

End point timeframe:

from first intake of study medication until 30 days after discontinuing faldaprevir, up to a maximum of 213 days

End point values	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[22]</sup>	75 <sup>[23]</sup>		
Units: percentage of participants				
number (not applicable)	88.4	88		

Notes:

[22] - FAS

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Laboratory test abnormalities by DAIDS grades**

End point title	Laboratory test abnormalities by DAIDS grades
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End point description:

This Outcome measure will be presented as summary of the percentage of patients with worst on-treatment Division of Acquired Immunodeficiency Syndrome (DAIDS) grade laboratory abnormalities for selected analytes (Haemoglobin, Alanine aminotransaminase (ALT), Aspartate aminotransaminase (AST) and Bilirubin total) with particular relevance to patients with HCV.

End point type	Secondary
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End point timeframe:

baseline (day 1, after first dose of randomised treatment) up to 7 days after the last intake of study drug

<b>End point values</b>	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[24]</sup>	75 <sup>[25]</sup>		
Units: percentage of participants				
number (not applicable)				
Haemoglobin, Grade 2	14	18.9		
Haemoglobin, Grade 3	11.6	8.1		
Haemoglobin, Grade 4	0	0		
ALT, Grade 2	7	6.7		
ALT, Grade 3	2.3	4		
ALT, Grade 4	2.3	0		
AST, Grade 2	4.7	10.7		
AST, Grade 3	2.3	2.7		
AST, Grade 4	2.3	0		
Bilirubin, total, Grade 2	32.6	37.3		
Bilirubin, total, Grade 3	39.5	29.3		
Bilirubin, total, Grade 4	11.6	13.3		

Notes:

[24] - FAS

[25] - FAS

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Changes from baseline in laboratory test values over time [Haemoglobin]**

End point title	Changes from baseline in laboratory test values over time [Haemoglobin]
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End point description:

This outcome measure will be presented as the mean value and the standard deviation at baseline, week 4, week 12, the minimum (min) value on treatment, maximum (max) value on treatment and last measured value on treatment. Analytes with particular relevance for patients with HCV have been selected: Haemoglobin, Alanine aminotransaminase (ALT), Aspartate aminotransaminase (AST) and Bilirubin total.

In this outcome measure Haemoglobin is presented.

End point type	Secondary
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End point timeframe:

baseline (the last observed measurement prior to administration of any randomised study medication), week 4, week 12 (after start of treatment)

End point values	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[26]</sup>	75 <sup>[27]</sup>		
Units: gram (g)/decilitre (dL)				
arithmetic mean (standard deviation)				
Baseline (N=43, 74)	14.8 (± 1.3)	14.8 (± 1.4)		
week 4 (N=41, 69)	12.6 (± 1.6)	12.7 (± 1.4)		
week 12 (N=43, 66)	11.7 (± 1.6)	11.5 (± 1.5)		
min value on treatment (N=43, 74)	11.1 (± 1.5)	11.3 (± 1.7)		
max value on treatment (N=43, 74)	13.7 (± 1.2)	14 (± 1.4)		
last value on treatment (N=43, 74)	11.4 (± 1.5)	11.8 (± 1.6)		

Notes:

[26] - FAS

[27] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: Changes from baseline in laboratory test values over time [ALT]

End point title	Changes from baseline in laboratory test values over time [ALT]
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End point description:

This outcome measure will be presented as the mean value and the standard deviation at baseline, week 4, week 12, the minimum (min) value on treatment, maximum (max) value on treatment and last measured value on treatment. Analytes with particular relevance for patients with HCV have been selected: Haemoglobin, Alanine aminotransaminase (ALT), Aspartate aminotransaminase (AST) and Bilirubin total.

In this outcome measure ALT is presented.

End point type	Secondary
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End point timeframe:

baseline (the last observed measurement prior to administration of any randomised study medication), week 4, week 12 (after start of treatment)

<b>End point values</b>	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[28]</sup>	75 <sup>[29]</sup>		
Units: Units (U)/Litre (L)				
arithmetic mean (standard deviation)				
Baseline (N=43, 75)	72 (± 79)	88 (± 63)		
week 4 (N=43, 73)	51 (± 71)	57 (± 49)		
week 12 (N=43, 67)	43 (± 40)	55 (± 62)		
min value on treatment (N=43, 75)	30 (± 20)	39 (± 38)		
max value on treatment (N=43, 75)	68 (± 91)	70 (± 62)		
last value on treatment (N=43, 75)	40 (± 26)	54 (± 52)		

Notes:

[28] - FAS

[29] - FAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Changes from baseline in laboratory test values over time [AST]

End point title	Changes from baseline in laboratory test values over time [AST]
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End point description:

This outcome measure will be presented as the mean value and the standard deviation at baseline, week 4, week 12, the minimum (min) value on treatment, maximum (max) value on treatment and last measured value on treatment. Analytes with particular relevance for patients with HCV have been selected: Haemoglobin, Alanine aminotransaminase (ALT), Aspartate aminotransaminase (AST) and Bilirubin total.

In this outcome measure AST is presented.

End point type	Secondary
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End point timeframe:

baseline (the last observed measurement prior to administration of any randomised study medication), week 4, week 12 (after start of treatment)

<b>End point values</b>	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[30]</sup>	75 <sup>[31]</sup>		
Units: U/L				
arithmetic mean (standard deviation)				
Baseline (N=43, 75)	54 (± 41)	68 (± 42)		
week 4 (N=43, 73)	48 (± 71)	46 (± 33)		
week 12 (N=43, 67)	41 (± 37)	48 (± 45)		
min value on treatment (N=43, 75)	30 (± 16)	35 (± 25)		
max value on treatment (N=43, 75)	63 (± 89)	62 (± 50)		
last value on treatment (N=43, 75)	40 (± 23)	49 (± 39)		

Notes:

[30] - FAS

[31] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline in laboratory test values over time [Bilirubin total]

End point title	Changes from baseline in laboratory test values over time [Bilirubin total]
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End point description:

This outcome measure will be presented as the mean value and the standard deviation at baseline, week 4, week 12, the minimum (min) value on treatment, maximum (max) value on treatment and last measured value on treatment. Analytes with particular relevance for patients with HCV have been selected: Haemoglobin, Alanine aminotransaminase (ALT), Aspartate aminotransaminase (AST) and Bilirubin total.

In this outcome measure Bilirubin total is presented.

End point type	Secondary
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End point timeframe:

baseline (the last observed measurement prior to administration of any randomised study medication), week 4, week 12 (after start of treatment)

End point values	Relapse	Non-relapse		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 <sup>[32]</sup>	75 <sup>[33]</sup>		
Units: milligram (mg)/dL				
arithmetic mean (standard deviation)				
Baseline (N=43, 75)	0.5 (± 0.2)	0.5 (± 0.2)		
week 4 (N=43, 74)	2.8 (± 1.6)	2.6 (± 1.7)		
week 12 (N=43, 67)	2.7 (± 1.8)	2.7 (± 1.9)		
min value on treatment (N=43, 75)	1.9 (± 1.3)	1.9 (± 1.5)		
max value on treatment (N=43, 75)	3.6 (± 2.1)	3.5 (± 2.2)		
last value on treatment (N=43, 75)	2.6 (± 1.8)	2.6 (± 1.9)		

Notes:

[32] - FAS

[33] - FAS

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

from first intake of study medication until 30 days after discontinuing faldaprevir, up to a maximum of 213 days

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

### Reporting groups

Reporting group title	Non-Relapse
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Reporting group description:

Faldaprevir (FDV) 240mg once daily combined with Pegylated interferon  $\alpha$ -2a (PegIFN)/ Ribavirin (RBV) for 24 weeks, followed by an additional 24 weeks of PegIFN/RBV for non-relapser patients.

Non-relapser are non-responder (null and partial) and breakthrough patients.

Null responders are patients who did not achieve  $> 2 \log_{10}$  decrease in HCV RNA from baseline during the treatment period.

Partial non-responders are patients who achieved  $> 2 \log_{10}$  decrease in HCV RNA from baseline but who never achieved an undetectable level of HCV RNA.

Breakthrough are patients who achieved an undetectable HCV RNA during the treatment period but had detectable HCV RNA at the end of treatment.

Reporting group title	Relapse
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Reporting group description:

Faldaprevir (FDV) 240 mg once daily combined with Pegylated interferon  $\alpha$ -2a (PegIFN)/ Ribavirin (RBV) for 24 weeks was administered for relapser patients.

At week 24, patients who did not achieve early treatment success (ETS) continue with an additional 24 weeks of PegIFN/RBV.

ETS is defined as Hepatitis C virus (HCV) Ribonucleic Acid (RNA)  $< 25$  International Units (IU)/millilitre (ml) (detected or undetected) at week 4 and  $< 25$  IU/ml (undetected) at week 8.

<b>Serious adverse events</b>	Non-Relapse	Relapse	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 75 (8.00%)	1 / 43 (2.33%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Presyncope			

subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
Ascites			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 75 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hepatobiliary disorders</b>			
Hepatic failure			
subjects affected / exposed	0 / 75 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Musculoskeletal and connective tissue disorders</b>			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Gastroenteritis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral fungal infection			

subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pneumonia</b>			
subjects affected / exposed	0 / 75 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolism and nutrition disorders</b>			
<b>Decreased appetite</b>			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Dehydration</b>			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Non-Relapse	Relapse	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	68 / 75 (90.67%)	38 / 43 (88.37%)	
<b>Vascular disorders</b>			
<b>Hypertension</b>			
subjects affected / exposed	1 / 75 (1.33%)	3 / 43 (6.98%)	
occurrences (all)	1	3	
<b>General disorders and administration site conditions</b>			
<b>Asthenia</b>			
subjects affected / exposed	12 / 75 (16.00%)	7 / 43 (16.28%)	
occurrences (all)	12	7	
<b>Chills</b>			
subjects affected / exposed	2 / 75 (2.67%)	3 / 43 (6.98%)	
occurrences (all)	2	3	
<b>Fatigue</b>			

subjects affected / exposed occurrences (all)	9 / 75 (12.00%) 9	14 / 43 (32.56%) 14	
Influenza like illness subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	5 / 43 (11.63%) 7	
Malaise subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 6	1 / 43 (2.33%) 1	
Pyrexia subjects affected / exposed occurrences (all)	8 / 75 (10.67%) 8	4 / 43 (9.30%) 4	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	11 / 75 (14.67%) 11	5 / 43 (11.63%) 5	
Dyspnoea subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 3	4 / 43 (9.30%) 4	
Psychiatric disorders			
Depression subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	3 / 43 (6.98%) 3	
Insomnia subjects affected / exposed occurrences (all)	14 / 75 (18.67%) 14	5 / 43 (11.63%) 5	
Irritability subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 6	2 / 43 (4.65%) 2	
Investigations			
Haemoglobin decreased subjects affected / exposed occurrences (all)	1 / 75 (1.33%) 1	3 / 43 (6.98%) 3	
Weight decreased subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 3	3 / 43 (6.98%) 3	
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 5	3 / 43 (6.98%) 3	
Dysgeusia subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	2 / 43 (4.65%) 2	
Headache subjects affected / exposed occurrences (all)	15 / 75 (20.00%) 16	10 / 43 (23.26%) 12	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	20 / 75 (26.67%) 24	9 / 43 (20.93%) 9	
Neutropenia subjects affected / exposed occurrences (all)	7 / 75 (9.33%) 7	2 / 43 (4.65%) 2	
Thrombocytopenia subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 5	1 / 43 (2.33%) 1	
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	0 / 43 (0.00%) 0	
Abdominal pain subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 4	6 / 43 (13.95%) 6	
Abdominal pain upper subjects affected / exposed occurrences (all)	8 / 75 (10.67%) 8	2 / 43 (4.65%) 2	
Diarrhoea subjects affected / exposed occurrences (all)	21 / 75 (28.00%) 24	14 / 43 (32.56%) 19	
Dry mouth subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	0 / 43 (0.00%) 0	
Dyspepsia			

subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 5	2 / 43 (4.65%) 3	
Nausea subjects affected / exposed occurrences (all)	34 / 75 (45.33%) 36	22 / 43 (51.16%) 25	
Stomatitis subjects affected / exposed occurrences (all)	2 / 75 (2.67%) 2	3 / 43 (6.98%) 3	
Vomiting subjects affected / exposed occurrences (all)	15 / 75 (20.00%) 22	11 / 43 (25.58%) 15	
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 7	12 / 43 (27.91%) 12	
Jaundice subjects affected / exposed occurrences (all)	10 / 75 (13.33%) 10	5 / 43 (11.63%) 5	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 6	4 / 43 (9.30%) 4	
Dry skin subjects affected / exposed occurrences (all)	8 / 75 (10.67%) 9	4 / 43 (9.30%) 4	
Eczema subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 6	1 / 43 (2.33%) 1	
Photosensitivity reaction subjects affected / exposed occurrences (all)	1 / 75 (1.33%) 1	3 / 43 (6.98%) 3	
Pruritus subjects affected / exposed occurrences (all)	23 / 75 (30.67%) 23	13 / 43 (30.23%) 16	
Rash			

subjects affected / exposed occurrences (all)	21 / 75 (28.00%) 26	12 / 43 (27.91%) 12	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 75 (5.33%)	2 / 43 (4.65%)	
occurrences (all)	4	2	
Back pain			
subjects affected / exposed	4 / 75 (5.33%)	0 / 43 (0.00%)	
occurrences (all)	5	0	
Muscle spasms			
subjects affected / exposed	4 / 75 (5.33%)	2 / 43 (4.65%)	
occurrences (all)	5	2	
Myalgia			
subjects affected / exposed	9 / 75 (12.00%)	3 / 43 (6.98%)	
occurrences (all)	11	3	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 75 (1.33%)	3 / 43 (6.98%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 75 (21.33%)	3 / 43 (6.98%)	
occurrences (all)	17	3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2011	<p>Visit windows changed to offer sites and patients more scheduling flexibility.</p> <p>The definition sustained virological response (SVR) was modified by clarifying that the planned end of treatment for this assessment would be based on cohort and achievement of ETS.</p> <p>Clarification of exclusion criteria: cervical cap deemed inferior barrier and was removed as a sufficient method of contraception per Health Canada.</p> <p>Exclusion criterion describing restriction of patients with decompensated liver disease was modified per Child-Turcotte-Pugh classification, and exclusion criteria for pre-existing psychiatric conditions were modified per an update of the Summary of Product Characteristics (SPC) for RBV.</p> <p>Clarified rules for stopping treatment in case of virological failure.</p> <p>Prohibited increasing the dose of drug up to 240mg after it had been reduced to 120mg during the trial.</p> <p>Removed restrictions on certain contraindicated medications.</p> <p>Added instructions on appropriate management of missed doses of drug.</p> <p>Clarified definition of eRVR and added progression of liver disease progression as other endpoint.</p> <p>Adopted Division of Acquired Immunodeficiency Syndrome (DAIDS) grading system for classifying AE intensity and laboratory tests.</p> <p>Allowed for blood sampling at the first screening visit for patients who were not fasting at the screening visit.</p> <p>Removed requirement for screening visit if the time period between the last study visit of one of the phase III predecessor studies and the first visit for 1220.48 was <math>\leq 14</math> weeks.</p> <p>Restricted the discontinuation of pegylated interferon <math>\alpha</math>-2a (PegIFN) for patients who discontinued FDV or ribavirin (RBV) early.</p> <p>Removed list of restricted concomitant medications and added reference to ISF to facilitate updated information as new potential interactions were identified.</p> <p>Definition of virological failure was described in more detail to include a repeat blood draw to determine whether patient could continue study medications.</p>

05 March 2012	<p>Change:</p> <p>Descriptions of rashes, instructions to discontinue FDV treatment in case of severe photosensitivity reaction with opportunity to continue PegIFN/RBV in conjunction with a dermatology specialist</p> <p>Primary efficacy endpoint from SVR24 to SVR12</p> <p>Secondary efficacy endpoint to add ALT and AST normalization post treatment</p> <p>Add:</p> <p>Procedure clarification for patients who discontinued early; Criteria/rules for stopping patient treatment due to lack of efficacy</p> <p>Description of AEs defined as always serious per BI SOPs</p> <p>Clarified:</p> <p>Standard of care with PegIFN, RBV</p> <p>Planned treatment interruptions/dose reductions should be considered for treatment compliance calculation</p> <p>AE definitions to include worsening of underlying diseases/pre-existing conditions, changes in vital signs, ECG, physical examination, laboratory values deemed clinically relevant</p> <p>Markers of liver disease progression would be assessed at (early) end of treatment</p> <p>Procedures for patients who prematurely discontinued from treatment or trial</p> <p>Handling of rules for imputing missing SVR12 or SVR24 data</p> <p>Calculation of Child-Turcotte-Pugh score for exclusion of such patients from trial</p> <p>Modified:</p> <p>Analyses for other efficacy endpoint: rapid virological response (VR), complete early VR, week 24 VR, extended rapid VR, ETR</p> <p>Rash management plan to include photosensitivity reaction gradings, no photo documentation for mild rashes, clarified the instructions for potentially life-threatening rashes</p> <p>Jaundice deemed non-specific, removed from list of sensitive markers indicative of liver disease progression</p> <p>Use of oral antivirals, oseltamivir and zanamivir: permitted during trial</p> <p>Planned interim analysis: database lock after last patient's 12 weeks post-treatment visit. Primary endpoint assessed for all patients. Safety and efficacy data were to be summarized</p>
09 July 2013	<p>Added that Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms (DRESS) syndrome had been reported in the FDV program and it was added as a potentially life-threatening example. Patients were to be monitored for the appearance of safety signals related to this syndrome.</p>
09 April 2014	<p>Removal of extended follow-up visit because sufficient long-term data had been collected as part of the clinical program. Sensitivity analyses were removed. Other secondary analyses were removed (ALT/AST normalization reference; RBV-associated anaemia; reason for further breakout) or added (ETS) to correct errors. Clarified that interim analysis would only performed if requested by regulatory agencies; one database lock would be performed at end of trial only.</p>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
24 June 2014	<p>Boehringer Ingelheim (BI) no longer has any internal HCV direct-acting antiviral agents required to develop an IFN-free clinical development program. As a result, BI withdrew all pending marketing applications for FDV worldwide and is discontinuing further HCV drug development. As a result, this trial was prematurely discontinued.</p>	-

Notes:

## Limitations and caveats

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

Due to the premature discontinuation of this trial an abbreviated report format was used.

Notes: