



Clinical trial results:

A randomized, double-blind, placebo-controlled trial of the efficacy and safety of DEB025/Alisporivir in combination with peg-IFN alfa2a and ribavirin in hepatitis C genotype 1 treatment-naïve patients

Summary

EudraCT number	2010-022867-37
Trial protocol	HU DE BE GB PL IT ES
Global end of trial date	13 August 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	CDEB025A2301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01318694
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 61-324-1111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 61-324-1111,

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	13 August 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate that in treatment-naïve chronic hepatitis C genotype 1 patients triple therapy with DEB025 plus peg-IFN α 2a/RBV leads to a superior SVR12 rate as compared to dual therapy with peg-IFN α 2a/RBV.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 126
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Korea, Republic of: 76
Country: Number of subjects enrolled	Taiwan: 58
Country: Number of subjects enrolled	Thailand: 88
Country: Number of subjects enrolled	Vietnam: 70
Country: Number of subjects enrolled	Hong Kong: 19
Country: Number of subjects enrolled	Russian Federation: 90
Country: Number of subjects enrolled	Argentina: 19
Country: Number of subjects enrolled	Mexico: 18
Country: Number of subjects enrolled	Canada: 47
Country: Number of subjects enrolled	Romania: 95
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	United Kingdom: 36
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	Poland: 81
Country: Number of subjects enrolled	Hungary: 53

Country: Number of subjects enrolled	Italy: 85
Worldwide total number of subjects	1077
EEA total number of subjects	445

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)	1045
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 1081 patients included in the randomized set, 4 patients were excluded from the Full Analysis Set (FAS) due to mis-randomization related to information entered in the IVRS system by mistake. These patients did not have a baseline visit and never started study medication.

Pre-assignment

Screening details:

Participants were screened for eligibility over a period of 42 days.

Period 1

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

Blinding implementation details:

The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Alisporivir 600 QD RGT

Arm description:

Triple therapy with a response-guided treatment duration (see below) with Peg-IFN α 2a and Ribavirin (P/R) plus alisporivir 600 mg twice daily (BID) for one week followed by P/R plus alisporivir 600 mg once daily (QD) for an additional 23 or 47 weeks based on week 4 hepatitis C virus (HCV) RNA results.

Response guided treatment:

- Patients with a viral load below the level of detection (LOD) at week 4 (< RVR4LOD) had to stop P/R and alisporivir study medications after 24 weeks.
- Patients with a viral load at or above the LOD at week 4 (\geq RVR4LOD) had to complete 48 weeks of P/R and alisporivir study treatment.

Arm type	Experimental
Investigational medicinal product name	Alisporivir
Investigational medicinal product code	
Other name	DEB025
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Three 200 mg soft gel capsules: twice daily (BID) for Week 1, once daily (QD) in the morning the remaining weeks

Investigational medicinal product name	Peg-IFN α 2a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Weekly dose of 180 μ g

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

Dosage and administration details:

200 mg tablets; patients < 75 Kg body weight at screening: 1000 mg daily, with 2 tablets in the morning and 3 tablets in the evening; ≥ 75 Kg: 1200 mg daily, with 3 tablets in the morning and 3 tablets in the evening. If a patient's weight increased from < 75 Kg to ≥ 75 Kg, the investigator could increase the dose to 1200 mg per day as per clinical practice. Likewise, the investigator could lower the dose from 1200 mg/day to 1000 mg/day as per clinical practice if the patient's weight decreased from ≥ 75 Kg to < 75 Kg.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Two placebo capsules to match alisporivir, QD in the evening after Week 1

Arm title	Arm B: Alisporivir 400 BID RGT
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Arm description:

Triple therapy with a response-guided treatment duration (see below) with Peg-IFNα2a and Ribavirin (P/R) plus alisporivir 400 mg twice daily (BID) for 24 or 48 weeks based on week 4 hepatitis C virus (HCV) RNA results.

Response guided treatment:

- Patients with a viral load below the level of detection (LOD) at week 4 (< RVR4LOD) had to stop P/R and alisporivir study medications after 24 weeks.
- Patients with a viral load at or above the LOD at week 4 (≥ RVR4LOD) had to complete 48 weeks of P/R and alisporivir study treatment.

Arm type	Experimental
Investigational medicinal product name	Alisporivir
Investigational medicinal product code	
Other name	DEB025
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Two 200 mg soft gel capsules BID for the duration of treatment

Investigational medicinal product name	Peg-IFNα2a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Weekly dose of 180 µg

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

Dosage and administration details:

200 mg tablets; patients < 75 Kg body weight at screening: 1000 mg daily, with 2 tablets in the morning and 3 tablets in the evening; ≥ 75 Kg: 1200 mg daily, with 3 tablets in the morning and 3 tablets in the evening. If a patient's weight increased from < 75 Kg to ≥ 75 Kg, the investigator could increase the dose to 1200 mg per day as per clinical practice. Likewise, the investigator could lower the dose from 1200 mg/day to 1000 mg/day as per clinical practice if the patient's weight decreased from ≥ 75 Kg to < 75 Kg.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One placebo capsule to match alisporivir: BID for Week 1, QD in the morning of remaining weeks

Arm title	Arm C: Alisporivir 600 QD
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Arm description:

Fixed-duration triple therapy with Peg-IFN α 2a and Ribavirin (P/R) plus alisporivir 600 mg twice daily (BID) for one week followed by P/R plus alisporivir 600 mg once daily (QD) for an additional 47 weeks.

Arm type	Experimental
Investigational medicinal product name	Alisporivir
Investigational medicinal product code	
Other name	DEB025
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Three 200 mg soft gel capsules: BID for Week 1, QD in the morning the remaining weeks

Investigational medicinal product name	Peg-IFN α 2a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Weekly dose of 180 μ g

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

Dosage and administration details:

200 mg tablets; patients < 75 Kg body weight at screening: 1000 mg daily, with 2 tablets in the morning and 3 tablets in the evening; \geq 75 Kg: 1200 mg daily, with 3 tablets in the morning and 3 tablets in the evening. If a patient's weight increased from < 75 Kg to \geq 75 Kg, the investigator could increase the dose to 1200 mg per day as per clinical practice. Likewise, the investigator could lower the dose from 1200 mg/day to 1000 mg/day as per clinical practice if the patient's weight decreased from \geq 75 Kg to < 75 Kg.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Two placebo capsules to match alisporivir, QD in the evening after Week 1

Arm title	Arm D: Peg-IFN α 2a and Ribavirin (P/R)
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Arm description:

Therapy with P/R and placebo for 48 weeks.

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

Dosage and administration details:

Week 1: three placebo capsules BID to match alisporivir; remaining weeks: three placebo capsules QD in the morning and two placebo capsules QD in the evening

Investigational medicinal product name	Peg-IFN α 2a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Weekly dose of 180 μ g

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

Dosage and administration details:

200 mg tablets; patients < 75 Kg body weight at screening: 1000 mg daily, with 2 tablets in the morning and 3 tablets in the evening; \geq 75 Kg: 1200 mg daily, with 3 tablets in the morning and 3 tablets in the evening. If a patient's weight increased from < 75 Kg to \geq 75 Kg, the investigator could increase the dose to 1200 mg per day as per clinical practice. Likewise, the investigator could lower the dose from 1200 mg/day to 1000 mg/day as per clinical practice if the patient's weight decreased from \geq 75 Kg to < 75 Kg.

Number of subjects in period 1	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD
Started	274	270	265
Completed treatment at week 24	96 ^[1]	94 ^[2]	1 ^[3]
Completed treatment at week 48	114 ^[4]	98 ^[5]	184 ^[6]
Completed	210	192	185
Not completed	64	78	80
Adverse event, serious fatal	-	1	-
Patient withdrew consent	11	14	12
Adverse event, non-fatal	17	33	31
Unsatisfactory therapeutic effect	22	21	26
Administrative problems	-	-	1
Non-compliance	4	4	6
Lost to follow-up	6	4	3
Protocol deviation	4	1	1

Number of subjects in period 1	Arm D: Peg-IFN α 2a and Ribavirin (P/R)
Started	268
Completed treatment at week 24	0 ^[7]
Completed treatment at week 48	170
Completed	170
Not completed	98
Adverse event, serious fatal	-

Patient withdrew consent	12
Adverse event, non-fatal	13
Unsatisfactory therapeutic effect	63
Administrative problems	-
Non-compliance	7
Lost to follow-up	2
Protocol deviation	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Complete treatment after 24 weeks is decided based on if the HCV RNA was below the limit of detection (LOD) after 4 weeks of treatment (Rapid Virologic Response – RVR).

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Complete treatment after 24 weeks is decided based on if the HCV RNA was below the limit of detection (LOD) after 4 weeks of treatment (Rapid Virologic Response – RVR).

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The treatment duration for this arm is 48 week.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Complete treatment after 48 weeks is decided as patients with a viral load at or above the level of detection (LOD) at week 4 (\geq RVR4LOD)

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Complete treatment after 48 weeks is decided as patients with a viral load at or above the level of detection (LOD) at week 4 (\geq RVR4LOD)

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Complete treatment after 48 weeks is decided as patients with a viral load at or above the level of detection (LOD) at week 4 (\geq RVR4LOD)

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The treatment duration for this arm is 48 week.

Period 2

Period 2 title	Open-label treatment
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Open-label ALV600 QD
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Arm description:

Patients from the Peg-IFN α 2a and Ribavirin (P/R) plus Alisporivir Placebo group who failed to achieve a decrease greater than or equal to 2 log $_{10}$ from baseline in serum hepatitis C virus (HCV) RNA concentration at any time within the first 12 weeks of treatment (Null non-responder), had a viral load above the level of detection (LOQ) at week 24, or had a viral breakthrough were offered open-label treatment with P/R plus alisporivir 600 mg twice daily (BID) for one week followed by P/R plus alisporivir 600 mg once daily (QD) for 47 weeks with 24 weeks of treatment-free follow-up.

Arm type	Experimental
Investigational medicinal product name	Alisporivir
Investigational medicinal product code	
Other name	DEB025
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Three 200 mg soft gel capsules: BID Week 1 and QD in the morning the remaining 47 weeks

Investigational medicinal product name	Peg-IFNa2a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Weekly dose of 180 µg

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

Dosage and administration details:

200 mg tablets; patients < 75 Kg body weight at screening: 1000 mg daily, with 2 tablets in the morning and 3 tablets in the evening; ≥ 75 Kg: 1200 mg daily, with 3 tablets in the morning and 3 tablets in the evening. If a patient's weight increased from < 75 Kg to ≥ 75 Kg, the investigator could increase the dose to 1200 mg per day as per clinical practice. Likewise, the investigator could lower the dose from 1200 mg/day to 1000 mg/day as per clinical practice if the patient's weight decreased from ≥ 75 Kg to < 75 Kg.

Number of subjects in period 2^[8]	Open-label ALV600 QD
Started	11
Completed	3
Not completed	8
Adverse event, non-fatal	1
Unsatisfactory therapeutic effect	6
Protocol deviation	1

Notes:

[8] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Open label treatment is relevant to only one arm of the double blind treatment period.

Baseline characteristics

Reporting groups

Reporting group title	Arm A: Alisporivir 600 QD RGT
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Reporting group description:

Triple therapy with a response-guided treatment duration (see below) with Peg-IFN α 2a and Ribavirin (P/R) plus alisporivir 600 mg twice daily (BID) for one week followed by P/R plus alisporivir 600 mg once daily (QD) for an additional 23 or 47 weeks based on week 4 hepatitis C virus (HCV) RNA results.

Response guided treatment:

- Patients with a viral load below the level of detection (LOD) at week 4 (< RVR4LOD) had to stop P/R and alisporivir study medications after 24 weeks.
- Patients with a viral load at or above the LOD at week 4 (\geq RVR4LOD) had to complete 48 weeks of P/R and alisporivir study treatment.

Reporting group title	Arm B: Alisporivir 400 BID RGT
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Reporting group description:

Triple therapy with a response-guided treatment duration (see below) with Peg-IFN α 2a and Ribavirin (P/R) plus alisporivir 400 mg twice daily (BID) for 24 or 48 weeks based on week 4 hepatitis C virus (HCV) RNA results.

Response guided treatment:

- Patients with a viral load below the level of detection (LOD) at week 4 (< RVR4LOD) had to stop P/R and alisporivir study medications after 24 weeks.
- Patients with a viral load at or above the LOD at week 4 (\geq RVR4LOD) had to complete 48 weeks of P/R and alisporivir study treatment.

Reporting group title	Arm C: Alisporivir 600 QD
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Reporting group description:

Fixed-duration triple therapy with Peg-IFN α 2a and Ribavirin (P/R) plus alisporivir 600 mg twice daily (BID) for one week followed by P/R plus alisporivir 600 mg once daily (QD) for an additional 47 weeks.

Reporting group title	Arm D: Peg-IFN α 2a and Ribavirin (P/R)
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Reporting group description:

Therapy with P/R and placebo for 48 weeks.

Reporting group values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD
Number of subjects	274	270	265
Age categorical			
Information on categorical age is provided for the Full Analysis Set (FAS). Four patients were excluded from the FAS due to mis-randomization related to information entered in the interactive voice response system (IVRS) system by mistake. These patients did not have a baseline visit and never started study medications. They were included in the all screened and randomized analysis sets, but excluded from the FAS and safety set (SAF).			
Units: Subjects			
>/=18 to 30 years	28	36	38
>30 to 50 years	141	118	124
>50 to 65 years	98	111	97
>65 to 70 years	7	5	6
Age continuous			
Information on age is provided for the Full Analysis Set (FAS). Four patients were excluded from the FAS due to mis-randomization related to information entered in the interactive voice response system (IVRS) system by mistake. These patients did not have a baseline visit and never started study medications. They were included in the all screened and randomized analysis sets, but excluded from the FAS and safety set (SAF).			
Units: years			
arithmetic mean	45.9	45.8	45.5
standard deviation	\pm 11.08	\pm 11.95	\pm 12.15

Gender categorical			
Information on gender is provided for the Full Analysis Set (FAS). Four patients were excluded from the FAS due to mis-randomization related to information entered in the interactive voice response system (IVRS) system by mistake. These patients did not have a baseline visit and never started study medications. They were included in the all screened and randomized analysis sets, but excluded from the FAS and safety set (SAF).			
Units: Subjects			
Female	113	106	134
Male	161	164	131

Reporting group values	Arm D: Peg-IFN α 2a and Ribavirin (P/R)	Total	
Number of subjects	268	1077	
Age categorical			
Information on categorical age is provided for the Full Analysis Set (FAS). Four patients were excluded from the FAS due to mis-randomization related to information entered in the interactive voice response system (IVRS) system by mistake. These patients did not have a baseline visit and never started study medications. They were included in the all screened and randomized analysis sets, but excluded from the FAS and safety set (SAF).			
Units: Subjects			
>/=18 to 30 years	26	128	
>30 to 50 years	132	515	
>50 to 65 years	105	411	
>65 to 70 years	5	23	
Age continuous			
Information on age is provided for the Full Analysis Set (FAS). Four patients were excluded from the FAS due to mis-randomization related to information entered in the interactive voice response system (IVRS) system by mistake. These patients did not have a baseline visit and never started study medications. They were included in the all screened and randomized analysis sets, but excluded from the FAS and safety set (SAF).			
Units: years			
arithmetic mean	46.3		
standard deviation	± 11.53	-	
Gender categorical			
Information on gender is provided for the Full Analysis Set (FAS). Four patients were excluded from the FAS due to mis-randomization related to information entered in the interactive voice response system (IVRS) system by mistake. These patients did not have a baseline visit and never started study medications. They were included in the all screened and randomized analysis sets, but excluded from the FAS and safety set (SAF).			
Units: Subjects			
Female	114	467	
Male	154	610	

End points

End points reporting groups

Reporting group title	Arm A: Alisporivir 600 QD RGT
Reporting group description: Triple therapy with a response-guided treatment duration (see below) with Peg-IFN α 2a and Ribavirin (P/R) plus alisporivir 600 mg twice daily (BID) for one week followed by P/R plus alisporivir 600 mg once daily (QD) for an additional 23 or 47 weeks based on week 4 hepatitis C virus (HCV) RNA results. Response guided treatment: <ul style="list-style-type: none">• Patients with a viral load below the level of detection (LOD) at week 4 (< RVR4LOD) had to stop P/R and alisporivir study medications after 24 weeks.• Patients with a viral load at or above the LOD at week 4 (\geq RVR4LOD) had to complete 48 weeks of P/R and alisporivir study treatment.	
Reporting group title	Arm B: Alisporivir 400 BID RGT
Reporting group description: Triple therapy with a response-guided treatment duration (see below) with Peg-IFN α 2a and Ribavirin (P/R) plus alisporivir 400 mg twice daily (BID) for 24 or 48 weeks based on week 4 hepatitis C virus (HCV) RNA results. Response guided treatment: <ul style="list-style-type: none">• Patients with a viral load below the level of detection (LOD) at week 4 (< RVR4LOD) had to stop P/R and alisporivir study medications after 24 weeks.• Patients with a viral load at or above the LOD at week 4 (\geq RVR4LOD) had to complete 48 weeks of P/R and alisporivir study treatment.	
Reporting group title	Arm C: Alisporivir 600 QD
Reporting group description: Fixed-duration triple therapy with Peg-IFN α 2a and Ribavirin (P/R) plus alisporivir 600 mg twice daily (BID) for one week followed by P/R plus alisporivir 600 mg once daily (QD) for an additional 47 weeks.	
Reporting group title	Arm D: Peg-IFN α 2a and Ribavirin (P/R)
Reporting group description: Therapy with P/R and placebo for 48 weeks.	
Reporting group title	Open-label ALV600 QD
Reporting group description: Patients from the Peg-IFN α 2a and Ribavirin (P/R) plus Alisporivir Placebo group who failed to achieve a decrease greater than or equal to 2 log $_{10}$ from baseline in serum hepatitis C virus (HCV) RNA concentration at any time within the first 12 weeks of treatment (Null non-responder), had a viral load above the level of detection (LOQ) at week 24, or had a viral breakthrough were offered open-label treatment with P/R plus alisporivir 600 mg twice daily (BID) for one week followed by P/R plus alisporivir 600 mg once daily (QD) for 47 weeks with 24 weeks of treatment-free follow-up.	

Primary: Percent of Patients Who Achieved Sustained Virologic Response by 12 Weeks (SVR12)

End point title	Percent of Patients Who Achieved Sustained Virologic Response by 12 Weeks (SVR12) ^[1]
End point description: SVR12 was defined as hepatitis C virus (HCV) RNA less than the limit of quantification (LOQ) at week 12 of follow-up (FU) after stopping treatment. LOQ was defined as HCV RNA < 25 International Units (IU)/mL. For this endpoint, n equals the number of patients who were at the corresponding category, M equals the total number of patients with a value for the corresponding exposure after imputation, and N equals the total number of patients in the treatment group. The percent shown is n/M; the value for "subjects analysed" equals N. This end point analyzed the Full Analysis Set (N), which included all patients to whom study treatment had been assigned.	
End point type	Primary
End point timeframe: 12 weeks after treatment completion	

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: Due to the clinical hold, the character of the study status changed from confirmatory to nonconfirmatory. Therefore, statistical comparison planned in the protocol was not done.

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	274 ^[2]	270 ^[3]	265 ^[4]	268 ^[5]
Units: percent of patients				
number (not applicable)				
Overall	68.6	68.9	69.4	52.5
≤ 12 weeks of treatment	30.3	38.2	40.6	30.4
> 12 to ≤ 16 weeks of treatment	65.1	68.1	65.2	40.9
> 16 to ≤ 20 weeks of treatment	78	78.8	79.7	60.7
> 20 to ≤ 24 weeks of treatment	82.5	80.3	73.5	66.7
> 24 weeks of treatment	75.6	90.3	76.5	60.4

Notes:

[2] - M were: Overall = 274; ≤12 = 33; >12-≤16 = 83; >16-≤20 = 59; >20-≤24 = 57; >24 = 41

[3] - M were: Overall = 270; ≤12 = 55; >12-≤16 = 69; >16-≤20 = 52; >20-≤24 = 61; >24 = 31

[4] - M were: Overall = 265; ≤12 = 32; >12-≤16 = 69; >16-≤20 = 64; >20-≤24 = 49; >24 = 51

[5] - M were: Overall = 265; ≤12 = 23; >12-≤16 = 88; >16-≤20 = 56; >20-≤24 = 45; >24 = 53

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Achieved Sustained Virologic Response by 24 Weeks (SVR24)

End point title	Percent of Patients Who Achieved Sustained Virologic Response by 24 Weeks (SVR24)
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End point description:

SVR24 was defined as hepatitis C virus (HCV) RNA less than the limit of quantification (LOQ) at week 24 of follow-up (FU) after stopping treatment. LOQ was defined as HCV RNA < 25 International Units (IU)/mL.

This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type	Secondary
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End point timeframe:

24 weeks after treatment completion

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	273	268	265	265
Units: percent of patients				
number (not applicable)	68.5	69	68.3	51.7

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Achieved Extended Rapid Virologic Response (eRVR)

End point title	Percent of Patients Who Achieved Extended Rapid Virologic Response (eRVR)
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End point description:

eRVR was defined as RVR less than the limit of quantification (LOQ) achieved and maintained until 12 weeks after the start of treatment. LOQ was defined as HCV RNA < 25 International Units (IU)/mL. This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type	Secondary
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End point timeframe:

12 weeks after treatment start

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	259	242	247	256
Units: percent of patients				
number (not applicable)	60.2	71.1	56.7	28.1

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Achieved Early Virologic Response (EVR)

End point title	Percent of Patients Who Achieved Early Virologic Response (EVR)
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End point description:

EVR was defined as serum hepatitis C virus (HCV) RNA reduction greater than or equal to 2Log₁₀ or serum HCV RNA less than the limit of quantification (LOQ) after 12 weeks of treatment. LOQ was defined as HCV RNA < 25 International Units (IU)/mL.

This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type	Secondary
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End point timeframe:

12 weeks after treatment start

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFNα2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	259	242	247	256
Units: percent of patients				
number (not applicable)	97.7	98.3	99.6	89.8

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Achieved Partial Early Virologic Response (pEVR)

End point title	Percent of Patients Who Achieved Partial Early Virologic Response (pEVR)
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End point description:

pEVR was defined as serum hepatitis C virus (HCV) RNA reduction greater than or equal to 2Log10 and greater than or equal to the limit of quantification (LOQ) after 12 weeks of treatment. LOQ was defined as HCV RNA < 25 International Units (IU)/mL.

This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type	Secondary
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End point timeframe:

12 weeks after treatment start

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFNα2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	259	242	247	256
Units: percent of patients				
number (not applicable)	8.1	2.1	10.5	19.5

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Achieved Complete Early Viral Response (cEVR)

End point title	Percent of Patients Who Achieved Complete Early Viral Response (cEVR)
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End point description:

cEVR was defined as serum hepatitis C virus (HCV) RNA less than the limit of quantification (LOQ) after

12 weeks of treatment. LOQ was defined as HCV RNA < 25 International Units (IU)/mL. This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type	Secondary
End point timeframe:	
12 weeks after treatment start	

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	259	242	247	256
Units: percent of patients				
number (not applicable)	89.6	96.3	89.1	70.3

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Achieved End-of-Alisporivir-Treatment Response (EDTR)

End point title	Percent of Patients Who Achieved End-of-Alisporivir-Treatment Response (EDTR)
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End point description:

EDTR was defined as hepatitis C virus (HCV) RNA less than the limit of quantification (LOQ) at the end of treatment with alisporivir (completed or prematurely discontinued). LOQ was defined as HCV RNA < 25 International Units (IU)/mL.

This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type	Secondary
End point timeframe:	
Whenever completion of alisporivir treatment occurred or 12 and 48 weeks after treatment completion	

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	271	267	264	264
Units: percent of patients				
number (not applicable)	90	93.6	90.2	75

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Achieved End-of-Treatment Response (ETR)

End point title	Percent of Patients Who Achieved End-of-Treatment Response (ETR)
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End point description:

ETR was defined as hepatitis C virus (HCV) RNA less than the limit of quantification (LOQ) at the end of treatment. LOQ was defined as HCV RNA < 25 International Units (IU)/mL.

This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type	Secondary
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End point timeframe:

Whenever treatment completion occurred or 12 and 48 weeks after treatment completion

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFNa2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	271	268	264	265
Units: percent of patients				
number (not applicable)	88.2	87.7	87.5	80

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Achieved Rapid Virologic Response (RVR)

End point title	Percent of Patients Who Achieved Rapid Virologic Response (RVR)
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End point description:

RVR was defined as serum hepatitis C virus (HCV) RNA less than the limit of quantification (LOQ) after 4 weeks of treatment. LOQ was defined as HCV RNA < 25 International Units (IU)/mL.

This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type	Secondary
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End point timeframe:

4 weeks after treatment start

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFNa2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	268	258	258	261
Units: percent of patients				
number (not applicable)	60.1	72.5	56.6	28.4

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Were Null Non-responders

End point title | Percent of Patients Who Were Null Non-responders

End point description:

A null non-responder was defined as a subject who failed to achieve a decrease of greater than or equal to 2log₁₀ from baseline in serum hepatitis C virus (HCV) RNA concentration at any time within the first 12 weeks of treatment.

This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type | Secondary

End point timeframe:

Within 12 weeks of treatment start

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFNα2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	273	268	265	265
Units: percent of patients				
number (not applicable)	2.2	2.2	1.5	7.5

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Were Partial Non-responders

End point title | Percent of Patients Who Were Partial Non-responders

End point description:

A partial non-responder was defined as a subject whose hepatitis C virus (HCV) RNA levels decreased greater than or equal to 2log₁₀ from baseline at any time within the first 12 weeks of treatment but never became undetectable during treatment.

This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type | Secondary

End point timeframe:

24 or 48 weeks after treatment start

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFNα2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	273	268	265	265
Units: percent of patients				
number (not applicable)	6.6	3.4	5.3	8.3

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Were Non-responders

End point title	Percent of Patients Who Were Non-responders
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End point description:

A non-responder was defined as a subject who failed to achieve undetectable levels of serum hepatitis C virus (HCV) RNA during treatment.

This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type	Secondary
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End point timeframe:

24 or 48 weeks after treatment start

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	273	268	265	265
Units: percent of patients				
number (not applicable)	8.8	5.6	6.8	15.8

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Achieved Sustained Virologic Response by 4 Weeks (SVR4)

End point title	Percent of Patients Who Achieved Sustained Virologic Response by 4 Weeks (SVR4)
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End point description:

SVR4 was defined as hepatitis C virus (HCV) RNA less than the limit of quantification (LOQ) at week 4 of follow-up (FU) after stopping treatment. LOQ was defined as HCV RNA < 25 International Units (IU)/mL. This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type	Secondary
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End point timeframe:

4 weeks after treatment completion

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	273	268	265	265
Units: percent of patients				
number (not applicable)	76.2	76.5	75.1	58.1

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Relapsed

End point title	Percent of Patients Who Relapsed
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End point description:

Relapse was defined as levels of hepatitis C virus (HCV) RNA greater than the limit of detection (LOD) during post-treatment follow-up (FU) in patients with HCV RNA less than LOD at the end of treatment who achieved end-of-treatment response (ETR) above the LOD and had ≥ 1 post-treatment HCV RNA measurement. LOD was defined as < 10 International Units (IU)/mL.

This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type	Secondary
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End point timeframe:

24 or 48 weeks after treatment completion

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	214	215	180
Units: percent of patients				
number (not applicable)	17.9	13.1	15.3	26.1

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients With Normalized Alanine Aminotransferase (ALT) at The End of Treatment

End point title	Percent of Patients With Normalized Alanine Aminotransferase (ALT) at The End of Treatment
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End point description:

Normalized ALT was defined as less than or equal to the upper limit of normal (ULN). This end point measured ALT in patients with abnormal (greater than the ULN) ALT at baseline and those with ≥ 1 ALT measurement during triple therapy for the triple therapy end point and ≥ 1 on-treatment ALT measurement for the treatment end point. ULN was defined as 37 International Units (IU)/L for females, 48 IU/L for males.

This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had

been assigned.

End point type	Secondary
End point timeframe:	24 or 48 weeks after treatment start

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	188	178	185	183
Units: percent of patients				
number (not applicable)				
Normalized at triple therapy end	92.6	93.3	88.6	82
Normalized at treatment end	80.9	80.3	80	78.7

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients With Normalized Alanine Aminotransferase (ALT) at The End of Study

End point title	Percent of Patients With Normalized Alanine Aminotransferase (ALT) at The End of Study
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End point description:

Normalized ALT was defined as less than or equal to the upper limit of normal (ULN). This end point measured ALT in patients with abnormal (greater than the ULN) ALT at baseline and those with $>=1$ post-baseline ALT measurement for the study end point. ULN was defined as 37 International Units (IU)/L for females, 48 IU/L for males.

This end point analyzed the Full Analysis Set, which included all patients to whom study treatment had been assigned.

End point type	Secondary
End point timeframe:	72 weeks

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	189	178	185	183
Units: percent of patients				
number (not applicable)	83.6	80.3	78.9	72.1

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Developed Thrombocytopenia

End point title | Percent of Patients Who Developed Thrombocytopenia

End point description:

Thrombocytopenia was defined as platelets less than $50 \times 10^9/L$ ($50 \times 10^3/\mu L$), corresponding to Division of Microbiology and Infectious Diseases (DMID) toxicity grade 3 or more during treatment between the different treatment arms. Only patients with a DMID grade less than 3 at baseline were counted. A patient with multiple grade 3/4 was counted only once.

This end point analyzed the Safety Set, which included all patients who received at least one dose of study medication.

End point type | Secondary

End point timeframe:

24 or 48 weeks

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	270	265	264	264
Units: percent of patients				
number (not applicable)	6.7	23	12.5	1.9

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Developed Neutropenia

End point title | Percent of Patients Who Developed Neutropenia

End point description:

Neutropenia was defined as neutrophils less than $0.75 \times 10^9/L$ ($0.75 \times 10^3/\mu L$) corresponding to a DMID toxicity grade 3 or more, during treatment between the different treatment arms. Only patients with a DMID grade less than 3 at baseline were counted. A patient with multiple grade 3/4 was counted only once.

This end point analyzed the Safety Set, which included all patients who received at least one dose of study medication.

End point type | Secondary

End point timeframe:

24 or 48 weeks

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	270	263	264	264
Units: percent of patients				
number (not applicable)	28.9	32.7	30.3	15.5

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Developed Anemia

End point title	Percent of Patients Who Developed Anemia
End point description: Anemia was defined as hemoglobin (Hb) less than 80g/L (< 8 g/dL), corresponding to a DMID toxicity grade 3 or more, during treatment between the different treatment arms. Only patients with a DMID grade less than 3 at baseline were counted. A patient with multiple grade 3/4 was counted only once. This end point analyzed the Safety Set, which included all patients who received at least one dose of study medication.	
End point type	Secondary
End point timeframe: 24 or 48 weeks	

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFN α 2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	271	267	264	264
Units: percent of patients				
number (not applicable)	1.8	3.7	0.8	1.9

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Who Developed Hyperbilirubinemia

End point title	Percent of Patients Who Developed Hyperbilirubinemia
End point description: Hyperbilirubinemia was defined as total bilirubin value greater than 5 \times the upper limit of normal (ULN) (DMID toxicity grade 3 or more) during treatment between the different treatment arms. Only patients with a DMID grade less than 3 at baseline were counted. A patient with multiple grade 3/4 was counted only once. ULN was defined as total bilirubin 21 μ mol/L. This end point analyzed the Safety Set, which included all patients who received at least one dose of study medication.	
End point type	Secondary
End point timeframe: 24 or 48 weeks	

End point values	Arm A: Alisporivir 600 QD RGT	Arm B: Alisporivir 400 BID RGT	Arm C: Alisporivir 600 QD	Arm D: Peg- IFNα2a and Ribavirin (P/R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	271	267	264	264
Units: percent of patients				
number (not applicable)	4.4	16.9	2.3	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Arm B: Alisporivir 400 BID RGT
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Reporting group description:

Triple therapy with a response-guided treatment duration (see below) with Peg-IFN α 2a and Ribavirin (P/R) plus alisporivir 400 mg twice daily (BID) for 24 or 48 weeks based on week 4 hepatitis C virus (HCV) RNA results.

Response guided treatment (RGT):

- Patients with a viral load below the level of detection (LOD) at week 4 (< RVR4LOD) had to stop P/R and alisporivir study medications after 24 weeks.
- Patients with a viral load at or above the LOD at week 4 (\geq RVR4LOD) had to complete 48 weeks of P/R and alisporivir study treatment.

Reporting group title	Arm A: Alisporivir 600 QD RGT
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Reporting group description:

Triple therapy with a response-guided treatment duration (see below) with Peg-IFN α 2a and Ribavirin (P/R) plus alisporivir 600 mg twice daily (BID) for one week followed by P/R plus alisporivir 600 mg once daily (QD) for an additional 23 or 47 weeks based on week 4 hepatitis C virus (HCV) RNA results.

Response guided treatment (RGT):

- Patients with a viral load below the level of detection (LOD) at week 4 (< RVR4LOD) had to stop P/R and alisporivir study medications after 24 weeks.
- Patients with a viral load at or above the LOD at week 4 (\geq RVR4LOD) had to complete 48 weeks of P/R and alisporivir study treatment.

Reporting group title	Arm C: Alisporivir 600 QD 48 week
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Reporting group description:

Fixed-duration triple therapy with Peg-IFN α 2a and Ribavirin (P/R) plus alisporivir 600 mg twice daily (BID) for one week followed by P/R plus alisporivir 600 mg once daily (QD) for an additional 47 weeks.

Reporting group title	Arm D: Peg-IFN α 2a and Ribavirin (P/R) 48 wk
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Reporting group description:

Therapy with P/R and placebo for 48 weeks.

Serious adverse events	Arm B: Alisporivir 400 BID RGT	Arm A: Alisporivir 600 QD RGT	Arm C: Alisporivir 600 QD 48 week
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 268 (10.45%)	24 / 273 (8.79%)	21 / 265 (7.92%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Breast cancer			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniopharyngioma			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Hepatocellular carcinoma			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leiomyosarcoma			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Pancreatic neoplasm			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary tumour benign			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic adenoma			

subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the cervix			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Hypertension			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	3 / 268 (1.12%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Vasculitis			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Drug interaction			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Influenza like illness			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipogranuloma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Multi-organ failure			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Pain			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Pyrexia			
subjects affected / exposed	2 / 268 (0.75%)	1 / 273 (0.37%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Bartholinitis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian disorder			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Epistaxis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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

Pulmonary fibrosis			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	2 / 265 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Major depression			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Schizophrenia, paranoid type			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Suicidal ideation			
subjects affected / exposed	2 / 268 (0.75%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			

subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Radius fracture			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive heart disease			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Tachycardia			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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 / 268 (0.37%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraventricular haemorrhage			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Paraesthesia			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 268 (0.37%)	1 / 273 (0.37%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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 / 268 (0.37%)	2 / 273 (0.73%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Febrile neutropenia			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 268 (0.00%)	2 / 273 (0.73%)	0 / 265 (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
Pancytopenia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Spontaneous haematoma			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Thrombocytopenia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Ear and labyrinth disorders			
Acute vestibular syndrome			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deafness neurosensory			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Dacryoadenitis acquired			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 268 (0.75%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Gastritis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Haematemesis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Pancreatitis			

subjects affected / exposed	1 / 268 (0.37%)	1 / 273 (0.37%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	3 / 268 (1.12%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 268 (0.75%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Cholecystitis acute			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatosplenomegaly			

subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Hyperthyroidism			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroiditis			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	2 / 265 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exostosis			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Bronchitis			
subjects affected / exposed	2 / 268 (0.75%)	1 / 273 (0.37%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Cellulitis			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicitis			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			

subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Nasal abscess			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Pneumonia			
subjects affected / exposed	1 / 268 (0.37%)	1 / 273 (0.37%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Salpingo-oophoritis			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 268 (0.00%)	2 / 273 (0.73%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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
Hypokalaemia			

subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Hypomagnesaemia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	0 / 265 (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
Hyponatraemia			
subjects affected / exposed	0 / 268 (0.00%)	0 / 273 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	0 / 265 (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

Serious adverse events	Arm D: Peg-IFN α 2a and Ribavirin (P/R) 48 wk		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 265 (10.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervix carcinoma			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Craniopharyngioma			

subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatocellular carcinoma			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leiomyosarcoma			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meningioma			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatic neoplasm			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pituitary tumour benign			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostatic adenoma			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of the cervix			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic dissection			

subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vasculitis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Drug interaction			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			

subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lipogranuloma			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multi-organ failure			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Bartholinitis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysfunctional uterine bleeding			

subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian disorder			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary fibrosis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillar hypertrophy			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mania			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Schizophrenia, paranoid type			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Radius fracture			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive heart disease			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hemiparesis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intraventricular haemorrhage			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 265 (0.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			

subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spontaneous haematoma			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Acute vestibular syndrome			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deafness neurosensory			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vertigo			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Dacryoadenitis acquired			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Diarrhoea				
subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoidal haemorrhage				
subjects affected / exposed	1 / 265 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	1 / 265 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 265 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	1 / 265 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				

subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 265 (0.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatosplenomegaly			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urticaria			

subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperthyroidism			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thyroiditis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Exostosis			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 265 (0.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Bronchopneumonia				
subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cervicitis				
subjects affected / exposed	1 / 265 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	1 / 265 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 265 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lobar pneumonia				
subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasal abscess				
subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary tuberculosis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Salpingo-oophoritis			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth abscess			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			

subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm B: Alisporivir 400 BID RGT	Arm A: Alisporivir 600 QD RGT	Arm C: Alisporivir 600 QD 48 week
Total subjects affected by non-serious adverse events			
subjects affected / exposed	261 / 268 (97.39%)	256 / 273 (93.77%)	250 / 265 (94.34%)
Vascular disorders			
Hypertension			
subjects affected / exposed	49 / 268 (18.28%)	29 / 273 (10.62%)	32 / 265 (12.08%)
occurrences (all)	59	31	36
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	46 / 268 (17.16%)	43 / 273 (15.75%)	46 / 265 (17.36%)
occurrences (all)	52	48	53
Chills			
subjects affected / exposed	30 / 268 (11.19%)	23 / 273 (8.42%)	33 / 265 (12.45%)
occurrences (all)	34	27	37
Fatigue			
subjects affected / exposed	97 / 268 (36.19%)	84 / 273 (30.77%)	87 / 265 (32.83%)
occurrences (all)	106	91	92
Influenza like illness			
subjects affected / exposed	52 / 268 (19.40%)	55 / 273 (20.15%)	38 / 265 (14.34%)
occurrences (all)	62	70	51
Injection site erythema			
subjects affected / exposed	10 / 268 (3.73%)	14 / 273 (5.13%)	17 / 265 (6.42%)
occurrences (all)	10	14	17
Irritability			

subjects affected / exposed occurrences (all)	16 / 268 (5.97%) 17	19 / 273 (6.96%) 19	21 / 265 (7.92%) 24
Pyrexia subjects affected / exposed occurrences (all)	92 / 268 (34.33%) 112	78 / 273 (28.57%) 101	81 / 265 (30.57%) 120
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	53 / 268 (19.78%) 56	47 / 273 (17.22%) 57	57 / 265 (21.51%) 68
Dyspnoea subjects affected / exposed occurrences (all)	26 / 268 (9.70%) 26	37 / 273 (13.55%) 40	23 / 265 (8.68%) 24
Epistaxis subjects affected / exposed occurrences (all)	25 / 268 (9.33%) 31	12 / 273 (4.40%) 12	15 / 265 (5.66%) 16
Oropharyngeal pain subjects affected / exposed occurrences (all)	13 / 268 (4.85%) 15	13 / 273 (4.76%) 15	19 / 265 (7.17%) 29
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	19 / 268 (7.09%) 19	16 / 273 (5.86%) 17	24 / 265 (9.06%) 26
Depression subjects affected / exposed occurrences (all)	25 / 268 (9.33%) 26	20 / 273 (7.33%) 25	26 / 265 (9.81%) 27
Insomnia subjects affected / exposed occurrences (all)	57 / 268 (21.27%) 63	49 / 273 (17.95%) 59	48 / 265 (18.11%) 55
Investigations			
Weight decreased subjects affected / exposed occurrences (all)	28 / 268 (10.45%) 28	24 / 273 (8.79%) 26	26 / 265 (9.81%) 29
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	34 / 268 (12.69%) 36	33 / 273 (12.09%) 36	25 / 265 (9.43%) 26

Dysgeusia subjects affected / exposed occurrences (all)	22 / 268 (8.21%) 23	14 / 273 (5.13%) 14	13 / 265 (4.91%) 14
Headache subjects affected / exposed occurrences (all)	93 / 268 (34.70%) 126	88 / 273 (32.23%) 117	93 / 265 (35.09%) 145
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	124 / 268 (46.27%) 140	113 / 273 (41.39%) 131	91 / 265 (34.34%) 108
Leukopenia subjects affected / exposed occurrences (all)	27 / 268 (10.07%) 33	48 / 273 (17.58%) 66	48 / 265 (18.11%) 61
Lymphopenia subjects affected / exposed occurrences (all)	7 / 268 (2.61%) 11	15 / 273 (5.49%) 17	16 / 265 (6.04%) 24
Neutropenia subjects affected / exposed occurrences (all)	80 / 268 (29.85%) 116	84 / 273 (30.77%) 127	86 / 265 (32.45%) 130
Thrombocytopenia subjects affected / exposed occurrences (all)	73 / 268 (27.24%) 85	47 / 273 (17.22%) 49	49 / 265 (18.49%) 58
Eye disorders			
Ocular icterus subjects affected / exposed occurrences (all)	14 / 268 (5.22%) 14	11 / 273 (4.03%) 13	5 / 265 (1.89%) 5
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	23 / 268 (8.58%) 27	17 / 273 (6.23%) 19	22 / 265 (8.30%) 26
Constipation subjects affected / exposed occurrences (all)	16 / 268 (5.97%) 19	12 / 273 (4.40%) 12	7 / 265 (2.64%) 9
Diarrhoea subjects affected / exposed occurrences (all)	26 / 268 (9.70%) 36	29 / 273 (10.62%) 36	36 / 265 (13.58%) 44
Dyspepsia			

subjects affected / exposed occurrences (all)	15 / 268 (5.60%) 16	21 / 273 (7.69%) 24	32 / 265 (12.08%) 33
Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	9 / 268 (3.36%) 10	10 / 273 (3.66%) 10	5 / 265 (1.89%) 6
Nausea subjects affected / exposed occurrences (all)	66 / 268 (24.63%) 73	65 / 273 (23.81%) 78	62 / 265 (23.40%) 71
Vomiting subjects affected / exposed occurrences (all)	39 / 268 (14.55%) 42	25 / 273 (9.16%) 28	28 / 265 (10.57%) 29
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	61 / 268 (22.76%) 70	32 / 273 (11.72%) 33	25 / 265 (9.43%) 26
Jaundice subjects affected / exposed occurrences (all)	20 / 268 (7.46%) 21	7 / 273 (2.56%) 7	3 / 265 (1.13%) 3
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	44 / 268 (16.42%) 44	58 / 273 (21.25%) 58	55 / 265 (20.75%) 55
Dry skin subjects affected / exposed occurrences (all)	22 / 268 (8.21%) 22	21 / 273 (7.69%) 21	30 / 265 (11.32%) 31
Pruritus subjects affected / exposed occurrences (all)	55 / 268 (20.52%) 69	58 / 273 (21.25%) 75	48 / 265 (18.11%) 58
Rash subjects affected / exposed occurrences (all)	39 / 268 (14.55%) 43	45 / 273 (16.48%) 51	45 / 265 (16.98%) 51
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	22 / 268 (8.21%) 22	15 / 273 (5.49%) 15	23 / 265 (8.68%) 23
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	30 / 268 (11.19%) 35	34 / 273 (12.45%) 36	38 / 265 (14.34%) 42
Back pain subjects affected / exposed occurrences (all)	14 / 268 (5.22%) 15	13 / 273 (4.76%) 13	14 / 265 (5.28%) 15
Muscle spasms subjects affected / exposed occurrences (all)	15 / 268 (5.60%) 18	8 / 273 (2.93%) 12	7 / 265 (2.64%) 8
Myalgia subjects affected / exposed occurrences (all)	53 / 268 (19.78%) 62	58 / 273 (21.25%) 71	56 / 265 (21.13%) 64
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 268 (1.49%) 4	13 / 273 (4.76%) 14	14 / 265 (5.28%) 18
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	59 / 268 (22.01%) 68	61 / 273 (22.34%) 64	58 / 265 (21.89%) 63
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	23 / 268 (8.58%) 25	11 / 273 (4.03%) 12	22 / 265 (8.30%) 25

Non-serious adverse events	Arm D: Peg-IFN α 2a and Ribavirin (P/R) 48 wk		
Total subjects affected by non-serious adverse events subjects affected / exposed	241 / 265 (90.94%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	7 / 265 (2.64%) 17		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	47 / 265 (17.74%) 54		
Chills			

subjects affected / exposed	21 / 265 (7.92%)		
occurrences (all)	30		
Fatigue			
subjects affected / exposed	83 / 265 (31.32%)		
occurrences (all)	95		
Influenza like illness			
subjects affected / exposed	38 / 265 (14.34%)		
occurrences (all)	49		
Injection site erythema			
subjects affected / exposed	8 / 265 (3.02%)		
occurrences (all)	9		
Irritability			
subjects affected / exposed	21 / 265 (7.92%)		
occurrences (all)	23		
Pyrexia			
subjects affected / exposed	74 / 265 (27.92%)		
occurrences (all)	98		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	51 / 265 (19.25%)		
occurrences (all)	58		
Dyspnoea			
subjects affected / exposed	24 / 265 (9.06%)		
occurrences (all)	25		
Epistaxis			
subjects affected / exposed	10 / 265 (3.77%)		
occurrences (all)	12		
Oropharyngeal pain			
subjects affected / exposed	11 / 265 (4.15%)		
occurrences (all)	13		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	27 / 265 (10.19%)		
occurrences (all)	32		
Depression			

subjects affected / exposed occurrences (all)	22 / 265 (8.30%) 26		
Insomnia subjects affected / exposed occurrences (all)	58 / 265 (21.89%) 63		
Investigations Weight decreased subjects affected / exposed occurrences (all)	16 / 265 (6.04%) 16		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	30 / 265 (11.32%) 34		
Dysgeusia subjects affected / exposed occurrences (all)	11 / 265 (4.15%) 12		
Headache subjects affected / exposed occurrences (all)	80 / 265 (30.19%) 104		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	85 / 265 (32.08%) 123		
Leukopenia subjects affected / exposed occurrences (all)	27 / 265 (10.19%) 37		
Lymphopenia subjects affected / exposed occurrences (all)	8 / 265 (3.02%) 12		
Neutropenia subjects affected / exposed occurrences (all)	66 / 265 (24.91%) 109		
Thrombocytopenia subjects affected / exposed occurrences (all)	14 / 265 (5.28%) 20		
Eye disorders			

Ocular icterus subjects affected / exposed occurrences (all)	4 / 265 (1.51%) 4		
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	14 / 265 (5.28%) 16		
Constipation subjects affected / exposed occurrences (all)	11 / 265 (4.15%) 12		
Diarrhoea subjects affected / exposed occurrences (all)	35 / 265 (13.21%) 39		
Dyspepsia subjects affected / exposed occurrences (all)	15 / 265 (5.66%) 16		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	14 / 265 (5.28%) 15		
Nausea subjects affected / exposed occurrences (all)	43 / 265 (16.23%) 51		
Vomiting subjects affected / exposed occurrences (all)	18 / 265 (6.79%) 21		
Hepatobiliary disorders			
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	2 / 265 (0.75%) 2		
Jaundice subjects affected / exposed occurrences (all)	1 / 265 (0.38%) 1		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	45 / 265 (16.98%) 45		
Dry skin			

<p>subjects affected / exposed occurrences (all)</p> <p>Pruritus</p> <p>subjects affected / exposed occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed occurrences (all)</p>	<p>22 / 265 (8.30%) 23</p> <p>54 / 265 (20.38%) 61</p> <p>44 / 265 (16.60%) 54</p>		
<p>Endocrine disorders</p> <p>Hypothyroidism</p> <p>subjects affected / exposed occurrences (all)</p>	<p>11 / 265 (4.15%) 11</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed occurrences (all)</p> <p>Muscle spasms</p> <p>subjects affected / exposed occurrences (all)</p> <p>Myalgia</p> <p>subjects affected / exposed occurrences (all)</p>	<p>28 / 265 (10.57%) 33</p> <p>19 / 265 (7.17%) 19</p> <p>10 / 265 (3.77%) 10</p> <p>52 / 265 (19.62%) 62</p>		
<p>Infections and infestations</p> <p>Upper respiratory tract infection</p> <p>subjects affected / exposed occurrences (all)</p>	<p>12 / 265 (4.53%) 15</p>		
<p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>subjects affected / exposed occurrences (all)</p> <p>Hypertriglyceridaemia</p> <p>subjects affected / exposed occurrences (all)</p>	<p>41 / 265 (15.47%) 44</p> <p>13 / 265 (4.91%) 18</p>		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2010	This amendment took into consideration feedback from the USA Food and Drug Administration (FDA). The agency recommended to evaluate an additional dose regimen to determine whether higher C _{min} values expected with a 400 mg BID dose translates into greater efficacy compared to a QD regimen. The sample size for each group, study design & objectives, treatment blinding, and statistical methodology were adapted to take into consideration this new treatment group.
22 February 2011	This amendment took into consideration feedback from the USA FDA and Health Canada. The FDA advised that the number of patients in the study was sufficient to provide 90% power for the primary endpoint if a significance level of < 0.00125 was used. In order to meet this standard, the sample size was increased by 180 randomized patients (from 860 to 1040 patients) divided equally across the treatment arms. Health Canada requested that the definition of post-menopausal status was modified, requiring 12 months of amenorrhea irrespective of the follicle-stimulating hormone level.
31 May 2011	This amendment introduced the following changes: * Provide an opportunity of triple therapy treatment with alisporivir and P/R to patients who did not respond to double therapy (P/R). An additional treatment arm (Open Label Arm D) has been added to the study design, schedule of evaluations, statistical analysis and other relevant sections. * Address the requests from the FDA to add an ECG monitoring plan was added with central ECG evaluation. In addition, the management of patients with ALT elevation was modified. * Allow more flexibility on the scheduling of evaluations (scheduling of bone density evaluation), and on the use of prohibited medications * Take into consideration recent scientific information * Vitamin D: This protocol amendment also includes monitoring of vitamin D following recent scientific advances in the field of viral hepatitis highlighting frequent vitamin D deficiency in the HCV infected population. * Pregnancy test: The hCG level required to declare the pregnancy test positive was changed from > 5 mIU/mL to > 10 mIU/mL to match the specifications of the test being used by the central laboratory. * To reflect current clinical practice (change in acceptable ANA level, method used to collect vital signs).
08 September 2011	This amendment introduced the following changes at the request of the USA FDA: * All patients with < 2 log ₁₀ decline in HCV RNA at week 12 were considered as a null-non responder regardless of treatment arm. These patients were discontinued from study treatments. Previously, only patients receiving placebo/P/R would have had discontinued treatment * The study title was changed to clarify which drugs were being studied as the terminology "standard of care" might be understood differently in different countries based on the treatment available locally * The interruption of alisporivir and the use of prohibited medications were clarified

27 April 2012	<p>This amendment introduced the following changes: By 16 Apr 2012, Novartis had received six SAE reports of acute pancreatitis (and one report of pancreatitis later interpreted as primary diabetic keto-acidosis with secondary enzyme elevations) in patients taking alisporivir /placebo and P/R. Health Authorities and Investigators were notified as per local regulatory requirements. The first five patients fully recovered and the last patient died. Subsequently, the FDA requested that the alisporivir program be put on partial clinical hold to reduce risk to patients and to re-evaluate the benefit/risk of alisporivir in combination with peg-IFN_{2a} to treat chronic hepatitis C in the context of these SAEs. To implement the FDA request, safety amendment (protocol amendment 5) was issued with immediate effect (urgent safety measure). Investigators were notified on 18th April to stop treatment with alisporivir /placebo.</p>
10 August 2012	<p>This amendment detailed changes in the study conduct and analysis plan as a consequence of the partial clinical hold:</p> <ul style="list-style-type: none"> * Relevant sections have been updated with the changes in study conduct triggered by the discontinuation of alisporivir /placebo * The definition of non-responders was clarified * The definition of SVR12, SVR24, and SVR48 was changed * The changes expected on liver biopsy for the diagnosis of chronic hepatitis C virus infection were clarified * Study purpose and objectives were changed to take into consideration the premature discontinuation of alisporivir /placebo treatment and change of primary endpoint * The study design was updated to include the premature discontinuation of alisporivir /placebo treatment in all patients, the closing of the enrolment to the open-label period and the unblinding of the HCV RNA results * Justification for change from SVR 24 to SVR 12 was added to the section on rationale of study design and in all other relevant sections. * Rationale for continuing P/R treatment despite alisporivir treatment discontinuation was added * The interim analysis was added * The administrative analysis was removed * Ribavirin dose change based on weight was added to the study medication sections * Unblinding of study treatment was modified * Management of ALT elevation was clarified * Guidelines for the management of hypertriglyceridemia were added * Guidelines for the management of hematologic adverse events were modified * Hematopoietic factors were removed from the list of prohibited medications * Requirement for male patient whose female partner is pregnant to immediately discontinue study treatment was added as possible reason for discontinuation * Visit schedule for patients discontinued study treatment was changed * The data to be collected for screening failures was modified * A wording error in the definition of adverse events was corrected * The timing and scope of the DMC analyses were changed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 April 2012	Protocol amendment 5 was issued with immediate effect (urgent safety measure). Investigators were notified on April 18th 2012 to stop treatment with alisporivir/placebo.	10 August 2012

Notes:

Limitations and caveats

None reported