



Clinical trial results:

A multicenter, open-label, randomized, 3-arm, phase II profiling trial of pharmacokinetics, pharmacodynamics and safety of DEB025/Alisporivir in combination with ribavirin therapy in chronic hepatitis C genotype 2 and 3 treatment naïve patients

Summary

EudraCT number	2012-004185-17
Trial protocol	SE DE GB PL
Global end of trial date	24 March 2015

Results information

Result version number	v1 (current)
This version publication date	14 April 2016
First version publication date	14 April 2016

Trial information

Trial identification

Sponsor protocol code	CDEB025A2222
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01970904
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 GmbH, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma GmbH, +41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 March 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 March 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to explore pharmacodynamic (i.e. HCV viral load), pharmacokinetic, and safety profiles between three treatment groups receiving different doses of alisporivir in combination with RBV during the first 12 weeks treatment in chronic hepatitis C GT 2 and 3 treatment naïve patients.

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:

ribavirin 1000 - 1200 mg/day was given as backbone therapy in all 3 arms together with doses of alisporivir

Evidence for comparator: -

Actual start date of recruitment	03 October 2013
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	Germany: 61
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Sweden: 35
Worldwide total number of subjects	147
EEA total number of subjects	147

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)	144
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 147 treatment naïve chronic hepatitis C GT2/3 patients randomized into one of the three treatment groups in a 1:1:1 ratio. Randomization was stratified by the viral load at screening ($\geq 800,000$ IU/mL [$5.903 \log_{10}$] or $< 800,000$ IU/mL [$5.903 \log_{10}$])

Period 1

Period 1 title	Treatment Period (12 or 24 weeks) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Alisporivir (DEB025) 200mg + Ribavirin

Arm description:

Alisporivir (200 mg twice daily, BID): one capsule (200 mg) BID for 12 or 24 weeks depending on the response at Week 2, and Ribavirin: 1000 mg/day or 1200 mg/day orally (depending on weight) in two divided doses for 12 or 24 weeks depending on the response at Week 2, respectively. The treatment was for 12 or 24 weeks based on Week 2 Hepatitis C virus (HCV) ribonucleic acid (RNA) results.

There was a 24 week post treatment follow up period during which patients did not receive any study medication.

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

Dosage and administration details:

100 or 200 mg soft gel capsules by mouth

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

Dosage and administration details:

The daily scheduled dose was 1000 mg/day orally for patients < 75 kg or 1200 mg/day for ≥ 75 kg of body weight at screening.

Arm title	Alisporivir (DEB025) 300mg + Ribavirin
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Arm description:

Alisporivir (300 mg BID): one capsule of 200 mg and one capsule of 100 mg or three capsules (100 mg) BID for 12 or 24 weeks depending on the response at Week 2, and Ribavirin: 1000 mg/day or 1200 mg/day orally (depending on weight) in two divided doses for 12 or 24 weeks depending on the responses at Week 2, respectively. The treatment was for 12 or 24 weeks based on Week 2 Hepatitis C virus (HCV) ribonucleic acid (RNA) results.

There was a 24 week post treatment follow up period during which patients did not receive any study medication.

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

Dosage and administration details:

The daily scheduled dose was 1000 mg/day orally for patients < 75 kg or 1200 mg/day for ≥ 75 kg of body weight at screening.

Investigational medicinal product name	Alisporivir
Investigational medicinal product code	DEB025
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

100 or 200 mg soft gel capsules by mouth

Arm title	Alisporivir (DEB025) 400mg + Ribavirin
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Arm description:

Alisporivir (400 mg BID): two capsules (200 mg) BID for 12 or 24 weeks depending on the response at Week 2, and

Ribavirin: 1000 mg/day or 1200 mg/day orally (depending on weight) in two divided doses for 12 or 24 weeks depending on the responses at Week 2, respectively.

The treatment was for 12 or 24 weeks based on Week 2 Hepatitis C virus (HCV) ribonucleic acid (RNA) results.

There was a 24 week post treatment follow up period during which patients did not receive any study medication.

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

Dosage and administration details:

100 or 200 mg soft gel capsules by mouth

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

Dosage and administration details:

The daily scheduled dose was 1000 mg/day orally for patients < 75 kg or 1200 mg/day for ≥ 75 kg of body weight at screening.

Number of subjects in period 1	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin
Started	48	50	49
Completed at week 12	4 ^[1]	4 ^[2]	6 ^[3]
Completed at week 24	19 ^[4]	28 ^[5]	21 ^[6]
Completed	23	32	27
Not completed	25	18	22
Adverse event, non-fatal	4	2	6

Non-compliance with study treatment	1	1	2
Patient/guardian decision	-	2	3
Lack of efficacy	20	13	11

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: Milestone data are based on week 12 and week 24 where as completed is all patients (week 12 and week 24) who completed the treatment.

[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: Milestone data are based on week 12 and week 24 where as completed is all patients (week 12 and week 24) who completed the treatment.

[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: Milestone data are based on week 12 and week 24 where as completed is all patients (week 12 and week 24) who completed the treatment.

[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: Milestone data are based on week 12 and week 24 where as completed is all patients (week 12 and week 24) who completed the treatment.

[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: Milestone data are based on week 12 and week 24 where as completed is all patients (week 12 and week 24) who completed the treatment.

[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: Milestone data are based on week 12 and week 24 where as completed is all patients (week 12 and week 24) who completed the treatment.

Baseline characteristics

Reporting groups

Reporting group title	Alisporivir (DEB025) 200mg + Ribavirin
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Reporting group description:

Alisporivir (200 mg twice daily, BID): one capsule (200 mg) BID for 12 or 24 weeks depending on the response at Week 2, and

Ribavirin: 1000 mg/day or 1200 mg/day orally (depending on weight) in two divided doses for 12 or 24 weeks depending on the response at Week 2, respectively.

The treatment was for 12 or 24 weeks based on Week 2 Hepatitis C virus (HCV) ribonucleic acid (RNA) results.

There was a 24 week post treatment follow up period during which patients did not receive any study medication.

Reporting group title	Alisporivir (DEB025) 300mg + Ribavirin
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Reporting group description:

Alisporivir (300 mg BID): one capsule of 200 mg and one capsule of 100 mg or three capsules (100 mg) BID for 12 or 24 weeks depending on the response at Week 2, and Ribavirin: 1000 mg/day or 1200

mg/day orally (depending on weight) in two divided

doses for 12 or 24 weeks depending on the responses at Week 2, respectively.

The treatment was for 12 or 24 weeks based on Week 2 Hepatitis C virus (HCV) ribonucleic acid (RNA) results.

There was a 24 week post treatment follow up period during which patients did not receive any study medication.

Reporting group title	Alisporivir (DEB025) 400mg + Ribavirin
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Reporting group description:

Alisporivir (400 mg BID): two capsules (200 mg) BID for 12 or 24 weeks depending on the response at Week 2, and

Ribavirin: 1000 mg/day or 1200 mg/day orally (depending on weight) in two divided doses for 12 or 24 weeks depending on the responses at Week 2, respectively.

The treatment was for 12 or 24 weeks based on Week 2 Hepatitis C virus (HCV) ribonucleic acid (RNA) results.

There was a 24 week post treatment follow up period during which patients did not receive any study medication.

Reporting group values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin
Number of subjects	48	50	49
Age categorical Units: Subjects			
Adults (18-64 years)	47	50	47
From 65-84 years	1	0	2
Age continuous Units: years			
arithmetic mean	45.3	41.4	41.7
standard deviation	± 10.11	± 10.86	± 11.8
Gender categorical Units: Subjects			
Female	17	20	23
Male	31	30	26

Reporting group values	Total		
Number of subjects	147		
Age categorical Units: Subjects			
Adults (18-64 years)	144		

From 65-84 years	3		
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Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	60		
Male	87		

End points

End points reporting groups

Reporting group title	Alisporivir (DEB025) 200mg + Ribavirin
Reporting group description: Alisporivir (200 mg twice daily, BID): one capsule (200 mg) BID for 12 or 24 weeks depending on the response at Week 2, and Ribavirin: 1000 mg/day or 1200 mg/day orally (depending on weight) in two divided doses for 12 or 24 weeks depending on the response at Week 2, respectively. The treatment was for 12 or 24 weeks based on Week 2 Hepatitis C virus (HCV) ribonucleic acid (RNA) results. There was a 24 week post treatment follow up period during which patients did not receive any study medication.	
Reporting group title	Alisporivir (DEB025) 300mg + Ribavirin
Reporting group description: Alisporivir (300 mg BID): one capsule of 200 mg and one capsule of 100 mg or three capsules (100 mg) BID for 12 or 24 weeks depending on the response at Week 2, and Ribavirin: 1000 mg/day or 1200 mg/day orally (depending on weight) in two divided doses for 12 or 24 weeks depending on the responses at Week 2, respectively. The treatment was for 12 or 24 weeks based on Week 2 Hepatitis C virus (HCV) ribonucleic acid (RNA) results. There was a 24 week post treatment follow up period during which patients did not receive any study medication.	
Reporting group title	Alisporivir (DEB025) 400mg + Ribavirin
Reporting group description: Alisporivir (400 mg BID): two capsules (200 mg) BID for 12 or 24 weeks depending on the response at Week 2, and Ribavirin: 1000 mg/day or 1200 mg/day orally (depending on weight) in two divided doses for 12 or 24 weeks depending on the responses at Week 2, respectively. The treatment was for 12 or 24 weeks based on Week 2 Hepatitis C virus (HCV) ribonucleic acid (RNA) results. There was a 24 week post treatment follow up period during which patients did not receive any study medication.	

Primary: Change in log transformed Hepatitis C virus (HCV) Ribonucleic acid (RNA) from baseline through Week 12

End point title	Change in log transformed Hepatitis C virus (HCV) Ribonucleic acid (RNA) from baseline through Week 12 ^[1]
End point description: Viral load was analyzed as continuous variables using data in log10 IU/mL units as reported by the central laboratory. Baseline is defined as the last non-missing value before first administration of study drug. At week 12 only patients with a value at both baseline and week 12 were included.	
End point type	Primary
End point timeframe: Baseline, Week 12	

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: There was no statistical hypothesis testing planned for this primary endpoint

End point values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	44	44	
Units: log10 IU/mL				
arithmetic mean (standard deviation)	-3.586 (± 1.9833)	-4.173 (± 2.0039)	-4.131 (± 1.8248)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Sustained Virologic Response at Week 12 follow up (SVR12)

End point title	Number of patients with Sustained Virologic Response at Week 12 follow up (SVR12)
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End point description:

SVR12 is sustained virologic response at week 12 follow up: HCV RNA undetectable (by < LLOQ) 12 weeks after end of treatment. LLOQ (Lower limit of Quantification) is defined as HCV RNA < 15 IU/mL. Definition Non-responder: Failure to achieve undetectable serum HCV RNA during treatment

Definition Null non-responder: Failure to achieve a decrease in serum HCV RNA concentration $\geq 2 \log_{10}$ from baseline to treatment week 12

Definition Partial Non-responder: HCV RNA decrease $\geq 2 \log_{10}$ from baseline to treatment week 12 but never undetectable during treatment

End point type	Secondary
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End point timeframe:

12 weeks after end of treatment (total 24 weeks or 36 weeks from baseline)

End point values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	50	49	
Units: Patients				
SVR12	18	27	25	
Non-Responder	23	12	7	
Null non-responder	10	6	2	
Partial non-responder	13	6	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with rapid virologic response (RVR) after 4 weeks of treatment

End point title	Number of patients with rapid virologic response (RVR) after 4 weeks of treatment
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End point description:

Rapid Virologic Response by LLOQ is defined as serum HCV RNA < LLOQ after 4 weeks of treatment where LLOQ (Lower limit of Quantification) is defined as HCV RNA < 15 IU/mL.

End point type	Secondary
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End point timeframe:

Baseline to week 4

End point values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	50	49	
Units: Patients	8	11	16	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with extremely rapid virologic response (eRVR) after 2 weeks of treatment

End point title	Number of patients with extremely rapid virologic response (eRVR) after 2 weeks of treatment
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End point description:

Extremely Rapid Virologic Response by LLOQ (eRVR) , also known as very Rapid Virologic Response by LLOQ (vRVR) is defined as serum HCV RNA < LLOQ after 2 weeks of treatment where LLOQ (Lower limit of Quantification) is defined as HCV RNA < 15 IU/mL.

End point type	Secondary
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End point timeframe:

Baseline to week 2

End point values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	50	49	
Units: Patients	3	5	7	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with early virologic response (EVR) and complete early virologic response (cEVR) after 12 weeks of treatment

End point title	Number of patients with early virologic response (EVR) and complete early virologic response (cEVR) after 12 weeks of treatment
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End point description:

Early virologic response (EVR) is defined as HCV RNA decrease $\geq 2 \log_{10}$ or HCV RNA < LLOQ after 12 weeks of treatment and complete early viral response (cEVR) is defined as serum HCV RNA < LLOQ after 12 weeks of treatment where LLOQ (Lower limit of Quantification) is defined as HCV RNA < 15 IU/mL.

End point type	Secondary
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End point timeframe:

Baseline to week 12

End point values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	50	49	
Units: Patients				
EVR	33	37	38	
cEVR	22	30	33	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with end of treatment response

End point title	Number of patients with end of treatment response
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End point description:

End of treatment response is defined as HCV RNA undetectable (by < LLOQ) at treatment end (completed or prematurely discontinued) where LLOQ (Lower limit of Quantification) is defined as HCV RNA < 15 IU/mL.

End point type	Secondary
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End point timeframe:

Baseline to End of treatment (12 weeks or 24 weeks)

End point values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	50	49	
Units: Patients	22	35	34	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with sustained virologic response 4 weeks after end of treatment

End point title	NUmber of patients with sustained virologic response 4 weeks after end of treatment
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End point description:

Sustained virologic response at Week 4 follow up (SVR4) is defined as HCV RNA undetectable (by <LLOQ) 4 weeks after end of treatment where LLOQ (Lower limit of Quantification) is defined as HCV RNA < 15 IU/mL.

End point type	Secondary
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End point timeframe:

4 weeks after end of treatment (total 16 weeks or 28 weeks from baseline)

End point values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	50	49	
Units: Patients	19	32	29	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with sustained virologic response 24 weeks after end of treatment

End point title	Number of patients with sustained virologic response 24 weeks after end of treatment
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End point description:

Sustained virologic response at Week 24 follow up (SVR24) is defined as HCV RNA undetectable (by < LLOQ) 24 weeks after end of treatment where LLOQ (Lower limit of Quantification) is defined as HCV RNA < 15 IU/mL.

End point type	Secondary
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End point timeframe:

24 weeks after end of treatment (total 36 weeks or 48 weeks from baseline)

End point values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	50	49	
Units: Patients	17	26	25	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with confirmed viral breakthrough during treatment

End point title	Number of patients with confirmed viral breakthrough during treatment
End point description: Viral breakthrough is defined as confirmed (by a separate blood draw): increase of HCV RNA by ≥ 1 log ₁₀ above nadir (where nadir is the lowest HCV RNA level during treatment) and HCV RNA ≥ 100 IU/mL (2 log ₁₀) while still on treatment, or HCV RNA ≥ 100 IU/mL (2 log ₁₀) after previously being undetectable while still on treatment.	
End point type	Secondary
End point timeframe: 12 weeks or 24 weeks	

End point values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	50	49	
Units: Patients	16	14	14	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with relapse (based on primary and secondary definition)

End point title	Number of patients with relapse (based on primary and secondary definition)
End point description: Primary definition of relapse : Patients with non-missing and positive follow-up HCV RNA > LLOQ results after imputation are considered as relapsers, if they fully completed assigned treatments and were End of treatment (ETR)	

responders.

Secondary definition of relapse: patients with any positive follow-up HCV RNA > LLOQ results (after imputation) or no follow-up HCV RNA assessments (at all) are considered as relapsers if they fully completed assigned treatments and were ETR responders.

LLOQ (Lower limit of Quantification) is defined as HCV RNA < 15 IU/mL.

End point type	Secondary
End point timeframe:	
12 weeks or 24 weeks of treatment	

End point values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	50	49	
Units: Patients				
Primary Definition of Relapse	5	8	8	
Secondary Definition of Relapse	5	9	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with normalized alanine aminotransferase (ALT) at end of treatment

End point title	Number of patients with normalized alanine aminotransferase (ALT) at end of treatment
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End point description:

ALT levels were assessed as part of clinical chemistry assessments throughout the study as a measure of clinical liver recovery. Abnormal ALT is defined as an ALT value $\geq$ ULN. Patients with abnormal ALT at baseline but normalized at end of treatment were reported in this endpoint.

End point type	Secondary
End point timeframe:	
After 12 weeks or 24 weeks of treatment	

End point values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	50	49	
Units: Patients	30	35	35	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with normalized alanine aminotransferase (ALT) at end of study

End point title	Number of patients with normalized alanine aminotransferase (ALT) at end of study
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End point description:

ALT levels were assessed as part of clinical chemistry assessments throughout the study as a measure of clinical liver recovery. Abnormal ALT is defined as an ALT value $\geq$ ULN. Patients with abnormal ALT at baseline and normalized ALT at end of study are reported in this endpoint.

End point type	Secondary
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End point timeframe:

36 to 48 weeks including post treatment follow up

End point values	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	50	49	
Units: Patients	15	23	24	

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 are reported in this record from First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Alisporivir (DEB025) 200mg + Ribavirin
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Reporting group description:

Alisporivir (200 mg twice daily, BID): one capsule (200 mg) BID for 12 or 24 weeks depending on the response at Week 2, and Ribavirin: 1000 mg/day or 1200 mg/day orally (depending on weight) in two divided doses for 12 or 24 weeks depending on the response at Week 2, respectively.

The treatment was for 12 or 24 weeks based on Week 2 Hepatitis C virus (HCV) ribonucleic acid (RNA) results.

Reporting group title	Alisporivir (DEB025) 400mg + Ribavirin
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Reporting group description:

Alisporivir (400 mg BID): two capsules (200 mg) BID for 12 or 24 weeks depending on the response at Week 2, and Ribavirin: 1000 mg/day or 1200 mg/day orally (depending on weight) in two divided doses for 12 or 24 weeks depending on the responses at Week 2, respectively.

The treatment was for 12 or 24 weeks based on Week 2 Hepatitis C virus (HCV) ribonucleic acid (RNA) results.

Reporting group title	Alisporivir (DEB025) 300mg + Ribavirin
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Reporting group description:

Alisporivir (300 mg BID): one capsule of 200 mg and one capsule of 100 mg or three capsules (100 mg) BID for 12 or 24 weeks depending on the response at Week 2, and Ribavirin: 1000 mg/day or 1200 mg/day orally (depending on weight) in two divided doses for 12 or 24 weeks depending on the responses at Week 2, respectively.

The treatment was for 12 or 24 weeks based on Week 2 Hepatitis C virus (HCV) ribonucleic acid (RNA) results.

Serious adverse events	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 48 (8.33%)	4 / 49 (8.16%)	1 / 49 (2.04%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
CHEMICAL PERITONITIS			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	0 / 49 (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
FEMUR FRACTURE			

subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	0 / 49 (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 / 48 (0.00%)	1 / 49 (2.04%)	0 / 49 (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
Nervous system disorders			
HYPERAESTHESIA			
subjects affected / exposed	0 / 48 (0.00%)	0 / 49 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOAESTHESIA			
subjects affected / exposed	0 / 48 (0.00%)	0 / 49 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	0 / 49 (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
ABDOMINAL PAIN			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	0 / 49 (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
HAEMATEMESIS			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
GALLBLADDER PERFORATION			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	0 / 49 (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

HYPERBILIRUBINAEMIA			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	0 / 49 (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
INSOMNIA			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	0 / 49 (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
Renal and urinary disorders			
RENAL IMPAIRMENT			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 48 (0.00%)	0 / 49 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JOINT SWELLING			
subjects affected / exposed	0 / 48 (0.00%)	0 / 49 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
SEPSIS			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	0 / 49 (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
UROSEPSIS			

subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	0 / 49 (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
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	0 / 49 (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

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

Non-serious adverse events	Alisporivir (DEB025) 200mg + Ribavirin	Alisporivir (DEB025) 400mg + Ribavirin	Alisporivir (DEB025) 300mg + Ribavirin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 48 (85.42%)	41 / 49 (83.67%)	41 / 49 (83.67%)
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	3 / 48 (6.25%)	13 / 49 (26.53%)	8 / 49 (16.33%)
occurrences (all)	3	15	10
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	3 / 48 (6.25%)	6 / 49 (12.24%)	3 / 49 (6.12%)
occurrences (all)	3	6	3
FATIGUE			
subjects affected / exposed	21 / 48 (43.75%)	22 / 49 (44.90%)	18 / 49 (36.73%)
occurrences (all)	21	26	18
FEELING COLD			
subjects affected / exposed	1 / 48 (2.08%)	3 / 49 (6.12%)	0 / 49 (0.00%)
occurrences (all)	1	3	0
MUCOSAL DRYNESS			
subjects affected / exposed	0 / 48 (0.00%)	3 / 49 (6.12%)	1 / 49 (2.04%)
occurrences (all)	0	3	1
PYREXIA			
subjects affected / exposed	3 / 48 (6.25%)	3 / 49 (6.12%)	5 / 49 (10.20%)
occurrences (all)	4	3	5
Respiratory, thoracic and mediastinal disorders			

COUGH			
subjects affected / exposed	3 / 48 (6.25%)	7 / 49 (14.29%)	5 / 49 (10.20%)
occurrences (all)	3	7	6
DYSPNOEA			
subjects affected / exposed	2 / 48 (4.17%)	9 / 49 (18.37%)	3 / 49 (6.12%)
occurrences (all)	2	9	3
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 48 (2.08%)	1 / 49 (2.04%)	4 / 49 (8.16%)
occurrences (all)	1	1	5
Psychiatric disorders			
DEPRESSED MOOD			
subjects affected / exposed	1 / 48 (2.08%)	5 / 49 (10.20%)	3 / 49 (6.12%)
occurrences (all)	1	5	3
DEPRESSION			
subjects affected / exposed	4 / 48 (8.33%)	3 / 49 (6.12%)	4 / 49 (8.16%)
occurrences (all)	4	3	4
INSOMNIA			
subjects affected / exposed	7 / 48 (14.58%)	7 / 49 (14.29%)	6 / 49 (12.24%)
occurrences (all)	8	7	6
SLEEP DISORDER			
subjects affected / exposed	3 / 48 (6.25%)	2 / 49 (4.08%)	3 / 49 (6.12%)
occurrences (all)	3	2	3
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	4 / 48 (8.33%)	5 / 49 (10.20%)	1 / 49 (2.04%)
occurrences (all)	4	5	1
DYSGEUSIA			
subjects affected / exposed	2 / 48 (4.17%)	3 / 49 (6.12%)	2 / 49 (4.08%)
occurrences (all)	2	3	2
HEADACHE			
subjects affected / exposed	22 / 48 (45.83%)	22 / 49 (44.90%)	22 / 49 (44.90%)
occurrences (all)	27	27	24
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	5 / 48 (10.42%)	7 / 49 (14.29%)	4 / 49 (8.16%)
occurrences (all)	5	9	4
Ear and labyrinth disorders			

VERTIGO subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	3 / 49 (6.12%) 3	1 / 49 (2.04%) 1
Eye disorders OCULAR ICTERUS subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	4 / 49 (8.16%) 4	1 / 49 (2.04%) 1
Gastrointestinal disorders ABDOMINAL PAIN subjects affected / exposed occurrences (all)	5 / 48 (10.42%) 5	2 / 49 (4.08%) 2	4 / 49 (8.16%) 4
ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	6 / 49 (12.24%) 7	6 / 49 (12.24%) 7
DIARRHOEA subjects affected / exposed occurrences (all)	6 / 48 (12.50%) 6	4 / 49 (8.16%) 4	9 / 49 (18.37%) 9
DYSPEPSIA subjects affected / exposed occurrences (all)	4 / 48 (8.33%) 4	3 / 49 (6.12%) 3	3 / 49 (6.12%) 3
MOUTH ULCERATION subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	3 / 49 (6.12%) 3	0 / 49 (0.00%) 0
NAUSEA subjects affected / exposed occurrences (all)	13 / 48 (27.08%) 16	16 / 49 (32.65%) 20	10 / 49 (20.41%) 12
VOMITING subjects affected / exposed occurrences (all)	7 / 48 (14.58%) 9	2 / 49 (4.08%) 3	3 / 49 (6.12%) 5
Hepatobiliary disorders HYPERBILIRUBINAEMIA subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	3 / 49 (6.12%) 4	2 / 49 (4.08%) 3
JAUNDICE subjects affected / exposed occurrences (all)	4 / 48 (8.33%) 5	3 / 49 (6.12%) 3	1 / 49 (2.04%) 1
Skin and subcutaneous tissue disorders			

ALOPECIA subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	3 / 49 (6.12%) 3	1 / 49 (2.04%) 1
PRURITUS subjects affected / exposed occurrences (all)	7 / 48 (14.58%) 8	4 / 49 (8.16%) 4	7 / 49 (14.29%) 7
DRY SKIN subjects affected / exposed occurrences (all)	5 / 48 (10.42%) 5	5 / 49 (10.20%) 5	9 / 49 (18.37%) 10
RASH subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	6 / 49 (12.24%) 6	3 / 49 (6.12%) 3
Endocrine disorders HYPOTHYROIDISM subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	1 / 49 (2.04%) 1	0 / 49 (0.00%) 0
Musculoskeletal and connective tissue disorders BACK PAIN subjects affected / exposed occurrences (all)	4 / 48 (8.33%) 4	2 / 49 (4.08%) 2	4 / 49 (8.16%) 4
ARTHRALGIA subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	2 / 49 (4.08%) 2	5 / 49 (10.20%) 5
MUSCLE SPASMS subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	1 / 49 (2.04%) 1	3 / 49 (6.12%) 3
Infections and infestations NASOPHARYNGITIS subjects affected / exposed occurrences (all)	6 / 48 (12.50%) 6	6 / 49 (12.24%) 7	9 / 49 (18.37%) 9
Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	4 / 49 (8.16%) 4	2 / 49 (4.08%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2013	- The definition of "Partial Early Virologic Response" was removed from " Definition of Virologic Response Parameters" table, and definition of viral breakthrough was amended for clarity. A typographical error in the definition of eRVR was corrected throughout the protocol - One Inclusion , 2 Exclusion criterion were amended for clarification. An abdominal ultrasound assessment was added to the screening visit table and eligibility assessment - The hypertensive criteria was clarified in the "hypertension management" and vital sign assessment for consistency. - The significant ALT elevation criterion was amended for consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

After a portfolio review, and in light of the advancement of several successful oral anti-HCV agents, Novartis decided to no longer focus on HCV development. This decision was not in any way affected or influenced by new safety data for alisporivir.

Notes: