



Clinical trial results:

A multicenter, open-label, randomized, 2-arm, phase II trial of pharmacodynamics, pharmacokinetics and safety of two dose regimens of DEB025/alisporivir in combination with ribavirin therapy in chronic hepatitis C genotype 2 and 3 patients who have previously failed interferon therapy or are intolerant or unable to take interferon.

Summary

EudraCT number	2013-003751-38
Trial protocol	FR
Global end of trial date	21 April 2015

Results information

Result version number	v1 (current)
This version publication date	07 May 2016
First version publication date	07 May 2016

Trial information

Trial identification

Sponsor protocol code	CDEB025A2233
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02094443
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 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +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	21 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 April 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate pharmacodynamics, pharmacokinetic between 2 treatment groups receiving different doses of DEB025 in combination with 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	20 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	52
EEA total number of subjects	25

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)	49
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Informed consent was obtained from each patient in writing at screening visit 1. The study was described to the patient by a study nurse, the investigator or a study coordinator, who answered any questions, and written information was also provided.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DEB300 + RBV

Arm description:

1 capsule of 200 mg and 1 capsule of 100 mg or 3 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.

Arm type	Experimental
Investigational medicinal product name	DEB025300
Investigational medicinal product code	
Other name	Alisporivir
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

DEB025 (300 mg BID): 1 capsule of 200 mg and 1 capsule of 100 mg or 3 capsules (100 mg) BID for 12 or 24 weeks depending on the response at Week 2

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

Dosage and administration details:

Ribavirin 1000 mg/day or 1200 mg/day orally (depending on weight)

Arm title	DEB400 + RBV
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Arm description:

DEB025 (400 mg BID): 2 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 response at Week 2, respectively.

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

Dosage and administration details:

Ribavirin 1000 mg/day or 1200 mg/day orally (depending on weight)

Investigational medicinal product name	DEB025400
Investigational medicinal product code	
Other name	Alisporivir
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

DEB025 (400 mg BID): 2 capsules (200 mg) BID for 12 or 24 weeks depending on the response at Week 2

Number of subjects in period 1	DEB300 + RBV	DEB400 + RBV
Started	26	26
Completed	11	9
Not completed	15	17
Physician decision	1	-
Adverse event, non-fatal	3	6
Patient/guardian decision	1	2
Lack of efficacy	10	8
Protocol deviation	-	1

Period 2

Period 2 title	Post-treatment follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	DEB300 + RBV

Arm description: -

Arm type	Experimental
Investigational medicinal product name	DEB025300
Investigational medicinal product code	
Other name	Alisporivir
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

DEB025 (300 mg BID): 1 capsule of 200 mg and 1 capsule of 100 mg or 3 capsules (100 mg) BID for 12 or 24 weeks depending on the response at Week 2

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

Dosage and administration details:

Ribavirin 1000 mg/day or 1200 mg/day orally (depending on weight)

Arm title	DEB400 + RBV
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	DEB025400
Investigational medicinal product code	
Other name	Alisporivir
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

DEB025 (400 mg BID): 2 capsules (200 mg) BID for 12 or 24 weeks depending on the response at Week 2

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

Dosage and administration details:

Ribavirin 1000 mg/day or 1200 mg/day orally (depending on weight)

Number of subjects in period 2	DEB300 + RBV	DEB400 + RBV
Started	23	23
Completed	11	13
Not completed	12	10
Study terminated by sponsor	9	7
Patient/guardian decision	2	1
Lost to follow-up	1	1
New therapy for study indication	-	1

Baseline characteristics

Reporting groups

Reporting group title	DEB300 + RBV
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Reporting group description:

1 capsule of 200 mg and 1 capsule of 100 mg or 3 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.

Reporting group title	DEB400 + RBV
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Reporting group description:

DEB025 (400 mg BID): 2 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 response at Week 2, respectively.

Reporting group values	DEB300 + RBV	DEB400 + RBV	Total
Number of subjects	26	26	52
Age categorical Units: Subjects			
Adults (18-64 years)	25	24	49
From 65-84 years	1	2	3
Age continuous Units: years			
arithmetic mean	53.4	54.5	
standard deviation	± 8.25	± 7.62	-
Gender categorical Units: Subjects			
Female	8	12	20
Male	18	14	32

End points

End points reporting groups

Reporting group title	DEB300 + RBV
Reporting group description:	
1 capsule of 200 mg and 1 capsule of 100 mg or 3 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.	
Reporting group title	DEB400 + RBV
Reporting group description:	
DEB025 (400 mg BID): 2 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 response at Week 2, respectively.	
Reporting group title	DEB300 + RBV
Reporting group description: -	
Reporting group title	DEB400 + RBV
Reporting group description: -	

Primary: Viral load drop from baseline through Week 12

End point title	Viral load drop from baseline through Week 12 ^[1]
End point description:	
Defined as the change in log transformed Hepatitis-C Virus (HCV) Ribonucleic acid (RNA) from baseline through Week 12. Baseline is defined as the last non-missing value before first administration of study drug.	
At each time point, only patients with a value at both Baseline and that time point are included.	
End point type	Primary
End point timeframe:	
Baseline through 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: No statistical analyses have been performed for this primary end point.

End point values	DEB300 + RBV	DEB400 + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26 ^[2]	26 ^[3]		
Units: IU/mL				
arithmetic mean (standard deviation)				
Baseline	6.323 (± 6.323)	6.343 (± 0.6396)		
Change at Day 3	-0.316 (± 0.5494)	-0.692 (± 0.8812)		
Change at Week 1	-0.785 (± 0.7705)	-1.564 (± 0.9481)		
Change at Day 10	-1.058 (± 0.9963)	-1.803 (± 1.1674)		
Change at Week 2	-1.507 (± 0.9645)	-2.606 (± 1.2005)		
Change at Week 3	-1.863 (± 1.2377)	-3.474 (± 1.3669)		
Change at Week 4	-2.596 (± 1.3034)	-3.84 (± 1.4611)		

Change at Week 6	-3.058 (± 1.7385)	-4.232 (± 1.5875)		
Change at Week 8	-3.438 (± 2.1797)	-3.98 (± 2.219)		
Change at Week 12	-3.935 (± 2.3361)	-3.855 (± 2.7506)		

Notes:

[2] - N= 26, 14, 24, 17, 23, 18, 23, 23, 21

[3] - N= 26, 17 24, 12, 24, 17, 24, 21, 22, 18

Statistical analyses

No statistical analyses for this end point

Secondary: Number (%) of patients who Sustained Virologic Response (SVR) 12

End point title	Number (%) of patients who Sustained Virologic Response (SVR) 12
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End point description:

Number of participants who maintain undetectable Hepatitis C virus 12 weeks after end of treatment between 2 treatment arms.

End point type	Secondary
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End point timeframe:

Week 12

End point values	DEB300 + RBV	DEB400 + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: percent				
number (confidence interval 95%)	19.2 (6.6 to 39.4)	26.9 (11.6 to 47.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed viral breakthrough, relapse, or normalized ALT

End point title	Confirmed viral breakthrough, relapse, or normalized ALT
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End point description:

Confirmed viral breakthrough is defined as two consecutive episodes of: increase of HCV RNA by ≥ 1 log₁₀ above nadir (where nadir is the lowest HCV RNA level during treatment) and HCV RNA ≥ 100 IU / mL (2 log₁₀) while still on treatment), or HCV RNA ≥ 100 IU / mL (2 log₁₀) after previously being undetectable while still on treatment.

Relapse is defined as patients with non-missing and positive follow-up HCV RNA results after imputation are considered as relapsers, if they fully completed assigned treatments and were ETR responders.

End point type	Secondary
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End point timeframe:

Week 12

End point values	DEB300 + RBV	DEB400 + RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26 ^[4]	26 ^[5]		
Units: percent				
number (not applicable)				
Confirmed viral breakthrough	23.1	34.6		
Confirmed viral breakthrough during treatment	23.1	34.6		
Relapse	19.2	19.2		
ALT abnormal at baseline/normalized treatment end	73.1	61.5		
ALT abnormal at baseline/normalized at study end	38.5	42.3		

Notes:

[4] - N= 6, 6, 5, 19, 10

[5] - N = 9, 9, 5, 16, 11

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	DEB400+RBV
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Reporting group description:

DEB025 (400 mg BID): 2 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 response at Week 2, respectively.

Reporting group title	DEB300+RBV
-----------------------	------------

Reporting group description:

1 capsule of 200 mg and 1 capsule of 100 mg or 3 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.

Serious adverse events	DEB400+RBV	DEB300+RBV	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 26 (11.54%)	3 / 26 (11.54%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
GENERAL PHYSICAL HEALTH DETERIORATION			

subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
EPIGLOTTITIS			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DEB400+RBV	DEB300+RBV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 26 (92.31%)	22 / 26 (84.62%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	5 / 26 (19.23%)	4 / 26 (15.38%)	
occurrences (all)	5	5	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	12 / 26 (46.15%)	5 / 26 (19.23%)	
occurrences (all)	13	5	
FATIGUE			
subjects affected / exposed	6 / 26 (23.08%)	6 / 26 (23.08%)	
occurrences (all)	6	6	

Respiratory, thoracic and mediastinal disorders			
DYSпноEA			
subjects affected / exposed	6 / 26 (23.08%)	5 / 26 (19.23%)	
occurrences (all)	7	5	
OROPHARYNGEAL PAIN			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	4 / 26 (15.38%)	1 / 26 (3.85%)	
occurrences (all)	4	1	
DEPRESSION			
subjects affected / exposed	3 / 26 (11.54%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
INSOMNIA			
subjects affected / exposed	4 / 26 (15.38%)	4 / 26 (15.38%)	
occurrences (all)	4	4	
IRRITABILITY			
subjects affected / exposed	2 / 26 (7.69%)	3 / 26 (11.54%)	
occurrences (all)	2	3	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	3 / 26 (11.54%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
HEADACHE			
subjects affected / exposed	7 / 26 (26.92%)	4 / 26 (15.38%)	
occurrences (all)	7	5	
SYNCOPE			
subjects affected / exposed	2 / 26 (7.69%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
ANAEMIA			

subjects affected / exposed occurrences (all)	7 / 26 (26.92%) 7	5 / 26 (19.23%) 5	
Eye disorders			
DRY EYE			
subjects affected / exposed	2 / 26 (7.69%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
OCULAR ICTERUS			
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
CONSTIPATION			
subjects affected / exposed	1 / 26 (3.85%)	3 / 26 (11.54%)	
occurrences (all)	1	3	
DIARRHOEA			
subjects affected / exposed	4 / 26 (15.38%)	2 / 26 (7.69%)	
occurrences (all)	4	3	
DRY MOUTH			
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
GASTROESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
NAUSEA			
subjects affected / exposed	4 / 26 (15.38%)	4 / 26 (15.38%)	
occurrences (all)	4	5	
VOMITING			
subjects affected / exposed	3 / 26 (11.54%)	2 / 26 (7.69%)	
occurrences (all)	3	3	
Skin and subcutaneous tissue disorders			

DRY SKIN subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 26 (3.85%) 1	
PRURITUS subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4	5 / 26 (19.23%) 5	
PRURITUS GENERALISED subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 26 (3.85%) 1	
RASH subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	3 / 26 (11.54%) 3	
Renal and urinary disorders DYSURIA subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 26 (0.00%) 0	
Musculoskeletal and connective tissue disorders MUSCLE SPASMS subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	2 / 26 (7.69%) 2	
Infections and infestations BRONCHITIS subjects affected / exposed occurrences (all) NASOPHARYNGITIS subjects affected / exposed occurrences (all) URINARY TRACT INFECTION subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1 0 / 26 (0.00%) 0 1 / 26 (3.85%) 2	2 / 26 (7.69%) 2 2 / 26 (7.69%) 2 3 / 26 (11.54%) 3	
Metabolism and nutrition disorders HYPERTRIGLYCERIDAEMIA subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 26 (7.69%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 February 2015	Novartis decided to no longer focus on development of compounds for treating Hepatitis-C Virus (HCV). The compound DEB025 had been returned to the company from which it was licensed. This decision was not in any way affected or influenced by new safety data for DEB025.	-

Notes:

Limitations and caveats

None reported