Clinical trial results:
Study To Evaluate Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Ritonavir-Boosted DANOPREVIR in Combination With Peginterferon Alfa-2a Plus Ribavirin in Treatment-naive Patients and with addition of RO5024048 in Previous Null Responder Patients With Chronic Hepatitis C Genotype 1 or 4 and Compensated Cirrhosis.

Summary

EudraCT number	2011-004129-28
Trial protocol	SK
Global end of trial date	28 August 2013

Results information

Result version number	v2 (current)
This version publication date	09 July 2016
First version publication date	06 August 2015
Version creation reason	• Correction of full data set Corrections due to EudraCT system errors.

Trial information

Trial identification

Sponsor protocol code	NP27946

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability, pharmacokinetics (PK) and antiviral activity of RO5190591/ritonavir (danoprevir/r) in combination with peginterferon and ribavirin in treatment-naïve genotype 1 or 4 chronic hepatitis C patients with compensated cirrhosis and danoprevir/r + RO5024048 in combination with peginterferon and ribavirin in null responder genotype 1 or 4 chronic hepatitis C patients with compensated cirrhosis.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequent amendments. All patients were informed verbally and in writing regarding the objectives, procedures and risks of study participation. The patients signed the informed consent form (ICF) that contained information about the objectives of the study, about the procedures followed during the study and about the risks and restrictions of the study, with special reference to possible side effects of the medication and potential interactions. The primary investigator (PI) was responsible for the care of the patients throughout the study. If the PI was not present in the clinical site, instructions were left for the staff and a telephone number where the PI could be reached.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 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	New Zealand: 9
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	France: 4
Worldwide total number of subjects	43
EEA total number of subjects	16

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)	43
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened for participation in this study within 56 days before dosing. If Screening was conducted between Day -56 and Day -35, inclusive, rescreen assessments had to be completed before dosing on Day 1. Eligible patients arrived at the study unit on Day -1 for safety assessments.

Period 1

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

Blinding implementation details:

This was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Treatment-naïve

Arm description:

All participants received peginterferon alfa-2a (PEG-IFN) 180 micrograms (µg) subcutaneously once weekly for 24 weeks and weight-based ribavirin (RBV) 1000-1200 milligrams per day (mg/day) in two divided doses orally for 24 weeks along with DNV/r 100/100 mg twice a day (BID) orally for 24 weeks.

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

Dosage and administration details:

All participants received DNV 100 mg BID, every 12 hours (q12h) administered orally for 24 weeks.

Investigational medicinal product name	Ritonavir
Investigational medicinal product code	
Other name	Norvir®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All participants received ritonavir 100 mg BID orally for 24 weeks.

Investigational medicinal product name	PEG-IFN alfa 2a
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

All participants received PEG-IFN 180 µg subcutaneously once weekly.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus®, RBV
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

All participants received weight-based RBV 1000-1200 mg/day in two divided doses orally for 24 weeks.

Arm title	Cohort 2: Previous null responders

Arm description:

All participants received PEG-IFN 180 µg subcutaneously once weekly and weight-based RBV 1000-1200 mg/day in two divided doses orally for 24 weeks along with RO5024048 1000 mg BID co-administered orally. Participants also received DNV/r 100/100 mg BID for 24 weeks.

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

Dosage and administration details:

All participants received DNV/r 100/100 mg BID q12h administered orally for 24 weeks.

Investigational medicinal product name	Ritonavir
Investigational medicinal product code	
Other name	Norvir®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All participants received ritonavir 100 mg BID orally for 24 weeks.

Investigational medicinal product name	RO5024048
Investigational medicinal product code	
Other name	Mericitabine
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

All participants received RO5024048 1000 mg BID 24 weeks.

Investigational medicinal product name	PEG-IFN alfa 2a
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

All participants received PEG-IFN 180 µg subcutaneously once weekly.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus®, RBV
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

All participants received weight-based RBV 1000-1200 mg/day in two divided doses orally for 24 weeks.

Number of subjects in period 1	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders
Started	23	20
Completed	16	20
Not completed	7	0
Insufficient therapeutic response	5	-
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-

Period 2

Period 2 title	Follow-up Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Treatment-naïve - Follow-Up

Arm description:

After Week 24 of treatment period, all study drugs were discontinued and participants who completed 24 weeks of treatment were followed at 4, 12, and 24 weeks after the last dose of all medications (corresponding to Study Weeks 28, 36, and 48).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Cohort 2: Previous null responders - Follow-Up

Arm description:

After Week 24 of treatment period, all study drugs were discontinued and participants who completed 24 weeks of treatment were followed at 4, 12, and 24 weeks after the last dose of all medications (corresponding to Study Weeks 28, 36, and 48).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Cohort 1: Treatment-naïve - Follow-Up	Cohort 2: Previous null responders - Follow-Up
Started	16	20
Completed	11	19
Not completed	5	1
Consent withdrawn by subject	1	1
Administrative reasons	1	-
Lost to follow-up	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Treatment-naïve
Reporting group description:	
All participants received peginterferon alfa-2a (PEG-IFN) 180 micrograms (µg) subcutaneously once weekly for 24 weeks and weight-based ribavirin (RBV) 1000-1200 milligrams per day (mg/day) in two divided doses orally for 24 weeks along with DNV/r 100/100 mg twice a day (BID) orally for 24 weeks.	
Reporting group title	Cohort 2: Previous null responders
Reporting group description:	
All participants received PEG-IFN 180 µg subcutaneously once weekly and weight-based RBV 1000-1200 mg/day in two divided doses orally for 24 weeks along with RO5024048 1000 mg BID co-administered orally. Participants also received DNV/r 100/100 mg BID for 24 weeks.	

Reporting group values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders	Total
Number of subjects	23	20	43
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	55.2	54.1	
standard deviation	± 5.48	± 4.83	-
Gender categorical			
Units: Subjects			
Female	9	7	16
Male	14	13	27

End points

End points reporting groups

Reporting group title	Cohort 1: Treatment-naïve

Reporting group description:

All participants received peginterferon alfa-2a (PEG-IFN) 180 micrograms (µg) subcutaneously once weekly for 24 weeks and weight-based ribavirin (RBV) 1000-1200 milligrams per day (mg/day) in two divided doses orally for 24 weeks along with DNV/r 100/100 mg twice a day (BID) orally for 24 weeks.

Reporting group title	Cohort 2: Previous null responders

Reporting group description:

All participants received PEG-IFN 180 µg subcutaneously once weekly and weight-based RBV 1000-1200 mg/day in two divided doses orally for 24 weeks along with RO5024048 1000 mg BID co-administered orally. Participants also received DNV/r 100/100 mg BID for 24 weeks.

Reporting group title	Cohort 1: Treatment-naïve - Follow-Up

Reporting group description:

After Week 24 of treatment period, all study drugs were discontinued and participants who completed 24 weeks of treatment were followed at 4, 12, and 24 weeks after the last dose of all medications (corresponding to Study Weeks 28, 36, and 48).

Reporting group title	Cohort 2: Previous null responders - Follow-Up

Reporting group description:

After Week 24 of treatment period, all study drugs were discontinued and participants who completed 24 weeks of treatment were followed at 4, 12, and 24 weeks after the last dose of all medications (corresponding to Study Weeks 28, 36, and 48).

Subject analysis set title	Pharmacokinetic Analysis Population- Cohort 1 treatment-naïve
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK Analysis Population comprised all patients who received at least one dose of study medication and for whom at least one post-baseline PK measurement was performed.

Subject analysis set title	Pharmacokinetic Analysis Population- Cohort 2 previous null-re
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK Analysis Population comprised all patients who received at least one dose of study medication and for whom at least one post-baseline PK measurement was performed.

Primary: Maximum Plasma Concentration (Cmax) and Plasma Concentration at 12 Hours Post-dose (C12h) for Danoprevir (DNV) and Ritonavir

End point title	Maximum Plasma Concentration (Cmax) and Plasma Concentration at 12 Hours Post-dose (C12h) for Danoprevir (DNV) and Ritonavir[1]

End point description:

Plasma concentrations for DNV and ritonavir were measured by specific and validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods. Blood samples were collected at the following times: Days 1 and 14 (serial PK): Pre-dose (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (Day 2 and Day 15, respectively) post morning dose.

End point type	Primary

End point timeframe:

Days 1 and 14

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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: ng/mL				
arithmetic mean (standard deviation)				
DNV-Cmax Day 1 (n=23,20)	381 (± 394)	437 (± 339)		
DNV-Cmax Day 14 (n=22,20)	333 (± 346)	355 (± 310)		
DNV-C12h Day 1 (n=23,20)	8.49 (± 14)	11 (± 20.3)		
DNV-C12h Day 14 (n=22,20)	7.97 (± 24.2)	3.97 (± 6.42)		
Ritonavir-Cmax Day 1 (n=23,20)	744 (± 400)	739 (± 401)		
Ritonavir-Cmax Day 14 (n=22,20)	1614 (± 587)	1449 (± 745)		
Ritonavir-C12h Day 1 (n=23,20)	209 (± 185)	201 (± 92.4)		
Ritonavir-C12h Day 14 (n=22,20)	391 (± 22.4)	369 (± 158)		

Statistical analyses

No statistical analyses for this end point

Primary: Cmax and C12h for RO4995855 and RO5012433

End point title	Cmax and C12h for RO4995855 and RO5012433[2][3]

End point description:

Plasma concentrations for RO4995855 (parent of pro-drug RO5024048) and RO5012433 (the metabolite of RO4995855) were measured by specific and validated LC-MS/MS methods. Blood samples were collected at the following times: Days 1 and 14 (serial PK): Pre-dose (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (Day 2 and Day 15, respectively) post morning dose.

End point type	Primary

End point timeframe:

Days 1 and 14

Notes:

[2] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.
[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: RO5024048 was not administered to Cohort 1 participants. Therefore, calculating AUC of RO4995855 and RO5012433 (metabolites of RO5024048) was not feasible in these participants.

End point values	Cohort 2: Previous null responders			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: ng/mL				
arithmetic mean (standard deviation)				
RO4995855-Cmax Day 1	7171 (± 2157)			
RO4995855-Cmax Day 14	9096 (± 2041)			
RO4995855-C12h Day 1	1680 (± 703)			
RO4995855-C12h Day 14	2106 (± 693)			
RO5012433 Cmax Day 1	407 (± 188)			
RO5012433 Cmax Day 14	827 (± 310)			

RO5012433 C12h Day 1	242 (± 105)			
RO5012433 C12h Day 14	532 (± 262)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Curve (AUC) for DNV and Ritonavir

End point title	Area Under the Curve (AUC) for DNV and Ritonavir[4]

End point description:

AUC is the area under the curve (mathematically known as integral) in a plot of concentration of drug in blood plasma against time. Typically, the area is computed starting at the time the drug is administered and ending when the concentration in plasma is negligible. Here the drug concentration is measured at certain discrete points in time and the trapezoidal rule is used to estimate AUC. Blood samples for DNV and ritonavir were collected at the following times: Days 1 and 14 (serial PK): Predose (within 60 min), 0.5, 1 ,2, 3, 4, 6, 8, 12, and 24 hours post morning dose. AUC 0-12 denotes Area Under the Concentration Curve from 0 to 12 hours and AUC tau is the AUC from 0 hours to the time of next dosing measured as hours times nanograms per milliliter (hr*ng/mL)

End point type	Primary

End point timeframe:

Days 1 and 14

Notes:

[4] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
DNV-AUC(0-12h) Day 1 (n=23,20)	957 (± 807)	1181 (± 863)		
DNV-AUC(0-tau) Day 14 (n=22,20)	926 (± 1227)	1078 (± 1144)		
Ritonavir-AUC(0-12h) Day 1 (n=23,20)	4288 (± 2323)	3956 (± 1817)		
Ritonavir-AUC(0-tau) Day 14 (n=22,20)	9574 (± 3672)	8566 (± 3723)		

Statistical analyses

No statistical analyses for this end point

Primary: AUC for RO4995855 and RO5012433

End point title	AUC for RO4995855 and RO5012433[5][6]

End point description:

AUC is the area under the curve (mathematically known as integral) in a plot of concentration of drug in blood plasma against time. Typically, the area is computed starting at the time the drug is administered and ending when the concentration in plasma is negligible. Here the drug concentration is measured at certain discrete points in time and the trapezoidal rule is used to estimate AUC. Blood samples were

collected at the following times: Days 1 and 14 (serial PK): Predose (within 60 min), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post morning dose. RO4995855 is the parent of RO5024048 and RO5012433 is the metabolite of RO4995855.

End point type	Primary

End point timeframe:

Days 1 and 14

Notes:

[5] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.
[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: RO5024048 was not administered to Cohort 1 participants. Therefore, calculating concentrations of RO4995855 and RO5012433 (metabolites of RO5024048) was not feasible in these participants.

End point values	Cohort 2: Previous null responders			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
RO4995855-AUC(0-12h) Day 1	45233 (± 14020)			
RO4995855-AUC(0-tau) Day 14	60733 (± 14468)			
RO5012433-AUC(0-12h) Day 1	3262 (± 1457)			
RO5012433-AUC(0-tau) Day 14	7944 (± 2972)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Attain Maximum Plasma Concentration (Tmax) for DNV and Ritonavir

End point title	Time to Attain Maximum Plasma Concentration (Tmax) for DNV and Ritonavir[7]

End point description:

Tmax is defined as the time in hours to attain maximum concentration of the specific drug. Blood samples were collected at the following times: Days 1 and 14 (serial PK): Pre-dose (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (Day 2 and Day 15, respectively) post morning dose.

End point type	Primary

End point timeframe:

Days 1 and 14

Notes:

[7] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: hours				
median (full range (min-max))				
DNV Day 1 (n=23,20)	2 (0.483 to 4.08)	2 (0.483 to 4.03)		
DNV Day 14 (n=22,20)	2.58 (0.483 to 4.07)	2 (0.5 to 4)		
Ritonavir Day 1 (n=23,20)	3.9 (1 to 6)	4 (0.483 to 6)		
Ritonavir Day 14 (n=22,20)	3.03 (1 to 4.17)	4 (0 to 8)		

Statistical analyses

No statistical analyses for this end point

Primary: Tmax for RO4995855 and RO5012433

End point title	Tmax for RO4995855 and RO5012433[8][9]

End point description:

Tmax is defined as the time in hours to attain maximum plasma concentration of the specified metabolite. Blood samples were collected at the following times: Days 1 and 14 (serial PK): Pre-dose (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (Day 2 and Day 15, respectively) post morning dose.

End point type	Primary

End point timeframe:

Days 1 and 14

Notes:

[8] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.
[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: RO5024048 was not administered to Cohort 1 participants. Therefore, calculating AUC of RO4995855 and RO5012433 (metabolites of RO5024048) was not feasible in these participants.

End point values	Cohort 2: Previous null responders			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: hours				
median (full range (min-max))				
RO4995855 Day 1	3 (1 to 6)			
RO4995855 Day 14	3 (1.02 to 4.02)			
RO5012433 Day 1	4.99 (3 to 11.9)			
RO5012433 Day 14	4 (1.02 to 12)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Volume of Distribution at Steady State After Non-intravenous Administration

End point title	Apparent Volume of Distribution at Steady State After Non-intravenous Administration[10]

End point description:

The volume of distribution (VD), also known as apparent volume of distribution, is a pharmacological, theoretical volume that the total amount of administered drug would have to occupy (if it were uniformly distributed), to provide the same concentration as it currently is in blood plasma. Blood samples were collected at the following times: Days 1 and 14 (serial PK): Pre-dose (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (Day 2 and Day 15, respectively) post morning dose.

End point type	Primary

End point timeframe:

Day 14

Notes:

[10] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: litre(s)				
arithmetic mean (standard deviation)				
DNV (n=21,20) Ritonavir (n=20,15)	517 (± 456) 78.8 (± 38)	536 (± 506) 113 (± 66)		

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Total Oral Clearance at Steady State

End point title	Apparent Total Oral Clearance at Steady State[11]

End point description:

The apparent total oral clearance at Steady State 1 is the volume of plasma cleared of the drug per unit time and is measured in liters per hour (L/hr). Blood samples were collected at the following times: Days 1 and 14 (serial PK): Pre-dose (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (Day 2 and Day 15, respectively) post morning dose.

End point type	Primary

End point timeframe:

Day 14

Notes:

[11] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: L/hr				
arithmetic mean (standard deviation)				
DNV (n=21,20)	215 (± 202)	223 (± 202)		
Ritonavir (n= 21,16)	12.1 (± 5.28)	13.6 (± 5.21)		

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Elimination Half Life (t1/2)for DNV and Ritonavir

End point title	Terminal Elimination Half Life (t1/2)for DNV and Ritonavir[12]

End point description:

t1/2 is the time required for the concentration of the drug to reach half of its original value. Blood samples were collected at the following times: Days 1 and 14 (serial PK): Pre-dose (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (Day 2 and Day 15, respectively) post morning dose.

End point type	Primary

End point timeframe:

Days 1 and 14

Notes:

[12] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: hours				
arithmetic mean (standard deviation)				
DNV Day 1 (n=22,20)	2.05 (± 0.572)	2.01 (± 0.858)		
DNV Day 14 (n=21,20)	1.83 (± 0.746)	1.57 (± 0.328)		
Ritonavir Day 1(n=19,12)	5.17 (± 2.05)	5.7 (± 2.04)		
Ritonavir Day 14 (n=20,15)	4.51 (± 1.01)	5.28 (± 1.48)		

Statistical analyses

No statistical analyses for this end point

Primary: t1/2 for RO4995855 and RO5012433

End point title	t1/2 for RO4995855 and RO5012433[13][14]

End point description:

t1/2 is the time required for the concentration of the drug to reach half of its original value. Blood samples were collected at the following times: Days 1 and 14 (serial PK): Pre-dose (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (Day 2 and Day 15, respectively) post morning dose.

End point type	Primary

End point timeframe:

Days 1 and 14

Notes:

[13] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.
[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: RO5024048 was not administered to Cohort 1 participants. Therefore, calculating AUC of RO4995855 and RO5012433 (metabolites of RO5024048) was not feasible in these participants.

End point values	Cohort 2: Previous null responders			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: hours				
arithmetic mean (standard deviation)				
RO4995855 Day 1 (n=18)	4.14 (± 0.52)			
RO4995855 Day 14 (n=20)	4.52 (± 1.34)			
RO5012433 Day 1 (n=9)	8.74 (± 3.48)			
RO5012433 Day 14 (n=13)	11.2 (± 3.31)			

Statistical analyses

No statistical analyses for this end point

Primary: Accumulation Ratio (AR) for DNV and Ritonavir

End point title	Accumulation Ratio (AR) for DNV and Ritonavir[15]

End point description:

Accumulation ratio was calculated as the ratio of AUC(0-tau, Day 14)/AUC(0-12h, Day 1). Blood samples were collected at the following times: Days 1 and 14 (serial PK): Pre-dose (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (Day 2 and Day 15, respectively) post morning dose.

End point type	Primary

End point timeframe:

Day 14

Notes:

[15] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: ratio				
arithmetic mean (standard deviation)				
DNV	0.91 (± 0.4)	0.84 (± 0.38)		
Ritonavir	2.47 (± 0.94)	2.25 (± 0.59)		

Statistical analyses

No statistical analyses for this end point

Primary: AR for RO4995855 and RO5012433

End point title	AR for RO4995855 and RO5012433[16][17]

End point description:

AR was calculated as the ratio of AUC(0-tau, Day 14)/AUC(0-12h, Day 1). Blood samples were collected at the following times: Days 1 and 14 (serial PK): Pre-dose (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (Day 2 and Day 15, respectively) post morning dose.

End point type	Primary

End point timeframe:

Day 14

Notes:

[16] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.
[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: RO5024048 was not administered to Cohort 1 participants. Therefore, calculating AUC of RO4995855 and RO5012433 (metabolites of RO5024048) was not feasible in these participants.

End point values	Cohort 2: Previous null responders			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: ratio				
arithmetic mean (standard deviation)				
RO4995855	1.42 (± 0.45)			
RO5012433	2.61 (± 0.78)			

Statistical analyses

No statistical analyses for this end point

Primary: Trough concentrations for PEG-IFN

End point title	Trough concentrations for PEG-IFN[18]

End point description:

The trough levels is the lowest concentration reached by the drug before the next dose is administered, as determined by therapeutic drug monitoring. The concentrations were measured as picograms per milliliter (pg/mL). Blood samples were collected at the following times: Days 1 and 14 (serial PK): Pre-dose (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (Day 2 and Day 15, respectively) post morning dose.

End point type	Primary

End point timeframe:

Predose Days 1, 8 and 15

Notes:

[18] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: pg/mL				
arithmetic mean (standard deviation)				
Day 1 predose (n=23,20)	0 (± 0)	0 (± 0)		
Day 8 predose (n=22,20)	5750.2 (± 3672.05)	4267.8 (± 3231.44)		
Day 15 predose (n=20,20)	7662.5 (± 3840.98)	6506 (± 5529.46)		

Statistical analyses

No statistical analyses for this end point

Primary: Trough Concentrations of RBV

End point title	Trough Concentrations of RBV[19]

End point description:

The trough levels is the lowest concentration reached by the drug before the next dose is administered, as determined by therapeutic drug monitoring. The concentrations were measured as nanograms per milliliter (ng/mL). Blood samples were collected at the following times: Days 1 and 14 (serial PK): Pre-dose (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (Day 2 and Day 15, respectively) post morning dose.

End point type	Primary

End point timeframe:

Predose Days 1, 8 and 15

Notes:

[19] - 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: As a Phase II study, there was no hypothesis testing, but descriptive statistical analyses were performed according to the protocol.

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 predose (n=23,20)	0 (± 0)	2.97 (± 13.282)		
Day 8 predose (n=22,20)	1469.1 (± 346.491)	1598.3 (± 801.375)		
Day 15 predose (n=19,20)	1848.4 (± 546.293)	1850.8 (± 607.411)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Hepatitis C Virus Ribonucleic Acid (HCV RNA) Levels

End point title	Changes From Baseline in Hepatitis C Virus Ribonucleic Acid (HCV RNA) Levels

End point description:

HCV RNA antiviral activity was summarized by cohort in the Efficacy Population. Efficacy Population comprised all patients who received at least one dose of study medication, and for whom at least one post-baseline efficacy measurement was performed. Summary statistics for changes from baseline HCV RNA levels throughout the study were provided. Before calculating the change from baseline in HCV RNA levels, the levels were log transformed (base 10) measured as International Units per milliliter (IU/mL). If at a particular visit the HCV RNA level was unquantifiable or undetectable, the level was imputed as 24.99 before being log transformed.

End point type	Secondary

End point timeframe:

Day 14, Weeks 4, 12, and 24

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: IU/mL				
arithmetic mean (standard deviation)				
Baseline(n=23,20)	6.5 (± 0.62)	6.4 (± 0.34)		
Change from Baseline at Day 14 predose	-4.6 (± 0.71)	-5 (± 0.39)		
Change from Baseline at Week 4 predose	-4.7 (± 1.04)	-5 (± 0.34)		
Change from Baseline at Week 12 predose	-4.8 (± 0.73)	-5 (± 0.34)		
Change from Baseline at Week 24 predose	-5 (± 0.69)	-5 (± 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Virological Response

End point title	Percentage of Participants with Virological Response

End point description:

Virological response is defined as HCV RNA under the lower limit of quantification; less than (<) 25 IU/mL. a : HCV RNA samples were obtained before administration of any of the study drugs RVR: participants with response at Week 4 and cEVR: participants with response at Week 12.

End point type	Secondary

End point timeframe:

Days 8 and 14 and Weeks 4, 12, and 24

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: Percentage of participants				
number (confidence interval 95%)				
Day 8 pre-dose (a){n=23,20}	26.1 (12.5 to 46.5)	35 (18.1 to 56.7)		
Day 14 pre-dose {n=23,20}	43.5 (25.6 to 63.2)	85 (64 to 94.8)		
Week 4 pre-dose (RVR){n=23,20}	73.9 (53.5 to 87.5)	100 (83.9 to 100)		
Week 12 pre-dose (cEVR){n=23,20}	73.9 (53.5 to 87.5)	100 (83.9 to 100)		
Week 24 pre-dose {n=23,20}	65.2 (44.9 to 81.2)	100 (83.9 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Virological Response at End of Treatment (EOT) and Sustained Virological Response (SVR)

End point title	Percentage of Participants with Virological Response at End of Treatment (EOT) and Sustained Virological Response (SVR)

End point description:

SVR4/12/24 is defined as sustained virological response at 4, 12, and 24 weeks after the last study drug administration. EOT = End of Treatment response; SVR4 = Sustained Virological Response 4 weeks after the last study drug administration; SVR12 = Sustained Virological Response 12 weeks after the

last study drug administration; SVR24 = Sustained Virological Response 24 weeks after the last study drug administration.

End point type	Secondary

End point timeframe:

EOT, SVR 4, 12, and 24

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: Percentage of participants				
number (confidence interval 95%)				
EOT	69.6 (49.1 to 84.4)	100 (83.9 to 100)		
SVR4	47.8 (29.2 to 67)	75 (53.1 to 88.8)		
SVR12	39.1 (22.2 to 59.2)	65 (43.3 to 81.9)		
SVR24	39.1 (22.2 to 59.2)	65 (43.3 to 81.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with EOT Response and Relapse at 4, 12, and 24 Weeks Follow-Up

End point title	Percentage of Participants with EOT Response and Relapse at 4, 12, and 24 Weeks Follow-Up

End point description:

Participants who had an EOT virological response and did not have an HCV RNA assessment during follow-up were excluded; these participants were not considered as having relapsed. Participants who achieved a virological response at the end of the follow-up period but had no HCV RNA assessment at the end of the actual treatment period were also considered EOT virological responders.
Relapse = number of participants who achieved a response at EOT but had a detectable HCV RNA at the last assessment post-treatment divided
by the number of participants with a virological response at the end of treatment who had at least one HCV RNA assessment post-treatment.

End point type	Secondary

End point timeframe:

EOT and 4, 12, and 24 weeks of treatment free follow-up

End point values	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: Percentage of participants				
number (confidence interval 95%)				
EOT (n=23,20)	69.6 (49.1 to 84.4)	100 (83.9 to 100)		
Relapse at Week 4 (n=15,20)	26.7 (10.9 to 52)	25 (11.2 to 46.9)		
Relapse at Week 12 (n=15,20)	40 (19.8 to 64.3)	35 (18.1 to 56.7)		
Relapse at Week 24 (n= 15,20	40 (19.8 to 64.3)	35 (18.1 to 56.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were continuously monitored daily starting after the time of informed consent through the final follow-up visit up to 24 weeks after EOT.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Cohort 1: Treatment-naïve

Reporting group description:

All patients received PEG-IFN 180 µg subcutaneously once weekly and weight-based RBV 1000-1200 mg/day in two divided doses orally for 24 weeks along with DNV/r 100/100 mg BID orally for 24 weeks.

Reporting group title	Cohort 2: Previous null responders

Reporting group description:

All patients received PEG-IFN 180 µg subcutaneously once weekly and weight-based RBV 1000-1200 mg/day in two divided doses orally for 24 weeks along with RO5024048 1000 mg BID co-administered orally.

Serious adverse events	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 23 (13.04%)	1 / 20 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hemobilia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Corneal infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1: Treatment-naïve	Cohort 2: Previous null responders	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 23 (95.65%)	20 / 20 (100.00%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 23 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Orthostatic hypotension			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 23 (34.78%)	4 / 20 (20.00%)	
occurrences (all)	8	4	
Influenza like illness			
subjects affected / exposed	4 / 23 (17.39%)	5 / 20 (25.00%)	
occurrences (all)	4	10	
Irritability			
subjects affected / exposed	3 / 23 (13.04%)	4 / 20 (20.00%)	
occurrences (all)	3	4	
Asthenia			
subjects affected / exposed	4 / 23 (17.39%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Injection site erythema			

subjects affected / exposed	3 / 23 (13.04%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Pyrexia			
subjects affected / exposed	2 / 23 (8.70%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Chills			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Discomfort			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Injection site haemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Injection site bruising			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Vaginal discharge			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 23 (21.74%)	1 / 20 (5.00%)	
occurrences (all)	5	1	
Dyspnoea			

subjects affected / exposed	0 / 23 (0.00%)	4 / 20 (20.00%)	
occurrences (all)	0	4	
Oropharyngeal pain			
subjects affected / exposed	2 / 23 (8.70%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Rhinorrhoea			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Oropharyngeal discomfort			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pulmonary fibrosis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 23 (13.04%)	2 / 20 (10.00%)	
occurrences (all)	3	2	
Depression			
subjects affected / exposed	2 / 23 (8.70%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Anxiety			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Confusional state			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Mood altered			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 23 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Alanine aminotransferase increased			

subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Haemoglobin decreased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 23 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Post-traumatic pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Tooth fracture			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 23 (17.39%)	7 / 20 (35.00%)	
occurrences (all)	4	16	
Dizziness			
subjects affected / exposed	3 / 23 (13.04%)	3 / 20 (15.00%)	
occurrences (all)	3	4	
Syncope			
subjects affected / exposed	3 / 23 (13.04%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Amnesia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Disturbance in attention			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Dysgeusia			

subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypoaesthesia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Mental impairment			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Tension headache			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 23 (34.78%)	6 / 20 (30.00%)	
occurrences (all)	11	7	
Neutropenia			
subjects affected / exposed	7 / 23 (30.43%)	6 / 20 (30.00%)	
occurrences (all)	9	10	
Thrombocytopenia			
subjects affected / exposed	3 / 23 (13.04%)	6 / 20 (30.00%)	
occurrences (all)	3	6	
Haemolytic Anaemia			
subjects affected / exposed	0 / 23 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Eye disorders			

Vision blurred			
subjects affected / exposed	2 / 23 (8.70%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Conjunctivitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Eye pruritus			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	5	
Visual impairment			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 23 (30.43%)	6 / 20 (30.00%)	
occurrences (all)	9	6	
Nausea			
subjects affected / exposed	6 / 23 (26.09%)	1 / 20 (5.00%)	
occurrences (all)	8	2	
Constipation			
subjects affected / exposed	0 / 23 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Vomiting			
subjects affected / exposed	3 / 23 (13.04%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Dyspepsia			
subjects affected / exposed	2 / 23 (8.70%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Abdominal pain			
subjects affected / exposed	2 / 23 (8.70%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Abdominal distension			

subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Aphthous stomatitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Epigastric discomfort			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Irritable bowel syndrome			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 23 (17.39%)	4 / 20 (20.00%)	
occurrences (all)	4	5	
Pruritus			
subjects affected / exposed	2 / 23 (8.70%)	3 / 20 (15.00%)	
occurrences (all)	2	3	
Alopecia			
subjects affected / exposed	4 / 23 (17.39%)	0 / 20 (0.00%)	
occurrences (all)	4	0	
Dry skin			
subjects affected / exposed	0 / 23 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Eczema			
subjects affected / exposed	2 / 23 (8.70%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Petechiae			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Myalgia			
subjects affected / exposed	3 / 23 (13.04%)	4 / 20 (20.00%)	
occurrences (all)	3	9	
Back pain			
subjects affected / exposed	2 / 23 (8.70%)	4 / 20 (20.00%)	
occurrences (all)	2	5	
Arthralgia			
subjects affected / exposed	2 / 23 (8.70%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Muscle spasms			
subjects affected / exposed	0 / 23 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Pain in extremity			
subjects affected / exposed	3 / 23 (13.04%)	0 / 20 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal pain			
subjects affected / exposed	2 / 23 (8.70%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Upper respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Bronchitis			
subjects affected / exposed	2 / 23 (8.70%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Urinary tract infection			

subjects affected / exposed	0 / 23 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	4	
Ear infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Fungal skin infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Otitis media			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 23 (13.04%)	3 / 20 (15.00%)	
occurrences (all)	3	3	
Dehydration			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2012	This amendment included changes in Sponsor's name and address, sample size, sample collection times and data summarizing methods. Study committee and data monitoring committee were included. Study drug references were corrected to accurately reflect the information in clinical study protocol. The collection and reporting time for unrelated SAEs following the last dose of study treatment was updated. Patient safety data on ongoing studies was updated.
01 October 2012	This amendment included changes according to which pregnancy and drug testing did not need to be performed on Day 13 or Day 14. Text was added to clarify that sites should use their own Electrocardiogram (ECG) readout/printouts. The electronic Case Report Form (eCRF) was updated. Serial and Trough Pharmacokinetic (PK) sampling times were amended. SAE and pregnancy reporting timeframe was changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported