Clinical trial results:
A phase II, randomized, double-blind, multicenter, active-controlled, parallel group study to evaluate the sustained virologic response of the HCV polymerase inhibitor prodrug RO5024048 in combination with Telaprevir and Pegasus/Copegus compared with Telaprevir and Pegasys/Copegus in patients with chronic Hepatitis C Genotype 1 virus infection who were prior null responders to treatment with Pegylated Interferon/Ribavirin.

Summary

EudraCT number	2011-002715-28
Trial protocol	GB DE ES IT
Global end of trial date	28 January 2014

Results information

Result version number	v1 (current)
This version publication date	22 April 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	NV27779

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01482390
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, +41 061 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, 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	28 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the difference in sustained virologic response 12 weeks after treatment (SVR-12) between each of the following three experimental treatment groups (regimens containing RO5024048, telaprevir, Pegasys, and Copegus) and the control treatment group (regimen containing telaprevir, Pegasys, and Copegus) in patients with previous null response to pegylated interferon/ribavirin (PEG-IFN/RBV) combination therapy, defined as a < 2 log10 IU/mL decrease in viral titer after at least 12 weeks of treatment with PEG-IFN/RBV.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice. All subjects signed an informed consent form.

Background therapy:

There were no background therapies indicated for this study.

Evidence for comparator: -

Actual start date of recruitment	14 November 2011
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	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	80
EEA total number of subjects	43

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)	78
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screened over a period of 12 weeks

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS

Arm description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple) (total treatment duration of 24 weeks), followed by a 24-week treatment-free follow-up period.

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

Dosage and administration details:

Total daily dose of 1000 mg (<75 kg) or 1200 mg (≥75 kg) taken orally within 30 minutes after meal or snack for 24 weeks

Investigational medicinal product name	Mericitabine
Investigational medicinal product code	
Other name	RO5024048
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered at a dose of 1000 mg orally twice daily within 30 minutes of eating meal or snack for 24 weeks

Investigational medicinal product name	Pegasys
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered at a dose of 180 µg via subcutaneous route once weekly for 24 weeks

Investigational medicinal product name	Telaprevir
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered at a dose of 750 mg orally three times daily (at recommended intervals of 7-9 hours) within 30 minutes after meal or snack for 12 weeks

Arm title	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS

Arm description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24−week treatment-free follow-up period.

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

Dosage and administration details:

Total daily dose of 1000 mg (<75 kg) or 1200 mg (≥75 kg) taken orally within 30 minutes after meal or snack for 48 weeks

Investigational medicinal product name	Mericitabine
Investigational medicinal product code	
Other name	RO5024048
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered at a dose of 1000 mg orally twice daily within 30 minutes of eating meal or snack for 24 weeks

Investigational medicinal product name	Pegasys
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered at a dose of 180 µg via subcutaneous route once weekly for 48 weeks

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

Dosage and administration details:

Administered at a dose of 750 mg orally three times daily (at recommended intervals of 7-9 hours) within 30 minutes after meal or snack for 12 weeks

Arm title	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS

Arm description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo (PLAC) + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24−week treatment-free follow-up period.

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

Dosage and administration details:

Total daily dose of 1000 mg (<75 kg) or 1200 mg (≥75 kg) taken orally within 30 minutes after meal or snack for 48 weeks

Investigational medicinal product name	Mericitabine
Investigational medicinal product code	
Other name	RO5024048
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered at a dose of 1000 mg orally twice daily within 30 minutes of eating meal or snack for 12 weeks

Investigational medicinal product name	Pegasys
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered at a dose of 180 µg via subcutaneous route once weekly for 48 weeks

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

Dosage and administration details:

Administered at a dose of 750 mg orally three times daily (at recommended intervals of 7-9 hours) within 30 minutes after meal or snack for 12 weeks

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

Dosage and administration details:

Administered 1000 mg orally twice daily for 12 weeks

Arm title	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS

Arm description:

Twelve weeks of therapy with mericitabine (MCB) placebo (PLAC), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24−week treatment-free follow-up period.

Arm type	Active comparator

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

Dosage and administration details:

Total daily dose of 1000 mg (<75 kg) or 1200 mg (≥75 kg) taken orally within 30 minutes after meal or snack for 48 weeks

Investigational medicinal product name	Pegasys
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered at a dose of 180 µg via subcutaneous route once weekly for 48 weeks

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

Dosage and administration details:

Administered at a dose of 750 mg orally three times daily (at recommended intervals of 7-9 hours) within 30 minutes after meal or snack for 12 weeks

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

Dosage and administration details:

Administered 1000 mg orally twice daily for 24 weeks

Number of subjects in period 1	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS
Started	21	24	24
Completed	18	22	24
Not completed	3	2	0
Physician decision	1	-	-
Not specified	1	-	-
Did not receive study drug	-	1	-
Lost to follow-up	-	1	-
Withdrawal by subject	1	-	-

Number of subjects in period 1	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS

Started	11
Completed	11
Not completed	0
Physician decision	-
Not specified	-
Did not receive study drug	-
Lost to follow-up	-
Withdrawal by subject	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple) (total treatment duration of 24 weeks), followed by a 24-week treatment-free follow-up period.

Reporting group title	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24−week treatment-free follow-up period.

Reporting group title	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo (PLAC) + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24−week treatment-free follow-up period.

Reporting group title	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB) placebo (PLAC), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24−week treatment-free follow-up period.

Reporting group values	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS
Number of subjects	21	24	24
Age categorical Units: Subjects			
<18 years	0	0	0
>=18-<=65 years	20	24	23
>65	1	0	1
Age continuous Units: years			
arithmetic mean	51.9	54	53.5
standard deviation	± 10.1	± 7.6	± 7.7
Gender categorical Units: Subjects			
Female	6	7	7
Male	15	17	17

Reporting group values	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS	Total	
Number of subjects	11	80	

Age categorical Units: Subjects			
<18 years	0	0	
>=18-<=65 years	11	78	
>65	0	2	
Age continuous Units: years			
arithmetic mean	52.8		
standard deviation	± 6.7	-	
Gender categorical Units: Subjects			
Female	2	22	
Male	9	58	

End points

End points reporting groups

Reporting group title	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple) (total treatment duration of 24 weeks), followed by a 24-week treatment-free follow-up period.

Reporting group title	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24−week treatment-free follow-up period.

Reporting group title	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo (PLAC) + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24−week treatment-free follow-up period.

Reporting group title	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB) placebo (PLAC), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24−week treatment-free follow-up period.

Subject analysis set title	Hepatitis C Virus (HCV)-resistance Monitoring Set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who received therapy were monitored for the presence of resistance mutations.

Primary: Percent of Subjects With Sustained Virological Response 12 Weeks After Treatment (SVR12)

End point title	Percent of Subjects With Sustained Virological Response 12 Weeks After Treatment (SVR12)[1]

End point description:

Response was defined as an unquantifiable (less than the lower limit of quantification [LLOQ]; <25 International Units [IU]/mL) serum HCV-RNA 12 weeks after the actual end of treatment (EOT) (a single last unquantifiable HCV-RNA within 8-20 weeks after the last day of study drug administration). Serum HCV RNA was assessed in all randomized patients by polymerase chain reaction (PCR) techniques using the Roche COBAS TaqMan HCV v2.0 Test.

End point type	Primary

End point timeframe:

Up to 60 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was conducted in this exploratory study. The primary efficacy endpoint (SVR12 [actual]) for each of the treatment groups was summarized by using descriptive statistics.

End point values	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	23	24	11
Units: percentage				
number (not applicable)	81	95.7	70.8	90.9

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With SVR4

End point title	Percent of Subjects With SVR4

End point description:

Response was defined as an unquantifiable (less than the lower limit of quantification [LLOQ]; <25 International Units [IU]/mL) serum HCV-RNA within 2 − 8 weeks after the last day of study drug administration. Serum HCV RNA was assessed in all randomized patients by polymerase chain reaction (PCR) techniques using the Roche COBAS TaqMan HCV v2.0 Test.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	23	24	11
Units: percentage				
number (not applicable)	85.7	95.7	70.8	90.9

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With SVR24

End point title	Percent of Subjects With SVR24

End point description:

Response was defined as an unquantifiable (less than the lower limit of quantification [LLOQ]; <25 International Units [IU]/mL) serum HCV-RNA ≥ 20 weeks after the last day of study drug administration. Serum HCV RNA was assessed in all randomized patients by polymerase chain reaction (PCR) techniques using the Roche COBAS TaqMan HCV v2.0 Test.

End point type	Secondary

End point timeframe:

Up to 72 weeks

End point values	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	23	24	11
Units: percentage				
number (not applicable)	76.2	95.7	70.8	90.9

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With Virologic Response Over Time From Week 2 to Week 48

End point title	Percent of Subjects With Virologic Response Over Time From Week 2 to Week 48

End point description:

Response was defined as an unquantifiable (less than the lower limit of quantification [LLOQ]; <25 International Units [IU]/mL) serum HCV-RNA. Serum HCV RNA was assessed in all randomized patients by polymerase chain reaction (PCR) techniques using the Roche COBAS TaqMan HCV v2.0 Test.

End point type	Secondary

End point timeframe:

Up to 48 weeks

End point values	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	23	24	11
Units: percentage				
number (not applicable)				
Week 2	85.7	65.2	70.8	54.5
Week 4	100	95.7	91.7	100
Week 12	100	95.7	91.7	90.9
Week 24	100	91.3	75	90.9
Week 48	0	78.3	54.2	81.8

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-resistant Mutations

End point title	Number of Subjects With Treatment-resistant Mutations

End point description:

Blood samples were collected throughout the study to monitor for the development of drug resistance. During the course of the study, phenotypic and/or sequence analyses were performed on samples from patients who experienced virologic breakthrough, partial response, non-response, or relapse. Patients who developed resistance to MCB and/or to telaprevir were monitored for the persistence of resistant mutation(s) during the follow-up period. The genotype of samples from telaprevir- and/or RO5024048-resistant subjects were determined through population sequencing of the non-structural protein 3/non-structural protein 4a (NS3-4a) and nonstructural protein 5B (NS5B) coding regions by using standard sequencing technology.

End point type	Secondary

End point timeframe:

60 weeks

End point values	Hepatitis C Virus (HCV)-resistance Monitoring Set			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: subjects				
Subjects with telaprevir resistance mutations	10			
Subjects with MCB resistance mutations	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events

End point title	Number of Subjects With Adverse Events

End point description:

Adverse events were systematically monitored throughout the study.

End point type	Secondary

End point timeframe:

60 weeks

End point values	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	23	24	11
Units: Subjects				
Serious adverse events	4	6	3	0
Non-serious adverse events	20	23	24	11

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration of RO4995855

End point title	Trough Concentration of RO4995855

End point description:

Trough concentration was defined as the minimum observed drug concentration during a dosing interval. Pharmacokinetic (PK) plasma and serum samples were collected from all patients to measure RO4995855, its metabolite (RO5012433), and telaprevir before the morning dose of all study drugs on Day 1 (baseline) and at Week 8. Plasma concentrations for RO4995855, RO5012433, and telaprevir were measured by specific and validated liquid chromatography tandem mass spectrometry methods. The value reported is the average trough plasma concentration for Week 8.

End point type	Secondary

End point timeframe:

Day 1 and Week 8

End point values	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	23	4
Units: ng/mL				
arithmetic mean (standard deviation)	3147.75 (± 1711.91)	2716.77 (± 1508.75)	3933.09 (± 1938.6)	1277 (± 2068)

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration of RO5012433

End point title	Trough Concentration of RO5012433

End point description:

Trough concentration was defined as the minimum observed drug concentration during a dosing interval. Pharmacokinetic (PK) plasma and serum samples were collected from all patients to measure

RO4995855, its metabolite (RO5012433), and telaprevir before the morning dose of all study drugs on Day 1 (baseline) and at Week 8. Plasma concentrations for RO4995855, RO5012433, and telaprevir were measured by specific and validated liquid chromatography tandem mass spectrometry methods. The value reported is the average trough plasma concentration for Week 8.

End point type	Secondary

End point timeframe:

Day 1 and week 8

End point values	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	23	4
Units: ng/mL				
arithmetic mean (standard deviation)	727.4 (± 373.47)	638.68 (± 307.73)	853.3 (± 407.2)	394 (± 669.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration of Telaprevir

End point title	Trough Concentration of Telaprevir

End point description:

Trough concentration was defined as the minimum observed drug concentration during a dosing interval. Pharmacokinetic (PK) plasma and serum samples were collected from all patients to measure RO4995855, its metabolite (RO5012433), and telaprevir before the morning dose of all study drugs on Day 1 (baseline) and at Week 8. Plasma concentrations for RO4995855, RO5012433, and telaprevir were measured by specific and validated liquid chromatography tandem mass spectrometry methods. The value reported is the average trough plasma concentration for Week 8.

End point type	Secondary

End point timeframe:

Day 1 and week 8

End point values	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	12	9	4
Units: ng/mL				
arithmetic mean (standard deviation)	2070.56 (± 1240.77)	2020.83 (± 465.31)	2288.89 (± 623.83)	1663.25 (± 614.95)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

48 week timeframe for reporting adverse events

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple) (total treatment duration of 24 weeks), followed by a 24-week treatment-free follow-up period.

Reporting group title	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24−week treatment-free follow-up period.

Reporting group title	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo (PLAC) + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24−week treatment-free follow-up period.

Reporting group title	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB) placebo (PLAC), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24−week treatment-free follow-up period.

Serious adverse events	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 21 (19.05%)	6 / 23 (26.09%)	3 / 24 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid cancer			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (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

Hepatocellular carcinoma			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	0 / 24 (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
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (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
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Ophthalmoplegia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 21 (9.52%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Major depression			

subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (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
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	0 / 24 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid cancer			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatocellular carcinoma			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Amnesia			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Ophthalmoplegia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS	Arm B-TVR 12WKS,MCB 24WKS, P/R 48WKS	Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 21 (95.24%)	23 / 23 (100.00%)	24 / 24 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Phlebitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 21 (19.05%)	5 / 23 (21.74%)	6 / 24 (25.00%)
occurrences (all)	4	5	7
Chest discomfort			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Chest pain			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Chills			
subjects affected / exposed	4 / 21 (19.05%)	3 / 23 (13.04%)	2 / 24 (8.33%)
occurrences (all)	4	3	2
Fatigue			
subjects affected / exposed	12 / 21 (57.14%)	14 / 23 (60.87%)	12 / 24 (50.00%)
occurrences (all)	13	15	12
Feeling abnormal			

subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	1 / 24 (4.17%)
occurrences (all)	1	1	1
Feeling hot			
subjects affected / exposed	2 / 21 (9.52%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Influenza like illness			
subjects affected / exposed	0 / 21 (0.00%)	5 / 23 (21.74%)	2 / 24 (8.33%)
occurrences (all)	0	5	2
Injection site rash			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Irritability			
subjects affected / exposed	1 / 21 (4.76%)	6 / 23 (26.09%)	4 / 24 (16.67%)
occurrences (all)	1	6	4
Local swelling			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	2 / 24 (8.33%)
occurrences (all)	0	2	2
Malaise			
subjects affected / exposed	2 / 21 (9.52%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	2	1	0
Pain			
subjects affected / exposed	1 / 21 (4.76%)	2 / 23 (8.70%)	1 / 24 (4.17%)
occurrences (all)	1	2	1
Pyrexia			
subjects affected / exposed	3 / 21 (14.29%)	4 / 23 (17.39%)	4 / 24 (16.67%)
occurrences (all)	3	4	5
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 21 (9.52%)	7 / 23 (30.43%)	10 / 24 (41.67%)
occurrences (all)	2	7	11
Dyspnoea			

subjects affected / exposed	1 / 21 (4.76%)	2 / 23 (8.70%)	3 / 24 (12.50%)
occurrences (all)	1	2	3
Dyspnoea exertional			
subjects affected / exposed	3 / 21 (14.29%)	7 / 23 (30.43%)	4 / 24 (16.67%)
occurrences (all)	3	7	4
Epistaxis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	2
Rhinorrhoea			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Sinus congestion			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 21 (9.52%)	1 / 23 (4.35%)	2 / 24 (8.33%)
occurrences (all)	2	1	2
Depressed mood			
subjects affected / exposed	1 / 21 (4.76%)	3 / 23 (13.04%)	2 / 24 (8.33%)
occurrences (all)	1	3	2
Depression			
subjects affected / exposed	1 / 21 (4.76%)	4 / 23 (17.39%)	2 / 24 (8.33%)
occurrences (all)	1	4	2
Emotional disorder			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Initial insomnia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	2 / 21 (9.52%)	4 / 23 (17.39%)	5 / 24 (20.83%)
occurrences (all)	2	4	5

Libido decreased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Mood altered			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Mood swings			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Restlessness			
subjects affected / exposed	2 / 21 (9.52%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	2	0	1
Sleep disorder			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	2 / 24 (8.33%)
occurrences (all)	0	2	2
Stress			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	3 / 24 (12.50%)
occurrences (all)	1	0	3
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

Tachycardia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Disturbance in attention			
subjects affected / exposed	0 / 21 (0.00%)	3 / 23 (13.04%)	2 / 24 (8.33%)
occurrences (all)	0	3	2
Dizziness			
subjects affected / exposed	3 / 21 (14.29%)	5 / 23 (21.74%)	2 / 24 (8.33%)
occurrences (all)	3	5	2
Dysgeusia			
subjects affected / exposed	5 / 21 (23.81%)	2 / 23 (8.70%)	2 / 24 (8.33%)
occurrences (all)	5	2	2
Headache			
subjects affected / exposed	9 / 21 (42.86%)	9 / 23 (39.13%)	9 / 24 (37.50%)
occurrences (all)	9	10	10
Hyperaesthesia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Hypoaesthesia			
subjects affected / exposed	1 / 21 (4.76%)	3 / 23 (13.04%)	0 / 24 (0.00%)
occurrences (all)	1	3	0
Lethargy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Memory impairment			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Paraesthesia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Parosmia			

subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 21 (28.57%)	10 / 23 (43.48%)	10 / 24 (41.67%)
occurrences (all)	6	10	10
Leukopenia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Lymph node pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 21 (0.00%)	3 / 23 (13.04%)	1 / 24 (4.17%)
occurrences (all)	0	3	1
Neutropenia			
subjects affected / exposed	4 / 21 (19.05%)	6 / 23 (26.09%)	3 / 24 (12.50%)
occurrences (all)	4	7	3
Thrombocytopenia			
subjects affected / exposed	0 / 21 (0.00%)	4 / 23 (17.39%)	1 / 24 (4.17%)
occurrences (all)	0	4	1
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hyperacusis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	2 / 24 (8.33%)
occurrences (all)	0	3	2
Ocular hyperaemia			

subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	2 / 24 (8.33%)
occurrences (all)	0	2	2
Visual acuity reduced			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	3 / 24 (12.50%)
occurrences (all)	0	0	3
Visual impairment			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Abdominal pain upper			
subjects affected / exposed	2 / 21 (9.52%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	2	0	1
Anal pruritus			
subjects affected / exposed	5 / 21 (23.81%)	3 / 23 (13.04%)	6 / 24 (25.00%)
occurrences (all)	5	4	6
Anorectal discomfort			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Cheilitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	2 / 21 (9.52%)	1 / 23 (4.35%)	2 / 24 (8.33%)
occurrences (all)	2	1	3
Dental caries			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0

Diarrhoea			
subjects affected / exposed	5 / 21 (23.81%)	8 / 23 (34.78%)	4 / 24 (16.67%)
occurrences (all)	6	10	4
Dry mouth			
subjects affected / exposed	0 / 21 (0.00%)	4 / 23 (17.39%)	3 / 24 (12.50%)
occurrences (all)	0	4	3
Dyspepsia			
subjects affected / exposed	3 / 21 (14.29%)	0 / 23 (0.00%)	3 / 24 (12.50%)
occurrences (all)	3	0	3
Frequent bowel movements			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Gingival pain			
subjects affected / exposed	2 / 21 (9.52%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	2	0	1
Haemorrhoids			
subjects affected / exposed	2 / 21 (9.52%)	1 / 23 (4.35%)	3 / 24 (12.50%)
occurrences (all)	2	1	3
Nausea			
subjects affected / exposed	9 / 21 (42.86%)	8 / 23 (34.78%)	7 / 24 (29.17%)
occurrences (all)	9	13	7
Oral pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Painful defaecation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Tongue disorder			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

Tongue dry			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 21 (9.52%)	4 / 23 (17.39%)	6 / 24 (25.00%)
occurrences (all)	2	6	6
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 21 (4.76%)	2 / 23 (8.70%)	1 / 24 (4.17%)
occurrences (all)	1	2	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 21 (14.29%)	3 / 23 (13.04%)	2 / 24 (8.33%)
occurrences (all)	3	3	2
Dermatitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Dermatitis psoriasiform			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	2 / 21 (9.52%)	3 / 23 (13.04%)	3 / 24 (12.50%)
occurrences (all)	2	3	3
Eczema			
subjects affected / exposed	1 / 21 (4.76%)	2 / 23 (8.70%)	3 / 24 (12.50%)
occurrences (all)	1	2	3
Erythema			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Night sweats			
subjects affected / exposed	1 / 21 (4.76%)	2 / 23 (8.70%)	1 / 24 (4.17%)
occurrences (all)	1	2	1
Photosensitivity reaction			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Pruritus			

subjects affected / exposed	7 / 21 (33.33%)	12 / 23 (52.17%)	9 / 24 (37.50%)
occurrences (all)	8	13	11
Pruritus generalised			
subjects affected / exposed	2 / 21 (9.52%)	3 / 23 (13.04%)	4 / 24 (16.67%)
occurrences (all)	2	3	5
Psoriasis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	6 / 21 (28.57%)	7 / 23 (30.43%)	14 / 24 (58.33%)
occurrences (all)	7	7	21
Rash erythematous			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Rash generalised			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	2
Rash macular			
subjects affected / exposed	2 / 21 (9.52%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	2	0	1
Rash maculo-papular			
subjects affected / exposed	1 / 21 (4.76%)	2 / 23 (8.70%)	1 / 24 (4.17%)
occurrences (all)	1	3	2
Skin discolouration			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Skin irritation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

Renal colic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 21 (19.05%)	6 / 23 (26.09%)	1 / 24 (4.17%)
occurrences (all)	4	8	1
Back pain			
subjects affected / exposed	4 / 21 (19.05%)	4 / 23 (17.39%)	3 / 24 (12.50%)
occurrences (all)	4	4	3
Flank pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	2 / 21 (9.52%)	1 / 23 (4.35%)	2 / 24 (8.33%)
occurrences (all)	2	1	2
Myalgia			
subjects affected / exposed	5 / 21 (23.81%)	6 / 23 (26.09%)	4 / 24 (16.67%)
occurrences (all)	5	6	4
Pain in jaw			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Ear infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Eye infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Hordeolum			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Infection			

subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	2 / 24 (8.33%)
occurrences (all)	0	2	2
Oral herpes			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Staphylococcal skin infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 21 (0.00%)	3 / 23 (13.04%)	1 / 24 (4.17%)
occurrences (all)	0	3	1
Urinary tract infection			
subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	4 / 24 (16.67%)
occurrences (all)	1	1	6
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 21 (23.81%)	5 / 23 (21.74%)	3 / 24 (12.50%)
occurrences (all)	5	5	3
Dehydration			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Gout			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1

Non-serious adverse events	Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)		
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Phlebitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	4		
Chest discomfort			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	6		
Feeling abnormal			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Injection site rash			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Irritability			

subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Local swelling			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	5		
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Dyspnoea exertional			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Rhinorrhoea			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Sinus congestion			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Depressed mood			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Emotional disorder			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Initial insomnia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Libido decreased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Mood altered			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Mood swings			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Restlessness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		

Sleep disorder subjects affected / exposed occurrences (all) Stress subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1		
Investigations Glomerular filtration rate decreased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 2 / 11 (18.18%) 2		
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 1 / 11 (9.09%) 2		
Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1		
Nervous system disorders Amnesia subjects affected / exposed occurrences (all) Disturbance in attention subjects affected / exposed occurrences (all) Dizziness	 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0		

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	5 / 11 (45.45%)		
occurrences (all)	5		
Hyperaesthesia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Memory impairment			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Parosmia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 11 (54.55%)		
occurrences (all)	7		
Leukopenia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

Lymph node pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Lymphopenia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hyperacusis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Ocular hyperaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Photophobia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Visual acuity reduced			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Visual impairment			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Anal pruritus			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Anorectal discomfort			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Cheilitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Dry mouth			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Frequent bowel movements			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

Gingival pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Oral pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Painful defaecation			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Tongue disorder			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Tongue dry			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			

Alopecia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Dermatitis				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Dermatitis psoriasiform				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Dry skin				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Eczema				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	2			
Erythema				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Night sweats				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Photosensitivity reaction				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Pruritus				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	9			
Pruritus generalised				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	2			
Psoriasis				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	2			
Rash				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	2			

Rash erythematous subjects affected / exposed occurrences (all) Rash generalised subjects affected / exposed occurrences (all) Rash macular subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all) Skin discolouration subjects affected / exposed occurrences (all) Skin irritation subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 9 0 / 11 (0.00%) 0 2 / 11 (18.18%) 4 1 / 11 (9.09%) 3 1 / 11 (9.09%) 2 1 / 11 (9.09%) 1		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Pollakiuria subjects affected / exposed occurrences (all) Renal colic subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Flank pain	1 / 11 (9.09%) 1 2 / 11 (18.18%) 2		

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Pain in jaw			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Eye infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hordeolum			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Oral candidiasis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Staphylococcal skin infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

Upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	4		
Dehydration			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gout			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2012	This amendment included the following changes: - Additional assessments were added for urine protein analyses – Safety follow-up measures during the study were clarified – Study drug-stopping rules were updated – The definition of the primary efficacy analysis population was revised – SVR4 and SVR24 were specified as secondary efficacy endpoints - Fibroscan assessment allowed to define a liver status - Number of 'cirrhotic' patients raised up to 50% - Screening period extended to 24 weeks. - Study changed from active controlled to placebo controlled.
10 July 2012	This amendment included the following changes: - Control Arm D (MCB-free arm) was removed. Patients enrolled to this arm were offered the option to switch to MCB in addition to their current medications - The 50% cap on patients with a prior null response and compensated cirrhosis was removed - Intensive PK/pharmacodynamic sampling was deleted. Sparse PK sampling from all patients (Week 8 trough concentration) was scheduled to enable the measurement of drug exposure - IP-10 samples were collected only at baseline - The SVR24 analysis was removed and treatment free follow-up was decreased from 24 to 12 weeks - The SAE reporting window was reduced from 1 working day to immediately (i.e., within 24 hours)
13 November 2012	This amendment included the following changes: - SVR24 was added as the secondary endpoint - The treatment-free follow-up Week 24 visit was reinstated
15 February 2013	The primary reason for the amendment was the addition of a Week 42 visit to the Schedule of Assessments, with the same procedures as the Week 30 visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported