



Clinical trial results:

A Phase II, Randomized, Double-Blind, Multicenter, Parallel Group Study to Evaluate the Sustained Virologic Response of the HCV Polymerase Inhibitor Prodrug RO5024048 in Combination With Boceprevir and Pegasys®/Copegus® in Patients With Chronic Hepatitis C Genotype 1 Virus Infection Who Were Prior Null Responders to Treatment With Pegylated Interferon/Ribavarin

Summary

EudraCT number	2011-002714-37
Trial protocol	DE ES IT
Global end of trial date	27 January 2014

Results information

Result version number	v1
This version publication date	08 April 2016
First version publication date	08 April 2016

Trial information

Trial identification

Sponsor protocol code	NV27780
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01482403
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F.Hoffmann-LaRoche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F.Hoffmann-LaRoche 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	27 January 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to estimate the difference in sustained virologic response 12 weeks after treatment (SVR-12) between each of the following two experimental treatment groups (regimens containing mericitabine [MCB, RO5024048], boceprevir (BCP), Pegasys®, and Copegus®) and the control treatment group (regimen containing BCP, Pegasys®, and Copegus®) in participants with previous null response to pegylated interferon alfa and ribavirin (PEG-IFN/RBV) combination therapy, defined as a less than (<) 2 natural logarithm of ten (log10) international units per milliliter (IU/mL) decrease in viral titer after at least 12 weeks of treatment with PEG-IFN/RBV. MCB in combination with BCP and Pegasys/Copegus administered for 24 weeks. MCB in combination with Pegasys/Copegus administered for 24 weeks followed by BCP and Pegasys/Copegus administered for 24 weeks.

Protection of trial subjects:

The study was conducted in full conformance with the International Conference on Harmonisation (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever affords greater protection to the participant. This study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting); U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws; and the European Union Clinical Trial Directive (2001/20/EC).

The investigator, or a person designated by the investigator was responsible for providing participants with an adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and obtaining signed informed consent from each participant prior to their participation in this study. Approval from the Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs) was obtained before study start and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. Approval from the IRB/IEC and regulatory authorities (as locally required) was obtained before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or administrative changes. The Sponsor also obtained approval from the relevant Competent Authority prior to starting the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 9

Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	Canada: 11
Worldwide total number of subjects	58
EEA total number of subjects	32

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)	53
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Fifty-eight participants were randomized (25 participants with MCB+BCP+P/C, 20 participants with P/C+MCB+BCP+/BCP+P/C, and 13 participants with P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C) and included in study.

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	MCB+BCP+Pegasys/Copegus (P/C)

Arm description:

Participants received 24 weeks of therapy with MCB 1000 milligrams (mg) oral tablets twice a day (BID), BCP 800 mg three times a day (TID) oral capsule, Pegasys 180 micrograms per week (µg/week) subcutaneously (SC) and Copegus 1000/1200 mg/day oral tablets for a total treatment duration of 24 weeks, followed by a 24-week treatment-free follow-up period.

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

Dosage and administration details:

MCB 1000 mg oral tablets BID for a total treatment duration of 24 weeks.

Arm title	MCB+BCP+P/C+BCP+P/C
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Arm description:

Participants received 24 weeks of therapy with MCB 1000 mg oral tablets BID + BCP 800 mg oral capsule TID + Pegasys 180 µg per week SC injection / Copegus 1000/1200 mg oral tablets followed by 24 weeks of therapy with BCP 800 mg oral capsule TID +Pegasys 180 µg per week SC injection / Copegus 1000/1200 mg oral tablets per day (triple) for a total treatment duration of 48 weeks, followed by a 24-week treatment-free follow-up period.

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

Dosage and administration details:

MCB 1000 mg oral tablets BID for a total treatment duration of 24 weeks.

Arm title	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C
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Arm description:

Participants received 4 weeks of therapy with MCB placebo (MCB pbo), BCP placebo + Pegasys/Copegus, then 20 weeks of therapy with MCB placebo + boceprevir + Pegasys/Copegus, and then 24 weeks of therapy with BCP + Pegasys/Copegus for a total treatment duration of 48 weeks, followed by a 24-week

treatment-free follow-up period.

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

Dosage and administration details:

Matching MCB oral placebo tablet was administered for 24 weeks of therapy.

Number of subjects in period 1	MCB+BCP+Pegasys/ Copegus (P/C)	MCB+BCP+P/C+BCP +P/C	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+ P/C
Started	25	20	13
Received At least 1 Dose of Study Drug	25	20	12
Completed	25	18	9
Not completed	0	2	4
Participant not dosed	-	-	1
Consent withdrawn by subject	-	-	2
Lost to follow-up	-	2	1

Baseline characteristics

Reporting groups

Reporting group title	MCB+BCP+Pegasys/Copegus (P/C)
Reporting group description: Participants received 24 weeks of therapy with MCB 1000 milligrams (mg) oral tablets twice a day (BID), BCP 800 mg three times a day (TID) oral capsule, Pegasys 180 micrograms per week (µg/week) subcutaneously (SC) and Copegus 1000/1200 mg/day oral tablets for a total treatment duration of 24 weeks, followed by a 24-week treatment-free follow-up period.	
Reporting group title	MCB+BCP+P/C+BCP+P/C
Reporting group description: Participants received 24 weeks of therapy with MCB 1000 mg oral tablets BID + BCP 800 mg oral capsule TID + Pegasys 180 µg per week SC injection / Copegus 1000/1200 mg oral tablets followed by 24 weeks of therapy with BCP 800 mg oral capsule TID + Pegasys 180 µg per week SC injection / Copegus 1000/1200 mg oral tablets per day (triple) for a total treatment duration of 48 weeks, followed by a 24-week treatment-free follow-up period.	
Reporting group title	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C
Reporting group description: Participants received 4 weeks of therapy with MCB placebo (MCB pbo), BCP placebo + Pegasys/Copegus, then 20 weeks of therapy with MCB placebo + boceprevir + Pegasys/Copegus, and then 24 weeks of therapy with BCP + Pegasys/Copegus for a total treatment duration of 48 weeks, followed by a 24-week treatment-free follow-up period.	

Reporting group values	MCB+BCP+Pegasys/ Copegus (P/C)	MCB+BCP+P/C+BCP +P/C	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+ P/C
Number of subjects	25	20	13
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	53.8 ± 8	53.3 ± 10.1	56 ± 8.1
Gender categorical Units: Subjects			
Female	8	7	5
Male	17	13	8

Reporting group values	Total		
Number of subjects	58		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	20		

Male	38		
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End points

End points reporting groups

Reporting group title	MCB+BCP+Pegasys/Copegus (P/C)
Reporting group description: Participants received 24 weeks of therapy with MCB 1000 milligrams (mg) oral tablets twice a day (BID), BCP 800 mg three times a day (TID) oral capsule, Pegasys 180 micrograms per week (µg/week) subcutaneously (SC) and Copegus 1000/1200 mg/day oral tablets for a total treatment duration of 24 weeks, followed by a 24-week treatment-free follow-up period.	
Reporting group title	MCB+BCP+P/C+BCP+P/C
Reporting group description: Participants received 24 weeks of therapy with MCB 1000 mg oral tablets BID + BCP 800 mg oral capsule TID + Pegasys 180 µg per week SC injection / Copegus 1000/1200 mg oral tablets followed by 24 weeks of therapy with BCP 800 mg oral capsule TID + Pegasys 180 µg per week SC injection / Copegus 1000/1200 mg oral tablets per day (triple) for a total treatment duration of 48 weeks, followed by a 24-week treatment-free follow-up period.	
Reporting group title	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C
Reporting group description: Participants received 4 weeks of therapy with MCB placebo (MCB pbo), BCP placebo + Pegasys/Copegus, then 20 weeks of therapy with MCB placebo + boceprevir + Pegasys/Copegus, and then 24 weeks of therapy with BCP + Pegasys/Copegus for a total treatment duration of 48 weeks, followed by a 24-week treatment-free follow-up period.	
Subject analysis set title	P/C+MCB Pbo+BCP Pbo (Up to Week 4)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received 4 weeks of therapy with MCB placebo, BCP placebo + Pegasys/Copegus.	
Subject analysis set title	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C (After Week 4)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Of the 13 participants randomized to P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C group, 5 participants receiving MCB followed Amendment D. For these participants, MCB was initiated at various time points after Week 4, depending on how long participants had been in the study at the time of implementation of amendment, and was given for various durations at the investigator's discretion.	

Primary: Percentage of Participants With a Sustained Virological Response at Week 12 After Treatment (SVR-12)

End point title	Percentage of Participants With a Sustained Virological Response at Week 12 After Treatment (SVR-12) ^[1]
End point description: SVR-12 (actual) outcome was defined as an unquantifiable (less than the lower limit of quantification [LLOQ]; less than [$<$]25 international units per milliliter [IU/mL]) serum hepatitis C virus ribonucleic acid (HCV RNA) 12 weeks after the actual end of treatment (a single last unquantifiable HCV RNA within 8-20 weeks after the last dose of study drug administration). Analysis population: Treated population; All randomized participants who received at least 1 dose of study drug. Participants were analyzed according to the treatment group they were randomized.	
End point type	Primary
End point timeframe: Week 12	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The study was of an exploratory nature; therefore only descriptive statistics were applied, and no statistical hypothesis testing was carried out.

End point values	MCB+BCP+Peg asys/Copegus (P/C)	MCB+BCP+P/C +BCP+P/C	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/ BCP+P/C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	20	12	
Units: percentage of participants				
number (confidence interval 95%)	60 (40.7 to 76.6)	70 (48.1 to 85.5)	33.3 (13.8 to 60.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Sustained Virological Response At Week 24 After Treatment (SVR-24)

End point title	Percentage of Participants With a Sustained Virological Response At Week 24 After Treatment (SVR-24)
End point description:	
SVR-24 (actual) outcome was defined as unquantifiable (less than the LLOQ [<25 IU/mL]) serum HCV RNA response outcome greater than or equal to 20 weeks after the last dose of study drug administration.	
Analysis population: Treated population; All randomized participants who received at least 1 dose of study drug. Participants were analyzed according to the treatment group they were randomized.	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	MCB+BCP+Peg asys/Copegus (P/C)	MCB+BCP+P/C +BCP+P/C	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/ BCP+P/C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	20	12	
Units: percentage of participants				
number (confidence interval 95%)	60 (40.7 to 76.6)	70 (48.1 to 85.5)	33.3 (13.8 to 60.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Sustained Virological Response at Week 4 After Treatment (SVR-4)

End point title	Percentage of Participants With a Sustained Virological Response at Week 4 After Treatment (SVR-4)
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End point description:

SVR-4 (actual) outcome was defined as unquantifiable (less than the LLOQ [<25 IU/mL]) serum HCV RNA response outcome within 2–8 weeks after the last day of study drug administration.

Analysis population: Treated population; All randomized participants who received at least 1 dose of study drug. Participants were analyzed according to the treatment group they were randomized.

End point type	Secondary
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End point timeframe:

Week 4

End point values	MCB+BCP+Peg asys/Copegus (P/C)	MCB+BCP+P/C +BCP+P/C	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/ BCP+P/C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	20	12	
Units: percentage of participants				
number (confidence interval 95%)	60 (40.7 to 76.6)	75 (53.1 to 88.8)	33.3 (13.8 to 60.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Virological Response by Week

End point title	Percentage of Participants With Virological Response by Week
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End point description:

Virological response was defined as unquantifiable HCV RNA level <25 IU/mL.

Analysis population: Treated population; All randomized participants who received at least 1 dose of study drug. Participants were analyzed according to the treatment group they were randomized.

Here, N = number of participants analyzed for this end point and n (number) = number of participants with available data at specified time point.

For Week 48, Arm A: "99999" signifies that the data was not possible to calculate since the treatment period was up to Week 24 only.

End point type	Secondary
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End point timeframe:

Weeks 2, 4, 12, 24, and 48

End point values	MCB+BCP+Peg asys/Copegus (P/C)	MCB+BCP+P/C +BCP+P/C	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/ BCP+P/C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	20	12	
Units: percentage of participants				
number (confidence interval 95%)				
Week 2 (n= 25, 20, 12)	76 (56.5 to 88.5)	55 (34.2 to 74.2)	0 (0 to 24.3)	

Week 4 (n= 25, 20, 12)	84 (65.3 to 93.6)	100 (83.9 to 100)	8.3 (1.5 to 35.4)	
Week 12 (n= 25, 20, 12)	84 (65.3 to 93.6)	100 (83.9 to 100)	75 (46.8 to 91.1)	
Week 24 (n= 25, 20, 12)	84 (65.3 to 93.6)	95 (76.4 to 99.1)	58.3 (32 to 80.7)	
Week 48 (n= 0, 20, 12)	99999 (99999 to 99999)	70 (48.1 to 85.5)	50 (25.4 to 74.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Documented Direct-Acting Antiviral (DAA) Resistance

End point title	Number of Participants With Documented Direct-Acting Antiviral (DAA) Resistance
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and Weeks 1, 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, and at weeks 4, 12, and 24 during treatment-free follow-up

End point values	MCB+BCP+Peg asys/Copegus (P/C)	MCB+BCP+P/C +BCP+P/C	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	20	12	
Units: participants				
number (not applicable)	4	4	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in HCV RNA

End point title	Change from Baseline to Week 24 in HCV RNA
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End point description:

Serum HCV RNA was assessed by polymerase chain reaction (PCR) techniques using the Roche COBAS TaqMan HCV v2.0 Test (less than the LLOQ; < 25 IU/mL).

Analysis population: Treated population; All randomized participants who received at least 1 dose of study drug. Participants were analyzed according to the treatment group they were randomized. Here, N= number of participants analyzed for this end point, and n= number of participants with available data for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	MCB+BCP+Peg asys/Copegus (P/C)	MCB+BCP+P/C +BCP+P/C	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/ BCP+P/C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	20	12	
Units: international unit(s)/millilitre				
arithmetic mean (standard deviation)				
Baseline (n= 25, 20, 12)	6.51 (± 0.52)	6.65 (± 0.37)	6.63 (± 0.42)	
Change at Week 24 (n= 21, 19, 7)	-5.44 (± 0.44)	-5.45 (± 0.37)	-5.32 (± 0.45)	

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration of RO4995855 by Week 0 and Week 8

End point title	Trough Concentration of RO4995855 by Week 0 and Week 8 ^[2]
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End point description:

RO4995855 is the parent drug of MCB (RO5024048). Trough concentration is the minimum observed drug concentration during a dosing interval. .

"9999" at Week 0 for MCB+BCP+P/C, MCB+BCP+P/C+BCP+P/C, P/C+MCB Pbo +BCP Pbo (up to Week 4) signifies that the geometric coefficient of variation was not calculable as the mean concentration was zero for all the participants.

Participants in P/C+MCB Pbo +BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C (after Week 4) group received MCB following Amendment D and "9999 and 99999" for Week 0 signifies that the data was not possible to calculate since the treatment period started after Week 4.

Analysis population: Treated population; All randomized participants who received at least 1 dose of study drug. Participants were analyzed according to the treatment group they were randomized. Here, N = number of participants analyzed for this end point and n= number of participants with available data at specified time point.

End point type	Secondary
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End point timeframe:

Week 0 and 8

Notes:

[2] - 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: Of the 13 participants randomized to P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C, 5 participants received MCB following amendment D. For these participants, MCB was initiated at various time points after Week 4 and was given for various durations at the Investigator's discretion. This created reporting data to 2 groups.

End point values	MCB+BCP+Peg asys/Copegus (P/C)	MCB+BCP+P/C +BCP+P/C	P/C+MCB Pbo+BCP Pbo (Up to Week 4)	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/ BCP+P/C (After Week 4)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	21	19	11	6
Units: nanogram(s) per milliliter				
geometric mean (geometric coefficient of variation)				
Week 0 (n= 21, 16, 11)	0 (± 9999)	0 (± 9999)	0 (± 9999)	9999 (± 99999)
Week 8 (n= 21, 19, 3, 6)	2967.62 (± 56.92)	3058.42 (± 2067.55)	516.7 (± 894.9)	28.33 (± 69.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration of RO5012433 by Week 0 and Week 8

End point title	Trough Concentration of RO5012433 by Week 0 and Week 8 ^[3]
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End point description:

RO5012433 is the metabolite of RO4995855. Trough concentration is the minimum observed drug concentration during a dosing interval.

"9999" at Week 0 for MCB+BCP+P/C, MCB+BCP+P/C+BCP+P/C, P/C+MCB Pbo +BCP Pbo (up to Week 4) signifies that the geometric coefficient of variation was not calculable as the mean concentration was zero for all the participants.

Participants in P/C+MCB Pbo +BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C (after Week 4) group received MCB following Amendment D and "9999 and 99999" for Week 0 signifies that the data was not possible to calculate since the treatment period started after Week 4.

Analysis population: Treated population; All randomized participants who received at least 1 dose of study drug. Participants were analyzed according to the treatment group they were randomized.

Here, N= number of participants analyzed for this end point and n= number of participants with available data at specified time point.

End point type	Secondary
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End point timeframe:

Week 0 and Week 8

Notes:

[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: Of the 13 participants randomized to P/C+MCB Pbo+BCP Pbo/MCB

Pbo+P/C+BCP/BCP+P/C, 5 participants received MCB following amendment D. For these participants, MCB was initiated at various time points after Week 4 and was given for various durations at the Investigator's discretion. This created reporting data to 2 groups.

End point values	MCB+BCP+Peg asys/Copegus (P/C)	MCB+BCP+P/C +BCP+P/C	P/C+MCB Pbo+BCP Pbo (Up to Week 4)	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/ BCP+P/C (After Week 4)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	21	19	11	6
Units: nanogram(s) per milliliter				
geometric mean (geometric coefficient of variation)				

Week 0 (n= 21, 16, 11)	0 (± 9999)	0 (± 9999)	0 (± 9999)	9999 (± 99999)
Week 8 (n= 21, 19, 3, 6)	523.05 (± 38.31)	599.16 (± 65.7)	120.7 (± 173.2)	47 (± 244.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration of Boceprevir by Week 0 and Week 8

End point title	Trough Concentration of Boceprevir by Week 0 and Week 8 ^[4]
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End point description:

Trough concentration is the minimum observed drug concentration during a dosing interval. "9999" at Week 0 for MCB+BCP+P/C, MCB+BCP+P/C+BCP+P/C, P/C+MCB Pbo +BCP Pbo (up to Week 4) signifies that the geometric coefficient of variation was not calculable as the mean concentration was zero for all the participants.

Participants in P/C+MCB Pbo +BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C (after Week 4) group received MCB following Amendment D and "9999 and 99999" for Week 0 signifies that the data was not possible to calculate since the treatment period started after Week 4.

Analysis population: Treated population; All randomized participants who received at least 1 dose of study drug. Participants were analyzed according to the treatment group they were randomized.

Here, N = number of participants analyzed for this end point and n= number of participants with available data at specified time point.

End point type	Secondary
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End point timeframe:

Week 0 and Week 8

Notes:

[4] - 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: Of the 13 participants randomized to P/C+MCB Pbo+BCP Pbo/MCB

Pbo+P/C+BCP/BCP+P/C, 5 participants received MCB following amendment D. For these participants, MCB was initiated at various time points after Week 4 and was given for various durations at the Investigator's discretion. This created reporting data to 2 groups.

End point values	MCB+BCP+Peg asys/Copegus (P/C)	MCB+BCP+P/C +BCP+P/C	P/C+MCB Pbo+BCP Pbo (Up to Week 4)	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C (After Week 4)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	22	19	11	9
Units: nanogram(s) per milliliter				
geometric mean (geometric coefficient of variation)				
Week 0 (n= 22, 18, 11)	0 (± 9999)	0 (± 9999)	0 (± 9999)	9999 (± 99999)
Week 8 (n= 21, 19, 9, 9)	390.41 (± 175.1)	349.75 (± 187.6)	133.38 (± 97.01)	133.38 (± 97.01)

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were recorded from Baseline through the end of 24-week treatment free follow-up period (up to a maximum of 72 weeks)

Adverse event reporting additional description:

All randomized participants who received at least one dose of study drug and had at least one post-baseline safety assessment.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	MCB+BCP+Pegasys/Copegus (P/C)
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Reporting group description:

Participants received 24 weeks of therapy with MCB 1000 mg oral tablets BID, BCP 800 mg TID oral capsule, Pegasys 180 µg/week SC and Copegus 1000/1200 mg/day oral tablets for a total treatment duration of 24 weeks, followed by a 24-week treatment-free follow-up period.

Reporting group title	MCB+BCP+P/C+BCP+P/C
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Reporting group description:

Participants received 24 weeks of therapy with MCB 1000 mg oral tablets BID +BCP 800 mg oral capsule TID + Pegasys 180 µg per week SC injection / Copegus 1000/1200 mg oral tablets followed by 24 weeks of therapy with BCP 800 mg oral capsule TID +Pegasys 180 µg per week SC injection /Copegus 1000/1200 mg oral tablets per day (triple) for a total treatment duration of 48 weeks, followed by a 24-week treatment-free follow-up period.

Reporting group title	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C
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Reporting group description:

Participants received 4 weeks of therapy with MCB placebo, BCP placebo + Pegasys/Copegus, then 20 weeks of therapy with MCB placebo + BCP + Pegasys/Copegus, and then 24 weeks of therapy with BCP + Pegasys/Copegus for a total treatment duration of 48 weeks, followed by a 24-week treatment-free follow-up period.

Serious adverse events	MCB+BCP+Pegasys/ Copegus (P/C)	MCB+BCP+P/C+BCP +P/C	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+ P/C
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)	3 / 20 (15.00%)	2 / 12 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	0 / 12 (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
Myocardial infarction			

subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (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			
Anaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (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

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

Non-serious adverse events	MCB+BCP+Pegasy/ Copegus (P/C)	MCB+BCP+P/C+BCP +P/C	P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+ P/C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)	20 / 20 (100.00%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			

Hypotension subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 12 (8.33%) 1
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	8 / 25 (32.00%) 8	8 / 20 (40.00%) 9	4 / 12 (33.33%) 4
Asthenia subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 8	6 / 20 (30.00%) 7	4 / 12 (33.33%) 4
Chills subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	6 / 20 (30.00%) 7	4 / 12 (33.33%) 4
Pyrexia subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 4	5 / 20 (25.00%) 6	4 / 12 (33.33%) 8
Irritability subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 6	3 / 20 (15.00%) 4	1 / 12 (8.33%) 1
Influenza like illness subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Malaise subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Chest pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	1 / 12 (8.33%) 1
Injection site erythema subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Feeling abnormal subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 12 (8.33%) 1
Feeling cold			

subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Injection site pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Local swelling			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Mucosal dryness			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Thirst			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Epididymitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Prostatitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 25 (24.00%)	5 / 20 (25.00%)	4 / 12 (33.33%)
occurrences (all)	7	6	5
Dyspnoea exertional			
subjects affected / exposed	5 / 25 (20.00%)	6 / 20 (30.00%)	0 / 12 (0.00%)
occurrences (all)	5	7	0
Oropharyngeal pain			

subjects affected / exposed	3 / 25 (12.00%)	2 / 20 (10.00%)	2 / 12 (16.67%)
occurrences (all)	5	2	2
Dyspnoea			
subjects affected / exposed	2 / 25 (8.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	2	3	1
Productive cough			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Respiratory tract congestion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sinus congestion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 25 (16.00%)	3 / 20 (15.00%)	0 / 12 (0.00%)
occurrences (all)	5	3	0
Anxiety			
subjects affected / exposed	3 / 25 (12.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	3	1	1
Depressed mood			
subjects affected / exposed	1 / 25 (4.00%)	2 / 20 (10.00%)	1 / 12 (8.33%)
occurrences (all)	1	2	1
Depression			
subjects affected / exposed	2 / 25 (8.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Sleep disorder			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Apathy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Mood swings			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Investigations			
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Neutrophil count decreased			
subjects affected / exposed	3 / 25 (12.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Body temperature increased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Burn oesophageal			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Ligament rupture			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	1	1	2
Palpitations			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	11 / 25 (44.00%)	11 / 20 (55.00%)	0 / 12 (0.00%)
occurrences (all)	11	11	0
Headache			

subjects affected / exposed	7 / 25 (28.00%)	7 / 20 (35.00%)	6 / 12 (50.00%)
occurrences (all)	7	8	15
Dizziness			
subjects affected / exposed	5 / 25 (20.00%)	5 / 20 (25.00%)	1 / 12 (8.33%)
occurrences (all)	8	5	1
Loss of consciousness			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Memory impairment			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Poor quality sleep			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 25 (40.00%)	13 / 20 (65.00%)	6 / 12 (50.00%)
occurrences (all)	10	17	6
Neutropenia			
subjects affected / exposed	3 / 25 (12.00%)	6 / 20 (30.00%)	3 / 12 (25.00%)
occurrences (all)	3	6	4
Thrombocytopenia			
subjects affected / exposed	2 / 25 (8.00%)	6 / 20 (30.00%)	3 / 12 (25.00%)
occurrences (all)	2	6	3
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 25 (8.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Vertigo			

subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Eye disorders			
Vision blurred subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	2 / 20 (10.00%) 2	0 / 12 (0.00%) 0
Dry eye subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Eye pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 20 (0.00%) 0	1 / 12 (8.33%) 1
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	1 / 12 (8.33%) 1
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Eczema eyelids subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 12 (8.33%) 1
Erythema of eyelid subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Periorbital oedema subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Retinal artery embolism subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	9 / 25 (36.00%) 9	8 / 20 (40.00%) 11	6 / 12 (50.00%) 9
Diarrhoea			

subjects affected / exposed	6 / 25 (24.00%)	3 / 20 (15.00%)	3 / 12 (25.00%)
occurrences (all)	8	3	7
Vomiting			
subjects affected / exposed	5 / 25 (20.00%)	5 / 20 (25.00%)	2 / 12 (16.67%)
occurrences (all)	6	7	4
Abdominal pain			
subjects affected / exposed	2 / 25 (8.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	2	1	1
Constipation			
subjects affected / exposed	0 / 25 (0.00%)	4 / 20 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Abdominal discomfort			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Abdominal distension			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Abdominal pain upper			
subjects affected / exposed	1 / 25 (4.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	2	2	0
Dyspepsia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	3	1	0
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Anal pruritus			
subjects affected / exposed	2 / 25 (8.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Dysphagia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Rectal haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	2
Change of bowel habit			

subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Chapped lips			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Frequent bowel movements			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Haematochezia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Melaena			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Proctalgia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	8 / 25 (32.00%)	7 / 20 (35.00%)	3 / 12 (25.00%)
occurrences (all)	8	9	3
Dry skin			

subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4	5 / 20 (25.00%) 5	2 / 12 (16.67%) 2
Rash			
subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 8	3 / 20 (15.00%) 4	1 / 12 (8.33%) 2
Alopecia			
subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	4 / 20 (20.00%) 4	1 / 12 (8.33%) 1
Eczema			
subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4	1 / 20 (5.00%) 1	1 / 12 (8.33%) 1
Erythema			
subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 4	2 / 20 (10.00%) 2	0 / 12 (0.00%) 0
Pruritus generalised			
subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Rash erythematous			
subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Rash maculo-papular			
subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Rash papular			
subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 20 (0.00%) 0	1 / 12 (8.33%) 1
Musculoskeletal and connective tissue disorders			

Myalgia			
subjects affected / exposed	5 / 25 (20.00%)	6 / 20 (30.00%)	3 / 12 (25.00%)
occurrences (all)	6	7	4
Arthralgia			
subjects affected / exposed	6 / 25 (24.00%)	6 / 20 (30.00%)	0 / 12 (0.00%)
occurrences (all)	8	7	0
Back pain			
subjects affected / exposed	2 / 25 (8.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Pain in extremity			
subjects affected / exposed	1 / 25 (4.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Muscular weakness			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Torticollis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Trigger finger			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 25 (8.00%)	1 / 20 (5.00%)	3 / 12 (25.00%)
occurrences (all)	3	1	3
Gingival abscess			
subjects affected / exposed	2 / 25 (8.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	3	1	0
Influenza			
subjects affected / exposed	2 / 25 (8.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Bronchitis			

subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Ear infection fungal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Oesophageal candidiasis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Subcutaneous abscess			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tooth abscess			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 25 (16.00%)	5 / 20 (25.00%)	2 / 12 (16.67%)
occurrences (all)	4	5	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2012	The primary reasons for the amendment were A. The study was changed from active control to placebo control. B. Several changes were made in response to feedback from the Food and Drug Administration (FDA): <ul style="list-style-type: none">– addition of urine protein analysis assessments;– revision of the definition of additional primary efficacy analysis population;– specification of SVR-24 and SVR-4 as secondary efficacy objectives;– clarification of safety follow-up measures;– update of drug-stopping rules.
27 July 2012	The primary reasons for the amendment were as follows: A. Removal of control P/C+MCB Pbo+BCP Pbo/MCB Pbo+P/C+BCP/BCP+P/C(MCB free arm). Participants enrolled to this arm were offered the option to receive MCB in addition to their current medications. B. The sample size was decreased from 100 to 60 participants. C.Intensive pharmacokinetic (PK)/pharmacodynamic (PD) sampling was deleted. Sparse PK sampling from all participants (Week 8 trough concentration) was scheduled to enable the measurement of drug exposure. D.IP-10 samples were collected only at baseline. E.The SVR-24 analysis was removed and treatment-free follow-up was decreased from 24 to 12 weeks. F.Serious adverse event reporting window was reduced from 1 working day to immediately (i.e., within 24 hours).
28 November 2012	The primary reason for the amendment was to address FDA concerns about the possibility of late virologic relapse: A. SVR-24 was added as the secondary endpoint. B. 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