



Clinical trial results:

A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir Co-administered With Ribavirin (RBV) in Adults With Genotype 4 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (AGATE-1)

Summary

EudraCT number	2014-001496-31
Trial protocol	DE BE AT ES IT GR FR
Global end of trial date	07 April 2017

Results information

Result version number	v1 (current)
This version publication date	19 January 2018
First version publication date	19 January 2018

Trial information

Trial identification

Sponsor protocol code	M11-665
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02265237
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co.KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 800-633-9110,
Scientific contact	Negar Niki Alami, AbbVie, negarniki.alami@abbvie.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	07 April 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study in HCV genotype 4-infected participants with compensated cirrhosis is to assess the safety and to compare the percentage of participants achieving a 12-week sustained virologic response (SVR12), [HCV ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks following treatment], to a clinically relevant threshold [based on SVR rates for HCV genotype 4-infected participants treated with pegylated interferon (pegIFN)/RBV].

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	France: 47
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Greece: 23
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	184
EEA total number of subjects	153

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)	150
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was divided into 2 parts with 184 total participants. Part I (Arms A and B) included participants who received either 12 or 16 weeks of treatment and Part II (Arms C and D) included participants who received 24 weeks of treatment. Enrollment into Part II opened once randomization in Part I was completed.

Pre-assignment

Screening details:

Safety analysis population: all participants who received at least 1 dose of study drug. One participant randomized to the arm B (16 weeks arm) was erroneously administered study drug for 12 weeks (as in arm A). Therefore this participant is included in arm A for the safety population.

Period 1

Period 1 title	As Enrolled (Overall Study) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) and Ribavirin dosed for 12 weeks for genotype 4 treatment naïve or treatment-experienced with IFN/RBV.

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

Dosage and administration details:

Ribavirin was administered based on subject's weight.

Investigational medicinal product name	ombitasvir/paritaprevir/ritonavir
Investigational medicinal product code	
Other name	norvir (ritonavir), paritaprevir (ABT-450), ombitasvir (ABT-267).
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ombitasvir/paritaprevir/ritonavir (25/150/100 mg)

Arm title	Arm B
------------------	-------

Arm description:

Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) and Ribavirin dosed for 16 weeks for genotype 4 treatment naïve or treatment-experienced with IFN/RBV.

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

Dosage and administration details:	
Ribavirin was administered based on subject's weight.	
Investigational medicinal product name	ombitasvir/paritaprevir/ritonavir
Investigational medicinal product code	
Other name	norvir (ritonavir), paritaprevir (ABT-450), ombitasvir (ABT-267).
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Ombitasvir/paritaprevir/ritonavir (25/150/100 mg)	
Arm title	Arm C
Arm description:	
Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) and Ribavirin dosed for 24 weeks for genotype 4 treatment naive and treatment-experienced with IFN/RBV.	
Arm type	Experimental
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Ribavirin was administered based on subject's weight.	
Investigational medicinal product name	ombitasvir/paritaprevir/ritonavir
Investigational medicinal product code	
Other name	norvir (ritonavir), paritaprevir (ABT-450), ombitasvir (ABT-267).
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Ombitasvir/paritaprevir/ritonavir (25/150/100 mg)	
Arm title	Arm D
Arm description:	
Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) and Ribavirin dosed for 24 weeks for genotype 4 SOF/pegIFN/RBV or SOF/RBV treatment-experienced.	
Arm type	Experimental
Investigational medicinal product name	ombitasvir/paritaprevir/ritonavir
Investigational medicinal product code	
Other name	norvir (ritonavir), paritaprevir (ABT-450), ombitasvir (ABT-267).
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Ombitasvir/paritaprevir/ritonavir (25/150/100 mg)	
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Ribavirin was administered based on subject's weight.	

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	59	61	61
Completed	54	58	51
Not completed	5	3	10
Consent withdrawn by subject	1	-	1
Adverse event, non-fatal	1	1	-
Unknown	2	-	3
Lost to follow-up	1	2	6

Number of subjects in period 1	Arm D
Started	3
Completed	2
Not completed	1
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Unknown	1
Lost to follow-up	-

Baseline characteristics

Reporting groups

Reporting group title	As Enrolled (Overall Study)
-----------------------	-----------------------------

Reporting group description:

Safety analysis population: all participants who received at least 1 dose of study drug.

Reporting group values	As Enrolled (Overall Study)	Total	
Number of subjects	184	184	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	56.6 ± 8.80	-	
Gender categorical Units: Subjects			
Female	54	54	
Male	130	130	

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) and Ribavirin dosed for 12 weeks for genotype 4 treatment naïve or treatment-experienced with IFN/RBV.	
Reporting group title	Arm B
Reporting group description: Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) and Ribavirin dosed for 16 weeks for genotype 4 treatment naïve or treatment-experienced with IFN/RBV.	
Reporting group title	Arm C
Reporting group description: Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) and Ribavirin dosed for 24 weeks for genotype 4 treatment naïve and treatment-experienced with IFN/RBV.	
Reporting group title	Arm D
Reporting group description: Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) and Ribavirin dosed for 24 weeks for genotype 4 SOF/pegIFN/RBV or SOF/RBV treatment-experienced.	

Primary: Percentage of Participants in Arms A, B and C With Sustained Virologic Response 12 Weeks Post-treatment (SVR12)

End point title	Percentage of Participants in Arms A, B and C With Sustained Virologic Response 12 Weeks Post-treatment (SVR12) ^{[1][2]}
End point description: SVR12 was defined as plasma hepatitis C virus ribonucleic acid (HCV RNA) level less than the lower limit of quantification (<LLOQ) 12 weeks after the last dose of study drug.	
End point type	Primary
End point timeframe: 12 weeks after the last actual dose of study drug	

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 lower confidence bound of the 2-sided 97.5% confidence interval for the percentage of participants with SVR12 in each arm (A, B and C) must exceed 67% to achieve superiority.

[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: Given the small number of participants planned to be enrolled in Arm D, this arm was not include in the primary or secondary endpoints in the protocol but rather was considered exploratory.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59 ^[3]	61 ^[4]	61 ^[5]	
Units: percentage of participants				
number (confidence interval 97.5%)	96.6 (86.7 to 99.2)	100.0 (92.4 to 100.0)	93.4 (82.6 to 97.7)	

Notes:

[3] - All subjects who received at least 1 dose of study drug; with missing data imputed as nonresponders

[4] - All subjects who received at least 1 dose of study drug; with missing data imputed as nonresponders

[5] - All subjects who received at least 1 dose of study drug; with missing data imputed as nonresponders

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With SVR12 in Participants Receiving 12 Weeks (Arm A) of Treatment Compared to Participants Receiving 16 Weeks of Treatment (Arm B)

End point title	Percentage of Participants With SVR12 in Participants Receiving 12 Weeks (Arm A) of Treatment Compared to Participants Receiving 16 Weeks of Treatment (Arm B) ^[6]
-----------------	---

End point description:

SVR12 was defined as plasma hepatitis C virus ribonucleic acid (HCV RNA) level less than the lower limit of quantification [<LLOQ]) 12 weeks after the last dose of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

12 weeks after the last actual dose of study drug

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point was assessed only for arms A and B, as it included a pair-wise comparison.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59 ^[7]	61 ^[8]		
Units: percentage of participants				
number (not applicable)	96.6	100		

Notes:

[7] - All subjects who received at least 1 dose of study drug; with missing data imputed as nonresponders

[8] - All subjects who received at least 1 dose of study drug; with missing data imputed as nonresponders

Statistical analyses

Statistical analysis title	Arm A vs Arm B
----------------------------	----------------

Statistical analysis description:

Within Part I (arm A and B), since superiority was demonstrated for both arms in the primary outcome measures, testing continued to the first secondary outcome measure.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.304
Method	Mantel-Haenszel
Parameter estimate	Stratum-Adjusted MH Difference
Point estimate	-3.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.85
upper limit	3.07

Notes:

[9] - Treatment differences (with 95% confidence intervals) and corresponding P-value for the specified comparisons were estimated using stratum adjusted Mantel-Haenszel (MH) proportion and continuity-corrected variance, adjusting for IFN/RBV treatment history (treatment-naïve or treatment-experienced).

Secondary: Percentage of Participants With SVR12 in Participants Receiving 16 Weeks (Arm B) of Treatment Compared to Participants Receiving 24 Weeks of Treatment (Arm C)

End point title	Percentage of Participants With SVR12 in Participants Receiving 16 Weeks (Arm B) of Treatment Compared to Participants Receiving 24 Weeks of Treatment (Arm C) ^[10]
-----------------	--

End point description:

SVR12 was defined as plasma hepatitis C virus ribonucleic acid (HCV RNA) level less than the lower limit of quantification [<LLOQ]) 12 weeks after the last dose of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

12 weeks after the last actual dose of study drug

Notes:

[10] - 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: This end point was assessed only for arms B and C, as it included a pair-wise comparison.

End point values	Arm B	Arm C		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61 ^[11]	57 ^[12]		
Units: percentage of participants				
number (not applicable)	100	93.4		

Notes:

[11] - All participants who received at least 1 dose of study drug; missing data imputed as nonresponders.

[12] - All participants who received at least 1 dose of study drug; missing data imputed as nonresponders.

Statistical analyses

Statistical analysis title	Arm B vs Arm C
----------------------------	----------------

Statistical analysis description:

Within Part II (arm C), since superiority was demonstrated for the primary end point, testing continued to the second secondary outcome measure.

Comparison groups	Arm B v Arm C
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.086
Method	Mantel-Haenszel
Parameter estimate	Stratum-Adjusted MH Difference
Point estimate	6.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	13.81

Notes:

[13] - Treatment differences (with 95% confidence intervals) and corresponding P-value for the specified comparisons were estimated using stratum adjusted Mantel-Haenszel proportion and continuity-corrected variance, adjusting for IFN/RBV treatment history (treatment-naïve or treatment-

experienced).

Secondary: Percentage of Participants in Arms A, B and C With On-treatment Virologic Failure

End point title	Percentage of Participants in Arms A, B and C With On-treatment Virologic Failure ^[14]
-----------------	---

End point description:

On-treatment virologic failure was defined as confirmed HCV RNA \geq LLOQ after HCV RNA $<$ LLOQ during treatment; confirmed increase of $> 1 \log_{10}$ IU/mL above the lowest value post-baseline in HCV RNA during treatment; or all on-treatment values of HCV RNA \geq LLOQ with at least 6 weeks of treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to Treatment Week 24 (end of treatment) or premature discontinuation from treatment

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Given the small number of participants planned to be enrolled in Arm D, this arm was not include in the primary or secondary endpoints in the protocol but rather was considered exploratory.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59 ^[15]	61 ^[16]	61 ^[17]	
Units: percentage of participants				
number (confidence interval 95%)	1.7 (0.3 to 9.0)	0.0 (0.0 to 5.9)	0.0 (0.0 to 5.9)	

Notes:

[15] - All participants who received at least 1 dose of study drug (ITT population).

[16] - All participants who received at least 1 dose of study drug (ITT population).

[17] - All participants who received at least 1 dose of study drug (ITT population).

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants in Arms A, B and C With Post-treatment Relapse

End point title	Percentage of Participants in Arms A, B and C With Post-treatment Relapse ^[18]
-----------------	---

End point description:

Post-treatment relapse was defined as confirmed HCV RNA \geq LLOQ between the end of treatment and 12 weeks after the last dose of study drug among participants with HCV RNA levels $<$ LLOQ at the end of treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

From the end of treatment through 12 weeks after the last dose of study drug

Notes:

[18] - 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: Given the small number of participants planned to be enrolled in Arm D, this arm was not include in the primary or secondary endpoints in the protocol but rather was considered exploratory.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57 ^[19]	59 ^[20]	56 ^[21]	
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 6.3)	0.0 (0.0 to 6.1)	0.0 (0.0 to 6.4)	

Notes:

[19] - ITT subjects with one post-treatment HCV RNA value, completed treatment, and <LLOQ at final visit.

[20] - ITT subjects with one post-treatment HCV RNA value, completed treatment, and <LLOQ at final visit.

[21] - ITT subjects with one post-treatment HCV RNA value, completed treatment, and <LLOQ at final visit.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) were collected from the time of study drug administration until 30 days after the last dose of study drug (up to 28 weeks).

Adverse event reporting additional description:

Safety analysis population: all participants who received at least 1 dose of study drug. One participant randomized to arm B (16 weeks arm) was erroneously administered study drug for 12 weeks (as in arm A). Therefore this participant is included in arm A for the safety population.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	19.1
--------------------	------

Reporting groups

Reporting group title	Arm A
-----------------------	-------

Reporting group description:

Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) and Ribavirin dosed for 12 weeks for genotype 4 treatment naïve or treatment-experienced with IFN/RBV.

Reporting group title	Arm B
-----------------------	-------

Reporting group description:

Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) and Ribavirin dosed for 16 weeks for genotype 4 treatment naïve or treatment-experienced with IFN/RBV.

Reporting group title	Arm C
-----------------------	-------

Reporting group description:

Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) and Ribavirin dosed for 24 weeks for genotype 4 treatment naïve and treatment-experienced with IFN/RBV.

Reporting group title	Arm D
-----------------------	-------

Reporting group description:

Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) and Ribavirin dosed for 24 weeks for genotype 4 SOF/pegIFN/RBV or SOF/RBV treatment-experienced.

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 60 (6.67%)	4 / 60 (6.67%)	3 / 61 (4.92%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
SCIATICA			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 61 (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	2 / 60 (3.33%)	0 / 60 (0.00%)	0 / 61 (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
HAEMORRHAGIC ANAEMIA			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 61 (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
Gastrointestinal disorders			
OESOPHAGEAL VARICES HAEMORRHAGE			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
HEPATOTOXICITY			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PORTAL VEIN THROMBOSIS			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
Psychiatric disorders			
MANIA			

subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 61 (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
SUICIDAL IDEATION			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
Musculoskeletal and connective tissue disorders			
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
CLOSTRIDIUM COLITIS			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
MENINGITIS			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
PNEUMONIA			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
PNEUMONIA KLEBSIELLA			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 61 (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

Serious adverse events	Arm D		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
SCIATICA			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HAEMORRHAGIC ANAEMIA			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
OESOPHAGEAL VARICES			
HAEMORRHAGE			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

HEPATOTOXICITY			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PORTAL VEIN THROMBOSIS			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
MANIA			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SUICIDAL IDEATION			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
CLOSTRIDIUM COLITIS			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MENINGITIS			

subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA KLEBSIELLA			
subjects affected / exposed	0 / 3 (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	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 60 (76.67%)	55 / 60 (91.67%)	50 / 61 (81.97%)
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	4 / 60 (6.67%)	1 / 60 (1.67%)	1 / 61 (1.64%)
occurrences (all)	5	2	1
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	11 / 60 (18.33%)	19 / 60 (31.67%)	15 / 61 (24.59%)
occurrences (all)	13	22	17
FATIGUE			
subjects affected / exposed	10 / 60 (16.67%)	20 / 60 (33.33%)	16 / 61 (26.23%)
occurrences (all)	11	29	17
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 60 (0.00%)	3 / 60 (5.00%)	1 / 61 (1.64%)
occurrences (all)	0	3	1
OEDEMA PERIPHERAL			
subjects affected / exposed	5 / 60 (8.33%)	4 / 60 (6.67%)	2 / 61 (3.28%)
occurrences (all)	5	4	2
PYREXIA			

subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	3 / 60 (5.00%) 4	1 / 61 (1.64%) 2
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	5 / 60 (8.33%)	5 / 60 (8.33%)	4 / 61 (6.56%)
occurrences (all)	5	5	4
DYSPNOEA EXERTIONAL			
subjects affected / exposed	2 / 60 (3.33%)	3 / 60 (5.00%)	0 / 61 (0.00%)
occurrences (all)	2	4	0
DYSPNOEA			
subjects affected / exposed	4 / 60 (6.67%)	4 / 60 (6.67%)	4 / 61 (6.56%)
occurrences (all)	4	4	4
NASAL CONGESTION			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences (all)	0	0	1
PARANASAL SINUS DISCOMFORT			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 61 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	3 / 60 (5.00%)	2 / 60 (3.33%)	3 / 61 (4.92%)
occurrences (all)	3	2	3
INSOMNIA			
subjects affected / exposed	5 / 60 (8.33%)	6 / 60 (10.00%)	5 / 61 (8.20%)
occurrences (all)	5	6	5
IRRITABILITY			
subjects affected / exposed	2 / 60 (3.33%)	1 / 60 (1.67%)	1 / 61 (1.64%)
occurrences (all)	2	1	1
SLEEP DISORDER			
subjects affected / exposed	2 / 60 (3.33%)	5 / 60 (8.33%)	0 / 61 (0.00%)
occurrences (all)	2	5	0
Investigations			
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	1 / 60 (1.67%)	3 / 60 (5.00%)	0 / 61 (0.00%)
occurrences (all)	1	3	0
HAEMOGLOBIN DECREASED			

subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3	8 / 60 (13.33%) 8	4 / 61 (6.56%) 4
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	4 / 60 (6.67%)	9 / 60 (15.00%)	0 / 61 (0.00%)
occurrences (all)	4	9	0
MEMORY IMPAIRMENT			
subjects affected / exposed	1 / 60 (1.67%)	4 / 60 (6.67%)	1 / 61 (1.64%)
occurrences (all)	1	4	1
HEADACHE			
subjects affected / exposed	14 / 60 (23.33%)	14 / 60 (23.33%)	13 / 61 (21.31%)
occurrences (all)	14	15	15
PARAESTHESIA			
subjects affected / exposed	2 / 60 (3.33%)	2 / 60 (3.33%)	0 / 61 (0.00%)
occurrences (all)	2	2	0
SOMNOLENCE			
subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	0 / 61 (0.00%)
occurrences (all)	0	2	0
SYNCOPE			
subjects affected / exposed	2 / 60 (3.33%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences (all)	2	0	1
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	7 / 60 (11.67%)	12 / 60 (20.00%)	7 / 61 (11.48%)
occurrences (all)	8	13	7
Ear and labyrinth disorders			
EAR PAIN			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 61 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	4 / 60 (6.67%)	1 / 60 (1.67%)	2 / 61 (3.28%)
occurrences (all)	4	1	2
ABDOMINAL PAIN			
subjects affected / exposed	2 / 60 (3.33%)	4 / 60 (6.67%)	6 / 61 (9.84%)
occurrences (all)	2	4	6
CONSTIPATION			

subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 5	1 / 60 (1.67%) 1	2 / 61 (3.28%) 2
DIARRHOEA subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	3 / 60 (5.00%) 3	2 / 61 (3.28%) 2
NAUSEA subjects affected / exposed occurrences (all)	6 / 60 (10.00%) 6	8 / 60 (13.33%) 9	5 / 61 (8.20%) 7
TOOTHACHE subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	3 / 60 (5.00%) 3	2 / 61 (3.28%) 2
VOMITING subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 4	3 / 60 (5.00%) 4	4 / 61 (6.56%) 4
Hepatobiliary disorders HYPERBILIRUBINAEMIA subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	2 / 60 (3.33%) 3	3 / 61 (4.92%) 3
JAUNDICE subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3	2 / 60 (3.33%) 2	4 / 61 (6.56%) 5
Skin and subcutaneous tissue disorders DRY SKIN subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	1 / 60 (1.67%) 1	4 / 61 (6.56%) 4
PRURITUS subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 5	14 / 60 (23.33%) 15	12 / 61 (19.67%) 13
PRURITUS GENERALISED subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	2 / 61 (3.28%) 2
RASH subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 6	3 / 60 (5.00%) 4	2 / 61 (3.28%) 2
Musculoskeletal and connective tissue disorders			

ARTHRALGIA			
subjects affected / exposed	3 / 60 (5.00%)	4 / 60 (6.67%)	1 / 61 (1.64%)
occurrences (all)	3	4	1
BACK PAIN			
subjects affected / exposed	1 / 60 (1.67%)	2 / 60 (3.33%)	5 / 61 (8.20%)
occurrences (all)	1	2	6
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	1 / 61 (1.64%)
occurrences (all)	0	1	1
MYALGIA			
subjects affected / exposed	3 / 60 (5.00%)	6 / 60 (10.00%)	3 / 61 (4.92%)
occurrences (all)	3	6	3
NECK PAIN			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 61 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
SINUSITIS			
subjects affected / exposed	0 / 60 (0.00%)	3 / 60 (5.00%)	0 / 61 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	2 / 60 (3.33%)	5 / 60 (8.33%)	2 / 61 (3.28%)
occurrences (all)	2	5	2
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 60 (0.00%)	4 / 60 (6.67%)	1 / 61 (1.64%)
occurrences (all)	0	4	1

Non-serious adverse events	Arm D		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
ASTHENIA			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>FATIGUE</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>INFLUENZA LIKE ILLNESS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>OEDEMA PERIPHERAL</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PYREXIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 3 (33.33%)</p> <p>2</p> <p>0 / 3 (0.00%)</p> <p>0</p> <p>0 / 3 (0.00%)</p> <p>0</p> <p>0 / 3 (0.00%)</p> <p>0</p> <p>0 / 3 (0.00%)</p> <p>0</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>COUGH</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DYSпноEA EXERTIONAL</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DYSпноEA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>NASAL CONGESTION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PARANASAL SINUS DISCOMFORT</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 3 (33.33%)</p> <p>1</p> <p>0 / 3 (0.00%)</p> <p>0</p> <p>0 / 3 (0.00%)</p> <p>0</p> <p>1 / 3 (33.33%)</p> <p>1</p> <p>1 / 3 (33.33%)</p> <p>1</p>		
<p>Psychiatric disorders</p> <p>ANXIETY</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>INSOMNIA</p>	<p>0 / 3 (0.00%)</p> <p>0</p>		

subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
IRRITABILITY			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
SLEEP DISORDER			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Investigations			
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
HAEMOGLOBIN DECREASED			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
MEMORY IMPAIRMENT			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
HEADACHE			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
PARAESTHESIA			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
SOMNOLENCE			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
SYNCOPE			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			

ANAEMIA subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Ear and labyrinth disorders EAR PAIN subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Gastrointestinal disorders ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all) ABDOMINAL PAIN subjects affected / exposed occurrences (all) CONSTIPATION subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) TOOTHACHE subjects affected / exposed occurrences (all) VOMITING subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 1 / 3 (33.33%) 1 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		
Hepatobiliary disorders HYPERBILIRUBINAEMIA subjects affected / exposed occurrences (all) JAUNDICE subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		
Skin and subcutaneous tissue disorders			

<p>DRY SKIN</p> <p>subjects affected / exposed</p> <p>0 / 3 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>PRURITUS</p> <p>subjects affected / exposed</p> <p>1 / 3 (33.33%)</p> <p>occurrences (all)</p> <p>2</p> <p>PRURITUS GENERALISED</p> <p>subjects affected / exposed</p> <p>1 / 3 (33.33%)</p> <p>occurrences (all)</p> <p>1</p> <p>RASH</p> <p>subjects affected / exposed</p> <p>1 / 3 (33.33%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Musculoskeletal and connective tissue disorders</p> <p>ARTHRALGIA</p> <p>subjects affected / exposed</p> <p>0 / 3 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>BACK PAIN</p> <p>subjects affected / exposed</p> <p>0 / 3 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>MUSCULOSKELETAL CHEST PAIN</p> <p>subjects affected / exposed</p> <p>1 / 3 (33.33%)</p> <p>occurrences (all)</p> <p>1</p> <p>MYALGIA</p> <p>subjects affected / exposed</p> <p>0 / 3 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>NECK PAIN</p> <p>subjects affected / exposed</p> <p>1 / 3 (33.33%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Infections and infestations</p> <p>SINUSITIS</p> <p>subjects affected / exposed</p> <p>0 / 3 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Metabolism and nutrition disorders</p> <p>DECREASED APPETITE</p> <p>subjects affected / exposed</p> <p>0 / 3 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			

HYPERGLYCAEMIA			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2015	The purpose of the amendment was to evaluate 24 weeks of treatment (Part II) in addition to the existing 12- and 16-week durations in this study. While internal simulation modeling suggested that the optimal treatment duration would be 12 or 16 weeks, this modeling had not been validated in subjects with cirrhosis. Thus, it was reasonable to also evaluate sustained virologic response (SVR) rates after 24 weeks of treatment. Additionally, a study arm for subjects with treatment history of prior virologic failure with sofosbuvir (SOF) plus pegylated interferon (pegIFN)/ribavirin (RBV) or SOF plus RBV was added as a possible re-treatment option for such subjects with limited approved re-treatment options for hepatitis C virus (HCV) genotype 4 (GT4) infection.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported