



Clinical trial results:

A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-II)

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-003088-23
Trial protocol	BE DE GB ES IT FR
Global end of trial date	24 September 2014

Results information

Result version number	v1 (current)
This version publication date	18 May 2016
First version publication date	18 May 2016

Trial information

Trial identification

Sponsor protocol code	M13-099
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01704755
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	Abbott House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire , United Kingdom, SL6 4XE
Public contact	Global Medical Information, AbbVie, 001 800-633-9110,
Scientific contact	Roger Trinh, MD, AbbVie, roger.trinh@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	24 September 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were to assess the safety and to compare the SVR12 rates (the percentage of subjects achieving a 12-week sustained virologic response, SVR12 [HCV ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks following treatment]) of coformulated ABT-450, ritonavir and ABT-267 (ABT-450/r/ABT-267) and ABT-333 coadministered with ribavirin (RBV) for 12 or 24 weeks to the historical SVR rate of telaprevir plus pegIFN and RBV in HCV genotype 1-infected adults with compensated cirrhosis.

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
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	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 49
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	France: 53
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	United States: 165
Worldwide total number of subjects	381
EEA total number of subjects	182

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)	332
From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included a screening period of 35 days.

Period 1

Period 1 title	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	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks

Arm description:

ABT-450/r/ABT-267 (150/100/25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based ribavirin (RBV; 1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg, divided twice daily) for 12 weeks

Arm type	Experimental
Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	
Other name	ABT-450 coformulated with ritonavir and ABT-267; ABT-450 also known as paritaprevir; ABT-267 also known as ombitasvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450/r/ABT-267 (150/100/25 mg once daily) for 12 weeks

Investigational medicinal product name	ABT-333
Investigational medicinal product code	
Other name	Dasabuvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

250 mg twice daily for 12 weeks

Investigational medicinal product name	Ribavirin (RBV)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg, divided twice daily for 12 weeks

Arm title	ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks
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Arm description:

ABT-450/r/ABT-267 (150/100/25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based ribavirin (RBV; 1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg, divided twice daily) for 24 weeks

Arm type	Experimental
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Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	
Other name	ABT-450 coformulated with ritonavir and ABT-267; ABT-450 also known as paritaprevir; ABT-267 also known as ombitasvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450/r/ABT-267 (150/100/25 mg once daily) for 24 weeks

Investigational medicinal product name	ABT-333
Investigational medicinal product code	
Other name	Dasabuvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

250 mg twice daily for 24 weeks

Investigational medicinal product name	Ribavirin (RBV)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg, divided twice daily for 24 weeks

Number of subjects in period 1^[1]	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks	ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks
Started	208	172
Completed study drug	204	163 ^[2]
Completed	196	165
Not completed	12	7
Consent withdrawn by subject	1	1
Adverse event, non-fatal	4	1
Withdrew consent and personal issues	1	-
Other (not specified)	3	1
Lost to follow-up	3	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: In the 12-week treatment group, one participant withdrew from the study before receiving study drug.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: In the 24-week treatment group, 9 participants prematurely discontinued study drug.

Baseline characteristics

Reporting groups

Reporting group title	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks
Reporting group description: ABT-450/r/ABT-267 (150/100/25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based ribavirin (RBV; 1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg, divided twice daily) for 12 weeks	
Reporting group title	ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks
Reporting group description: ABT-450/r/ABT-267 (150/100/25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based ribavirin (RBV; 1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg, divided twice daily) for 24 weeks	

Reporting group values	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks	ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks	Total
Number of subjects	208	172	380
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	57.1	56.5	
standard deviation	± 7.01	± 7.87	-
Gender categorical Units: Subjects			
Female	62	51	113
Male	146	121	267

End points

End points reporting groups

Reporting group title	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks
Reporting group description: ABT-450/r/ABT-267 (150/100/25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based ribavirin (RBV; 1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg, divided twice daily) for 12 weeks	
Reporting group title	ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks
Reporting group description: ABT-450/r/ABT-267 (150/100/25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based ribavirin (RBV; 1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg, divided twice daily) for 24 weeks	
Subject analysis set title	Overall study
Subject analysis set type	Full analysis
Subject analysis set description: All participants who received at least 1 dose of study drug.	

Primary: Percentage of Participants With Sustained Virologic Response 12 Weeks Post-treatment

End point title	Percentage of Participants With Sustained Virologic Response 12 Weeks Post-treatment ^[1]
End point description: The percentage of participants with sustained virologic response (plasma Hepatitis C virus ribonucleic acid [HCV RNA] level less than the lower limit of quantitation [< LLOQ]) 12 weeks after the last dose of study drug. Primary efficacy endpoints were: noninferiority of 12-week Tx to the SVR rate for telaprevir plus pegIFN and RBV therapy; superiority of 12-week Tx to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; noninferiority of 24-week Tx to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; and superiority of 24-week Tx to the historical SVR rate for telaprevir plus pegIFN and RBV therapy. Based on a 2-sided significance level of 0.05 and assuming that 68% of subjects in each arm would achieve SVR12, a total of 380 subjects provides ≥ 90% power to demonstrate non-inferiority and superiority with a 2-sided 97.5% lower confidence bound greater than 43% and 54%, respectively, based on the normal approximation of a single binomial proportion.	
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% CI for the percentage of participants with sustained virologic response at 12 weeks after treatment must have exceeded 43% to achieve noninferiority. The lower confidence bound of the 2-sided 97.5% CI for the percentage of participants with sustained virologic response at 12 weeks after treatment must have exceeded 54% to achieve superiority.	

End point values	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks	ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208 ^[2]	172 ^[3]		
Units: Percentage of participants				
number (confidence interval 97.5%)	91.8 (87.6 to 96.1)	96.5 (93.4 to 99.7)		

Notes:

[2] - All randomized participants who received at least 1 dose of study drug.

[3] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Sustained Virologic Response 12 Weeks Post-treatment in the 24-week Arm Compared to the 12-week Arm

End point title	Percentage of Participants With Sustained Virologic Response 12 Weeks Post-treatment in the 24-week Arm Compared to the 12-week Arm
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End point description:

A sustained virologic response is defined as plasma Hepatitis C virus ribonucleic acid (HCV RNA) less than the lower limit of quantification (< LLOQ) 12 weeks after the last dose of study drug.

End point type	Secondary
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End point timeframe:

12 weeks after the last actual dose of study drug

End point values	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks	ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208 ^[4]	172 ^[5]		
Units: Percentage of participants				
number (not applicable)	91.8	96.5		

Notes:

[4] - All randomized participants who received at least 1 dose of study drug.

[5] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Logistic Regression
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Statistical analysis description:

To test the hypothesis that the percentages of participants who achieved sustained virologic response 12 weeks after treatment was different between the two treatment groups, the percentages were compared using a logistic regression model with treatment group, baseline log(subscript)10(subscript) HCV RNA level, HCV subgenotype (1a, non-1a), IL28B genotype (CC, non CC), and peginterferon-ribavirin treatment history (treatment-naïve or treatment-experienced) as predictors.

Comparison groups	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks v ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks
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Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.051
Method	Regression, Logistic

Secondary: Percentage of Participants in Each Arm With On-treatment Virologic Failure During the Treatment Period

End point title	Percentage of Participants in Each Arm With On-treatment Virologic Failure During the Treatment Period
End point description: Virologic failure during treatment was defined as rebound (confirmed HCV RNA greater than or equal to the lower limit of quantitation [\geq LLOQ] after HCV RNA < LLOQ during treatment, or confirmed increase from the lowest value post baseline in HCV RNA [2 consecutive HCV RNA measurements > 1 log(subscript)10(subscript) IU/mL above the lowest value post baseline] at any time point during treatment), or fail to suppress (HCV RNA \geq LLOQ persistently during treatment with at least 6 weeks [\geq 36 days] of treatment).	
End point type	Secondary
End point timeframe: Baseline (Day 1), and Treatment Weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24	

End point values	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks	ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208 ^[6]	172 ^[7]		
Units: Percentage of participants				
number (confidence interval 95%)	0.5 (0 to 1.4)	1.7 (0 to 3.7)		

Notes:

[6] - All randomized participants who received at least 1 dose of study drug.

[7] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Virologic Relapse After Treatment

End point title	Percentage of Participants With Virologic Relapse After Treatment
End point description: Participants were considered to have virologic relapse after treatment if they had confirmed quantifiable plasma Hepatitis C virus ribonucleic acid (HCV RNA) \geq lower limit of quantification (LLOQ) between the end of treatment and 12 weeks after the last dose of study drug among participants who completed treatment with HCV RNA < LLOQ at the end of treatment.	
End point type	Secondary
End point timeframe: within 12 weeks after the last dose of study drug	

End point values	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks	ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203 ^[8]	164 ^[9]		
Units: Percentage of Participants				
number (confidence interval 95%)	5.9 (2.7 to 9.2)	0.6 (0 to 1.8)		

Notes:

[8] - Subjects had at least 1 dose of study drug with HCV RNA < LLOQ at last Tx visit and finished Tx.

[9] - Subjects had at least 1 dose of study drug with HCV RNA < LLOQ at last Tx visit and finished Tx.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of study drug administration until 30 days after the last dose, 16 weeks for the 12-week treatment group and 28 weeks for the 24-week treatment group.

Adverse event reporting additional description:

Serious adverse events were collected from the time of informed consent until the end of participation in the study (up to 72 weeks).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks
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Reporting group description:

ABT-450/r/ABT-267 (150/100/25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based ribavirin (RBV; 1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg, divided twice daily) for 12 weeks

Reporting group title	ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks
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Reporting group description:

ABT-450/r/ABT-267 (150/100/25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based ribavirin (RBV; 1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg, divided twice daily) for 24 weeks

Serious adverse events	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks	ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 208 (6.25%)	7 / 172 (4.07%)	
number of deaths (all causes)	3	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			

subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 208 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 208 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 208 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 208 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intracranial aneurysm			
subjects affected / exposed	0 / 208 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 208 (0.48%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematemesis			

subjects affected / exposed	0 / 208 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 208 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 208 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heptatitis acute			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rhabdomyolysis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Candidiasis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Lactic acidosis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ABT-450/r/ABT-267 and ABT-333, plus RBV for 12 weeks	ABT-450/r/ABT-267 and ABT-333, plus RBV for 24 weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	175 / 208 (84.13%)	146 / 172 (84.88%)	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	12 / 208 (5.77%)	9 / 172 (5.23%)	
occurrences (all)	13	10	
Nervous system disorders			
Dizziness			
subjects affected / exposed	18 / 208 (8.65%)	10 / 172 (5.81%)	
occurrences (all)	20	14	
Headache			
subjects affected / exposed	58 / 208 (27.88%)	53 / 172 (30.81%)	
occurrences (all)	71	60	
Memory impairment			
subjects affected / exposed	5 / 208 (2.40%)	12 / 172 (6.98%)	
occurrences (all)	5	12	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 208 (7.21%)	17 / 172 (9.88%)	
occurrences (all)	17	25	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	29 / 208 (13.94%)	22 / 172 (12.79%)	
occurrences (all)	38	31	
Fatigue			
subjects affected / exposed	68 / 208 (32.69%)	80 / 172 (46.51%)	
occurrences (all)	80	89	
Irritability			

subjects affected / exposed	16 / 208 (7.69%)	21 / 172 (12.21%)	
occurrences (all)	17	23	
Oedema peripheral			
subjects affected / exposed	12 / 208 (5.77%)	10 / 172 (5.81%)	
occurrences (all)	12	11	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	6 / 208 (2.88%)	9 / 172 (5.23%)	
occurrences (all)	6	10	
Abdominal pain upper			
subjects affected / exposed	12 / 208 (5.77%)	16 / 172 (9.30%)	
occurrences (all)	13	16	
Diarrhoea			
subjects affected / exposed	31 / 208 (14.90%)	29 / 172 (16.86%)	
occurrences (all)	33	34	
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 208 (3.37%)	10 / 172 (5.81%)	
occurrences (all)	7	10	
Nausea			
subjects affected / exposed	37 / 208 (17.79%)	35 / 172 (20.35%)	
occurrences (all)	39	39	
Vomiting			
subjects affected / exposed	6 / 208 (2.88%)	14 / 172 (8.14%)	
occurrences (all)	7	15	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	15 / 208 (7.21%)	2 / 172 (1.16%)	
occurrences (all)	15	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 208 (11.54%)	19 / 172 (11.05%)	
occurrences (all)	24	23	
Dyspnoea			
subjects affected / exposed	12 / 208 (5.77%)	21 / 172 (12.21%)	
occurrences (all)	12	23	
Dyspnoea exertional			

subjects affected / exposed occurrences (all)	13 / 208 (6.25%) 13	11 / 172 (6.40%) 11	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	18 / 208 (8.65%)	11 / 172 (6.40%)	
occurrences (all)	20	11	
Pruritus			
subjects affected / exposed	38 / 208 (18.27%)	33 / 172 (19.19%)	
occurrences (all)	43	37	
Pruritus generalised			
subjects affected / exposed	10 / 208 (4.81%)	12 / 172 (6.98%)	
occurrences (all)	11	12	
Rash			
subjects affected / exposed	23 / 208 (11.06%)	25 / 172 (14.53%)	
occurrences (all)	24	30	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	15 / 208 (7.21%)	14 / 172 (8.14%)	
occurrences (all)	16	14	
Depression			
subjects affected / exposed	8 / 208 (3.85%)	12 / 172 (6.98%)	
occurrences (all)	8	13	
Insomnia			
subjects affected / exposed	32 / 208 (15.38%)	32 / 172 (18.60%)	
occurrences (all)	35	32	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 208 (4.81%)	14 / 172 (8.14%)	
occurrences (all)	11	15	
Back pain			
subjects affected / exposed	4 / 208 (1.92%)	13 / 172 (7.56%)	
occurrences (all)	5	13	
Muscle spasms			
subjects affected / exposed	14 / 208 (6.73%)	14 / 172 (8.14%)	
occurrences (all)	15	16	
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	13 / 208 (6.25%) 14	13 / 172 (7.56%) 16	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 208 (1.92%) 4	13 / 172 (7.56%) 14	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	12 / 208 (5.77%) 12	14 / 172 (8.14%) 15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2012	<ul style="list-style-type: none">• update secondary endpoints to remove RVR and EOTR, and to include virologic failure during treatment and relapse post-treatment• update the thresholds for the primary endpoints to be based on historical SVR rates from telaprevir plus pegIFN and RBV therapy• clarify inclusion/exclusion criteria to ensure the appropriate subject population was enrolled• update the plan for resistance analysis throughout the protocol in order to clarify and more accurately reflect plans for assessing resistance development;• update RBV toxicity management to clarify parameters for management of hemoglobin decreases;• to update sponsor from Abbott to AbbVie
07 March 2013	<ul style="list-style-type: none">• update the definition of relapse to prior pegIFN and RBV treatment to allow the measurement of a detectable HCV RNA to be within 52 weeks post-treatment due to clinical practice standards of assessment of HCV RNA in some regions• clarify that some study visits during the Treatment Period and Post-Treatment Period may have been conducted outside the study site• update to include that depo-progesterone may not have been an effective form of contraception for a female subject in the trial• update to provide guidance to address female subjects with borderline serum hCG test results• update Section 5.2.1 Inclusion Criterion No. 4. Rationale for update: To include that depo-progesterone may have been an effective form of contraception for female partners of male subjects in the trial• update to provide guidance to address subjects with steatosis and steatohepatitis• allow subjects with ALT up to $7 \times \text{ULN}$ and/or AST up to $7 \times \text{ULN}$ to enroll in the trial in accordance with the typical liver function tests of this patient population• update Section 5.3.1.1 Study Procedures (Screening: Liver Biopsy or FibroScan) to be consistent with Inclusion Criterion No. 11• add urine archive specimen for toxicity management of CrCl and tests for management of transaminase elevations• clarify that subjects who became pregnant must have discontinued the study drug, but may have continued to be monitored in the Post-Treatment Period• update Management of Transaminase Elevations in Section 6.7.4, including Table 10 to be consistent with Exclusion Criterion No. 17 to allow for management of subjects with ALT/AST $> 7 \times \text{ULN}$• make minor clerical updates throughout the protocol for clarification and consistency
08 April 2013	<ul style="list-style-type: none">• prohibit the use of hormonal contraceptives during study drug administration
07 May 2013	<ul style="list-style-type: none">• update the approximate number of subjects to be enrolled into the study from approximately 300 to approximately 380

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24725237>