Clinical trial results:
A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1a Chronic Hepatitis C Virus (HCV) Infection (PEARL-IV)

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	2012-005522-29
Trial protocol	GB
Global end of trial date	07 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	M14-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01833533
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	Yan Luo, MD, PhD, AbbVie, yan.luo@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 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and antiviral activity of ABT-450/ritonavir/ABT- 267 (ABT-450/r/ABT-267; ABT-450 also known as paritaprevir; ABT-267 also known as ombitasvir) and ABT-333 (also known as dasabuvir) with and without ribavirin (RBV) in patients with chronic hepatitis C virus genotype 1a (HCV GT1a) infection without 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	14 March 2013
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	United Kingdom: 27
Country: Number of subjects enrolled	Canada: 31
Country: Number of subjects enrolled	United States: 247
Worldwide total number of subjects	305
EEA total number of subjects	27

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)	282
From 65 to 84 years	23

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	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	ABT-450/r/ABT-267 and ABT-333, Plus RBV

Arm description:

ABT-450/r/ABT-267 (150 mg/ 100 mg/ 25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks

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

Dosage and administration details:

ABT-450 (150 mg) coformulated with ritonavir (100 mg) and ABT-267 (25 mg)

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

Dosage and administration details:

250 mg twice daily

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

Dosage and administration details:

Weight-based (dosed 1,000 or 1,200 mg daily divided twice a day)

Arm title	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV

Arm description:

ABT-450/r/ABT-267 (150 mg/ 100 mg/ 25 mg once daily) and ABT-333 (250 mg twice daily) for 12 weeks plus placebo RBV (twice daily) for 12 weeks

Arm type	Experimental

Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	
Other name	ABT-267 also known as ombitasvir, ABT-450 also known as paritaprevir, Viekirax
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450 (150 mg) coformulated with ritonavir (100 mg) and ABT-267 (25 mg)

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

Dosage and administration details:

250 mg twice daily

Investigational medicinal product name	Placebo for Ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

twice daily

Number of subjects in period 1	ABT-450/r/ABT-267 and ABT-333, Plus RBV	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV
Started	100	205
Completed	94	184
Not completed	6	21
Not specified	2	7
To enter an extension study	-	4
Adverse event	-	1
Lost to follow-up	4	9

Baseline characteristics

Reporting groups	
Reporting group title	ABT-450/r/ABT-267 and ABT-333, Plus RBV
Reporting group description:	
ABT-450/r/ABT-267 (150 mg/ 100 mg/ 25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks	
Reporting group title	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV
Reporting group description:	
ABT-450/r/ABT-267 (150 mg/ 100 mg/ 25 mg once daily) and ABT-333 (250 mg twice daily) for 12 weeks plus placebo RBV (twice daily) for 12 weeks	

Reporting group values	ABT-450/r/ABT-267 and ABT-333, Plus RBV	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV	Total
Number of subjects	100	205	305
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	51.6	51.4	
standard deviation	± 10.99	± 10.64	-
Gender categorical			
Units: Subjects			
Female	30	76	106
Male	70	129	199

End points

End points reporting groups

Reporting group title	ABT-450/r/ABT-267 and ABT-333, Plus RBV
Reporting group description:	
ABT-450/r/ABT-267 (150 mg/ 100 mg/ 25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks	
Reporting group title	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV
Reporting group description:	
ABT-450/r/ABT-267 (150 mg/ 100 mg/ 25 mg once daily) and ABT-333 (250 mg twice daily) for 12 weeks plus placebo RBV (twice daily) for 12 weeks	

Primary: Percentage of Subjects With Sustained Virologic Response 12 Weeks After Treatment; Primary Analyses

End point title	Percentage of Subjects With Sustained Virologic Response 12 Weeks After Treatment; Primary Analyses[1]
End point description:	
The percentage of subjects 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. The LLOQ for the assay was 25 IU/mL. Subjects with missing data were counted as non-responders. The primary endpoints were noninferiority of the percentage of subjects who achieved sustained virologic response 12 weeks after treatment in each treatment arm compared with the historical control rate for noncirrhotic, treatment-naïve subjects with HCV GT1a infection treated with telaprevir and peginterferon (pegIFN)/RBV. Based on a 2-sided significance level of 0.05 and underlying rates of ≥90% (arm with RBV; n=100) and ≥85% (arm with placebo RBV; n=200), a total of 300 subjects provides >95% power to demonstrate noninferiority of each regimen to the historical rate (75%) (based on the normal approximation of a single binomial proportion in a one-sample test for superiority)	
End point type	Primary
End point timeframe:	
12 weeks after last 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 95% CI must exceed 65% to achieve noninferiority. 95% CI calculated using the normal approximation to the binomial distribution.

End point values	ABT-450/r/ABT-267 and ABT-333, Plus RBV	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[2]	205[3]		
Units: percentage of subjects				
number (confidence interval 95%)	97 (93.7 to 100)	90.2 (86.2 to 94.3)		

Notes:

[2] - All randomized subjects who received at least 1 dose of study drug (ITT population)

[3] - All randomized subjects who received at least 1 dose of study drug (ITT population)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Hemoglobin Decrease to Below the Lower Limit of Normal (LLN) At End of Treatment

End point title	Percentage of Subjects With Hemoglobin Decrease to Below the Lower Limit of Normal (LLN) At End of Treatment

End point description:

The percentage of subjects with a decrease in hemoglobin from greater than or equal to the lower limit of normal (≥ LLN) at baseline to < LLN at the end of treatment.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12 (End of Treatment)

End point values	ABT-450/r/ABT-267 and ABT-333, Plus RBV	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[4]	203[5]		
Units: percentage of subjects				
number (not applicable)	42	3.9		

Notes:

[4] - Subjects in ITT population who had hemoglobin ≥ LLN reference range at baseline

[5] - Subjects in ITT population who had hemoglobin ≥ LLN reference range at baseline

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	ABT-450/r/ABT-267 and ABT-333, Plus RBV v ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Fisher exact

Secondary: Percentage of Subjects With Sustained Virologic Response 12 Weeks After Treatment; Secondary Analyses

End point title	Percentage of Subjects With Sustained Virologic Response 12 Weeks After Treatment; Secondary Analyses

End point description:

The percentage of subjects with sustained virologic response (plasma HCV RNA less than the lower limit of quantitation [< LLOQ]) 12 weeks after the last dose of study drug. Subjects with missing data were counted as non-responders. The secondary endpoints were superiority of the percentage of subjects who achieved sustained virologic response 12 weeks after treatment in each treatment arm compared with the historical control rate for noncirrhotic, treatment-naïve subjects with HCV GT1a infection treated with telaprevir and pegIFN/RBV (75%) (the lower confidence bound must exceed 75% to achieve superiority); and noninferiority of the percentage of subjects who achieved sustained virologic response 12 weeks after treatment with ABT-450/r/ABT-267 and ABT-333, plus placebo RBV compared with ABT-450/r/ABT-267 and ABT-333, plus RBV (see statistical analysis 1).

End point type	Secondary

End point timeframe:

12 weeks after last dose of study drug

End point values	ABT-450/r/ABT-267 and ABT-333, Plus RBV	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[6]	205[7]		
Units: percentage of subjects				
number (confidence interval 95%)	97 (93.7 to 100)	90.2 (86.2 to 94.3)		

Notes:

[6] - ITT population

[7] - ITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Based on a 2-sided significance level of 0.05 and an underlying rate of ≥90% in the ABT-450/r/ABT-267 and ABT-333, plus RBV arm (n=100) and ≥85% in the ABT-450/r/ABT-267 and ABT-333, plus Placebo RBV arm (n=200), a total of 300 subjects provides >95% power to demonstrate noninferiority of the ABT-450/r/ABT-267 and ABT-333, plus RBV arm compared with the ABT-450/r/ABT-267 and ABT-333, plus Placebo RBV arm (normal approximation of a single binomial proportion in a one-sample test for superiority).

Comparison groups	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV v ABT-450/r/ABT-267 and ABT-333, Plus RBV
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	difference in percentage of subjects
Point estimate	-6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	-1.5

Notes:

[8] - Noninferiority of the rate of sustained virologic response at 12 weeks after treatment in the ABT-450/r/ABT-267 and ABT-333, plus placebo RBV treatment group as compared with the ABT-450/r/ABT-267 and ABT-333, plus RBV treatment group was analyzed using a noninferiority margin of -10.5%; the lower confidence bound of the 2-sided 95% CI (calculated using normal approximation to the binomial distribution) for the difference in percentage of subjects must exceed -10.5% to achieve noninferiority

Secondary: Percentage of Subjects With Virologic Failure During Treatment

End point title	Percentage of Subjects With Virologic Failure During Treatment

End point description:

Virologic failure during treatment was defined as rebound (confirmed HCV RNA greater than or equal to the lower limit of quantitation [≥ 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 log10 IU/mL above the lowest value post baseline] at any time point during treatment), or failure to suppress (HCV RNA ≥ LLOQ persistently during treatment with at least 6 weeks [≥ 36 days] of treatment).

End point type	Secondary

End point timeframe:

Baseline (Day 1), and Treatment Weeks 1, 2, 4, 6, 8, 10, and 12

End point values	ABT-450/r/ABT-267 and ABT-333, Plus RBV	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[9]	205[10]		
Units: percentage of subjects				
number (not applicable)				
Rebound	1	2.9		
Failure to suppress	0	0		

Notes:

[9] - ITT population

[10] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Virologic Relapse After Treatment

End point title	Percentage of Subjects With Virologic Relapse After Treatment

End point description:

Subjects who completed treatment with plasma HCV RNA less than the lower limit of quantification (<LLOQ) at the end of treatment were considered to have virologic relapse if they had confirmed HCV RNA ≥ LLOQ during the post-treatment period. 95% CI calculated using the normal approximation to the binomial distribution.

End point type	Secondary

End point timeframe:

Between End of Treatment (Week 12) and Post-treatment (up to Week 12 Post-Treatment)

End point values	ABT-450/r/ABT-267 and ABT-333, Plus RBV	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[11]	194[12]		
Units: percentage of subjects				
number (confidence interval 95%)	1 (0 to 3)	5.2 (2 to 8.3)		

Notes:

[11] - Subjects in ITT population who had HCV RNA <LLOQ at final treatment visit and completed treatment

[12] - Subjects in ITT population who had HCV RNA <LLOQ at final treatment visit and completed treatment

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the time of study drug administration to 30 days after last dose of study drug (16 weeks); SAEs were also collected from the time that informed consent was obtained until the end of the study (up to 65 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	ABT-450/r/ABT-267 and ABT-333, Plus RBV

Reporting group description:

ABT-450/r/ABT-267 (150 mg/ 100 mg/ 25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks

Reporting group title	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV

Reporting group description:

ABT-450/r/ABT-267 (150 mg/ 100 mg/ 25 mg once daily) and ABT-333 (250 mg twice daily) for 12 weeks plus placebo RBV (twice daily) for 12 weeks

Serious adverse events	ABT-450/r/ABT-267 and ABT-333, Plus RBV	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 100 (3.00%)	1 / 205 (0.49%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 205 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 205 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 100 (1.00%)	0 / 205 (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			
Diverticulitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
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	ABT-450/r/ABT-267 and ABT-333, Plus Placebo RBV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 100 (81.00%)	138 / 205 (67.32%)	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	7 / 100 (7.00%)	0 / 205 (0.00%)	
occurrences (all)	8	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 100 (8.00%)	13 / 205 (6.34%)	
occurrences (all)	9	13	
Headache			
subjects affected / exposed	25 / 100 (25.00%)	58 / 205 (28.29%)	
occurrences (all)	29	64	
Memory impairment			
subjects affected / exposed	1 / 100 (1.00%)	14 / 205 (6.83%)	
occurrences (all)	1	14	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 100 (5.00%)	0 / 205 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	46 / 100 (46.00%)	72 / 205 (35.12%)	
occurrences (all)	55	84	
Irritability			
subjects affected / exposed	8 / 100 (8.00%)	14 / 205 (6.83%)	
occurrences (all)	9	14	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 100 (14.00%)	33 / 205 (16.10%)	
occurrences (all)	16	37	
Dyspepsia			
subjects affected / exposed	5 / 100 (5.00%)	5 / 205 (2.44%)	
occurrences (all)	5	5	
Nausea			
subjects affected / exposed	21 / 100 (21.00%)	28 / 205 (13.66%)	
occurrences (all)	25	31	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 100 (5.00%)	12 / 205 (5.85%)	
occurrences (all)	7	12	
Dyspnoea exertional			
subjects affected / exposed	7 / 100 (7.00%)	1 / 205 (0.49%)	
occurrences (all)	7	2	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	6 / 100 (6.00%)	2 / 205 (0.98%)	
occurrences (all)	6	2	
Pruritus			
subjects affected / exposed	10 / 100 (10.00%)	12 / 205 (5.85%)	
occurrences (all)	10	12	
Rash			
subjects affected / exposed	5 / 100 (5.00%)	11 / 205 (5.37%)	
occurrences (all)	5	11	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 100 (17.00%)	16 / 205 (7.80%)	
occurrences (all)	17	16	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 100 (9.00%)	5 / 205 (2.44%)	
occurrences (all)	10	5	
Back pain			

subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 5	12 / 205 (5.85%) 14	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 7	8 / 205 (3.90%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2013	The purpose of this amendment is to prohibit the use of hormonal contraceptives during study drug administration.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported