Clinical trial results:
A Randomized, Open-Label, Multicenter Study to Evaluate the Safety and Antiviral Activity of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin in Treatment-Experienced Subjects with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection (PEARL–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	2011-005740-95
Trial protocol	SE AT BE NL IT PT
Global end of trial date	13 October 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	M13-389

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01674725
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	Jeffrey Enejosa, MD, AbbVie, jeffrey.enejosa@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	13 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 October 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 1b (HCV GT1b) 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 August 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	Switzerland: 13
Country: Number of subjects enrolled	Turkey: 30
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Austria: 22
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Italy: 45
Worldwide total number of subjects	187
EEA total number of subjects	111

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)	156
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 187 subjects were randomized; 1 subject did not receive study drug and was excluded from the analyses.

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

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	Tablet
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

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

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

Number of subjects in period 1[1]	ABT-450/r/ABT-267 and ABT-333, Plus RBV	ABT-450/r/ABT-267 and ABT-333
Started	91	95
Completed	89	94
Not completed	2	1
Adverse event	1	-
Lost to follow-up	-	1
Withdrawal by subject	1	-

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: A total of 187 subjects were randomized; 1 subject did not receive study drug and was excluded from the intent-to-treat (ITT) and safety populations.

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
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	

Reporting group values	ABT-450/r/ABT-267 and ABT-333, Plus RBV	ABT-450/r/ABT-267 and ABT-333	Total
Number of subjects	91	95	186
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54.2	54.2	
standard deviation	± 10.9	± 10.51	-
Gender categorical Units: Subjects			
Female	46	38	84
Male	45	57	102

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
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	

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-experienced subjects with HCV GT1b infection treated with telaprevir and peginterferon (pegIFN)/RBV. Based on a 2-sided significance level of 0.05 and underlying rates of ≥90% (n=90 in each arm), a total of 180 subjects provides >90% 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% confidence interval for the percentage of subjects with sustained virologic response at 12 weeks after treatment must exceed 64% to achieve noninferiority. 95% CI was calculated using the normal approximation to the binomial distribution (ABT-450/r/ABT-267 and ABT-333) or the Wilson score method for the single proportion because the point estimate was 100% (ABT-450/r/ABT-267 and ABT-333, plus RBV).

End point values	ABT-450/r/ABT-267 and ABT-333, Plus RBV	ABT-450/r/ABT-267 and ABT-333		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[2]	91[3]		
Units: percentage of subjects				
number (confidence interval 95%)	97.7 (94.6 to 100)	100 (95.9 to 100)		

Notes:

[2] - ITT GT1b population: All subjects with HCV GT1b infection who received at least 1 dose of study drug
[3] - ITT GT1b population: All subjects with HCV GT1b infection who received at least 1 dose of study drug

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		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[4]	91[5]		
Units: percentage of subjects				
number (not applicable)	42	5.5		

Notes:

[4] - Subjects in the ITT HCV GT1b population with hemoglobin ≥ LLN reference range at baseline

[5] - Subjects in the ITT HCV GT1b population with 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
Number of subjects included in analysis	179
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-experienced subjects with HCV GT1b 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 RBV compared with ABT-450/r/ABT-267 and ABT-333 (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		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[6]	91[7]		
Units: percentage of subjects				
number (confidence interval 95%)	97.7 (94.6 to 100)	100 (95.9 to 100)		

Notes:

[6] - ITT GT1b population

[7] - ITT GT1b population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

95% CI was calculated using the normal approximation to the binomial distribution.

Comparison groups	ABT-450/r/ABT-267 and ABT-333, Plus RBV v ABT-450/r/ABT-267 and ABT-333
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Percentage of subjects
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	5.4

Notes:

[8] - The noninferiority of the rate of sustained virologic response at 12 weeks after treatment for the ABT-450/r/ABT-267 and ABT-333 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% confidence interval for the difference in percentage of subjects with sustained virologic response at 12 weeks after treatment 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		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[9]	91[10]		
Units: percentage of subjects				
number (not applicable)				
Rebound	0	0		
Failure to Suppress	0	0		

Notes:

[9] - ITT GT1b population

[10] - ITT GT1b 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 was calculated using the Wilson score method for the single proportion because the point estimate was 0%.

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		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[11]	91[12]		
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 4.3)	0 (0 to 4.1)		

Notes:

[11] - ITT GT1b population with HCV RNA < LLOQ at the final treatment visit and completed treatment

[12] - ITT GT1b population with HCV RNA < LLOQ at the 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 participation in the study (up to 64 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

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

Serious adverse events	ABT-450/r/ABT-267 and ABT-333, Plus RBV	ABT-450/r/ABT-267 and ABT-333	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 91 (2.20%)	2 / 95 (2.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 91 (1.10%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 91 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			

subjects affected / exposed	1 / 91 (1.10%)	0 / 95 (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			
Cellulitis			
subjects affected / exposed	0 / 91 (0.00%)	1 / 95 (1.05%)	
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	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 91 (78.02%)	62 / 95 (65.26%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 91 (5.49%)	4 / 95 (4.21%)	
occurrences (all)	5	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 91 (12.09%)	7 / 95 (7.37%)	
occurrences (all)	13	8	
Fatigue			
subjects affected / exposed	29 / 91 (31.87%)	16 / 95 (16.84%)	
occurrences (all)	37	19	
Irritability			
subjects affected / exposed	5 / 91 (5.49%)	1 / 95 (1.05%)	
occurrences (all)	5	1	
Pyrexia			
subjects affected / exposed	6 / 91 (6.59%)	8 / 95 (8.42%)	
occurrences (all)	7	8	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	3 / 91 (3.30%)	7 / 95 (7.37%)	
occurrences (all)	3	8	
Dyspnoea			
subjects affected / exposed	8 / 91 (8.79%)	2 / 95 (2.11%)	
occurrences (all)	8	2	
Dyspnoea exertional			
subjects affected / exposed	5 / 91 (5.49%)	1 / 95 (1.05%)	
occurrences (all)	5	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 91 (14.29%)	3 / 95 (3.16%)	
occurrences (all)	14	3	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	8 / 91 (8.79%)	0 / 95 (0.00%)	
occurrences (all)	9	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	5 / 91 (5.49%)	2 / 95 (2.11%)	
occurrences (all)	5	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 91 (8.79%)	3 / 95 (3.16%)	
occurrences (all)	9	3	
Headache			
subjects affected / exposed	22 / 91 (24.18%)	22 / 95 (23.16%)	
occurrences (all)	30	25	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 91 (10.99%)	0 / 95 (0.00%)	
occurrences (all)	11	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	5 / 91 (5.49%)	1 / 95 (1.05%)	
occurrences (all)	7	1	
Diarrhoea			

subjects affected / exposed	12 / 91 (13.19%)	12 / 95 (12.63%)	
occurrences (all)	14	15	
Nausea			
subjects affected / exposed	19 / 91 (20.88%)	6 / 95 (6.32%)	
occurrences (all)	21	6	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	5 / 91 (5.49%)	2 / 95 (2.11%)	
occurrences (all)	5	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	13 / 91 (14.29%)	8 / 95 (8.42%)	
occurrences (all)	19	10	
Rash			
subjects affected / exposed	8 / 91 (8.79%)	1 / 95 (1.05%)	
occurrences (all)	8	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 91 (6.59%)	6 / 95 (6.32%)	
occurrences (all)	8	8	
Myalgia			
subjects affected / exposed	6 / 91 (6.59%)	4 / 95 (4.21%)	
occurrences (all)	6	5	
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 91 (2.20%)	6 / 95 (6.32%)	
occurrences (all)	2	7	
Nasopharyngitis			
subjects affected / exposed	6 / 91 (6.59%)	6 / 95 (6.32%)	
occurrences (all)	7	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 91 (9.89%)	2 / 95 (2.11%)	
occurrences (all)	9	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2012	The purpose of this amendment was to clarify when Arms 3 and 4 were opened for enrollment; remove RBV from list of previous anti-HCV agents prohibited in exclusion criteria; correct time frame for qualifying biopsy from 3 years to 24 months; remove requirement for consenting pregnant partners.
17 February 2012	The purpose of this amendment was to clarify that subjects may not have used other anti-HCV agents with exception of pegIFN/RBV combination therapy.
25 May 2012	The purpose of this amendment was to remove the 8-week arms (Arms 3 and 4); replace extended virologic response (eRVR) with end of treatment response (EOTR) as a secondary endpoint; revise treatment futility criteria; update options for treatment for subjects currently undergoing treatment in a study arm or subgenotype that was terminated due to futility criteria being met and allow for use of pegIFN and RBV as an add-on therapy; modify definitions for null responders and nonresponder/partial responders; clarify conditions under which a subject may have been allowed to re-screen; clarify contraception requirements; clarify screening requirements (FibroTest or FibroScan, liver diagnostic testing, HCV genotype 1 result, platelet results, discontinuation of pegIFN/RBV within 2 months of the screening visit); and clarify recording of medications.
24 September 2012	The purpose of this amendment was to stop further enrollment of HCV GT1a-infected subjects and only allow HCV GT1b-infected subjects to be enrolled, and provide options for the HCV GT1a-infected subjects who were currently enrolled; removing HCV subgenotype from primary and secondary analyses and update screening and inclusion/exclusion criteria.
28 November 2012	The purpose of this amendment was to modify the protocol to a Phase 3 study; increase sample size of the study and change randomization for 1:1 for all pegIFN/RBV treatment experienced populations (null responders, nonresponders/partial responders, and relapsers); change the investigational product supply to use the combination ABT-450/r/ABT-267 tablet and to adjust the dose and strength of the ABT-333 tablet; and change the primary and secondary endpoints to compare SVR12 rate of each arm with the historical SVR rate of telaprevir plus pegIFN/RBV.
29 January 2013	The purpose of this amendment was to update the definition of relapsers to expand the timeframe for testing from 24 weeks to 52 weeks to allow subjects that may have detectable viral load documentation more than 24 weeks after treatment; update to allow testing of the genotype/subgenotype if not known prior to completing all the screening procedures; update inclusion criteria (include that depo-progesterone may not be an effective form of contraception for a female subject, depo-progesterone may be an effective form of contraception for female partners of male subjects in the trial); update exclusion criteria (provide guidance for female subjects with borderline human chorionic gonadotropin (hCG) test results; add a contraindicated medication; provide guidance to address subjects with steatosis and steatohepatitis; update absolute neutrophil count (ANC) and international normalized ratio (INR); update conditions for discontinuation and follow-up of subects who become pregnant; add a data monitoring committee DMC).
08 April 2013	The purpose of this amendment was 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