



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-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	2012-002035-29
Trial protocol	DE GB CZ PT IE NL IT DK ES
Global end of trial date	23 October 2014

Results information

Result version number	v1 (current)
This version publication date	22 May 2016
First version publication date	22 May 2016

Trial information

Trial identification

Sponsor protocol code	M13-098
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01715415
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	Jeff Enejosa, MD, AbbVie, jeff.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	23 October 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 October 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 compare the percentage of subjects achieving sustained virologic response 12 weeks postdosing (SVR12; HCV ribonucleic acid [RNA] < lower limit of quantitation [LLOQ] 12 weeks following treatment) after 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 coadministered with RBV (the direct-acting antiviral agent [DAA] combination regimen) to the historical SVR rate of telaprevir plus pegylated interferon (pegIFN) and RBV therapy and to assess the safety of the DAA combination regimen versus placebo for 12 weeks in pegIFN/RBV treatment-experienced HCV genotype 1-infected adults without cirrhosis.

Protection of trial subjects:

All subjects entering the study had to sign an informed consent that was explained to them and questions encouraged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 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	Netherlands: 7
Country: Number of subjects enrolled	Portugal: 20
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	France: 37
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Ireland: 12
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Russian Federation: 24
Country: Number of subjects enrolled	United States: 149
Worldwide total number of subjects	395
EEA total number of subjects	188

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)	362
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

One subject in the Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV arm was randomized but did not received treatment; this subject was not included in the Safety Population and is accounted for in the Pre-assignment Milestones below.

Pre-assignment period milestones

Number of subjects started	395
Number of subjects completed	394

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomized but not treated: 1
----------------------------	-------------------------------

Period 1

Period 1 title	Double-blind Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

AbbVie, investigators, and subjects were blinded to drug assignment and virologic results for the duration of the Double-blind Treatment Period.

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

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

Arm description:

Double-blind 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 to 1,200 mg/day divided twice daily) for 12 weeks

Arm type	Experimental
Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	ABT-450/r/ABT-267
Other name	ABT-267 also known as ombitasvir, ABT-450 also known as paritaprevir, (with ABT-333) Viekira PAK
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

At the double-blind (DB) Day 1 Visit, subjects were administered study drugs by the study site personnel and received instructions for self-administration of all study drugs from Study Day 2 through Study Week 12 of the DB Treatment Period.

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

Dosage and administration details:

At the DB Day 1 Visit, subjects were administered study drugs by the study site personnel and received

instructions for self-administration of all study drugs from Study Day 2 through Study Week 12 of the DB Treatment Period.

Investigational medicinal product name	ABT-333
Investigational medicinal product code	ABT-333
Other name	dasabuvir, (with ABT-450/r/ABT-267) Viekira PAK
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

At the DB Day 1 Visit, subjects were administered study drugs by the study site personnel and received instructions for self-administration of all study drugs from Study Day 2 through Study Week 12 of the DB Treatment Period.

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

Arm description:

Double-blind placebo for 12 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

At the DB Day 1 Visit, subjects were administered study drugs by the study site personnel and received instructions for self-administration of all study drugs from Study Day 2 through Study Week 12 of the DB Treatment Period.

Number of subjects in period 1^[1]	ABT-450/r/ABT-267 and ABT-333, Plus RBV	Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV
Started	297	97
Completed	292	96
Not completed	5	1
Not specified	1	-
Adverse event	3	-
Withdrawal by subject	1	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: One subject in the Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV arm were randomized but did not received treatment; these subjects were not included in the Safety Population. The Pre-assignment Milestones, above, accounts for the worldwide number enrolled.

Period 2

Period 2 title	Open-label Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV
Arm description: Open-label ABT-450/r/ABT-267 (150 mg/100 mg/25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based RBV (RBV; dosed 1,000 to 1,200 mg/day divided twice daily) for 12 weeks	
Arm type	Experimental
Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	ABT-450/r/ABT-267
Other name	ABT-267 also known as ombitasvir, ABT-450 also known as paritaprevir, (with ABT-333) Viekira PAK
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects entering the open-label (OL) Treatment Period were given drugs at the DB Week 12 Visit, along with instructions to begin dosing the next day.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects entering the OL Treatment Period were given drugs at the DB Week 12 Visit, along with instructions to begin dosing the next day.

Investigational medicinal product name	ABT-333
Investigational medicinal product code	ABT-333
Other name	dasabuvir, (with ABT-450/r/ABT-267) Viekira PAK
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects entering the OL Treatment Period were given drugs at the DB Week 12 Visit, along with instructions to begin dosing the next day.

Number of subjects in period 2^[2]	Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV
Started	96
Completed	94
Not completed	2
Adverse event	1
Subject noncompliant	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only subjects in the Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV arm (n=96) were continued on to Period 2, per protocol.

Baseline characteristics

Reporting groups

Reporting group title	ABT-450/r/ABT-267 and ABT-333, Plus RBV
Reporting group description: Double-blind 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 to 1,200 mg/day divided twice daily) for 12 weeks	
Reporting group title	Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV
Reporting group description: Double-blind placebo for 12 weeks	

Reporting group values	ABT-450/r/ABT-267 and ABT-333, Plus RBV	Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV	Total
Number of subjects	297	97	394
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	51.7 ± 10.26	54.9 ± 8.46	-
Gender categorical Units: Subjects			
Female	130	37	167
Male	167	60	227

End points

End points reporting groups

Reporting group title	ABT-450/r/ABT-267 and ABT-333, Plus RBV
Reporting group description: Double-blind 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 to 1,200 mg/day divided twice daily) for 12 weeks	
Reporting group title	Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV
Reporting group description: Double-blind placebo for 12 weeks	
Reporting group title	Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV
Reporting group description: Open-label ABT-450/r/ABT-267 (150 mg/100 mg/25 mg once daily) and ABT-333 (250 mg twice daily), plus weight-based RBV (RBV; dosed 1,000 to 1,200 mg/day divided twice daily) for 12 weeks	
Subject analysis set title	ABT-450/r/ABT-267 and ABT-333, Plus RBV
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention-to-treat (ITT) Population: All randomized subjects in the ABT-450/r/ABT-267 and ABT-333, Plus RBV arm who received at least 1 dose of blinded study drug.	
Subject analysis set title	Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention-to-treat (ITT) Population: All randomized subjects in the Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV arm who received at least 1 dose of blinded study drug.	

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

End point title	Percentage of Subjects With Sustained Virologic Response 12 Weeks After Treatment ^[1]
End point description: The percentage of subjects with sustained virologic response (plasma HCV RNA level < 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 active 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: See attached zip file (M-13-098 Statistical Analysis for Primary Endpoint.pdf) for the statistical analysis data, which could not be entered directly due to EudraCT system limitations.

End point values	ABT-450/r/ABT-267 and ABT-333, Plus RBV			
Subject group type	Subject analysis set			
Number of subjects analysed	297			
Units: percentage of subjects				
number (not applicable)	96.3			

Attachments (see zip file)	M13-098 Statistical Analysis for Primary Endpoint.pdf
-----------------------------------	---

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Normalization of Alanine Aminotransferase (ALT) at Final Treatment Visit During the Double-Blind Treatment Period

End point title	Percentage of Subjects With Normalization of Alanine Aminotransferase (ALT) at Final Treatment Visit During the Double-Blind Treatment Period
End point description:	Normalization is defined as alanine aminotransferase less than or equal to the upper limit of normal (ULN) at final treatment visit for subjects with alanine aminotransferase greater than ULN at baseline.
End point type	Secondary
End point timeframe:	At 12 weeks

End point values	ABT-450/r/ABT-267 and ABT-333, Plus RBV	Placebo Followed by ABT-450/r/ABT-267 and ABT-333, Plus RBV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224 ^[2]	78 ^[3]		
Units: percentage of subjects				
number (not applicable)	96.9	12.8		

Notes:

[2] - Subjects in the ITT population who had ALT $\geq$ ULN of the reference range at baseline

[3] - Subjects in the ITT population who had ALT $\geq$ ULN of the reference range at baseline

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	In order to control the Type I error rate at 0.05, a fixed-sequence testing procedure was used to proceed through the primary and the first 3 secondary endpoints.
Comparison groups	Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV v ABT-450/r/ABT-267 and ABT-333, Plus RBV

Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Secondary: Percentage of HCV Genotype 1a-infected Subjects With Sustained Virologic Response 12 Weeks After Treatment

End point title	Percentage of HCV Genotype 1a-infected Subjects With Sustained Virologic Response 12 Weeks After Treatment
-----------------	--

End point description:

The percentage of subjects with sustained virologic response (plasma HCV RNA level < LLOQ) 12 weeks after the last dose of study drug. One subject, who had genotype 1 HCV with an indeterminate subgenotype, is not included in this analysis.

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

End point timeframe:

12 weeks after the last actual dose of active study drug

End point values	ABT-450/r/ABT-267 and ABT-333, Plus RBV			
Subject group type	Subject analysis set			
Number of subjects analysed	173 ^[4]			
Units: percentage of subjects				
number (not applicable)	96			

Notes:

[4] - Subjects in ITT population with HCV genotype 1a who received at least 1 dose of blinded study drug.

Attachments (see zip file)	M13-098 Statistical Analysis for Secondary Endpoint 3.docx
-----------------------------------	--

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of HCV Genotype 1b-infected Subjects With Sustained Virologic Response 12 Weeks After Treatment

End point title	Percentage of HCV Genotype 1b-infected Subjects With Sustained Virologic Response 12 Weeks After Treatment
-----------------	--

End point description:

The percentage of subjects with sustained virologic response (HCV RNA level < LLOQ) 12 weeks after the last dose of study drug. One subject, who had genotype 1 HCV with an indeterminate subgenotype, is not included in this analysis.

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

End point timeframe:

12 weeks after the last actual dose of active study drug

End point values	ABT-450/r/ABT-267 and ABT-333, Plus RBV			
Subject group type	Subject analysis set			
Number of subjects analysed	123 ^[5]			
Units: percentage of subjects				
number (not applicable)	96.7			

Notes:

[5] - Subjects in ITT population with HCV genotype 1b who received at least 1 dose of blinded study drug.

Attachments (see zip file)	M13-098 Statistical Analysis for Secondary Endpoint 4.docx.pdf
-----------------------------------	--

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With On-treatment Virologic Failure During the Double-blind Treatment Period: ABT-450/r/ ABT-267 and ABT-333, Plus RBV Arm

End point title	Percentage of Subjects With On-treatment Virologic Failure During the Double-blind Treatment Period: ABT-450/r/ ABT-267 and ABT-333, Plus RBV Arm
-----------------	---

End point description:

Virologic failure was defined as rebound (HCV RNA $\geq$ LLOQ after HCV RNA $<$ LLOQ or increase in HCV RNA of at least 1 log₁₀ IU/mL) or failure to suppress (all on-treatment values of plasma HCV RNA $\geq$ LLOQ with at least 36 days of treatment) during treatment.

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

End point timeframe:

12 weeks after the last actual dose of active study drug

End point values	ABT-450/r/ABT-267 and ABT-333, Plus RBV			
Subject group type	Subject analysis set			
Number of subjects analysed	297			
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Virologic Relapse After Treatment: ABT-450/r/ABT-267 and ABT-333, Plus RBV Arm

End point title	Percentage of Subjects With Virologic Relapse After Treatment: ABT-450/r/ABT-267 and ABT-333, Plus RBV Arm
End point description:	
Subjects were considered to have virologic relapse after treatment if they had confirmed quantifiable plasma HCV RNA $\geq$ LLOQ between the end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment with HCV RNA $<$ LLOQ at the end of treatment.	
End point type	Secondary
End point timeframe:	
Within 12 weeks post-treatment	

End point values	ABT-450/r/ABT-267 and ABT-333, Plus RBV			
Subject group type	Subject analysis set			
Number of subjects analysed	293 ^[6]			
Units: percentage of subjects				
number (confidence interval 95%)	2.4 (0.6 to 4.1)			

Notes:

[6] - Subjects with HCV RNA $<$ LLOQ at the final treatment visit who completed treatment in the DB period.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from the start of active study drug administration (DB or OL active) to 30 days after the last dose of active study drug (total 16 weeks).

Adverse event reporting additional description:

DB Placebo Arm: AEs collected from start of placebo until 30 days following discontinuation of placebo and prior to the OL period (if applicable; total 16 weeks). Serious AEs collected from informed consent until the end of participation in the study (12 weeks, DB period; 12 weeks, OL period + 48-week post-treatment period; total up to 72 weeks).

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

Dictionary used

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

Dictionary version	16.0
--------------------	------

Reporting groups

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

Reporting group description:

Double-blind 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 to 1,200 mg/day divided twice daily) for 12 weeks

Reporting group title	Double Blind Placebo
-----------------------	----------------------

Reporting group description:

Double-blind placebo for 12 weeks

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

Reporting group description:

Open-label 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 to 1,200 mg/day divided twice daily) for 12 weeks

Serious adverse events	Double Blind ABT-450/r/ABT-267 and ABT-333, Plus RBV	Double Blind Placebo	Open Label ABT-450/r/ABT-267 and ABT-333, Plus RBV
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 297 (2.02%)	1 / 97 (1.03%)	3 / 96 (3.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 297 (0.00%)	1 / 97 (1.03%)	0 / 96 (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
BRADYCARDIA			
subjects affected / exposed	1 / 297 (0.34%)	0 / 97 (0.00%)	0 / 96 (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

Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 297 (0.34%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIZZINESS			
subjects affected / exposed	1 / 297 (0.34%)	0 / 97 (0.00%)	0 / 96 (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			
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 297 (0.34%)	0 / 97 (0.00%)	0 / 96 (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
NAUSEA			
subjects affected / exposed	1 / 297 (0.34%)	0 / 97 (0.00%)	0 / 96 (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
VOMITING			
subjects affected / exposed	1 / 297 (0.34%)	0 / 97 (0.00%)	0 / 96 (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			
BILE DUCT STONE			
subjects affected / exposed	0 / 297 (0.00%)	0 / 97 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	1 / 297 (0.34%)	0 / 97 (0.00%)	0 / 96 (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
Skin and subcutaneous tissue disorders			
ANGIOEDEMA			

subjects affected / exposed	0 / 297 (0.00%)	0 / 97 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
CALCULUS URETERIC			
subjects affected / exposed	0 / 297 (0.00%)	0 / 97 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE ACUTE			
subjects affected / exposed	1 / 297 (0.34%)	0 / 97 (0.00%)	0 / 96 (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
Infections and infestations			
PNEUMONIA			
subjects affected / exposed	1 / 297 (0.34%)	0 / 97 (0.00%)	0 / 96 (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

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

Non-serious adverse events	Double Blind ABT-450/r/ABT-267 and ABT-333, Plus RBV	Double Blind Placebo	Open Label ABT-450/r/ABT-267 and ABT-333, Plus RBV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	254 / 297 (85.52%)	74 / 97 (76.29%)	74 / 96 (77.08%)
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	25 / 297 (8.42%)	5 / 97 (5.15%)	5 / 96 (5.21%)
occurrences (all)	27	6	5
DYSGEUSIA			
subjects affected / exposed	10 / 297 (3.37%)	5 / 97 (5.15%)	3 / 96 (3.13%)
occurrences (all)	10	5	3
HEADACHE			
subjects affected / exposed	108 / 297 (36.36%)	34 / 97 (35.05%)	18 / 96 (18.75%)
occurrences (all)	126	37	21
Blood and lymphatic system disorders			

ANAEMIA subjects affected / exposed occurrences (all)	16 / 297 (5.39%) 19	0 / 97 (0.00%) 0	3 / 96 (3.13%) 3
General disorders and administration site conditions ASTHENIA subjects affected / exposed occurrences (all) FATIGUE subjects affected / exposed occurrences (all) IRRITABILITY subjects affected / exposed occurrences (all)	47 / 297 (15.82%) 60 99 / 297 (33.33%) 99 16 / 297 (5.39%) 17	11 / 97 (11.34%) 13 22 / 97 (22.68%) 23 8 / 97 (8.25%) 8	13 / 96 (13.54%) 15 16 / 96 (16.67%) 17 6 / 96 (6.25%) 6
Gastrointestinal disorders ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all) CONSTIPATION subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) DYSPEPSIA subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) VOMITING subjects affected / exposed occurrences (all)	16 / 297 (5.39%) 17 4 / 297 (1.35%) 4 39 / 297 (13.13%) 40 18 / 297 (6.06%) 19 59 / 297 (19.87%) 66 19 / 297 (6.40%) 21	6 / 97 (6.19%) 6 6 / 97 (6.19%) 6 12 / 97 (12.37%) 14 3 / 97 (3.09%) 3 17 / 97 (17.53%) 18 0 / 97 (0.00%) 0	9 / 96 (9.38%) 10 0 / 96 (0.00%) 0 8 / 96 (8.33%) 8 7 / 96 (7.29%) 7 13 / 96 (13.54%) 13 3 / 96 (3.13%) 3
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	32 / 297 (10.77%) 33	5 / 97 (5.15%) 5	11 / 96 (11.46%) 11

DYSпноEA			
subjects affected / exposed	37 / 297 (12.46%)	10 / 97 (10.31%)	13 / 96 (13.54%)
occurrences (all)	40	10	13
DYSпноEA EXERTIONAL			
subjects affected / exposed	12 / 297 (4.04%)	5 / 97 (5.15%)	8 / 96 (8.33%)
occurrences (all)	13	5	8
Skin and subcutaneous tissue disorders			
DRY SKIN			
subjects affected / exposed	22 / 297 (7.41%)	3 / 97 (3.09%)	5 / 96 (5.21%)
occurrences (all)	23	3	5
PRURITUS			
subjects affected / exposed	41 / 297 (13.80%)	5 / 97 (5.15%)	12 / 96 (12.50%)
occurrences (all)	43	5	12
PRURITUS GENERALISED			
subjects affected / exposed	11 / 297 (3.70%)	5 / 97 (5.15%)	3 / 96 (3.13%)
occurrences (all)	11	5	3
RASH			
subjects affected / exposed	26 / 297 (8.75%)	6 / 97 (6.19%)	8 / 96 (8.33%)
occurrences (all)	27	8	9
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	14 / 297 (4.71%)	4 / 97 (4.12%)	7 / 96 (7.29%)
occurrences (all)	14	4	7
DEPRESSED MOOD			
subjects affected / exposed	5 / 297 (1.68%)	5 / 97 (5.15%)	1 / 96 (1.04%)
occurrences (all)	5	5	1
INSOMNIA			
subjects affected / exposed	42 / 297 (14.14%)	7 / 97 (7.22%)	10 / 96 (10.42%)
occurrences (all)	46	7	11
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	19 / 297 (6.40%)	7 / 97 (7.22%)	2 / 96 (2.08%)
occurrences (all)	20	8	2
BACK PAIN			
subjects affected / exposed	15 / 297 (5.05%)	3 / 97 (3.09%)	3 / 96 (3.13%)
occurrences (all)	15	3	3

MYALGIA subjects affected / exposed occurrences (all)	23 / 297 (7.74%) 23	10 / 97 (10.31%) 10	5 / 96 (5.21%) 6
Infections and infestations NASOPHARYNGITIS subjects affected / exposed occurrences (all)	21 / 297 (7.07%) 24	5 / 97 (5.15%) 5	8 / 96 (8.33%) 8
Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all)	20 / 297 (6.73%) 21	2 / 97 (2.06%) 2	4 / 96 (4.17%) 5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2012	The purpose of this amendment was to: • update secondary endpoints to remove rapid virological response and end-of-treatment response, which are irrelevant in the absence of SVR, and to include rebound and relapse rates which are relevant in clinical practice when using DAAs; • clarify inclusion/exclusion criteria to ensure the appropriate subject population was enrolled; • clarify the timing of efficacy analyses based on the availability of post-treatment virologic data; • update plan for resistance analysis throughout the protocol in order to clarify and more accurately reflect plans for assessing resistance development; • update RBV toxicity management in a manner that aligns with the RBV label; • address inconsistencies throughout the protocol.
01 March 2013	The purpose of this amendment was to: • include SVR12 rates within HCV subgenotypes (1a, 1b) as secondary endpoints. • update the thresholds for success of the primary and secondary efficacy 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 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 the timing of primary and follow-up efficacy analyses based on the availability of post-treatment virologic data. • address inconsistencies throughout the protocol.
08 April 2013	• prohibit the use of hormonal contraceptives during study drug administration. Rationale: Hormonal contraceptives are not expected to be effective when dosed with the DAA regimen and may be associated with an increased risk for ALT elevation. • correct typographical error for sponsor/emergency contact mobile number.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported