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-Naïve Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-I)

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	2012-002019-25
Trial protocol	SE GB HU DE AT IT ES
Global end of trial date	09 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	M11-646

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01716585
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	Nancy Shulman, MD, AbbVie, nancy.shulman@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	09 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 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 show the noninferiority in sustained virologic response 12 weeks postdosing (SVR12) rates (the percentage of subjects achieving a 12-week sustained virologic response [HCV ribonucleic acid {RNA} < lower limit of quantitation {LLOQ} 12 weeks following therapy]) 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 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	27 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	Spain: 36
Country: Number of subjects enrolled	Sweden: 29
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	Hungary: 25
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Australia: 37
Country: Number of subjects enrolled	Canada: 41
Country: Number of subjects enrolled	New Zealand: 10
Country: Number of subjects enrolled	Switzerland: 23
Country: Number of subjects enrolled	United States: 266
Worldwide total number of subjects	636
EEA total number of subjects	259

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)	607
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 4 subjects in the ABT-450/r/ABT-267 and ABT-333, Plus RBV arm and 1 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, and are accounted for in the Pre-assignment Milestones below.

Pre-assignment period milestones

Number of subjects started	636
Number of subjects completed	631

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomized but not treated: 5

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 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	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	473	158
Completed	464	157
Not completed	9	1
Subject Noncompliant	1	-
Adverse Event	2	1
Not Specified	1	-
Withdrawal by Subject	3	-
Lost to follow-up	2	-

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 4 subjects in the ABT-450/r/ABT-267 and ABT-333, Plus RBV arm and 1 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 table 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 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	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	157
Completed	150
Not completed	7
Adverse Event	2
Virologic Failure	2
Withdrawal by Subject	3

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=157) 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 or 1,200 mg daily divided twice a day) 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	473	158	631
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	49.4	51.2	
standard deviation	± 10.98	± 10.23	-
Gender categorical			
Units: Subjects			
Female	202	85	287
Male	271	73	344

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 or 1,200 mg daily divided twice a day) 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 or 1,200 mg daily divided twice a day) 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:	
Intent-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:	
Intent-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 (M11-646 Primary Endpoint Statistical Analysis.docx) 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	473			
Units: percentage of subjects				
number (not applicable)	96.4			

Attachments (see zip file)	M11-646 Primary Endpoint Statistical Analysis.docx

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	363[2]	114[3]		
Units: percentage of subjects				
number (not applicable)	97	15.8		

Notes:

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

[3] - Subjects in the ITT population who had ALT ≥ 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 will be used to proceed through the primary and first 3 secondary efficacy endpoints in the order numbered below.

Comparison groups	ABT-450/r/ABT-267 and ABT-333, Plus RBV v Placebo Followed by ABT-450/r/ ABT-267 and ABT-333, Plus RBV
Number of subjects included in analysis	477
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.

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	322[4]			
Units: percentage of subjects				
number (not applicable)	95.7			

Notes:

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

Attachments (see zip file)	M11-646 Secondary Endpoint 3 Statistical Analysis.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 (plasma HCV RNA level < LLOQ) 12 weeks after the last dose of study drug.

End point type	Secondary

End point timeframe:

12 weeks after the last actual dose of 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	151[5]			
Units: percentage of subjects				
number (not applicable)	98			

Notes:

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

Attachments (see zip file)	M11-646 Secondary Endpoint 4 Statistical Analysis.docx

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 ≥ 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 ≥ 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	473			
Units: percentage of subjects				
number (confidence interval 95%)	0.2 (0 to 0.6)			

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 ≥ 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	463[6]			
Units: percentage of subjects				
number (confidence interval 95%)	1.5 (0.4 to 2.6)			

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/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 or 1,200 mg daily divided twice a day) 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 or 1,200 mg daily divided twice a day) 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	10 / 473 (2.11%)	0 / 158 (0.00%)	2 / 157 (1.27%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NON-SMALL CELL LUNG CANCER			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Injury, poisoning and procedural complications			
LUMBAR VERTEBRAL FRACTURE			

subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
OVERDOSE			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
Vascular disorders			
AORTIC STENOSIS			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
Cardiac disorders			
SINUS TACHYCARDIA			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
VENTRICULAR EXTRASYSTOLES			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
Nervous system disorders			
ENCEPHALOPATHY			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
General disorders and administration site conditions			
CHILLS			

subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
DIARRHOEA			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
NAUSEA			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
VOMITING			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
Hepatobiliary disorders			
BILIARY COLIC			
subjects affected / exposed	0 / 473 (0.00%)	0 / 158 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
Respiratory, thoracic and mediastinal			

disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
HYPOXIA			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
MEDIASTINAL MASS			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
LOBAR PNEUMONIA			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	1 / 473 (0.21%)	0 / 158 (0.00%)	0 / 157 (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
SUBCUTANEOUS ABSCESS			
subjects affected / exposed	0 / 473 (0.00%)	0 / 158 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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	391 / 473 (82.66%)	108 / 158 (68.35%)	117 / 157 (74.52%)
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	38 / 473 (8.03%)	6 / 158 (3.80%)	5 / 157 (3.18%)
occurrences (all)	40	6	5
HEADACHE			
subjects affected / exposed	156 / 473 (32.98%)	42 / 158 (26.58%)	26 / 157 (16.56%)
occurrences (all)	182	54	31
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	24 / 473 (5.07%)	0 / 158 (0.00%)	14 / 157 (8.92%)
occurrences (all)	25	0	15
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	59 / 473 (12.47%)	6 / 158 (3.80%)	10 / 157 (6.37%)
occurrences (all)	80	10	11
FATIGUE			
subjects affected / exposed	164 / 473 (34.67%)	45 / 158 (28.48%)	35 / 157 (22.29%)
occurrences (all)	182	49	38
IRRITABILITY			
subjects affected / exposed	26 / 473 (5.50%)	4 / 158 (2.53%)	6 / 157 (3.82%)
occurrences (all)	26	4	6
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	29 / 473 (6.13%)	5 / 158 (3.16%)	8 / 157 (5.10%)
occurrences (all)	31	7	9
DIARRHOEA			
subjects affected / exposed	65 / 473 (13.74%)	11 / 158 (6.96%)	19 / 157 (12.10%)
occurrences (all)	77	12	24
DRY MOUTH			
subjects affected / exposed	19 / 473 (4.02%)	9 / 158 (5.70%)	0 / 157 (0.00%)
occurrences (all)	19	10	0
DYSPEPSIA			

subjects affected / exposed	26 / 473 (5.50%)	7 / 158 (4.43%)	6 / 157 (3.82%)
occurrences (all)	29	7	6
NAUSEA			
subjects affected / exposed	112 / 473 (23.68%)	22 / 158 (13.92%)	24 / 157 (15.29%)
occurrences (all)	129	23	28
VOMITING			
subjects affected / exposed	23 / 473 (4.86%)	6 / 158 (3.80%)	9 / 157 (5.73%)
occurrences (all)	25	6	12
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	34 / 473 (7.19%)	8 / 158 (5.06%)	7 / 157 (4.46%)
occurrences (all)	40	8	8
DYSPNOEA			
subjects affected / exposed	38 / 473 (8.03%)	4 / 158 (2.53%)	12 / 157 (7.64%)
occurrences (all)	39	4	12
DYSPNOEA EXERTIONAL			
subjects affected / exposed	24 / 473 (5.07%)	3 / 158 (1.90%)	8 / 157 (5.10%)
occurrences (all)	25	3	8
Skin and subcutaneous tissue disorders			
DRY SKIN			
subjects affected / exposed	27 / 473 (5.71%)	2 / 158 (1.27%)	7 / 157 (4.46%)
occurrences (all)	29	2	7
PRURITUS			
subjects affected / exposed	80 / 473 (16.91%)	7 / 158 (4.43%)	16 / 157 (10.19%)
occurrences (all)	87	7	16
RASH			
subjects affected / exposed	51 / 473 (10.78%)	9 / 158 (5.70%)	8 / 157 (5.10%)
occurrences (all)	62	9	9
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	22 / 473 (4.65%)	5 / 158 (3.16%)	8 / 157 (5.10%)
occurrences (all)	23	6	8
INSOMNIA			
subjects affected / exposed	67 / 473 (14.16%)	12 / 158 (7.59%)	21 / 157 (13.38%)
occurrences (all)	70	12	22
SLEEP DISORDER			

subjects affected / exposed	24 / 473 (5.07%)	4 / 158 (2.53%)	4 / 157 (2.55%)
occurrences (all)	25	4	4
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	23 / 473 (4.86%)	9 / 158 (5.70%)	9 / 157 (5.73%)
occurrences (all)	23	11	9
BACK PAIN			
subjects affected / exposed	22 / 473 (4.65%)	7 / 158 (4.43%)	9 / 157 (5.73%)
occurrences (all)	26	7	10
MYALGIA			
subjects affected / exposed	21 / 473 (4.44%)	8 / 158 (5.06%)	6 / 157 (3.82%)
occurrences (all)	23	9	7
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	33 / 473 (6.98%)	10 / 158 (6.33%)	11 / 157 (7.01%)
occurrences (all)	36	11	13
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	22 / 473 (4.65%)	8 / 158 (5.06%)	10 / 157 (6.37%)
occurrences (all)	24	8	11
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	37 / 473 (7.82%)	5 / 158 (3.16%)	11 / 157 (7.01%)
occurrences (all)	39	6	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2012	The purpose of this amendment was to: ● update the thresholds for the primary endpoints to be based on historical SVR rates from telaprevir plus pegIFN and RBV therapy. ● update secondary endpoints to remove rapid virologic response and end-of-treatment response and to include rebound and relapse rates. ● 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. ● incorporate Administrative Changes. ● address inconsistencies throughout the protocol.
08 April 2013	The purpose of this amendment was to: ● prohibit the use of hormonal contraceptives during study drug administration. Rationale: Hormonal contraceptives were not expected to be effective when dosed with the DAA regimen and could have been associated with an increased risk for ALT elevation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported