Clinical trial results:
An Open-Label Study to Evaluate the Safety, Antiviral Activity and Pharmacokinetics of Direct-Acting Antiviral Agent (DAA) Treatment in Combination with Peginterferon Alpha-2a and Ribavirin (pegIFN/RBV) in Chronic Hepatitis C Virus (HCV) Infected Subjects Who Have Experienced Virologic Failure in a Previous Abbott DAA Combination Study

Summary

EudraCT number	2011-005393-32
Trial protocol	GB ES DE BE HU SE AT NL IT CZ IE SK PT
Global end of trial date	08 May 2017

Results information

Result version number	v1 (current)
This version publication date	09 May 2018
First version publication date	09 May 2018

Trial information

Trial identification

Sponsor protocol code	M13-101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01609933
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 800-633-9110,
Scientific contact	Mariem Charafeddine, AbbVie, mariem.charafeddine@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	08 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A study to evaluate the safety and effect of treatment with experimental antiviral drugs in combination with peginterferon alpha-2a and ribavirin in people with hepatitis C virus who did not respond to treatment in a previous AbbVie/Abbott combination study.

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	18 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	United States: 17
Worldwide total number of subjects	32
EEA total number of subjects	13

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	32
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All subjects who received at least 1 dose of study drug were included in the intent-to-treat (ITT) population; the safety population is the same as the ITT population.

Pre-assignment

Screening details:

The study included a 42-day screening period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	2-DAA + PegIFN/RBV

Arm description:

2-direct-acting antiviral (2-DAA: ABT-450 [paritaprevir] 200 mg once daily [QD], ritonavir 100 mg QD, ABT-267 [ombitasvir] 25 mg QD) plus pegylated interferon alpha-2a (pegIFN) 180 mcg once weekly and Ribavirin (RBV) weight-based dosing, 1000 to 1200 mg divided twice daily (BID) for 24 weeks (Substudy 1) and followed by pegIFN and RBV alone for an additional 24 weeks (Substudy 2).

Arm type	Experimental
Investigational medicinal product name	ABT-450/r
Investigational medicinal product code	
Other name	ABT-450 also known as paritaprevir and r is also know as ritonavir
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450 (tablets) dosed with ritonavir (capsules or tablets) administered orally

Investigational medicinal product name	ABT-267
Investigational medicinal product code	
Other name	ABT-267 also known as ombitasvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-267 (tablets)

Investigational medicinal product name	pegylated interferon alpha-2a (pegIFN)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

pegIFN alpha-2a (syringe)

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

Dosage and administration details:
Ribavirin (tablets)

Number of subjects in period 1	2-DAA + PegIFN/RBV
Started	32
Completed	28
Not completed	4
Adverse event, serious fatal	1
Consent withdrawn by subject	3

Baseline characteristics

Reporting groups	
Reporting group title	2-DAA + PegIFN/RBV
Reporting group description:	
2-direct-acting antiviral (2-DAA: ABT-450 [paritaprevir] 200 mg once daily [QD], ritonavir 100 mg QD, ABT-267 [ombitasvir] 25 mg QD) plus pegylated interferon alpha-2a (pegIFN) 180 mcg once weekly and Ribavirin (RBV) weight-based dosing, 1000 to 1200 mg divided twice daily (BID) for 24 weeks (Substudy 1) and followed by pegIFN and RBV alone for an additional 24 weeks (Substudy 2).	

Reporting group values	2-DAA + PegIFN/RBV	Total	
Number of subjects	32	32	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	51.4		
standard deviation	± 9.77	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	25	25	
Race categorical Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	2	
White	30	30	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	2-DAA + PegIFN/RBV

Reporting group description:

2-direct-acting antiviral (2-DAA: ABT-450 [paritaprevir] 200 mg once daily [QD], ritonavir 100 mg QD, ABT-267 [ombitasvir] 25 mg QD) plus pegylated interferon alpha-2a (pegIFN) 180 mcg once weekly and Ribavirin (RBV) weight-based dosing, 1000 to 1200 mg divided twice daily (BID) for 24 weeks (Substudy 1) and followed by pegIFN and RBV alone for an additional 24 weeks (Substudy 2).

Primary: Percentage of Participants Achieving Sustained Virologic Response 12 Weeks Post Treatment (SVR12)

End point title	Percentage of Participants Achieving Sustained Virologic Response 12 Weeks Post Treatment (SVR12)[1]

End point description:

SVR12 was defined as hepatitis C virus ribonucleic acid (HCV RNA) level less than lower limit of quantitation [LLOQ] 12 weeks after the last dose of study drugs (DAAs plus pegIFN alpha-2a and RBV).

End point type	Primary

End point timeframe:

12 weeks after last dose of study drugs (DAAs plus pegIFN alpha-2a and RBV)

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: Descriptive data are summarized for this end point per protocol.

End point values	2-DAA + PegIFN/RBV			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: percentage of participants				
number (confidence interval 95%)	81.3 (64.7 to 91.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Virologic Response 24 Weeks Post Treatment (SVR24)

End point title	Percentage of Participants Achieving Virologic Response 24 Weeks Post Treatment (SVR24)

End point description:

SVR24 was defined as HCV RNA level less than the LLOQ 24 weeks after the last dose of study drugs (DAAs plus pegIFN alpha-2a and RBV).

End point type	Secondary

End point timeframe:

24 weeks after last dose of study drugs (DAAs plus pegIFN alpha-2a and RBV)

End point values	2-DAA + PegIFN/RBV			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of participants				
number (confidence interval 95%)	78.1 (61.2 to 89.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Extended Rapid Virologic Response (eRVR)

End point title	Percentage of Participants With Extended Rapid Virologic Response (eRVR)

End point description:

eRVR was defined as HCV RNA level < LLOQ at Substudy 1 treatment weeks 4 through 12 without a confirmed HCV RNA >= LLOQ

End point type	Secondary

End point timeframe:

Treatment weeks 4 through 12 of Substudy 1 (DAAs plus pegIFN alpha-2a and RBV)

End point values	2-DAA + PegIFN/RBV			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of participants				
number (confidence interval 95%)	87.5 (71.9 to 95.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events

End point title	Number of Subjects With Adverse Events

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. The investigator assessed the relationship of each event to the use of study drug as either probably related, possibly related, probably not related or not related. A serious adverse event (SAE) is an event that results in death, is lifethreatening, requires or prolongs

hospitalization, results in a congenital anomaly, persistent or significant disability/incapacity or is an important medical event that, based on medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above. Treatment-emergent events (TEAEs/TESAEs) are defined as any event that began or worsened in severity after initiation of study drug through 30 days post-DAA dosing. For more details on AEs, see the AE section.

End point type	Secondary

End point timeframe:

From first dose of study drug through 30 days after last dose of study drug (DAAs plus pegIFN alpha-2a and RBV) (up to 28 weeks).

End point values	2-DAA + PegIFN/RBV			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: subjects				
2-DAA TEAE	29			
2-DAA TESAE	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) were collected from first dose of study drug through 30 days after the last dose of DAA (2-DAA + pegIFN alpha-2a and RBV) dosing (up to 28 weeks).

Adverse event reporting additional description:

TEAEs and TESAEs are defined as any AE with an onset date that is after the first dose of study drug through 30 days after the last dose of DAAs (up to 28 weeks) and were collected whether elicited or spontaneously reported by the participant.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	2-DAA + PegIFN/RBV

Reporting group description:

2-direct-acting antiviral (2-DAA: ABT-450 [paritaprevir] 200 mg once daily [QD], ritonavir 100 mg QD, ABT-267 [ombitasvir] 25 mg QD) plus pegylated interferon alpha-2a (pegIFN) 180 mcg once weekly and Ribavirin (RBV) weight-based dosing, 1000 to 1200 mg divided twice daily (BID) for 24 weeks and followed by pegIFN and RBV alone for an additional 24 weeks.

Serious adverse events	2-DAA + PegIFN/RBV		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 32 (3.13%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	2-DAA + PegIFN/RBV		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 32 (87.50%)		
Investigations			

Neutrophil count decreased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all)	 3 / 32 (9.38%) 7 2 / 32 (6.25%) 2 5 / 32 (15.63%) 7		
Nervous system disorders Disturbance in attention subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 3 / 32 (9.38%) 3 14 / 32 (43.75%) 27		
Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	 2 / 32 (6.25%) 2 7 / 32 (21.88%) 10		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Feeling abnormal subjects affected / exposed occurrences (all)	 2 / 32 (6.25%) 2 3 / 32 (9.38%) 3 11 / 32 (34.38%) 13 2 / 32 (6.25%) 2		

Influenza like illness			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	6		
Pain			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Anal pruritus			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	7		
Dry mouth			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	9 / 32 (28.13%)		
occurrences (all)	9		
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	6		
Pruritus			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	8		
Rash			
subjects affected / exposed	8 / 32 (25.00%)		
occurrences (all)	9		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	8 / 32 (25.00%)		
occurrences (all)	10		
Irritability			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	4		
Muscle spasms			

subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Viral infection			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	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 included the following: to add text to the benefit and risks section; clarify screening procedures; clarify that that subjects continue into Substudy 2 after completing or discontinuing Substudy 1; clarify that sites may substitute serum pregnancy testing for urine pregnancy testing only if required per local regulations; added clinical laboratory and IP-10 testing to Table 2 at the Discontinuation visit; added subgenotypes to the exploratory analyses text.
17 April 2012	The purpose of this amendment included the following: to exclude subjects with prior null or partial response to PegIFN/RBV in whom resistant variants associated with decreased susceptibility to ABT-450 and/or ABT-267 were detected; increased the enrollment time up to 1 year after virologic failure in the previous study; revised the Screening Visit procedures; clarified inclusion criteria text for woman of child bearing potential and define postmenopausal state; clarified inclusion criteria for male subjects who had partners of childbearing potential; added exclusion criteria to exclude use of herbal supplements and colony stimulating factors; added non-efficacy (futility) criteria; added information for the management of neuropsychiatric complications; added text to provide information on managing complications due to peginterferon therapy; and removed Abbott Realtime HCV testing, as exploratory analysis of HCV RNA results using 2 platforms was no longer planned.
26 July 2012	The purpose of this amendment included the following: added a pre-screening visit to study procedures; updated the number of weeks of treatment with ABT-450 and ABT-267 in active clinical trials to 24 weeks; added inclusion criteria and exclusion criteria text to limit the enrollment to subjects with genotype 1 chronic HCV infection; added inclusion criteria text regarding HCV RNA level at pre-screening; clarified exclusion criteria text to align with how population sequencing was performed; added exclusion criteria related to the gap between the time the subject failed treatment in the previous AbbVie/Abbott DAA combination study and the start of this study; clarified that medical history will only be an update at the Screening Visit and Substudy 1 Day 1 Visit of new information that was not already recorded in the previous Abbott study; added text to clarify what treatment was planned after the subject ended their participation in this study; clarified physical examination procedures; added text regarding clinical laboratory tests to confirm post-menopausal status; corrected centrifuge speed text; added storage condition instructions for ritonavir; clarified text regarding assigning subjects; clarified drug accountability documentation; and updated references to include the newest versions of ABT-450 and ABT-267 Investigator's Brochures.

22 March 2013	The purpose of this amendment included the following: revised inclusion/exclusion criteria and study procedures; revised the number of participating subjects in the study from 250 to 150; updated the description of the Treatment Period and the Post-Treatment Period including descriptions of study visits; modified inclusion criteria regarding effective contraceptive methods for female subjects; clarified exclusion criteria text to indicate that pregnancy should be avoided within 7 months after last dose of RBV study drug; added a table of medications contraindicated for use with ABT-450 and ABT-267 to exclusion criteria text; added urine albumin test to Substudy 1 Day 1 visit; deleted comprehensive physical examination from the Post Treatment Period; deleted the 1-year restriction for subjects to enroll into this study from discontinuation of the previous study; added clarifying text to the following sections: Prohibited Therapy, Pregnancy, Discontinuation of Individual Subject, Method of Assigning Subjects to Treatment Groups, Treatment Compliance, Drug Accountability, and Appropriateness of Measurements; updated the Toxicity Management; updated the Statistical Methods and Determination of Sample Size text; updated the Resistance Variables text; incorporated Administrative Changes 2 and 3; and provided clarifying text to address the Sponsor change from Abbott Laboratories (Abbott) to AbbVie.
09 April 2013	The purpose of this amendment was to add text that prohibited the use of hormonal contraceptives during study drug administration.
17 June 2013	The purpose of this amendment included the following: updated the Introduction text; updated the discussion text regarding the risk of treatment failure for subjects who previously failed pegIFN/RBV plus telaprevir; updates throughout to include subjects who failed pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study; clarified the expectations for rescreening procedures and eligibility; updated and clarified eligibility determination for both male and female subjects; amended the eligibility determination for subjects who failed telaprevir plus PegIFN/RBV therapy in the previous AbbVie study; updated the eligibility criterion for contraindicated medications; modified the hemoglobin exclusion criterion text; amended the prohibited therapy text; modified the study activities table and text; amended the treatment compliance and drug accountability text; updated the primary contact information for protocol deviations; and updated the resistance analyses to be performed; and added an appendix with clinical toxicity grade information.
25 September 2013	The purpose of this amendment included the following: Amended the Pre-Screening and Screening sections regarding timing of the discontinuation visit from the previous AbbVie/Abbott DAA combination study; revised the assessments not required to be re-tested during the re-screening visit; clarified subjects that would not be permitted to re-screen and were excluded from the study; updated the Post-Treatment follow-up period text to allow subjects the ability to enroll in a follow-up study; amended the post-treatment therapy section; modified the study activities table and text; amended the information provided to the subjects; modified the Medication Event Monitoring System caps distribution text; amended the Non-Efficacy (Futility) Criteria text; updated the type of treatments dispensed in this study to include the possibility of receiving ritonavir tablets; for PegIFN, amended the treatment compliance and drug accountability text; amended the hematologic toxicities table to remove extra management criteria and to add another management criterion; amended the Statistical Methods and Resistance Analyses text; and corrected the protocol signatories in Appendix B.
11 June 2014	The purpose of this amendment included the following: amended the number of subjects from approximately 150 to up to 150; updated the Introduction text to ensure that the most current drug development information was included; amended the toxicity management for Grades 1 and 2 laboratory abnormalities and modified instructions regarding the management of total bilirubin and/or hepatic transaminase and creatinine clearance decreases.

25 July 2014	The purpose of this amendment included the following: updated the section for hormonal contraception to more clearly define the acceptable approaches to contraception during the study, and updated the information about the medication that is contraindicated for use with the study drug regimen.
26 June 2015	The purpose of this amendment included the following: corrected the number of subjects to be enrolled; updated the Study Designated Physician details; updated the collection time point for HCV RNA level at screening and changed the collection time for archive plasma samples; removed the collection of Medication Event Monitoring System caps data; removed interim analyses; clarified in the protocol how and when samples were to be disposed of; corrected RBV dispensing text; updated the SAE section; and added contact information for subject safety concerns or medical emergencies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: