Clinical trial results:
A Randomized, Double-Blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 2 Infection (ENDURANCE-2)

Summary

EudraCT number	2015-002348-14
Trial protocol	BE PT LT IT
Global end of trial date	23 February 2017

Results information

Result version number	v1 (current)
This version publication date	02 February 2018
First version publication date	02 February 2018

Trial information

Trial identification

Sponsor protocol code	M15-464

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02640482
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	Neddie Zadeikis, AbbVie, neddie.zadeikis@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 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 February 2017
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 efficacy of ABT-493/ABT-530 in adults with genotype 2 chronic hepatitis C virus (HCV) infection.

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	27 November 2015
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	Italy: 54
Country: Number of subjects enrolled	Korea, Republic of: 65
Country: Number of subjects enrolled	Taiwan: 41
Country: Number of subjects enrolled	United States: 53
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	France: 45
Country: Number of subjects enrolled	Lithuania: 18
Worldwide total number of subjects	304
EEA total number of subjects	145

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)	203
From 65 to 84 years	101
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Safety population: All participants who received at least one dose of study drug.

Pre-assignment

Screening details:

A total of 304 subjects were enrolled of which 302 received at least 1 dose of study drug and were included in the intent-to-treat (ITT) population (N=302; 202 in Arm A and 100 in Arm B). Most efficacy analyses were performed on Arm A only (N=202) and excluded prior sofosbuvir (SOF) + ribavirin (RBV) ± pegylated-interferon (pegIFN) failures (N=6).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A DB Active Drug

Arm description:

ABT-493/ABT-530 (300 mg/120 mg) coformulated once daily (QD) for 12 weeks (double-blind [DB] treatment period)

Arm type	Experimental
Investigational medicinal product name	ABT-493/ABT-530
Investigational medicinal product code	
Other name	ABT-493 also known as glecaprevir, ABT-530 also known as pibrentasvir, MAVIRET
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet; ABT-493 coformulated with ABT-530 administered orally

Arm title	Arm B DB Placebo Then OL Active

Arm description:

Placebo for ABT-493/ABT-530 QD for 12 weeks (DB treatment period) followed by ABT-493/ABT-530 (300 mg/120 mg) coformulated once daily (QD) for 12 weeks (open-label [OL] treatment period)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet administered orally

Investigational medicinal product name	ABT-493/ABT-530
Investigational medicinal product code	
Other name	ABT-493 also known as glecaprevir, ABT-530 also known as pibrentasvir, MAVIRET
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet; ABT-493 coformulated with ABT-530 administered orally.

Number of subjects in period 1[1]	Arm A DB Active Drug	Arm B DB Placebo Then OL Active
Started	202	100
Completed	199	100
Not completed	3	0
Lost to follow-up	3	-

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 304 subjects were enrolled of which 302 received at least 1 dose of study drug and were included in the intent-to-treat (ITT) population (N = 302; 202 subjects in Arm A and 100 subjects in Arm B). Most efficacy analyses were performed on Arm A only (N = 202) and excluded prior SOF + RBV ± pegIFN failures (N = 6).

Baseline characteristics

Reporting groups	
Reporting group title	Arm A DB Active Drug
Reporting group description:	
ABT-493/ABT-530 (300 mg/120 mg) coformulated once daily (QD) for 12 weeks (double-blind [DB] treatment period)	
Reporting group title	Arm B DB Placebo Then OL Active
Reporting group description:	
Placebo for ABT-493/ABT-530 QD for 12 weeks (DB treatment period) followed by ABT-493/ABT-530 (300 mg/120 mg) coformulated once daily (QD) for 12 weeks (open-label [OL] treatment period)	

Reporting group values	Arm A DB Active Drug	Arm B DB Placebo Then OL Active	Total
Number of subjects	202	100	302
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	56.77	57.60	
standard deviation	± 12.79	± 12.04	-
Gender categorical			
Units: Subjects			
Female	104	55	159
Male	98	45	143

End points

End points reporting groups

Reporting group title	Arm A DB Active Drug
Reporting group description:	
ABT-493/ABT-530 (300 mg/120 mg) coformulated once daily (QD) for 12 weeks (double-blind [DB] treatment period)	
Reporting group title	Arm B DB Placebo Then OL Active
Reporting group description:	
Placebo for ABT-493/ABT-530 QD for 12 weeks (DB treatment period) followed by ABT-493/ABT-530 (300 mg/120 mg) coformulated once daily (QD) for 12 weeks (open-label [OL] treatment period)	

Primary: Percentage of Participants With Sustained Virologic Response 12 Weeks Post-treatment (SVR12) in Arm A DB Active Drug Excluding Prior SOF + Ribavirin (RBV) ± pegIFN Failures: Noninferiority Analysis

End point title	Percentage of Participants With Sustained Virologic Response 12 Weeks Post-treatment (SVR12) in Arm A DB Active Drug Excluding Prior SOF + Ribavirin (RBV) ± pegIFN Failures: Noninferiority Analysis[1][2]

End point description:

SVR12 was defined as plasma HCV RNA level <LLOQ 12 weeks after the last dose of study drug. The primary efficacy endpoint was the noninferiority of the percentage of participants who achieved SVR12 in Arm A Double Blind (DB) Active Drug excluding prior SOF + RBV ± pegIFN failures compared with the historical control rate for patients treated with the current standard of care (SOC) (SOF + RBV for 12 weeks). The lower confidence bound of the 2-sided 95% confidence interval (95% CI) for the percentage of participants with SVR12 must exceed 89% to achieve noninferiority.

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: The noninferiority of the rate of sustained virologic response at 12 weeks after treatment for Arm A as compared with the historical rate for patients treated with the current standard of care (SOF + RBV for 12 weeks) was analyzed; the lower confidence bound of the 2-sided 95% CI for the percentage of participants with sustained virologic response at 12 weeks after treatment must exceed 89% to achieve noninferiority.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary endpoint included Arm A.

End point values	Arm A DB Active Drug			
Subject group type	Reporting group			
Number of subjects analysed	196[3]			
Units: Percentage of participants				
number (confidence interval 95%)	99.5 (98.5 to 100)			

Notes:

[3] - ITT participants in Arm A excluding participants with prior SOF + RBV ± pegIFN failures.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With SVR12 in Arm A DB Active Drug Excluding Prior SOF + RBV ± pegIFN Failures: Superiority Analysis

End point title	Percentage of Participants With SVR12 in Arm A DB Active Drug Excluding Prior SOF + RBV ± pegIFN Failures: Superiority Analysis[4]

End point description:

SVR12 was defined as plasma HCV RNA level <LLOQ 12 weeks after the last dose of study drug. The secondary efficacy endpoint was the superiority of the percentage of participants who achieved SVR12 in Arm A Double Blind (DB) Active Drug excluding prior SOF + RBV ± pegIFN failures compared with the historical control rate for patients treated with the current standard of care (SOC) (SOF + RBV for 12 weeks). The lower confidence bound of the 2-sided 95% CI for the percentage of participants with SVR12 must exceed 95% to achieve superiority.

End point type	Secondary

End point timeframe:

12 weeks after the last actual dose of active study drug

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The secondary endpoint included Arm A.

End point values	Arm A DB Active Drug			
Subject group type	Reporting group			
Number of subjects analysed	196[5]			
Units: Percentage of participants				
number (confidence interval 95%)	99.5 (98.5 to 100)			

Notes:

[5] - ITT participants in Arm A excluding participants with prior SOF + RBV ± pegIFN failures.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With On-treatment Virologic Failure in Arm A DB Active Drug Excluding Prior SOF + RBV ± pegIFN Failures

End point title	Percentage of Participants With On-treatment Virologic Failure in Arm A DB Active Drug Excluding Prior SOF + RBV ± pegIFN Failures[6]

End point description:

On-treatment virologic failure was defined as confirmed increase of > 1 log(subscript)10(subscript) IU/mL above the lowest value of post-baseline HCV RNA during treatment; confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at end of treatment with at least 6 weeks of treatment.

End point type	Secondary

End point timeframe:

Up to Week 12 post baseline

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The secondary endpoint included Arm A.

End point values	Arm A DB Active Drug			
Subject group type	Reporting group			
Number of subjects analysed	196[7]			
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 1.9)			

Notes:

[7] - ITT participants in Arm A excluding participants with prior SOF + RBV ± pegIFN failures.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Post-treatment Relapse in Arm A DB Active Drug Excluding Prior SOF + RBV ± pegIFN Failures

End point title	Percentage of Participants With Post-treatment Relapse in Arm A DB Active Drug Excluding Prior SOF + RBV ± pegIFN Failures[8]

End point description:

Post-treatment relapse was defined as confirmed HCV RNA ≥ LLOQ between the end of DB treatment and 12 weeks after the last dose of active study drug among participants who completed treatment with HCV RNA levels < LLOQ at the end of treatment, excluding reinfection.

End point type	Secondary

End point timeframe:

Between End of Treatment (Week 12) and 12 weeks after the last dose of Arm A DB active drug (up to Week 24)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The secondary endpoint included Arm A.

End point values	Arm A DB Active Drug			
Subject group type	Reporting group			
Number of subjects analysed	195[9]			
Units: Percentage of participants				
number (confidence interval 95%)	0 (0 to 1.9)			

Notes:

[9] - ITT: Arm A, HCV RNA <LLOQ at final treatment, completed DB, excluding prior SOF+RBV±pegIFN failures

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With SVR12 in Arm A DB Active Drug With Prior SOF + RBV ± pegIFN Failure

End point title	Percentage of Participants With SVR12 in Arm A DB Active Drug With Prior SOF + RBV ± pegIFN Failure[10]

End point description:

SVR12 was defined as HCV RNA level <LLOQ 12 weeks after the last dose of active study drug.

End point type	Secondary

End point timeframe:

12 weeks after the last actual dose of active study drug

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The secondary endpoint included Arm A.

End point values	Arm A DB Active Drug			
Subject group type	Reporting group			
Number of subjects analysed	6[11]			
Units: Percentage of participants				
number (not applicable)	100			

Notes:

[11] - ITT participants in Arm A DB with prior SOF + RBV ± pegIFN failures.

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 initial study drug administration until 30 days after the last dose of study drug (up to 16 weeks) in both the double-blind (DB) open-label (OL) periods.

Adverse event reporting additional description:

TEAEs and TESAEs are defined as any AE or SAE with an onset date after the first dose of study drug until 30 days after the last dose of study drug (or until prior to the first dose of open-label active drug for subjects who received DB placebo then OL active study drug) and 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	Arm A DB Active Drug

Reporting group description:

ABT-493/ABT-530 (300 mg/120 mg) coformulated once daily (QD) for 12 weeks (double-blind [DB] treatment period)

Reporting group title	Arm B DB Placebo

Reporting group description:

Placebo for ABT-493/ABT-530 QD for 12 weeks (DB treatment period)

Reporting group title	Arm B OL Active Drug

Reporting group description:

ABT-493/ABT-530 (300 mg/120 mg) coformulated once daily (QD) for 12 weeks (open-label [OL] treatment period)

Serious adverse events	Arm A DB Active Drug	Arm B DB Placebo	Arm B OL Active Drug
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 202 (1.49%)	1 / 100 (1.00%)	1 / 100 (1.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 202 (0.50%)	0 / 100 (0.00%)	0 / 100 (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
Joint dislocation			
subjects affected / exposed	1 / 202 (0.50%)	0 / 100 (0.00%)	0 / 100 (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			
Haemorrhoids			
subjects affected / exposed	1 / 202 (0.50%)	0 / 100 (0.00%)	0 / 100 (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	1 / 202 (0.50%)	0 / 100 (0.00%)	0 / 100 (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
Musculoskeletal and connective tissue disorders			
Rhuematoid arthritis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 100 (1.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	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	Arm A DB Active Drug	Arm B DB Placebo	Arm B OL Active Drug
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 202 (37.13%)	38 / 100 (38.00%)	31 / 100 (31.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 202 (0.99%)	5 / 100 (5.00%)	2 / 100 (2.00%)
occurrences (all)	2	5	2
Nervous system disorders			
Dizzness			
subjects affected / exposed	6 / 202 (2.97%)	5 / 100 (5.00%)	1 / 100 (1.00%)
occurrences (all)	6	6	1
Headache			
subjects affected / exposed	24 / 202 (11.88%)	12 / 100 (12.00%)	8 / 100 (8.00%)
occurrences (all)	32	12	8
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	19 / 202 (9.41%)	8 / 100 (8.00%)	5 / 100 (5.00%)
occurrences (all)	21	8	5
Fatigue			
subjects affected / exposed	23 / 202 (11.39%)	10 / 100 (10.00%)	5 / 100 (5.00%)
occurrences (all)	24	10	5
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	20 / 202 (9.90%)	3 / 100 (3.00%)	5 / 100 (5.00%)
occurrences (all)	20	3	5
Nausea			
subjects affected / exposed	15 / 202 (7.43%)	4 / 100 (4.00%)	8 / 100 (8.00%)
occurrences (all)	16	4	8
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	4 / 202 (1.98%)	5 / 100 (5.00%)	1 / 100 (1.00%)
occurrences (all)	4	6	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	12 / 202 (5.94%)	6 / 100 (6.00%)	5 / 100 (5.00%)
occurrences (all)	12	6	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2015	The purpose of this amendment was to revise the inclusion criteria, to add a list of potential birth control options, and to expand the categories of treatment-experienced subjects allowed (allowed sofosbuvir [SOF] + ribavirin [RBV] ± pegIFN treatment failures in the study). In addition, this amendment specified a reflex assay used for determination of Chronic Hepatitis C Virus (HCV) genotype/subtype and updated the historical control rate of the Sustained Virologic Response 12 Weeks Post-treatment (SVR12) for primary and secondary efficacy endpoints and the determination of sample size to accommodate the expanded study population
14 October 2015	The purpose of this amendment was to update the inclusion criteria to require only 1 effective method of contraception and added text detailing allowable methods of contraceptives. In addition, this amendment included an update to the definitions of prior treatment experience, removed prior SOF + RBV ± pegIFN failures from the analysis of the primary endpoint and made it a separate secondary endpoint, and allowed an increase of the total sample size for the study to up to 321 subjects, particularly to increase the sample size of subjects who failed a previous SOF-containing regimen.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported