Clinical trial results:
A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy (ABT-493 and/or ABT-530) in Subjects Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection

Summary

EudraCT number	2015-000452-24
Trial protocol	BE DE
Global end of trial date	04 December 2019

Results information

Result version number	v1 (current)
This version publication date	09 October 2020
First version publication date	09 October 2020

Trial information

Trial identification

Sponsor protocol code	M13-576

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02441283
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@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	04 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a long-term, Phase 2/3, multicenter, follow-up study to evaluate the durability of sustained virologic response (SVR), persistence of direct-acting antiviral agent (DAA) resistance, and clinical outcomes for subjects who received glecaprevir (ABT-493) and/or pibrentasvir (ABT-530) in prior AbbVie Phase 2 or 3 clinical studies for the treatment of chronic hepatitis C virus (HCV) infection. The subject must have completed the follow-up period of the prior eligible AbbVie study. To be included in the analyses, the subject must not have been retreated prior to enrolling in this study. Subjects were followed for a total of approximately 3 years after their last dose of DAA in the previous HCV clinical study. The 3 years were inclusive of any post-treatment period in the prior study, as well as any gaps between the end of the prior study and enrollment in this 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	22 June 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	Australia: 39
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	New Zealand: 12
Country: Number of subjects enrolled	Puerto Rico: 24
Country: Number of subjects enrolled	United States: 222
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Germany: 6
Worldwide total number of subjects	377
EEA total number of subjects	62

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)	320
From 65 to 84 years	57
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Full Analysis Set (FAS):subjects who rcvd ABT-493 and/or ABT-530 in a prior Phase 2/3 study and weren't retreated prior to enrolling in this study. 3 subjects were retreated prior to enrollment in this study and 4 didn't receive ABT-493 and/or ABT-540 in prior study and were excluded from the FAS. Baseline data= values at time of prior study start.

Period 1

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

Arms

Arm title	HCV-infected Participants

Arm description:

Hepatitis C virus (HCV)-infected participants who received ABT-493 and/or ABT-530 in prior Phase 2 or 3 clinical studies with these agents for the treatment of chronic HCV and were not retreated prior to entering this study. No AbbVie study drug was administered in this study.

Arm type	Experimental
Investigational medicinal product name	Glecaprevir
Investigational medicinal product code	
Other name	ABT-493
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-493 was not administered in this study. This study was a follow-up for participants who received the drug in prior studies.

Investigational medicinal product name	Pibrentasvir
Investigational medicinal product code	
Other name	ABT-530
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-530 was not administered in this study. This study was a follow-up for participants who received the drug in prior studies.

Number of subjects in period 1	HCV-infected Participants
Started	377
Completed	287
Not completed	90
Death	1
Other, not specified	32
Withdrew consent	15
Lost to follow-up	42

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

Full Analysis Set (FAS): all subjects who received ABT-493 and/or ABT-530 in a prior Phase 2/3 study and were not retreated prior to enrolling in this study. Three subjects who received retreatment prior to enrollment in this study and four subjects who did not receive ABT-493 and/or ABT-540 in a prior study were excluded from the FAS.

Reporting group values	Overall Study	Total	
Number of subjects	377	377	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 54.1 ± 10.96	 -	
Gender categorical Units: Subjects			
Female	172	172	
Male	205	205	

End points

End points reporting groups

Reporting group title	HCV-infected Participants

Reporting group description:

Hepatitis C virus (HCV)-infected participants who received ABT-493 and/or ABT-530 in prior Phase 2 or 3 clinical studies with these agents for the treatment of chronic HCV and were not retreated prior to entering this study. No AbbVie study drug was administered in this study.

Primary: Percentage of Participants Who Maintained a Sustained Virologic Response (SVR) Out of Those Who Achieved SVR12 in a Prior Study With an ABT-493- and/or ABT-530-containing Regimen

End point title	Percentage of Participants Who Maintained a Sustained Virologic Response (SVR) Out of Those Who Achieved SVR12 in a Prior Study With an ABT-493- and/or ABT-530-containing Regimen[1]

End point description:

Maintaining a sustained virologic response (SVR) is defined as having Hepatitis C virus ribonucleic acid (HCV RNA) value consistently below the lower limit of quantification (< LLOQ) from the end of treatment in the previous study throughout Study M13-576 (this study).

End point type	Primary

End point timeframe:

From the end of treatment in the previous study up to 3 years post-treatment

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: Statistical analysis was not applicable for this endpoint.

End point values	HCV-infected Participants			
Subject group type	Reporting group			
Number of subjects analysed	376[2]			
Units: Percentage of participants				
number (not applicable)	99.5			

Notes:

[2] - Subjects rcvd ABT-493 +/- ABT-530 in prior Phase 2/3 study and weren't retreated before this study

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Relapsed or Had a New Hepatitis C Virus (HCV) Infection at Any Time up to the Last Follow-up in This Study Among Participants Who Achieved SVR12 in a Prior Study With an ABT-493- and/or ABT-530-containing Regimen

End point title	Percentage of Participants Who Relapsed or Had a New Hepatitis C Virus (HCV) Infection at Any Time up to the Last Follow-up in This Study Among Participants Who Achieved SVR12 in a Prior Study With an ABT-493- and/or ABT-530-containing Regimen[3]

End point description:

Relapse was defined as confirmed Hepatitis C virus ribonucleic acid (HCV RNA) greater than or equal to the lower limit of quantification (≥ LLOQ) between end of treatment and up to and including the last

HCV RNA measurement collected in this study for a participant with HCV RNA < LLOQ at Final Treatment Visit who completed treatment, excluding reinfection. HCV reinfection was defined as confirmed HCV RNA ≥ LLOQ after the end of treatment in a participant who had HCV RNA < LLOQ at Final Treatment Visit, along with the post-treatment detection of a different HCV genotype, subtype, or clade compared with baseline, as determined by phylogenetic analysis of the NS3 or NS5A, and/or NS5B gene sequences.

End point type	Primary

End point timeframe:

From the end of treatment in the previous study up to 3 years post-treatment

Notes:

[3] - 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: Statistical analysis was not applicable for this endpoint.

End point values	HCV-infected Participants			
Subject group type	Reporting group			
Number of subjects analysed	376[4]			
Units: percentage of participants				
number (not applicable)				
Relapse overall	0.3			
Reinfection overall	0.3			

Notes:

[4] - Subjects rcvd ABT-493 +/- ABT-530 in prior Phase 2/3 study and weren't retreated before this study

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Persistence of Resistance-Associated Amino Acid Variants Among Those Experiencing Virologic Failure

End point title	Number of Participants With Persistence of Resistance-Associated Amino Acid Variants Among Those Experiencing Virologic Failure[5]

End point description:

Plasma samples for HCV resistance testing were collected at study visits. The variants in nonstructural viral protein 3 (NS3) and nonstructural viral protein 5A (NS5A) at amino acid positions of interest were analyzed by next generation sequencing relative to baseline and prototypic reference sequences.

End point type	Primary

End point timeframe:

From Day 1 to Month 12

Notes:

[5] - 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: Statistical analysis was not applicable for this endpoint.

End point values	HCV-infected Participants			
Subject group type	Reporting group			
Number of subjects analysed	1[6]			
Units: participants				
NS3 Variants at Months 3, 6, and 12	1			
NS5A Variants at Months 3, 6, and 12	1			

Notes:

[6] - Subjects w/ virologic failure in prior/current study and NS3/4A and/or NS5A sequencing data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Medical Events Related to Progression of Liver Disease or Hepatitis C Virus Infection

End point title	Number of Participants With Medical Events Related to Progression of Liver Disease or Hepatitis C Virus Infection

End point description:

Any events (i.e., diagnoses) related to liver disease progression and/or HCV infection considered to be clinically significant by the investigator that began or worsened after Day 1 were documented until the end of the study or initiation of re-treatment for HCV (if applicable). Significant events related to liver disease progression include the development of cirrhosis, events indicative of hepatic decompensation, (including: variceal bleeding, new ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepato-renal syndrome, hepatic hydrothorax or other evidence of hepatic decompensation considered to be significant by the investigator), change in the Child-Pugh category (e.g., change from Child-Pugh Class A to Child-Pugh Class B), the occurrence of hepatocellular carcinoma, liver transplantation and/or death.

End point type	Secondary

End point timeframe:

After Day 1 up to 3 years post-treatment

End point values	HCV-infected Participants			
Subject group type	Reporting group			
Number of subjects analysed	377[7]			
Units: participants				
Medical events related to liver disease or HCV inf	7			
Development of cirrhosis	0			
Liver decompensation (Variceal bleeding)	0			
Liver decompensation (Ascites)	0			
Liver decomp (spontaneous bacterial peritonitis)	0			
Liver decompensation (hepatic encephalopathy)	0			
Liver decompensation (hepatorenal syndrome)	0			
Liver decompensation (hepatic hydrothorax)	0			
Liver decompensation (other [PI's discretion])	0			
Change in Child-Pugh Score in subject w/cirrhosis	0			
Hepatocellular carcinoma (HCC)	5			

Liver transplantation occurred	0			
Death	0			
Regenerated node in the liver	1			
Cholangiocarcinoma/differentiated adenocarcinoma	1			

Notes:

[7] - Subjects rcvd ABT-493 +/- ABT-530 in prior Phase 2/3 study and weren't retreated before this study

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Concentration of Interferon Gamma-induced Protein 10 (IP-10) Over Time

End point title	Mean Concentration of Interferon Gamma-induced Protein 10 (IP-10) Over Time

End point description:

A plasma sample for IP-10 testing was collected at study visits for all participants, until the end of the study or initiation of re-treatment for HCV (if applicable). IP-10 is used to assess liver fibrosis in participants with chronic liver disease. Values of 999 in the standard deviation fields in the table below indicate not calculable due to n=1 subject.

End point type	Secondary

End point timeframe:

From Day 1 up to 3 years post-treatment

End point values	HCV-infected Participants			
Subject group type	Reporting group			
Number of subjects analysed	374[8]			
Units: ng/L				
arithmetic mean (standard deviation)				
Day 1 (n=374)	146.884 (± 116.6272)			
Month 3 (n=363)	147.606 (± 118.5143)			
Month 6 (n=336)	148.959 (± 119.0047)			
Month 12 (n=1)	224.400 (± 999)			
Month 18 (n=7)	133.300 (± 50.2647)			
Month 24 (n=234)	140.185 (± 97.2769)			
Month 30 (n=88)	164.244 (± 276.9176)			
Month 36 (n=1)	120.600 (± 999)			

Notes:

[8] - Subjects rcvd ABT-493 +/- ABT-530 in prior Phase 2/3 study and weren't retreated before this study

Statistical analyses

No statistical analyses for this end point

Secondary: Mean FibroTest Score Over Time

End point title	Mean FibroTest Score Over Time

End point description:

A serum sample for FibroTest evaluation was collected at study visits for all participants, until the end of the study or initiation of re treatment for HCV (if applicable). FibroTest uses six biomarkers to generate a score that correlates to the degree of liver damage in participants. Scores range from 0 to 1, with higher scores indicating more severe liver fibrosis. The value of 999 in the standard deviation field in the table below indicates not calculable due to n=1 subject.

End point type	Secondary

End point timeframe:

From Day 1 up to 3 years post-treatment

End point values	HCV-infected Participants			
Subject group type	Reporting group			
Number of subjects analysed	367[9]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 1 (n=367)	0.354 (± 0.2341)			
Month 3 (n=347)	0.363 (± 0.2383)			
Month 6 (n=333)	0.353 (± 0.2311)			
Month 12 (n=2)	0.405 (± 0.0919)			
Month 18 (n=5)	0.272 (± 0.1281)			
Month 24 (n=227)	0.321 (± 0.2156)			
Month 30 (n=68)	0.261 (± 0.1667)			
Month 36 (n=1)	0.190 (± 999)			

Notes:

[9] - Subjects rcvd ABT-493 +/- ABT-530 in prior Phase 2/3 study and weren't retreated before this study

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Aspartate Transaminase to Platelet Ratio Index (APRI) Over Time

End point title	Mean Aspartate Transaminase to Platelet Ratio Index (APRI) Over Time

End point description:

A serum sample for aspartate transaminase evaluation and platelets were collected at study visits for all participants, until the end of the study or initiation of re-treatment for HCV (if applicable). The aspartate transaminase to platelet ratio index (APRI) is used to assess liver fibrosis in participants with chronic liver disease. Scores range from 0 to ≥ 2.0, with scores < 0.5 predictive of no liver fibrosis; scores >1.5 significant fibrosis; and scores > 2.0 indicative of cirrhosis. The value of 999 in the standard deviation field in the table below indicates not calculable due to n=1 subject.

End point type	Secondary

End point timeframe:

From Day 1 up to 3 years post-treatment

End point values	HCV-infected Participants			
Subject group type	Reporting group			
Number of subjects analysed	367[10]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 1 (n=367)	0.317 (± 0.2268)			
Month 3 (n=352)	0.303 (± 0.2171)			
Month 6 (n=333)	0.298 (± 0.2101)			
Month 12 (n=1)	0.230 (± 999)			
Month 18 (n=5)	0.262 (± 0.0589)			
Month 24 (n=232)	0.275 (± 0.1620)			
Month 30 (n=69)	0.227 (± 0.1084)			
Month 36 (n=2)	0.215 (± 0.1768)			

Notes:

[10] - Subjects rcvd ABT-493 +/- ABT-530 in prior Phase 2/3 study and weren't retreated before this study

Statistical analyses

No statistical analyses for this end point

Secondary: Mean FibroScan scores over time

End point title	Mean FibroScan scores over time

End point description:

The FibroScan test is used to assess liver fibrosis in participants with chronic liver disease. This was not performed as a study procedure, but any available results from source documents were summarized. For participants with Hepatitis C infection, a Fibroscan score of 2-7 kPa indicates no liver scarring or mild scarring; a score of 8 or 9 is associated with moderate liver scarring ; 9-14 indicates severe liver scarring; and 14 or higher is indicative of advanced liver scarring, cirrhosis. The value of 999 in the standard deviation field in the table below indicates not calculable due to n=1 subject.

End point type	Secondary

End point timeframe:

Up to 3 years post-treatment

End point values	HCV-infected Participants			
Subject group type	Reporting group			
Number of subjects analysed	23[11]			
Units: kPa				
arithmetic mean (standard deviation)				
Day 1 (n=7)	13.014 (± 12.6850)			
Month 3 (n=5)	6.880 (± 4.6677)			
Month 6 (n=10)	10.780 (± 5.9260)			
Month 12 (n=10)	7.700 (± 4.2208)			
Month 18 (n=8)	6.913 (± 2.8002)			
Month 24 (n=23)	6.757 (± 3.1564)			
Month 30 (n=1)	9.400 (± 999)			

Notes:

[11] - Subjects rcvd ABT-493 +/- ABT-530 in prior Phase 2/3 study and weren't retreated before this study

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

SAEs reasonably related to interventional study procedures or to ABT-530 and/or ABT-493 Tx in the prior study were collected from Day 1 through the last study procedure or discontinuation from study, whichever was later, up to 3 years post-treatment.

Adverse event reporting additional description:

An adverse event is any untoward medical occurrence as a result of a study procedure or considered by the investigator to be reasonably related to exposure to ABT-493 and/or ABT-530 in the prior study. Deaths were collected as a medical event from consent until study end. SAEs outside of the study time frame and nonserious AEs were not collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	HCV-infected Participants-- FAS

Reporting group description:

Full Analysis Set (FAS): all participants who received ABT-493 and/or ABT-530 in a prior Phase 2 /3 study and were not retreated prior to enrolling in this study. Three participants who received retreatment prior to enrollment in this study and four participants who did not receive ABT-493 and/or ABT-530 in a prior study were excluded from the FAS.

Serious adverse events	HCV-infected Participants-- FAS		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 377 (0.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	HCV-infected Participants-- FAS		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 377 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Nonserious adverse events were not collected for this study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2015	Amendment 1 • Included the reporting of any SAEs considered by the investigator to be reasonably related to exposure to ABT-530 and/or ABT-493 in the prior study because it was possible that a subject enrolled in this study may have experienced a SAE that the investigator believed to be reasonably related to their exposure to ABT-530 and/or ABT-493 in the prior study • Included the requirement to record, in the CRF, the concomitant medications used to treat SAEs considered to be related to the subject's exposure to ABT-530 and/or ABT-493 in the previous study • Clarified the use of the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 and provided a revised LLOQ of 15 IU/mL for all HCV genotypes using this assay • Added Protocol M15-410 to Appendix C • Added the Child-Pugh classification definitions to Appendix D
19 July 2016	Amendment 2 • Changed Phase from 2 to 2/3 to reflect addition of subjects from Phase 3 studies • Revised Secondary Objectives to include all laboratory tests/scores: those required by study to be presented in final analysis • Changed anticipated no. of subjects/sites to reflect potential enrollment from Phase 3 studies • Clarified that all subjects failing Tx in prior study would be offered this study if they had not/would not be receiving immediate Tx in AbbVie Study M15-942 • Added Exclusion Criterion 3 (Subjects experiencing non-virologic treatment failure due to premature discontinuation of study drug in prior study of ABT-493/ABT-530 may not participate), to exclude any non-virologic treatment failure who did not complete study drug • Added Exclusion Criterion 4 (Subjects enrolling in Study M15-942 for retreatment are not eligible for Study M13-576), to specify that subjects who were re-treated in Study M15-942 could not enroll because they could not be in both studies • Appendix D: expanded list of Phase 3 studies from which subjects could be enrolled • Revised to allow for re-treatment with commercially available HCV medications any time after treatment with study drugs in prior AbbVie HCV Phase 2/3 studies (prior to/during participation in Study M13-576). Subjects who were re-treated were to be followed to SVR12, to assess posttreatment Wk 12 (SVR12) outcomes of HCV re-treatment among subjects who experienced a virology failure in a prior study • Added requirement for a posttreatment Wk 12 (SVR12) visit for all re-treated VFs, since SVR12 assessment is generally accepted standard for SVR • Added requirement for Child-Pugh Score and Classification for all cirrhotic subjects at Day 1 and every 6 mos • Removed archived serum sample requirement • Updated sequencing method for resistance analysis to more sensitive deep sequencing

09 October 2017	Amendment 3 • Removed collection of alpha fetoprotein, as it is an unreliable test for screening for liver disease including HCC and was no longer recommended in the AASLD HCV guidelines current at the time • Clarified Inclusion Criterion 3 by adding a sentence to note that subjects who had been re-treated with a commercially available anti-HCV treatment were able to enroll in the study greater than 2 years after the last dose of the AbbVie DAA therapy from the previous AbbVie clinical study. The 2-year timeframe did not apply to subjects who had been re-treated, for whom blood samples were not to be collected to evaluate the persistence of resistance substitutions • Screening for HCC by liver ultrasound was added to the final study visit for cirrhotic subjects, in order to screen them for development of HCC as part of long-term follow-up

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported