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

Summary

EudraCT number	2012-003073-26
Trial protocol	GB IE DE ES HU AT BE DK PT PL CZ IT
Global end of trial date	20 October 2016

Results information

Result version number	v1 (current)
This version publication date	21 October 2017
First version publication date	21 October 2017

Trial information

Trial identification

Sponsor protocol code	M13-102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01773070
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	Rebecca Craft, AbbVie, rebecca.craft@abbvie.com
Scientific contact	Mariem Charafeddine MD, 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	20 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study are as follows:
●Assess the persistence of specific HCV amino acid variants associated with drug resistance in subjects who experience virologic failure.
●Assess the durability of response for subjects who achieved SVR12 with a regimen including an AbbVie DAA.

Protection of trial subjects:

Participant and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 June 2013
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	Spain: 56
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	United States: 328
Worldwide total number of subjects	478
EEA total number of subjects	117

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)	434
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who received ABT-450, ABT-333 or ABT-267 at any dose level in an eligible prior AbbVie Phase 2 or 3 study for the treatment of chronic HCV and met other inclusion/exclusion criteria had the option to enroll in this follow-up study.

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	All Subjects

Arm description:

Subjects who received ABT-450, ABT-333 or ABT-267 at any dose level in an eligible prior AbbVie Phase 2 or 3 study for the treatment of chronic HCV, followed for up to 3 years post-treatment.

Arm type	non-interventional
Investigational medicinal product name	ABT-450/ritonavir
Investigational medicinal product code	
Other name	ABT-450 also known as paritaprevir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450 coformulated with ritonavir. Drug is not administered -- this study is follow-up for subjects previously receiving the drug.

Investigational medicinal product name	ABT-333
Investigational medicinal product code	
Other name	dasabuvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Drug is not administered -- this study is follow-up for subjects previously receiving the drug.

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

Dosage and administration details:

Drug is not administered -- this study is follow-up for subjects previously receiving the drug.

Number of subjects in period 1	All Subjects
Started	478
Completed	397
Not completed	81
Consent withdrawn by subject	24
Death	3
Not specified	15
Lost to follow-up	39

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	478	478	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 53 ± 9.85	 -	
Gender categorical Units: Subjects			
Female	227	227	
Male	251	251	

End points

End points reporting groups

Reporting group title	All Subjects

Reporting group description:

Subjects who received ABT-450, ABT-333 or ABT-267 at any dose level in an eligible prior AbbVie Phase 2 or 3 study for the treatment of chronic HCV, followed for up to 3 years post-treatment.

Subject analysis set title	NS3, NS5A, NS5B Resistance Analyses: GT1a-Infected Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

GT1a-infected participants who experienced virologic failure after receiving ABT-450, ABT-333 or ABT-267, and had not achieved SVR12 and had postbaseline sequencing data for NS3, NS5A, or NS5B at given time point.

Primary: Percentage of Subjects Who Experienced Relapse12overall With and Without New HCV Infection

End point title	Percentage of Subjects Who Experienced Relapse12overall With and Without New HCV Infection[1]

End point description:

Relapse is defined as a confirmed HCV RNA ≥ LLOQ at any time during the post-treatment period for a subject who had HCV RNA < LLOQ at the end of treatment. Relapse12overall is defined as a confirmed HCV RNA ≥ LLOQ at any time after the SVR12 assessment time point for a subject who achieved SVR12 and had post-SVR12 HCV RNA data available. SVR12 is defined as HCV RNA < LLOQ in the SVR12 window (12 weeks after the last actual dose of study drug) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window. New HCV infection is defined as re-infection with a different HCV isolate.

Subjects who did not have any post-treatment HCV RNA values were excluded from the relapse analyses.

End point type	Primary

End point timeframe:

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: Descriptive statistics are presented, per protocol.

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	457			
Units: percentage of subjects				
number (not applicable)				
Relapse12overall With New HCV Infection	0.2			
Relapse12overall Without New HCV Infection	0.2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of HCV Genotype (GT)1a-Infected Subjects With Persistence of

Treatment-Emergent Substitutions in NS3, NS5A, or NS5B

End point title	Number of HCV Genotype (GT)1a-Infected Subjects With Persistence of Treatment-Emergent Substitutions in NS3, NS5A, or NS5B[2]

End point description:

The persistence of specific hepatitis C amino acid variants (treatment-emergent substitutions) associated with drug resistance in NS3, NS5A, or NS5B was evaluated in subjects who had not achieved SVR12. Post-baseline time points were calculated relative to the last dose of study drug in the previous study.

End point type	Primary

End point timeframe:

from the last dose of study drug in the previous study up to 3 years post-treatment

Notes:

[2] - 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 statistics are presented, per protocol.

End point values	NS3, NS5A, NS5B Resistance Analyses: GT1a-Infected Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	18[3]			
Units: subjects				
number (not applicable)				
NS3: time of failure; n=18	7			
NS3: post-treatment week 48; n=7	0			
NS5A: time of failure; n=18	13			
NS5A: post-treatment week 48; n=10	10			
NS5A: post-treatment week 96; n=8	6			
NS5A: post-treatment week 132; n=8	4			
NS5B: time of failure; n=15	7			
NS5B: post-treatment week 24; n=4	3			
NS5B: post-treatment week 96; n=5	1			

Notes:

[3] - n=number of subjects with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Experienced Relapse12 Without and With New HCV Infection

End point title	Percentage of Subjects Who Experienced Relapse12 Without and With New HCV Infection

End point description:

Relapse is defined as a confirmed HCV RNA ≥ LLOQ at any time during the post-treatment period for a subject who had HCV RNA < LLOQ at the end of treatment. Relapse12 is defined as a confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR12 assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment.

Subjects who did not have any post-treatment HCV RNA values were excluded from the relapse analyses.

End point type	Secondary

End point timeframe:

From the end of treatment through 12 weeks post-treatment

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	458[4]			
Units: percentage of participants				
number (not applicable)				
Relapse12 Without New HCV Infection	2			
Relapse12 With New HCV Infection	0			

Notes:

[4] - Subjects with HCV RNA < LLOQ at Final Treatment Visit who completed treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Experienced Relapse24 Without and With New HCV Infection

End point title	Percentage of Subjects Who Experienced Relapse24 Without and With New HCV Infection

End point description:

Relapse is defined as a confirmed HCV RNA ≥ LLOQ at any time during the post-treatment period for a subject who had HCV RNA < LLOQ at the end of treatment. Relapse24 is defined as a confirmed HCV RNA ≥ LLOQ within the sustained virologic response at Week 24 post-dosing (SVR24) window for a subject who achieved SVR12 and had HCV RNA data available in the SVR24 window.

Subjects who did not have any post-treatment HCV RNA values were excluded from the relapse analyses.

End point type	Secondary

End point timeframe:

From the end of treatment through 24 weeks post-treatment

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	403[5]			
Units: percentage of subjects				
number (not applicable)				
Relapse24 Without New HCV Infection	0.2			
Relapse24 With New HCV Infection	0			

Notes:

[5] - Subjects who achieved SVR12 and had HCV RNA data available in the SVR24 window.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Experienced Relapseoverall Without and With New HCV Infection

End point title	Percentage of Subjects Who Experienced Relapseoverall Without and With New HCV Infection

End point description:

Relapse is defined as a confirmed HCV RNA ≥ LLOQ at any time during the post-treatment period for a subject who had HCV RNA < LLOQ at the end of treatment. Relapseoverall was defined as a confirmed HCV RNA ≥ LLOQ between end of treatment and up to and including the last HCV RNA measurement collected in the Post-Treatment Period for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment.

Subjects who did not have any post-treatment HCV RNA values were excluded from the relapse analyses.

End point type	Secondary

End point timeframe:

Up to 3 years post-treatment

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	458[6]			
Units: percentage of subjects				
number (not applicable)				
Relapseoverall Without New HCV Infection	2.2			
Relapseoverall With New HCV Infection	0.2			

Notes:

[6] - Subjects with HCV RNA < LLOQ at Final Treatment Visit who completed treatment.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From last dose of direct-acting antiviral agent treatment in the previous study to last HCV RNA assessment in M13-102 (mean [SD] duration: 146.3 [28.16] weeks).

Adverse event reporting additional description:

Per protocol, only serious adverse events that the investigator considered to be causally related to study procedures (i.e., venipunctures) were collected in this study. Non-serious adverse events were not collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	All subjects

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 478 (0.00%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 478 (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: Non-serious adverse events were not collected in this study, per protocol.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2013	• Clarify the collection of events related to HCV or liver disease. • Add that some study visits and visit activities (including but not limited to vital signs, clinical laboratory tests, and concomitant medication assessment) could be conducted in the home or in a non-hospital/clinic environment at the request of the Investigator and with the agreement of the subject. • Incorporate Administrative Changes
22 November 2013	• Update the list of abbreviations and definition of terms. • Increase the anticipated number of subjects from ~500 to ~2000 and the anticipated number of sites from ~125 to ~350 to reflect potential enrollment from all eligible prior sites. • Add that it was preferable that subjects complete the full Post-treatment Period of the prior study before enrolling in Study M13-102. • Remove vital signs from the list of study activities that could be conducted in the home or non-hospital/clinic environment because vital signs were not assessed in this study. • Clarify that only prior studies being submitted as a US IND were eligible and provide a list of eligible prior studies. • Delete the inclusion criterion that subjects were required to commit to up to 3 years of participation in the study. • Prohibit the use of any investigational medication while participating in the Study M13-102. • Clarify that the study visit that fell closest to 3 years since the subject's last dose of an AbbVie DAA was considered the final visit. • Add that study visits were ideally to take place within 3 weeks of the planned visit date, and visits that occurred more than a specified number of weeks later than planned were to be considered as the next visit in the schedule. • Clarify that only mortality events related to liver disease (not all deaths) were to be collected. • Clarify the central laboratory location to where samples were to be shipped and analyzed/stored. • Add the LLOD levels for HCV genotypes 2, 3, and 4. • Change providing archive plasma and serum samples from mandatory to preferable. • Clarify that only SAEs that the investigator considered causally related to a study procedure would be collected.
22 November 2013	(continued) • Add that pregnancies in subjects who entered Study M13-102 within 7 months of the last dose of study drug in a prior study were to be reported for the prior study (not Study M13-102) according to the requirements of the prior study. • Update contact names and contact information throughout the protocol. • Clarify and provide additional details regarding the resistance analyses.

28 April 2014	• Decrease the number of anticipated subjects from ~2000 to ~500. • Add that subjects were required to have completed the Post-treatment Period of the prior study before enrolling in Study M13-102. • Clarify that visits that were allowed to occur outside of the primary clinic would be arranged by the Investigator and had to be pre-approved by the sponsor. • Remove measurement of IP-10 and clinical chemistry testing at Months 12 and 18. • Update the description of the resistance analyses. • Update how the sample size was determined. • Update the contact information for adverse event reporting. • Update contact names and contact information throughout the protocol. • Update the basis for the number of subjects enrolled in the study. • Update reference list to include more recent Investigator Brochures. • Update the list of eligible prior studies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported