Clinical trial results:
A Single Arm, Open-label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis

Summary

EudraCT number	2016-004967-38
Trial protocol	GR PL PT HU CZ BG IE ES GB RO
Global end of trial date	08 November 2019

Results information

Result version number	v1 (current)
This version publication date	30 July 2020
First version publication date	30 July 2020

Trial information

Trial identification

Sponsor protocol code	M16-135

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03089944
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	08 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A Phase 3b, single arm, open-label, multicenter study in treatment naïve adults with chronic HCV infection and compensated cirrhosis to assess the safety of 8 weeks of treatment with glecaprevir/pibrentasvir and to demonstrate the efficacy of the sustained virologic response 12 weeks post dosing (SVR12) rates of 8 weeks of treatment with glecaprevir/pibrentasvir compared to the historical SVR12 rates of 12 weeks of treatment with glecaprevir/pibrentasvir.

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	28 April 2017
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: 12
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Bulgaria: 20
Country: Number of subjects enrolled	Czech Republic: 17
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Puerto Rico: 20
Country: Number of subjects enrolled	Romania: 21
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	United States: 89
Country: Number of subjects enrolled	Vietnam: 9

Worldwide total number of subjects	343
EEA total number of subjects	156

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)	257
From 65 to 84 years	85
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The intent to treat (ITT) population included 343 subjects that enrolled and received ≥ 1 dose of study drug. The Per Protocol (PP) Population, a subset of ITT, excluded subjects who experienced breakthrough, or discontinued treatment prior to Week 8, or had no HCV RNA value in SVR12 visit window or later for reasons other than virologic failure.

Period 1

Period 1 title	GLE/PIB for 8 weeks (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks

Arm description:

Glecaprevir (GLE)/Pibrentasvir (PIB) 300 mg/120 mg administered orally once daily (QD) for 8 weeks.

Arm type	Experimental
Investigational medicinal product name	Glecaprevir/Pibrentasvir tablet
Investigational medicinal product code	
Other name	ABT-493, ABT-530
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received glecaprevir (GLE)/pibrentasvir(PIB) 300 mg/120 mg orally (with food) once daily for 8 weeks.

Number of subjects in period 1	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks
Started	343
Completed	331
Not completed	12
Adverse event, non-fatal	1
Other, not specified	1
Lost to follow-up	8
Withdrew consent	2

Baseline characteristics

Reporting groups	
Reporting group title	GLE/PIB for 8 weeks

Reporting group description: -

Reporting group values	GLE/PIB for 8 weeks	Total	
Number of subjects	343	343	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57.61		
standard deviation	± 10.58	-	
Gender categorical Units: Subjects			
Female	126	126	
Male	217	217	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	43	43	
Not Hispanic or Latino	300	300	

End points

End points reporting groups

Reporting group title	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks

Reporting group description:

Glecaprevir (GLE)/Pibrentasvir (PIB) 300 mg/120 mg administered orally once daily (QD) for 8 weeks.

Primary: Percentage of Participants With Sustained Virologic Response 12 Weeks Post-treatment (SVR12) in Hepatitis C Virus (HCV) Genotype (GT) 1,2,4,5 and 6-infected Participants in the Per Protocol (PP) Population

End point title	Percentage of Participants With Sustained Virologic Response 12 Weeks Post-treatment (SVR12) in Hepatitis C Virus (HCV) Genotype (GT) 1,2,4,5 and 6-infected Participants in the Per Protocol (PP) Population[1]

End point description:

SVR12 was defined as plasma hepatitis C virus ribonucleic acid (HCV RNA) level less than the lower limit of quantification (<LLOQ; less than 15 IU/mL) 12 weeks after the last dose of study drug. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration was demonstrated if the lower bound of the 2-sided 95% confidence interval (CI) for the percentage of participants with HCV GT1, GT2, GT4, GT5, or GT6 infection in the 8 week treatment duration achieving SVR12 was greater than 94% in the PP population. Efficacy analyses were performed following a fixed-sequence testing procedure to control the type I error rate. The percentage of participants achieving SVR12 was summarized with a 2-sided 95% CI, calculated using the normal approximation to the binomial distribution. If the number of participants who failed to achieve SVR12 rate was less than 5, the Wilson's score method was used to calculate the CI.

End point type	Primary

End point timeframe:

12 weeks after last dose of 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 statistical analysis are presented in the Endpoint Data Table, per protocol.

End point values	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks			
Subject group type	Reporting group			
Number of subjects analysed	274[2]			
Units: percentage of participants				
number (confidence interval 95%)				
Percentage with SVR12 (PP)	100 (98.6 to 100.0)			

Notes:

[2] - Per Protocol (PP) Population

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With SVR12 in HCV GT 1,2,4,5 and 6-infected Participants in the Intent-To-Treat (ITT) Population

End point title	Percentage of Participants With SVR12 in HCV GT 1,2,4,5 and 6-infected Participants in the Intent-To-Treat (ITT) Population[3]

End point description:

SVR12 was defined as HCV RNA level less than the LLOQ (less than 15 IU/mL) 12 weeks after the last dose of study drug. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration was demonstrated if the lower bound of the 2-sided 95% CI for the percentage of participants with HCV GT1, GT2, GT4, GT5, or GT6 infection in the 8 week treatment duration achieving SVR12 was greater than 93% in the ITT population. Primary efficacy analyses were performed following a fixed-sequence testing procedure to control the type I error rate. The percentage of participants achieving SVR12 was summarized with a 2-sided 95% CI, calculated using the normal approximation to the binomial distribution. If the number of participants who failed to achieve SVR12 rate was less than 5, the Wilson's score method was used to calculate the CI.

End point type	Primary

End point timeframe:

12 weeks after last dose of study drug

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: The statistical analysis are presented in the Endpoint Data Table, per protocol.

End point values	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks			
Subject group type	Reporting group			
Number of subjects analysed	280[4]			
Units: percentage of participants				
number (confidence interval 95%)				
Percentage with SVR12 (ITT)	98.2 (96.7 to 99.8)			

Notes:

[4] - Intent to treat (ITT) population: Participants who received at least one dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With SVR12 in HCV GT1-6-infected Participants in the PP Population

End point title	Percentage of Participants With SVR12 in HCV GT1-6-infected Participants in the PP Population

End point description:

SVR12 was defined as HCV RNA level less than the LLOQ (less than 15 IU/mL) 12 weeks after the last dose of study drug. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration was demonstrated if the lower bound of the 2-sided 95% CI for the percentage of participants with HCV GT1, GT2, GT3, GT4, GT5, or GT6 infection in the 8 week treatment duration achieving SVR12 was greater than 94% in the PP population. These efficacy analyses were performed only if success was demonstrated for both primary efficacy analyses, following a fixed-sequence testing procedure.

End point type	Secondary

End point timeframe:

12 weeks after last dose of study drug

End point values	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks			
Subject group type	Reporting group			
Number of subjects analysed	335[5]			
Units: percentage of participants				
number (confidence interval 95%)				
With SVR12 in HCV GT1-6-infected PP Population	99.7 (98.3 to 99.9)			

Notes:

[5] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With SVR12 in HCV GT1-6-infected Participants in the ITT Population

End point title	Percentage of Participants With SVR12 in HCV GT1-6-infected Participants in the ITT Population

End point description:

SVR12 was defined as HCV RNA level less than the LLOQ (less than 15 IU/mL) 12 weeks after the last dose of study drug. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration was demonstrated if the lower bound of the 2-sided 95% CI for the percentage of participants with HCV GT1, GT2, GT3, GT4, GT5, or GT6 infection in the 8 week treatment duration achieving SVR12 was greater than 93% in the ITT population. These efficacy analyses were performed only if success was demonstrated for both primary efficacy analyses, following a fixed-sequence testing procedure.

End point type	Secondary

End point timeframe:

12 weeks after the last dose of study drug

End point values	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks			
Subject group type	Reporting group			
Number of subjects analysed	343[6]			
Units: Percentage of participants				
number (confidence interval 95%)				
With SVR12 in HCV GT-1-6-infected in ITT	97.7 (96.1 to 99.3)			

Notes:

[6] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With On-treatment Virologic Failure in the

ITT Population

End point title	Percentage of Participants With On-treatment Virologic Failure in the ITT Population

End point description:

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

End point type	Secondary

End point timeframe:

8 weeks on treatment

End point values	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks			
Subject group type	Reporting group			
Number of subjects analysed	343[7]			
Units: Percentage of participants				
number (confidence interval 95%)				
With On-treatment Virologic Failure in ITT	0 (0.0 to 1.1)			

Notes:

[7] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Post-treatment Relapse

End point title	Percentage of Participants With Post-treatment Relapse

End point description:

Post-treatment relapse was defined as confirmed HCV RNA ≥ LLOQ between the end of treatment and 12 weeks after the last dose of study drug among participants who completed treatment as planned (defined as study drug duration ≥ 52 days for participants assigned to 8 weeks of treatment) and with HCV RNA levels < LLOQ at the end of treatment excluding participants who had been reinfected.

End point type	Secondary

End point timeframe:

Up to 12 weeks after the last dose of study drug

End point values	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks			
Subject group type	Reporting group			
Number of subjects analysed	336[8]			
Units: Percentage of Participants				
number (confidence interval 95%)				

Participants with Post treatment Relapse	0.3 (0.1 to 1.7)			

Notes:

[8] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of HCV GT3-infected Participants Who Achieved SVR12 in the PP Population

End point title	Percentage of HCV GT3-infected Participants Who Achieved SVR12 in the PP Population

End point description:

SVR12 was defined as HCV RNA level less than the LLOQ (less than 15 IU/mL) 12 weeks after the last dose of study drug.

End point type	Secondary

End point timeframe:

12 weeks after the last dose of study drug

End point values	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks			
Subject group type	Reporting group			
Number of subjects analysed	61[9]			
Units: Percentage of participants				
number (confidence interval 95%)				
HCV GT3-infected Who Achieved SVR12 in PP	98.4 (91.3 to 99.7)			

Notes:

[9] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of HCV GT3-infected Participants Who Achieved SVR12 in the ITT Population

End point title	Percentage of HCV GT3-infected Participants Who Achieved SVR12 in the ITT Population

End point description:

SVR12 was defined as HCV RNA level less than the LLOQ (less than 15 IU/mL) 12 weeks after the last dose of study drug.

End point type	Secondary

End point timeframe:

12 weeks after the last dose of study drug

End point values	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks			
Subject group type	Reporting group			
Number of subjects analysed	63[10]			
Units: Percentage of Participants				
number (confidence interval 95%)				
HCV GT3-infected Who Achieved SVR12 in ITT	95.2 (86.9 to 98.4)			

Notes:

[10] - ITT population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) were defined as any adverse event with an onset date that was on or after the first dose of study drug and no more than 30 days after the last dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks

Reporting group description:

Glecaprevir (GLE)/Pibrentasvir (PIB) 300 mg/120 mg administered orally once daily (QD) for 8 weeks.

Serious adverse events	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 343 (1.75%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 343 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 343 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 343 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oedema peripheral			

subjects affected / exposed	1 / 343 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 343 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 343 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 343 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 343 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Glecaprevir (GLE)/Pibrentasvir (PIB) for 8 weeks		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 343 (23.91%)		
Nervous system disorders			
Headache			
subjects affected / exposed	28 / 343 (8.16%)		
occurrences (all)	31		
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed occurrences (all)	30 / 343 (8.75%) 31		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 19 / 343 (5.54%) 19		
Skin and subcutaneous tissue disorders Pruritis subjects affected / exposed occurrences (all)	 29 / 343 (8.45%) 31		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2017	This amendment clarified the protocol deviation process, specified that participants experiencing virologic failure will be offered retreatment and excluded participants with a medical history of solid organ transplantation.
06 September 2017	This amendment included an update to Primary Efficacy Endpoints, based on regulatory authority feedback, the analysis of SVR12 based on the ITT population has been elevated from a secondary to a primary efficacy endpoint , references to non-inferiority have been removed, and the Wilson score method will be used to calculate the confidence intervals for the primary efficacy endpoints if the number of SVR12 non-responders is less than 5, clarification of pregnancy test requirements during the study,include additional language on empiric use of lactulose and rifaximin and to clarify the list of approved and investigational anti-HCV compounds and that historical presence of HCC within the previous 5 years is exclusionary,clarify that specific statins must be discontinued at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug, clarify when study procedures to be performed, and clarify that the Physical Exam and labs are to be drawn for FibroTest and Child-Pugh scores.
11 June 2018	Allow for the enrollment of participants infected with HCV Genotype 3 to evaluate the efficacy and safety of an 8-week treatment regimen in a treatment-naïve cirrhotic patient population inclusive of patients with HCV GT3 infection. Update prohibited therapy based on the marketing approval of GLE/PIB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported