Clinical trial results:
A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir/Pibrentasvir in Renally-Impaired Adults with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (EXPEDITION-5)

Summary

EudraCT number	2016-004182-60
Trial protocol	SE ES DE PL GR
Global end of trial date	05 June 2018

Results information

Result version number	v1 (current)
This version publication date	22 February 2019
First version publication date	22 February 2019

Trial information

Trial identification

Sponsor protocol code	M16-127

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03069365
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	05 June 2018
Is this the analysis of the primary	No

completion data?	
Global end of trial reached?	Yes
Global end of trial date	05 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a Phase 3b, open-label, non-randomized, multicenter study to evaluate the efficacy and safety of glecaprevir/pibrentasvir (GLE/PIB) in participants with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without liver cirrhosis or with compensated liver cirrhosis and with chronic renal impairment in participants who were either HCV treatment-naïve (TN) or prior treatment-experienced (TE) with interferon (IFN) or pegylated interferon (PegIFN) with or without ribavirin (RBV), or sofosbuvir (SOF) plus RBV with or without pegIFN. The study included a 42-day screening period, a treatment period of either 8, 12, or 16 weeks, and a 24-week post-treatment period. The duration of treatment was determined by product labeling.

Protection of trial subjects:

Prior to the initiation of any screening or study-specific procedures, the investigator or his or her representative explained the nature of the study to the subject or his or her representative and answered all questions regarding this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 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	Spain: 7
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Puerto Rico: 5
Worldwide total number of subjects	101
EEA total number of subjects	53

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)	71
From 65 to 84 years	29
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study enrollment was monitored to meet the following non-mutually exclusive enrollment criteria: (1) up to approximately 40 subjects with Stage 3b chronic kidney disease (CKD), (2) up to approximately 75 hepatitis C virus genotype 1 (HCV GT1)-infected subjects, (3) up to approximately 30 subjects with compensated cirrhosis.

Pre-assignment

Screening details:

Subjects were HCV treatment-naive (no prior dose of any approved or investigational regimen) or treatment-experienced HCV genotype 1 – 6-infected adult male and female subjects with or without compensated cirrhosis, who had CKD Stage 3b, 4, or 5. Subjects had up to 42 days after the Screening Visit to confirm eligibility and enroll into the study.

Period 1

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

Arms

Arm title	GLE/PIB for 8, 12, or 16 weeks

Arm description:

HCV genotype 1,2,4-6 non-cirrhotic, treatment-naive or treatment-experienced; genotype 3 non-cirrhotic, treatment-naïve participants treated with glecaprevir/pibrentasvir (GLE/PIB)- three 100 mg/40 mg co-formulated tablets once daily with food for 8 weeks;

HCV genotype 1,2,4-6 compensated cirrhosis, treatment-naive or treatment-experienced; genotype 3 compensated cirrhosis, treatment-naïve participants treated with glecaprevir/pibrentasvir (GLE/PIB)- three 100 mg/40 mg co-formulated tablets once daily with food for 12 weeks;

HCV genotype 3 non-cirrhotic or with compensated cirrhosis, treatment-experienced participants treated with glecaprevir/pibrentasvir (GLE/PIB)- three 100 mg/40 mg co-formulated tablets once daily with food for 16 weeks

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

Dosage and administration details:

Three 100 mg/40 mg co-formulated tablets once daily with food for 8, 12, or 16 weeks

Number of subjects in period 1	GLE/PIB for 8, 12, or 16 weeks
Started	101
Completed	100
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	GLE/PIB for 8, 12, or 16 weeks

Reporting group description:

HCV genotype 1,2,4-6 non-cirrhotic, treatment-naive or treatment-experienced; genotype 3 non-cirrhotic, treatment-naïve participants treated with glecaprevir/pibrentasvir (GLE/PIB)- three 100 mg/40 mg co-formulated tablets once daily with food for 8 weeks;

HCV genotype 1,2,4-6 compensated cirrhosis, treatment-naive or treatment-experienced; genotype 3 compensated cirrhosis, treatment-naïve participants treated with glecaprevir/pibrentasvir (GLE/PIB)- three 100 mg/40 mg co-formulated tablets once daily with food for 12 weeks;

HCV genotype 3 non-cirrhotic or with compensated cirrhosis, treatment-experienced participants treated with glecaprevir/pibrentasvir (GLE/PIB)- three 100 mg/40 mg co-formulated tablets once daily with food for 16 weeks

Reporting group values	GLE/PIB for 8, 12, or 16 weeks	Total	
Number of subjects	101	101	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Intent to treat population: all participants who received at least 1 dose of study drug			
Units: years			
arithmetic mean	59.03		
standard deviation	± 11.00	-	
Gender categorical			
Intent to treat population: all participants who received at least 1 dose of study drug			
Units: Subjects			
Female	41	41	
Male	60	60	

End points

End points reporting groups

Reporting group title	GLE/PIB for 8, 12, or 16 weeks

Reporting group description:

HCV genotype 1,2,4-6 non-cirrhotic, treatment-naive or treatment-experienced; genotype 3 non-cirrhotic, treatment-naïve participants treated with glecaprevir/pibrentasvir (GLE/PIB)- three 100 mg/40 mg co-formulated tablets once daily with food for 8 weeks;

HCV genotype 1,2,4-6 compensated cirrhosis, treatment-naive or treatment-experienced; genotype 3 compensated cirrhosis, treatment-naïve participants treated with glecaprevir/pibrentasvir (GLE/PIB)- three 100 mg/40 mg co-formulated tablets once daily with food for 12 weeks;

HCV genotype 3 non-cirrhotic or with compensated cirrhosis, treatment-experienced participants treated with glecaprevir/pibrentasvir (GLE/PIB)- three 100 mg/40 mg co-formulated tablets once daily with food for 16 weeks

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

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

End point description:

SVR12 was defined as hepatitis C virus ribonucleic acid (HCV RNA) level less than the lower limit of quantification (LLOQ) 12 weeks after the last actual dose of study drug. Participants with missing data after backwards imputation were counted as non-responders.

End point type	Primary

End point timeframe:

12 weeks after the last actual 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: Statistical analyses were not performed for this endpoint.

End point values	GLE/PIB for 8, 12, or 16 weeks			
Subject group type	Reporting group			
Number of subjects analysed	101[2]			
Units: Percentage of participants				
number (confidence interval 95%)	97.0 (91.6 to 99.0)			

Notes:

[2] - Intent to treat population: all participants who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With On-treatment Virologic Failure

End point title	Percentage of Participants With On-treatment Virologic Failure

End point description:

On-treatment virologic failure was defined as:
• Confirmed increase from nadir in hepatitis C virus ribonucleic acid (HCV RNA) defined as confirmed increase of >
1 log (subscript)10(subscript) IU/mL above nadir during treatment; or
• Confirmed HCV RNA greater than or equal to 100 IU/mL after HCV RNA less than the lower limit of quantification (LLOQ) during study drug treatment; or
• HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment

End point type	Secondary

End point timeframe:

Up to 16 weeks

End point values	GLE/PIB for 8, 12, or 16 weeks			
Subject group type	Reporting group			
Number of subjects analysed	101[3]			
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.0 to 3.7)			

Notes:

[3] - Intent to treat population: all participants who received at least 1 dose of study drug

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 hepatitis C virus ribonucleic acid (HCV RNA) ≥ the lower limit of quantification (LLOQ) between the end of treatment and 12 weeks after the last dose of study drug among participants who completed treatment as planned with HCV RNA < LLOQ at the end of treatment and had post-treatment HCV RNA data; participants who had been shown to be reinfected were not considered to have relapsed.

End point type	Secondary

End point timeframe:

Up to 12 weeks after the last dose of study drug

End point values	GLE/PIB for 8, 12, or 16 weeks			
Subject group type	Reporting group			
Number of subjects analysed	98[4]			
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.0 to 3.8)			

Notes:

[4] - Subjects rcvd ≥ 1 dose of drug, completed Tx, HCV RNA < LLOQ at last Tx, ≥ 1 post-Tx HCV RNA value

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 the time of study drug administration until 30 days after the last dose of study drug (up to 20 weeks).

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	GLE/PIB for 8, 12, or 16 Weeks

Reporting group description:

Glecaprevir/pibrentasvir (GLE/PIB): three 100 mg/40 mg co-formulated tablets once daily with food

Serious adverse events	GLE/PIB for 8, 12, or 16 Weeks		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 101 (11.88%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
EXTREMITY NECROSIS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PERIPHERAL ARTERY STENOSIS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VENOUS STENOSIS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

PLEURAL EFFUSION			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PULMONARY OEDEMA			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
MYELOPATHY			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PRESYNCOPE			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ILEUS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
NEPHROLITHIASIS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 101 (0.99%)		

occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HYPOKALAEMIA			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 101 (0.99%)		
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	GLE/PIB for 8, 12, or 16 Weeks		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 101 (26.73%)		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			

PRURITUS subjects affected / exposed occurrences (all)	16 / 101 (15.84%) 16		
PRURITUS GENERALISED subjects affected / exposed occurrences (all)	6 / 101 (5.94%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2017	Amendment 1 • Removed the lab test soluble erythropoietin receptor (sEpoR) • Clarified the timing and process around distributing the dosing card to subjects • Removed hepatitis B surface antigen (HbsAg) testing from Day 1 • Removed the word "separate" from the Subject Information and Consent section as the optional pharmacogenetic informed consent form (ICF) may have been included in the Main ICF • Corrected an administrative error to show that Study Drug would not be dispensed at Screening, but instead at Day 1, and that study drug accountability and review of study drug adherence would not occur at Screening; clarified that Hepatitis C testing would occur at Screening as well as Hepatitis B and HIV testing; removed HBsAg testing on Day 1.
27 July 2017	Amendment 2 • Updated the method for the calculation of the two-sided 95% CI for the primary efficacy endpoint to use the normal approximation to the binomial distribution, unless the number of SVR12 non-responders was less than 5, where the Wilson score method would be used • Clarified that all prohibited medications had to be discontinued 14 days or 10 half-lives prior to initiating GLE/PIB and could be resumed 14 days after last dose of study drug • Clarified that any historical presence of hepatocellular carcinoma (HCC) was exclusionary; also clarified that prior or current empiric use of lactulose/rifaximin for neurologic indications was exclusionary • Clarified the Screening procedures for HCC in the Screening period, treatment period, and post-treatment period • Clarified when protocol deviations were to be reported to regulatory authorities
30 January 2018	Amendment 3 • Clarified that serum samples for tumor necrosis factor-alpha (TNF-α) would not be collected and analyzed. Instead, the Archive Plasma samples collected throughout the study would be analyzed for TNF-α • Corrected analyses of the signature amino acid position of HCV GT3 • Clarified that Hematology/Chemistry/Coagulation would only be performed if the subject discontinued prior to post-treatment Week 4 unless the patient was cirrhotic, in which case labs were to be collected to test international normalized ratio (INR), total bilirubin, and albumin in the post-treatment period

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported