



## Clinical trial results:

### A Single Arm, Open Label, Multicenter Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults With Chronic Hepatitis C Virus (HCV) Genotypes 1 - 6 Infection and Aspartate Aminotransferase to Platelet Ratio Index (APRI) Less Than or Equal to 1

#### Summary

EudraCT number	2016-004876-23
Trial protocol	GB ES DE BG PL
Global end of trial date	13 August 2018

#### Results information

Result version number	v1 (current)
This version publication date	28 August 2019
First version publication date	28 August 2019

#### Trial information

##### Trial identification

Sponsor protocol code	M16-133
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03212521
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Abbvie Deutschland GmbH & Co.KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 011 0800-633-9110,
Scientific contact	Ana Pires dos Santos, AbbVie, ana.pires@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	13 August 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 August 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the efficacy (by achieving high sustained virologic response 12 weeks postdosing [SVR12] rate) and safety of 8 weeks of treatment with the glecaprevir/pibrentasvir combination regimen in treatment-naïve adults with hepatitis C virus (HCV) genotypes 1 – 6 infection with aminotransferase/platelet ratio index (APRI)  $\leq 1$ .

Protection of trial subjects:

All subjects entering the study had to sign an informed consent that was explained to them and questions encouraged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 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	Germany: 19
Country: Number of subjects enrolled	Bulgaria: 25
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Puerto Rico: 5
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	United States: 70
Worldwide total number of subjects	230
EEA total number of subjects	114

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)	207
From 65 to 84 years	23
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at 40 sites in Bulgaria, Canada, France, Germany, Poland, Russian Federation, Spain, United Kingdom, and the United States (including Puerto Rico).

### Pre-assignment

Screening details:

This study enrolled adults with any genotype hepatitis C virus infection who were treatment-naïve and had an aminotransferase/platelet ratio index (APRI)  $\leq 1$ .

### 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	Glecaprevir/Pibrentasvir
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Arm description:

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

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

Dosage and administration details:

Glecaprevir/pibrentasvir 100 mg/40 mg co-formulated tablets taken orally as 3 tablets once a day.

Number of subjects in period 1	Glecaprevir/Pibrentasvir
Started	230
Completed	223
Not completed	7
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Other	1
Lost to follow-up	4

## Baseline characteristics

### Reporting groups

Reporting group title	Glecaprevir/Pibrentasvir
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Reporting group description:

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

Reporting group values	Glecaprevir/Pibrentasvir	Total	
Number of subjects	230	230	
Age categorical			
Units: Subjects			
Adults (18-64 years)	207	207	
From 65-84 years	23	23	
Age continuous			
Units: years			
median	48		
full range (min-max)	19 to 82	-	
Gender categorical			
Units: Subjects			
Female	113	113	
Male	117	117	
Race			
Units: Subjects			
White	207	207	
Black or African American	13	13	
Asian	10	10	
Ethnicity			
Units: Subjects			
Hispanic or Latino	25	25	
Not Hispanic or Latino	205	205	
Hepatitis C Virus (HCV) Genotype			
Units: Subjects			
Genotype 1	151	151	
Genotype 2	33	33	
Genotype 3	35	35	
Genotype 4	9	9	
Genotype 5	0	0	
Genotype 6	2	2	
Aminotransferase/Platelet Ratio Index (APRI)			
<p>APRI is used to determine the likelihood of hepatic fibrosis and cirrhosis in patients with hepatitis C. APRI is calculated from the level of aspartate aminotransferase (AST) measured in a blood test (international units per liter [IU/L]) and platelet count (platelets/cubic millimeter) according to the following formula:</p> $APRI = [(AST/upper\ limit\ of\ the\ normal\ range\ (ULN)\ of\ AST) \times 100] / Platelet\ count$ <p>APRI scores of less than or equal to 1 have a good performance characteristic for excluding the presence of cirrhosis.</p>			
Units: ratio			
median	0.41		
full range (min-max)	0.13 to 1.00	-	

HCV Ribonucleic Acid (RNA) Concentration Units: Log IU/mL			
median	6.29		
full range (min-max)	2.22 to 7.74	-	

## End points

### End points reporting groups

Reporting group title	Glecaprevir/Pibrentasvir
Reporting group description:	
Participants received oral glecaprevir/pibrentasvir (300 mg/120 mg) once daily with food for 8 weeks.	

### Primary: Percentage of Participants in the Modified Intention-to-Treat Population With Sustained Virologic Response 12 Weeks Post-treatment (SVR12)

End point title	Percentage of Participants in the Modified Intention-to-Treat Population With Sustained Virologic Response 12 Weeks Post-treatment (SVR12) <sup>[1]</sup>
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#### End point description:

SVR12 was defined as plasma hepatitis C virus ribonucleic acid (HCV RNA) level less than the lower limit of quantification (LLOQ; 15 IU/mL) 12 weeks after the last dose of study drug.

The 95% confidence interval (95%CI) was calculated using the Wilson's score method.

The modified intention-to-treat (mITT) population includes all enrolled participants who received at least 1 dose of study drug, excluding participants who did not achieve SVR12 for reasons other than virologic failure, such as missing SVR12 data (5 participants) or premature study drug discontinuation (3 participants).

Efficacy was to be established if the lower bound of the 95%CI was greater than the threshold of 92.4%, based on the historical rate observed in glecaprevir/pibrentasvir registrational studies in treatment-naïve, non-cirrhotic patients (98.4%) minus a margin of 6%.

End point type	Primary
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#### End point timeframe:

12 weeks after the last actual dose of study drug, Week 20

#### 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: Efficacy for the 8-week regimen in this single-group study was to be established by demonstrating similarity to the historical control regimen of glecaprevir/pibrentasvir administered for 8 weeks in treatment naïve non cirrhotic patients.

<b>End point values</b>	Glecaprevir/Pibrentasvir			
Subject group type	Reporting group			
Number of subjects analysed	222 <sup>[2]</sup>			
Units: percentage of participants				
number (confidence interval 95%)	100 (98.3 to 100.0)			

#### Notes:

[2] - Modified intention-to-treat population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants in the Intention-to-Treat Population With SVR12

End point title	Percentage of Participants in the Intention-to-Treat Population With SVR12
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#### End point description:

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

The intention-to-treat (ITT) population included all enrolled participants who received at least 1 dose of study drug.

The 95% confidence interval was calculated using the normal approximation to the binomial distribution. Efficacy was to be established if the lower bound of the 95%CI was greater than the threshold of 91.4%, based on the mITT threshold minus an expected 1% rate of non-virological SVR failures.

End point type	Secondary
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End point timeframe:

12 weeks after the last actual dose of study drug, Week 20

<b>End point values</b>	Glecaprevir/Pib rentasvir			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: percentage of participants				
number (confidence interval 95%)	96.5 (94.2 to 98.9)			

## 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
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End point description:

Post-treatment relapse was defined as confirmed HCV RNA  $\geq$  LLOQ between the end of treatment and 12 weeks after the last dose of study drug among participants who completed treatment with HCV RNA levels  $<$  LLOQ at the end of treatment.

End point type	Secondary
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End point timeframe:

From the end of treatment (Week 8) through 12 weeks after the last dose of study drug (Week 20)

<b>End point values</b>	Glecaprevir/Pib rentasvir			
Subject group type	Reporting group			
Number of subjects analysed	225 <sup>[3]</sup>			
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 1.7)			

Notes:

[3] - Subjects with HCV RNA  $<$  15 IU/mL at the end of treatment and at least 1 post-treatment HCV RNA value

## 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
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**End point description:**

On-treatment virologic failure was defined as one of the following conditions:

- confirmed HCV RNA  $\geq 100$  IU/mL after HCV RNA  $< 15$  IU/mL during the Treatment Period; or
- confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements  $> 1$  log IU/mL above nadir) at any time point during the Treatment Period; or
- HCV RNA  $\geq 15$  IU/mL at end of treatment with at least 6 weeks of treatment, where the HCV RNA value must be collected on or after Study Drug Day 36 and study drug duration  $\geq 36$  days.

The intention-to-treat (ITT) population included all enrolled participants who received at least 1 dose of study drug.

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End point type	Secondary
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End point timeframe:

Up to 8 weeks

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<b>End point values</b>	Glecaprevir/Pib rentasvir			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 1.6)			

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**Statistical analyses**

No statistical analyses for this end point

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## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through 30 days after the last dose of study drug; 12 weeks

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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### Reporting groups

Reporting group title	Glecaprevir/Pibrentasvir
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Reporting group description:

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

Serious adverse events	Glecaprevir/Pibrentasvir		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 230 (1.74%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
JOINT DISLOCATION			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
LIMB TRAUMATIC AMPUTATION			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
UTERINE HAEMORRHAGE			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
ANGIOEDEMA			

subjects affected / exposed	2 / 230 (0.87%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Glecaprevir/Pibrentasvir		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 230 (20.00%)		
Nervous system disorders			
<b>DIZZINESS</b>			
subjects affected / exposed	8 / 230 (3.48%)		
occurrences (all)	8		
<b>HEADACHE</b>			
subjects affected / exposed	29 / 230 (12.61%)		
occurrences (all)	32		
General disorders and administration site conditions			
<b>FATIGUE</b>			
subjects affected / exposed	17 / 230 (7.39%)		
occurrences (all)	17		
<b>ASTHENIA</b>			
subjects affected / exposed	8 / 230 (3.48%)		
occurrences (all)	8		
Gastrointestinal disorders			
<b>NAUSEA</b>			
subjects affected / exposed	10 / 230 (4.35%)		
occurrences (all)	10		
Skin and subcutaneous tissue disorders			
<b>PRURITUS</b>			
subjects affected / exposed	10 / 230 (4.35%)		
occurrences (all)	11		
Infections and infestations			
<b>NASOPHARYNGITIS</b>			
subjects affected / exposed	9 / 230 (3.91%)		
occurrences (all)	9		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2017	<ul style="list-style-type: none"><li>• Updated Section 5, Study Activities, to change the allowed concomitant rosuvastatin dose from 10 mg to 5 mg based upon the anticipated European Union Summary of Product Characteristics label recommendation under Subsection 5.1, Eligibility Criteria, Concomitant Medications.</li><li>• Updated Section 5, Study Activities, to add Subsection 5.2, Contraception Recommendations.</li><li>• Updated Section 6, Safety Considerations, to add regulatory definition of serious adverse events under subsection Medical Complaints/Adverse Events and Serious Adverse Events.</li><li>• Updated Section 6, Safety Considerations, to add definition of adverse event severity grade under subsection Adverse Event Definition of Severity Grade.</li><li>• Updated Section 6, Safety Considerations, to add the definition of reasonable possibility and no reasonable possibility under the subsection Adverse Event Severity and Relationship to Study Drug.</li><li>• Updated Section 6, Safety Considerations, under subsection Medical Complaints/Adverse Events and Serious Adverse Events, to add the requirement by the Investigator to report a serious adverse event to the Sponsor within 24 hours of becoming aware of a serious adverse event.</li><li>• Updated Section 6, Safety Considerations, under subsection Medical Complaints/Adverse Events and Serious Adverse Events, to add the statement that adverse events will be monitored throughout the study to identify any which may indicate a risk to subjects.</li><li>• Updated Section 10, Data Quality Assurance, to add statement regarding the use of a quality management system to define quality tolerance limits.</li><li>• Updated Appendix D, Activity Schedule to include a list of what vital signs will be measured: systolic and diastolic blood pressure, pulse, and body temperature.</li><li>• Updated Appendix D, Activity Schedule to add HIV-1 RNA and flow cytometry to the Post-Treatment Week 4 Visit study activities.</li></ul>
18 September 2017	<ul style="list-style-type: none"><li>• Updated Subsection 5.1, Eligibility Criteria, Demographic and Laboratory Assessments, Criterion 3, to clarify the definition of HBV to clarify the population that is not at risk of HBV reactivation and therefore can be included in the study.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported