



Clinical trial results:

An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Subjects with Genotypes 1 – 6 Chronic Hepatitis C Virus (HCV) Infection (DORA)

Summary

EudraCT number	2016-004102-34
Trial protocol	ES BE DE GB
Global end of trial date	12 September 2022

Results information

Result version number	v1 (current)
This version publication date	11 March 2023
First version publication date	11 March 2023

Trial information

Trial identification

Sponsor protocol code	M16-123
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03067129
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	1 North Waukegan Road, North Chicago, IL, United States, 60064
Public contact	Global Medical Services, AbbVie, 001 800-633-9110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 800-633-9110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001832-PIP01-15
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 September 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were to:

- Assess the steady state area under the concentration-time curve (AUC), and to assess the pharmacokinetics (PK) of glecaprevir/pibrentasvir (GLE/PIB) in paediatric subjects following multiple dosing by age group;
- Evaluate the safety and tolerability of GLE/PIB by age group, cirrhosis status, and across all subjects;
- Evaluate the percentage of subjects with sustained virologic response for 12 weeks post-treatment (SVR12) in HCV Genotype 1 – 6 infected paediatric subjects (US FDA only, otherwise secondary).

Protection of trial subjects:

Subject 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	20 March 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	33 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Puerto Rico: 6
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 58
Worldwide total number of subjects	129
EEA total number of subjects	26

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)	81
Adolescents (12-17 years)	48
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 38 sites in North America, Europe, and Japan.

Cohort 1 enrolled adolescent subjects aged 12 to < 18 years old. Subsequently, children aged 9 to < 12 (Cohort 2), 6 to < 9 (Cohort 3), and 3 to < 6 (Cohort 4) years old were enrolled in parallel.

Pre-assignment

Screening details:

In each cohort, subjects were first enrolled into an intense pharmacokinetics (IPK) portion to characterize the PK and safety in each age group, followed by a non-IPK safety/efficacy part. PK samples from the first 6 subjects in the IPK part were analyzed to determine the final dose used for the remaining IPK participants and in the non-IPK group.

Pre-assignment period milestones

Number of subjects started	129
Number of subjects completed	127

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Enrolled but not dosed: 2
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Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: 12 to < 18 years old

Arm description:

Adolescents aged 12 to < 18 years old received the adult formulation of glecaprevir (GLE)/pibrentasvir (PIB) 100 mg/40 mg co-formulated film-coated tablets for a once daily (QD) total dose of 300 mg/120 mg by mouth for 8, 12, or 16 weeks depending on hepatitis C virus (HCV) genotype, cirrhosis status, and prior treatment experience.

Arm type	Experimental
Investigational medicinal product name	Glecaprevir (GLE)/Pibrentasvir (PIB)
Investigational medicinal product code	ABT-493/ABT-530
Other name	MAVYRET®, MAVIRET®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

GLE/PIB was provided as 100 mg/40 mg film-coated tablets taken orally at GLE 300 mg/PIB 120 mg (three × GLE 100 mg/PIB 40 mg tablets) QD and with food.

Arm title	Cohort 2: 9 to < 12 years old
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Arm description:

Children aged 9 to < 12 years old received a paediatric formulation of GLE + PIB as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience. The final dose for children weighing 30 to < 45 kg was GLE 250 mg + PIB 100 mg.

Arm type	Experimental
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Investigational medicinal product name	Glecaprevir + Pibrentasvir Paediatric Formulation
Investigational medicinal product code	ABT-493 + ABT-530
Other name	
Pharmaceutical forms	Film-coated granules
Routes of administration	Oral use

Dosage and administration details:

The initial proposed dose for paediatric participants 9 to < 12 years old (30 to < 45 kg) was GLE 200 mg + PIB 75 mg. After PK analysis from the first 6 enrolled participants the dose was adjusted to GLE 250 mg + PIB 100 mg.

The paediatric formulation was to be administered by mixing the granules with a small amount (1-2 teaspoons) of a soft food vehicle, such as hazelnut spread, Greek yogurt, or peanut butter.

Arm title	Cohort 3: 6 to < 9 years old
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Arm description:

Children aged 6 to < 9 years old received a paediatric formulation of GLE + PIB as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience. The final dose for children weighing ≥ 20 to < 30 kg was GLE 200 mg + PIB 80 mg; one participant received GLE 250 mg + PIB 100 mg based on weight at screening.

Arm type	Experimental
Investigational medicinal product name	Glecaprevir + Pibrentasvir Paediatric Formulation
Investigational medicinal product code	ABT-493 + ABT-530
Other name	
Pharmaceutical forms	Film-coated granules
Routes of administration	Oral use

Dosage and administration details:

The initial proposed dose for paediatric participants 6 to < 9 years old (20 to < 30 kg) was GLE 160 mg + PIB 60 mg. After PK analysis from the first 6 enrolled participants the dose was adjusted to GLE 200 mg + PIB 80 mg.

The paediatric formulation was to be administered by mixing the granules with a small amount (1-2 teaspoons) of a soft food vehicle, such as hazelnut spread, Greek yogurt, or peanut butter.

Arm title	Cohort 4: 3 to < 6 years old
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Arm description:

Children aged 3 to < 6 years old received a paediatric formulation of GLE + PIB as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience. The final dose for children weighing 12 to < 20 kg was GLE 150 mg + PIB 60 mg; one participant received GLE 200 mg + PIB 80 mg based on weight at screening.

Arm type	Experimental
Investigational medicinal product name	Glecaprevir + Pibrentasvir Paediatric Formulation
Investigational medicinal product code	ABT-493 + ABT-530
Other name	
Pharmaceutical forms	Film-coated granules
Routes of administration	Oral use

Dosage and administration details:

The initial proposed dose for paediatric participants 3 to < 6 years old (12 to < 20 kg) was GLE 120 mg + PIB 45 mg. After PK analysis from the first 5 enrolled participants the dose was adjusted to GLE 150 mg + PIB 60 mg.

The paediatric formulation was to be administered by mixing the granules with a small amount (1-2 teaspoons) of a soft food vehicle, such as hazelnut spread, Greek yogurt, or peanut butter.

Number of subjects in period 1^[1]	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old
Started	47	29	27
Completed	42	24	22
Not completed	5	5	5
Consent withdrawn by subject	-	-	1
Partially dosed; refused to swallow entire dose	-	-	-
Lost to follow-up	5	5	4

Number of subjects in period 1^[1]	Cohort 4: 3 to < 6 years old
Started	24
Completed	18
Not completed	6
Consent withdrawn by subject	2
Partially dosed; refused to swallow entire dose	1
Lost to follow-up	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Two participants enrolled but did not receive study drug and are therefore not included in the baseline period.

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1: 12 to < 18 years old
Reporting group description: Adolescents aged 12 to < 18 years old received the adult formulation of glecaprevir (GLE)/pibrentasvir (PIB) 100 mg/40 mg co-formulated film-coated tablets for a once daily (QD) total dose of 300 mg/120 mg by mouth for 8, 12, or 16 weeks depending on hepatitis C virus (HCV) genotype, cirrhosis status, and prior treatment experience.	
Reporting group title	Cohort 2: 9 to < 12 years old
Reporting group description: Children aged 9 to < 12 years old received a paediatric formulation of GLE + PIB as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience. The final dose for children weighing 30 to < 45 kg was GLE 250 mg + PIB 100 mg.	
Reporting group title	Cohort 3: 6 to < 9 years old
Reporting group description: Children aged 6 to < 9 years old received a paediatric formulation of GLE + PIB as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience. The final dose for children weighing ≥ 20 to < 30 kg was GLE 200 mg + PIB 80 mg; one participant received GLE 250 mg + PIB 100 mg based on weight at screening.	
Reporting group title	Cohort 4: 3 to < 6 years old
Reporting group description: Children aged 3 to < 6 years old received a paediatric formulation of GLE + PIB as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience. The final dose for children weighing 12 to < 20 kg was GLE 150 mg + PIB 60 mg; one participant received GLE 200 mg + PIB 80 mg based on weight at screening.	

Reporting group values	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old
Number of subjects	47	29	27
Age categorical			
Age at Baseline is reported; Cohorts were defined in the interactive response technology (IRT) system as age group at Screening which may differ from Baseline age.			
Units: Subjects			
12 to < 18 years	47	0	0
9 to < 12 years	0	29	1
6 to < 9 years	0	0	26
3 to < 6 years	0	0	0
Age continuous			
Units: years			
median	14	10	7
full range (min-max)	12 to 17	9 to 11	6 to 9
Gender categorical			
Units: Subjects			
Female	26	15	17
Male	21	14	10
Race			
Units: Subjects			
White	35	21	18
Black or African American	4	1	1

Asian	6	5	5
American Indian or Alaska Native	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Multiple	2	1	3
Ethnicity Units: Subjects			
Hispanic or Latino	5	5	4
Not Hispanic or Latino	42	24	23
Weight Units: Subjects			
12 to < 20 kg	0	0	1
20 to < 30 kg	0	2	25
30 to < 45 kg	3	27	1
≥ 45 kg	44	0	0
Hepatitis C Virus Genotype Units: Subjects			
Genotype 1	37	19	22
Genotype 2	3	2	0
Genotype 3	4	8	3
Genotype 4	3	0	2
Genotype 5	0	0	0
Genotype 6	0	0	0
Prior HCV Treatment History Units: Subjects			
Naive	36	27	27
Experienced	11	2	0
Baseline Fibrosis Stage			
Fibrosis stage was determined by biopsy score, FibroScan score (if biopsy not available), or FibroTest score (if biopsy and FibroScan not available) and is equivalent to the liver biopsy Metavir score: F0: no fibrosis; F1: portal fibrosis without septa; F2: portal fibrosis with few septa; F3: numerous septa without cirrhosis; F4: cirrhosis.			
Units: Subjects			
F0-F1	45	28	26
F2	1	1	1
F3	1	0	0
F4	0	0	0
Co-infection with Human Immunodeficiency Virus (HIV) Units: Subjects			
Yes	2	0	1
No	45	29	26
HCV Ribonucleic Acid (RNA) Level			
HCV RNA quantified by Roche COBAS Ampliprep/COBAS TaqMan HCV Quantitative Test, version 2.0.			
Units: Log IU/mL			
median	6.20	6.20	5.89
full range (min-max)	4.63 to 7.18	4.79 to 7.19	4.53 to 7.15
Reporting group values	Cohort 4: 3 to < 6 years old	Total	
Number of subjects	24	127	

Age categorical			
Age at Baseline is reported; Cohorts were defined in the interactive response technology (IRT) system as age group at Screening which may differ from Baseline age.			
Units: Subjects			
12 to < 18 years	0	47	
9 to < 12 years	0	30	
6 to < 9 years	0	26	
3 to < 6 years	24	24	
Age continuous			
Units: years			
median	4		
full range (min-max)	3 to 5	-	
Gender categorical			
Units: Subjects			
Female	12	70	
Male	12	57	
Race			
Units: Subjects			
White	16	90	
Black or African American	1	7	
Asian	4	20	
American Indian or Alaska Native	1	2	
Native Hawaiian or Other Pacific Islander	1	1	
Multiple	1	7	
Ethnicity			
Units: Subjects			
Hispanic or Latino	4	18	
Not Hispanic or Latino	20	109	
Weight			
Units: Subjects			
12 to < 20 kg	23	24	
20 to < 30 kg	1	28	
30 to < 45 kg	0	31	
≥ 45 kg	0	44	
Hepatitis C Virus Genotype			
Units: Subjects			
Genotype 1	17	95	
Genotype 2	0	5	
Genotype 3	7	22	
Genotype 4	0	5	
Genotype 5	0	0	
Genotype 6	0	0	
Prior HCV Treatment History			
Units: Subjects			
Naive	24	114	
Experienced	0	13	
Baseline Fibrosis Stage			
Fibrosis stage was determined by biopsy score, FibroScan score (if biopsy not available), or FibroTest score (if biopsy and FibroScan not available) and is equivalent to the liver biopsy Metavir score: F0: no fibrosis; F1: portal fibrosis without septa;			

F2: portal fibrosis with few septa; F3: numerous septa without cirrhosis; F4: cirrhosis.			
Units: Subjects			
F0-F1	24	123	
F2	0	3	
F3	0	1	
F4	0	0	
Co-infection with Human Immunodeficiency Virus (HIV)			
Units: Subjects			
Yes	0	3	
No	24	124	
HCV Ribonucleic Acid (RNA) Level			
HCV RNA quantified by Roche COBAS Ampliprep/COBAS TaqMan HCV Quantitative Test, version 2.0.			
Units: Log IU/mL			
median	5.83		
full range (min-max)	3.43 to 6.90	-	

End points

End points reporting groups

Reporting group title	Cohort 1: 12 to < 18 years old
Reporting group description: Adolescents aged 12 to < 18 years old received the adult formulation of glecaprevir (GLE)/pibrentasvir (PIB) 100 mg/40 mg co-formulated film-coated tablets for a once daily (QD) total dose of 300 mg/120 mg by mouth for 8, 12, or 16 weeks depending on hepatitis C virus (HCV) genotype, cirrhosis status, and prior treatment experience.	
Reporting group title	Cohort 2: 9 to < 12 years old
Reporting group description: Children aged 9 to < 12 years old received a paediatric formulation of GLE + PIB as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience. The final dose for children weighing 30 to < 45 kg was GLE 250 mg + PIB 100 mg.	
Reporting group title	Cohort 3: 6 to < 9 years old
Reporting group description: Children aged 6 to < 9 years old received a paediatric formulation of GLE + PIB as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience. The final dose for children weighing \geq 20 to < 30 kg was GLE 200 mg + PIB 80 mg; one participant received GLE 250 mg + PIB 100 mg based on weight at screening.	
Reporting group title	Cohort 4: 3 to < 6 years old
Reporting group description: Children aged 3 to < 6 years old received a paediatric formulation of GLE + PIB as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience. The final dose for children weighing 12 to < 20 kg was GLE 150 mg + PIB 60 mg; one participant received GLE 200 mg + PIB 80 mg based on weight at screening.	
Subject analysis set title	Cohorts 2-4: 3 to < 12 years old
Subject analysis set type	Intention-to-treat
Subject analysis set description: Children aged 3 to < 12 years old received a paediatric formulation of GLE + PIB at a final dose of GLE 250 mg + PIB 100 mg (children 9 to < 12 years of age), GLE 200 mg + PIB 80 mg (children 6 to < 9 years of age), or GLE 150 mg + PIB 60 mg (children 3 to < 6 years of age) as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience.	
Subject analysis set title	Total
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants in Cohorts 1-4.	

Primary: Steady-state Area Under the Plasma Concentration-time Curve From Time Zero to 24 Hours Postdose (AUC0-24) of Glecaprevir

End point title	Steady-state Area Under the Plasma Concentration-time Curve From Time Zero to 24 Hours Postdose (AUC0-24) of Glecaprevir ^[1]
End point description: The area under the plasma concentration-time curve (AUC) is a method of measurement of the total exposure of a drug in blood plasma. The steady-state exposure of GLE was measured up to 24 hours after dosing at Week 2 and estimated using non-compartmental analysis. PK analyses were assessed in participants with intense pharmacokinetic samples who received the final dose regimen of GLE + PIB. One participant in Cohort 4 who received GLE 200 mg + PIB 80 mg based on weight (> 20 kg) and was summarized in Cohort 3 for PK analyses based on the actual dose received.	
End point type	Primary
End point timeframe: Week 2 from predose to 24 hours post-dose	

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: No hypotheses were tested in this open-label study.

End point values	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14 ^[2]	13 ^[3]	13 ^[4]	12 ^[5]
Units: ng*h/mL				
geometric mean (confidence interval 95%)	4790 (3520 to 6500)	7870 (4140 to 14900)	6860 (4080 to 11500)	7520 (3870 to 14600)

Notes:

[2] - Participants with IPK samples

[3] - Participants with IPK samples who received the final dose regimen of GLE + PIB

[4] - Participants with IPK samples who received the final dose regimen of GLE + PIB

[5] - Participants with IPK samples who received the final dose regimen of GLE + PIB

Statistical analyses

No statistical analyses for this end point

Primary: Steady-state AUC0-24 of Pibrentasvir

End point title	Steady-state AUC0-24 of Pibrentasvir ^[6]
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End point description:

The area under the plasma concentration-time curve (AUC) is a method of measurement of the total exposure of a drug in blood plasma. The steady-state exposure of PIB was measured up to 24 hours after dosing at Week 2 and estimated using non-compartmental analysis.

PK analyses were assessed in participants with intense pharmacokinetic samples who received the final dose regimen of GLE + PIB. One participant in Cohort 4 who received GLE 200 mg + PIB 80 mg based on weight (> 20 kg) and was summarized in Cohort 3 for PK analyses based on the actual dose received.

End point type	Primary
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End point timeframe:

Week 2 from predose to 24 hours post-dose

Notes:

[6] - 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: No hypotheses were tested in this open-label study.

End point values	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14 ^[7]	13 ^[8]	13 ^[9]	12 ^[10]
Units: ng*hour/mL				
geometric mean (confidence interval 95%)	1380 (1150 to 1660)	2200 (1460 to 3310)	1640 (1230 to 2190)	1790 (1350 to 2370)

Notes:

[7] - Participants with IPK samples

[8] - Participants with IPK samples who received the final dose regimen of GLE + PIB

[9] - Participants with IPK samples who received the final dose regimen of GLE + PIB

[10] - Participants with IPK samples who received the final dose regimen of GLE + PIB

Statistical analyses

Secondary: Percentage of Participants With Sustained Virologic Response 12 Weeks Post Treatment (SVR12)

End point title	Percentage of Participants With Sustained Virologic Response 12 Weeks Post Treatment (SVR12)
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End point description:

SVR12 is defined as hepatitis C virus ribonucleic acid (HCV RNA) less than the lower limit of quantification (LLOQ; 15 IU/mL) 12 weeks after the last actual dose of study drug. Plasma HCV RNA levels were collected using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0.

SVR12 was considered a primary efficacy endpoint by the US regulatory agency and was considered secondary outside of the US.

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

Backward imputation, where applicable, was used to impute missing data. Participants with missing data after backwards imputation were counted as nonresponders.

End point type	Secondary
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End point timeframe:

12 weeks after last dose of study drug (Week 20, 24, or 28 depending on treatment duration)

End point values	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47 ^[11]	29 ^[12]	27 ^[13]	24 ^[14]
Units: percentage of participants				
number (confidence interval 95%)	100 (92.4 to 100.0)	93.1 (78.0 to 98.1)	100 (87.5 to 100.0)	95.8 (79.8 to 99.3)

Notes:

[11] - Intention-to-treat population

[12] - Intention-to-treat population

[13] - Intention-to-treat population

[14] - Intention-to-treat population

End point values	Cohorts 2-4: 3 to < 12 years old	Total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80 ^[15]	127 ^[16]		
Units: percentage of participants				
number (confidence interval 95%)	96.3 (89.5 to 98.7)	97.6 (93.3 to 99.2)		

Notes:

[15] - Intention-to-treat population

[16] - Intention-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (C_{max}) of Glecaprevir

End point title	Maximum Plasma Concentration (C _{max}) of Glecaprevir
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End point description:

PK analyses were assessed in participants with intense pharmacokinetic samples who received the final dose regimen of GLE + PIB. One participant in Cohort 4 who received GLE 200 mg + PIB 80 mg based on weight (> 20 kg) and was summarized in Cohort 3 for PK analyses based on the actual dose received.

End point type	Secondary
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End point timeframe:

Week 2 from predose to 24 hours post-dose.

End point values	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14 ^[17]	13 ^[18]	13 ^[19]	12 ^[20]
Units: ng/mL				
geometric mean (confidence interval 95%)	1040 (733 to 1480)	1370 (773 to 2440)	1600 (926 to 2770)	1530 (711 to 3290)

Notes:

[17] - Participants with IPK samples

[18] - Participants with IPK samples who received the final dose regimen of GLE + PIB

[19] - Participants with IPK samples who received the final dose regimen of GLE + PIB

[20] - Participants with IPK samples who received the final dose regimen of GLE + PIB

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance (CL/F) of Glecaprevir From Plasma

End point title	Apparent Clearance (CL/F) of Glecaprevir From Plasma
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End point description:

PK analyses were assessed in participants with intense pharmacokinetic samples who received the final dose regimen of GLE + PIB. One participant in Cohort 4 who received GLE 200 mg + PIB 80 mg based on weight (> 20 kg) and was summarized in Cohort 3 for PK analyses based on the actual dose received.

End point type	Secondary
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End point timeframe:

Week 2 from predose to 24 hours pose-dose

End point values	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14 ^[21]	13 ^[22]	13 ^[23]	12 ^[24]
Units: litres/hour				
geometric mean (confidence interval 95%)	62.6 (46.1 to 85.1)	31.8 (16.7 to 60.3)	29.1 (17.3 to 49.0)	19.9 (10.2 to 38.7)

Notes:

[21] - Participants with IPK samples

[22] - Participants with IPK samples who received the final dose regimen of GLE + PIB

[23] - Participants with IPK samples who received the final dose regimen of GLE + PIB

[24] - Participants with IPK samples who received the final dose regimen of GLE + PIB

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration of Pibrentasvir

End point title	Maximum Plasma Concentration of Pibrentasvir
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End point description:

PK analyses were assessed in participants with intense pharmacokinetic samples who received the final dose regimen of GLE + PIB. One participant in Cohort 4 who received GLE 200 mg + PIB 80 mg based on weight (> 20 kg) and was summarized in Cohort 3 for PK analyses based on the actual dose received.

End point type	Secondary
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End point timeframe:

Week 2 from predose to 24 hours post-dose

End point values	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14 ^[25]	13 ^[26]	13 ^[27]	12 ^[28]
Units: ng/mL				
geometric mean (confidence interval 95%)	174 (148 to 205)	225 (164 to 310)	197 (154 to 251)	233 (184 to 296)

Notes:

[25] - Participants with IPK samples

[26] - Participants with IPK samples who received the final dose regimen of GLE + PIB

[27] - Participants with IPK samples who received the final dose regimen of GLE + PIB

[28] - Participants with IPK samples who received the final dose regimen of GLE + PIB

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance of Pibrentasvir

End point title	Apparent Clearance of Pibrentasvir
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End point description:

PK analyses were assessed in participants with intense pharmacokinetic samples who received the final dose regimen of GLE + PIB. One participant in Cohort 4 who received GLE 200 mg + PIB 80 mg based on weight (> 20 kg) and was summarized in Cohort 3 for PK analyses based on the actual dose received.

End point type	Secondary
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End point timeframe:

Week 2 from predose to 24 hours post-dose

End point values	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14 ^[29]	13 ^[30]	13 ^[31]	12 ^[32]
Units: litres/hour				
geometric mean (confidence interval 95%)	86.9 (72.4 to 104)	45.4 (30.1 to 68.5)	48.7 (36.6 to 64.8)	33.6 (25.4 to 44.5)

Notes:

[29] - Participants with IPK samples

[30] - Participants with IPK samples who received the final dose regimen of GLE + PIB

[31] - Participants with IPK samples who received the final dose regimen of GLE + PIB

[32] - Participants with IPK samples who received the final dose regimen of GLE + PIB

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced On-treatment Virologic Failure

End point title	Percentage of Participants Who Experienced On-treatment Virologic Failure
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End point description:

On-treatment virologic failure is defined as meeting one of the following:

- A confirmed (defined as two consecutive HCV RNA measurements) increase of > 1 log IU/mL above nadir during treatment;
- Confirmed HCV RNA \geq 100 IU/mL after HCV RNA < 15 IU/mL during treatment;
- HCV RNA \geq 15 IU/mL at the end of treatment with at least 6 weeks of treatment.

End point type	Secondary
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End point timeframe:

Up to Week 8, 12, or 16 (depending on treatment duration)

End point values	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47 ^[33]	29 ^[34]	27 ^[35]	24 ^[36]
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 7.6)	0.0 (0.0 to 11.7)	0.0 (0.0 to 12.5)	0.0 (0.0 to 13.8)

Notes:

[33] - Intention-to-treat population

[34] - Intention-to-treat population

[35] - Intention-to-treat population

[36] - Intention-to-treat population

End point values	Cohorts 2-4: 3 to < 12 years old	Total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80 ^[37]	127 ^[38]		

Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 4.6)	0.0 (0.0 to 2.9)		

Notes:

[37] - Intention-to-treat population

[38] - Intention-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Post-treatment Relapse up to 12 Weeks Post Treatment

End point title	Percentage of Participants With Post-treatment Relapse up to 12 Weeks Post Treatment
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End point description:

Post-treatment relapse is defined as confirmed HCV RNA \geq 15 IU/mL 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 < 15 IU/mL at the end of treatment; excluding participants who had been shown to be re-infected.

End point type	Secondary
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End point timeframe:

Up to 12 weeks after the last dose of study drug (Week 20, 24, or 28 depending on treatment duration)

End point values	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47 ^[39]	28 ^[40]	27 ^[41]	23 ^[42]
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 7.6)	3.6 (0.6 to 17.7)	0.0 (0.0 to 12.5)	0.0 (0.0 to 14.3)

Notes:

[39] - Participants who completed treatment as planned with HCV RNA < 15 IU/mL at the end of treatment

[40] - Participants who completed treatment as planned with HCV RNA < 15 IU/mL at the end of treatment

[41] - Participants who completed treatment as planned with HCV RNA < 15 IU/mL at the end of treatment

[42] - Participants who completed treatment as planned with HCV RNA < 15 IU/mL at the end of treatment

End point values	Cohorts 2-4: 3 to < 12 years old	Total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78 ^[43]	125 ^[44]		
Units: percentage of participants				
number (confidence interval 95%)	1.3 (0.2 to 6.9)	0.8 (0.1 to 4.4)		

Notes:

[43] - Participants who completed treatment as planned with HCV RNA < 15 IU/mL at the end of treatment

[44] - Participants who completed treatment as planned with HCV RNA < 15 IU/mL at the end of treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with New HCV Infection (Reinfection)

End point title	Percentage of Participants with New HCV Infection (Reinfection)
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End point description:

Reinfection is defined as confirmed HCV RNA ≥ 15 IU/mL in the post-treatment period in a participant who had HCV RNA < 15 IU/mL at the Final Treatment Visit, along with post-treatment detection of a different HCV genotype, subtype, or clade compared with Baseline, as determined by phylogenetic analysis of the nonstructural viral protein 3 (NS3) or NS5A, and/or NS5B gene sequences.

End point type	Secondary
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End point timeframe:

From the end of treatment up to post-treatment Week 144

End point values	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47 ^[45]	29 ^[46]	27 ^[47]	24 ^[48]
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 7.6)	0.0 (0.0 to 11.7)	0.0 (0.0 to 12.5)	0.0 (0.0 to 13.8)

Notes:

[45] - Intention-to-treat population

[46] - Intention-to-treat population

[47] - Intention-to-treat population

[48] - Intention-to-treat population

End point values	Cohorts 2-4: 3 to < 12 years old	Total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80 ^[49]	127 ^[50]		
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 4.6)	0.0 (0.0 to 2.9)		

Notes:

[49] - Intention-to-treat population

[50] - Intention-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Questionnaire Question 1: How Convenient or Inconvenient Was it to Prepare the Dose?

End point title	Palatability Questionnaire Question 1: How Convenient or Inconvenient Was it to Prepare the Dose? ^[51]
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End point description:

For each participant who received the paediatric formulation (Cohorts 2 - 4), the parent(s)/guardian(s) completed a Palatability Questionnaire to provide feedback on the perception of the dosage form. The Palatability Questionnaire included 6 questions related to the administration and ingestion of the paediatric GLE + PIB formulation.

Question 1 "How Convenient or Inconvenient Was it to Prepare the Dose?" was answered as "very

convenient", "convenient", "borderline", "inconvenient", or "very inconvenient".

End point type	Secondary
End point timeframe:	
Final treatment visit (up to Week 8, 12, or 16, depending on treatment duration)	
Notes:	

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Assessment of palatability/acceptability of the paediatric formulation was not conducted in adolescents (Cohort 1).

End point values	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old	Cohorts 2-4: 3 to < 12 years old
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	28 ^[52]	27 ^[53]	23 ^[54]	78 ^[55]
Units: participants				
Very convenient	7	9	9	25
Convenient	13	10	8	31
Borderline	2	7	4	13
Inconvenient	6	1	1	8
Very inconvenient	0	0	1	1

Notes:

[52] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[53] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[54] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[55] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Questionnaire Question 2: How Long Did it Typically Take for the Child to Take the Dose?

End point title	Palatability Questionnaire Question 2: How Long Did it Typically Take for the Child to Take the Dose? ^[56]
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End point description:

For each participant who received the paediatric formulation (Cohorts 2 - 4), the parent(s)/guardian(s) completed a Palatability Questionnaire to provide feedback on the perception of the dosage form. The Palatability Questionnaire included 6 questions related to the administration and ingestion of the paediatric GLE + PIB formulation.

Question 2 "How Long Did it Typically Take for the Child to Take the Dose?" was answered as "5 minutes or less", "5 to 15 minutes", "15 to 30 minutes", or "more than 30 minutes".

End point type	Secondary
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End point timeframe:

Final treatment visit (up to Week 8, 12, or 16, depending on duration of treatment)

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Assessment of palatability/acceptability of the paediatric formulation was not conducted in adolescents (Cohort 1).

End point values	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old	Cohorts 2-4: 3 to < 12 years old
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	28 ^[57]	27 ^[58]	23 ^[59]	78 ^[60]
Units: participants				
5 minutes or less	22	23	21	66
5 to 15 minutes	5	4	2	11
15 to 30 minutes	1	0	0	1
More than 30 minutes	0	0	0	0

Notes:

[57] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[58] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[59] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[60] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Questionnaire Question 3: Were You Able to Successfully Administer the Whole Dose to the Child With 1 to 2 Teaspoons (5 to 10 mL) of Soft Food?

End point title	Palatability Questionnaire Question 3: Were You Able to Successfully Administer the Whole Dose to the Child With 1 to 2 Teaspoons (5 to 10 mL) of Soft Food? ^[61]
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End point description:

For each participant who received the paediatric formulation (Cohorts 2 - 4), the parent(s)/guardian(s) completed a Palatability Questionnaire to provide feedback on the perception of the dosage form. The Palatability Questionnaire included 6 questions related to the administration and ingestion of the paediatric GLE + PIB formulation.

Question 3 "Were You Able to Successfully Administer the Whole Dose to the Child With 1 to 2 Teaspoons (5 to 10 mL) of Soft Food?" was answered as "Yes" or "No".

End point type	Secondary
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End point timeframe:

Final treatment visit (up to Week 8, 12, or 16, depending on treatment duration)

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Assessment of palatability/acceptability of the paediatric formulation was not conducted in adolescents (Cohort 1).

End point values	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old	Cohorts 2-4: 3 to < 12 years old
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	28 ^[62]	27 ^[63]	23 ^[64]	78 ^[65]
Units: participants				
Yes	20	19	19	58
No	8	8	3	19
Missing	0	0	1	1

Notes:

[62] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[63] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[64] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Questionnaire Question 4: Did You Experience Any Resistance When Feeding the Child the Medicine?

End point title	Palatability Questionnaire Question 4: Did You Experience Any Resistance When Feeding the Child the Medicine? ^[66]
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End point description:

For each participant who received the paediatric formulation (Cohorts 2 - 4), the parent(s)/guardian(s) completed a Palatability Questionnaire to provide feedback on the perception of the dosage form. The Palatability Questionnaire included 6 questions related to the administration and ingestion of the paediatric GLE + PIB formulation. Question 4 "Did You Experience Any Resistance When Feeding the Child the Medicine?" was answered as "Yes" or "No".

End point type	Secondary
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End point timeframe:

Final treatment visit (up to Week 8, 12, or 16 depending on treatment duration)

Notes:

[66] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Assessment of palatability/acceptability of the paediatric formulation was not conducted in adolescents (Cohort 1).

End point values	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old	Cohorts 2-4: 3 to < 12 years old
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	28 ^[67]	27 ^[68]	23 ^[69]	78 ^[70]
Units: participants				
Yes	6	4	7	17
No	22	23	15	60
Missing	0	0	1	1

Notes:

[67] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[68] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[69] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[70] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Questionnaire Question 4a: Type of Feeding Resistance

End point title	Palatability Questionnaire Question 4a: Type of Feeding Resistance ^[71]
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End point description:

For each participant who received the paediatric formulation (Cohorts 2 - 4), the parent(s)/guardian(s) completed a Palatability Questionnaire to provide feedback on the perception of the dosage form. The

Palatability Questionnaire included 6 questions related to the administration and ingestion of the paediatric GLE + PIB formulation. Question 4a "Type of feeding resistance?" tracks feeding resistance experienced at any time during treatment, and was answered as "Did not like taste of medicine", "Did not like texture of medicine", "Did not like the soft food used", "Did not like to swallow the amount of medicine", or "Unrelated to the medicine".

End point type	Secondary
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End point timeframe:

Up to final treatment visit (up to Week 8, 12, or 16 depending on treatment duration)

Notes:

[71] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Assessment of palatability/acceptability of the paediatric formulation was not conducted in adolescents (Cohort 1).

End point values	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old	Cohorts 2-4: 3 to < 12 years old
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	28 ^[72]	27 ^[73]	23 ^[74]	78 ^[75]
Units: participants				
Did not like taste of medicine	3	5	7	15
Did not like texture of medicine	2	2	5	9
Did not like the soft food used	3	2	0	5
Did not like to swallow the amount of medicine	3	2	3	8
Unrelated to the medicine	0	0	1	1
Missing	0	0	1	1

Notes:

[72] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[73] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[74] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[75] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Questionnaire Question 5: How Easy or Difficult Was it for the Child to Swallow the Medicine?

End point title	Palatability Questionnaire Question 5: How Easy or Difficult Was it for the Child to Swallow the Medicine? ^[76]
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End point description:

For each participant who received the paediatric formulation (Cohorts 2 - 4), the parent(s)/guardian(s) completed a Palatability Questionnaire to provide feedback on the perception of the dosage form. The Palatability Questionnaire included 6 questions related to the administration and ingestion of the paediatric GLE/PIB formulation. Question 5 "How Easy or Difficult Was it for the Child to Swallow the Medicine?" was answered as "very easy", "easy", "borderline", "difficult", or "very difficult."

End point type	Secondary
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End point timeframe:

Final treatment visit (up to Week 8, 12, or 16, depending on treatment duration)

Notes:

[76] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Assessment of palatability/acceptability of the paediatric formulation was not conducted in adolescents (Cohort 1).

End point values	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old	Cohort 4: 3 to < 6 years old	Cohorts 2-4: 3 to < 12 years old
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	28 ^[77]	27 ^[78]	23 ^[79]	78 ^[80]
Units: participants				
Very easy	10	8	11	29
Easy	13	16	10	39
Borderline	4	3	1	8
Difficult	1	0	0	1
Very difficult	0	0	0	0
Missing	0	0	1	1

Notes:

[77] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[78] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[79] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

[80] - Intention-to-treat population who completed the Palatability Questionnaire at final treatment visit

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported from first dose of study drug up to 30 days after last dose (up to 20 weeks depending on the duration of treatment). Deaths are reported through Post Treatment Week 144.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	Cohort 1: 12 to < 18 years old
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Reporting group description:

Adolescents aged 12 to < 18 years old received the adult formulation of GLE/PIB 100 mg/40 mg co-formulated film-coated tablets for a once daily total dose of 300 mg/120 mg by mouth for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience.

Reporting group title	Cohort 2: 9 to < 12 years old
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Reporting group description:

Children aged 9 to < 12 years old received a paediatric formulation of GLE + PIB as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience. The final dose for children weighing 30 to < 45 kg was GLE 250 mg + PIB 100 mg.

Reporting group title	Cohort 3: 6 to < 9 years old
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Reporting group description:

Children aged 6 to < 9 years old received a paediatric formulation of GLE + PIB as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience. The final dose for children weighing ≥ 20 to < 30 kg was GLE 200 mg + PIB 80 mg; one participant received GLE 250 mg + PIB 100 mg based on weight at screening.

Reporting group title	Cohort 4: 3 to < 6 years old
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Reporting group description:

Children aged 3 to < 6 years old received a paediatric formulation of GLE + PIB as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience. The final dose for children weighing 12 to < 20 kg was GLE 150 mg + PIB 60 mg; one participant received GLE 200 mg + PIB 80 mg based on weight at screening.

Reporting group title	Cohorts 2-4: 3 to < 12 years old
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Reporting group description:

Children aged 3 to < 12 years old received a paediatric formulation of GLE + PIB at a final dose of GLE 250 mg + PIB 100 mg (children 9 to < 12 years of age), GLE 200 mg + PIB 80 mg (children 6 to < 9 years of age), or GLE 150 mg + PIB 60 mg (children 3 to < 6 years of age) as small film-coated granules taken with a small amount of food once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience.

Reporting group title	All Subjects
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Reporting group description:

Participants in Cohorts 1-4 received glecaprevir and pibrentasvir based on age and weight once daily for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience.

Serious adverse events	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)	0 / 29 (0.00%)	0 / 27 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
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Serious adverse events	Cohort 4: 3 to < 6 years old	Cohorts 2-4: 3 to < 12 years old	All Subjects
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 80 (0.00%)	0 / 127 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Cohort 1: 12 to < 18 years old	Cohort 2: 9 to < 12 years old	Cohort 3: 6 to < 9 years old
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 47 (65.96%)	15 / 29 (51.72%)	16 / 27 (59.26%)
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	0 / 47 (0.00%)	0 / 29 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Nervous system disorders			
HEADACHE			
subjects affected / exposed	8 / 47 (17.02%)	3 / 29 (10.34%)	6 / 27 (22.22%)
occurrences (all)	12	3	6
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	5 / 47 (10.64%)	1 / 29 (3.45%)	3 / 27 (11.11%)
occurrences (all)	5	1	3
PYREXIA			
subjects affected / exposed	5 / 47 (10.64%)	1 / 29 (3.45%)	2 / 27 (7.41%)
occurrences (all)	6	1	3
Ear and labyrinth disorders			
MOTION SICKNESS			
subjects affected / exposed	0 / 47 (0.00%)	2 / 29 (6.90%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
ABDOMINAL PAIN			

subjects affected / exposed	2 / 47 (4.26%)	2 / 29 (6.90%)	1 / 27 (3.70%)
occurrences (all)	2	2	1
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 47 (2.13%)	2 / 29 (6.90%)	1 / 27 (3.70%)
occurrences (all)	1	2	1
DIARRHOEA			
subjects affected / exposed	3 / 47 (6.38%)	2 / 29 (6.90%)	4 / 27 (14.81%)
occurrences (all)	3	2	4
NAUSEA			
subjects affected / exposed	4 / 47 (8.51%)	2 / 29 (6.90%)	2 / 27 (7.41%)
occurrences (all)	4	2	2
VOMITING			
subjects affected / exposed	5 / 47 (10.64%)	1 / 29 (3.45%)	6 / 27 (22.22%)
occurrences (all)	5	1	6
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	2 / 47 (4.26%)	1 / 29 (3.45%)	1 / 27 (3.70%)
occurrences (all)	2	1	1
DYSPNOEA			
subjects affected / exposed	0 / 47 (0.00%)	0 / 29 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
NASAL CONGESTION			
subjects affected / exposed	4 / 47 (8.51%)	0 / 29 (0.00%)	0 / 27 (0.00%)
occurrences (all)	4	0	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	5 / 47 (10.64%)	1 / 29 (3.45%)	0 / 27 (0.00%)
occurrences (all)	5	1	0
RHINORRHOEA			
subjects affected / exposed	0 / 47 (0.00%)	0 / 29 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
PRURITUS			
subjects affected / exposed	0 / 47 (0.00%)	2 / 29 (6.90%)	1 / 27 (3.70%)
occurrences (all)	0	2	1
RASH			

subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	2 / 29 (6.90%) 3	1 / 27 (3.70%) 1
Infections and infestations LICE INFESTATION subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 29 (0.00%) 0	0 / 27 (0.00%) 0
NASOPHARYNGITIS subjects affected / exposed occurrences (all)	11 / 47 (23.40%) 12	4 / 29 (13.79%) 5	1 / 27 (3.70%) 1
UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	9 / 47 (19.15%) 11	1 / 29 (3.45%) 1	3 / 27 (11.11%) 6
VIRAL INFECTION subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 29 (0.00%) 0	2 / 27 (7.41%) 2
Metabolism and nutrition disorders INCREASED APPETITE subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 29 (0.00%) 0	0 / 27 (0.00%) 0

Non-serious adverse events	Cohort 4: 3 to < 6 years old	Cohorts 2-4: 3 to < 12 years old	All Subjects
Total subjects affected by non-serious adverse events subjects affected / exposed	17 / 24 (70.83%)	48 / 80 (60.00%)	79 / 127 (62.20%)
Cardiac disorders PALPITATIONS subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 80 (2.50%) 2	2 / 127 (1.57%) 2
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	12 / 80 (15.00%) 12	20 / 127 (15.75%) 24
General disorders and administration site conditions FATIGUE subjects affected / exposed occurrences (all) PYREXIA	3 / 24 (12.50%) 3	7 / 80 (8.75%) 7	12 / 127 (9.45%) 12

subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	5 / 80 (6.25%) 6	10 / 127 (7.87%) 12
Ear and labyrinth disorders MOTION SICKNESS subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 80 (2.50%) 2	2 / 127 (1.57%) 2
Gastrointestinal disorders ABDOMINAL PAIN subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	3 / 80 (3.75%) 3	5 / 127 (3.94%) 5
ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3	5 / 80 (6.25%) 6	6 / 127 (4.72%) 7
DIARRHOEA subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	8 / 80 (10.00%) 8	11 / 127 (8.66%) 11
NAUSEA subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	5 / 80 (6.25%) 5	9 / 127 (7.09%) 9
VOMITING subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 4	11 / 80 (13.75%) 11	16 / 127 (12.60%) 16
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	5 / 24 (20.83%) 6	7 / 80 (8.75%) 8	9 / 127 (7.09%) 10
DYSPNOEA subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	3 / 80 (3.75%) 3	3 / 127 (2.36%) 3
NASAL CONGESTION subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 80 (0.00%) 0	4 / 127 (3.15%) 4
OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 80 (1.25%) 1	6 / 127 (4.72%) 6
RHINORRHOEA			

subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	2 / 80 (2.50%) 2	2 / 127 (1.57%) 2
Skin and subcutaneous tissue disorders PRURITUS subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	3 / 80 (3.75%) 3	3 / 127 (2.36%) 3
RASH subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	3 / 80 (3.75%) 4	4 / 127 (3.15%) 5
Infections and infestations LICE INFESTATION subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	2 / 80 (2.50%) 2	2 / 127 (1.57%) 2
NASOPHARYNGITIS subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	6 / 80 (7.50%) 7	17 / 127 (13.39%) 19
UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	6 / 80 (7.50%) 9	15 / 127 (11.81%) 20
VIRAL INFECTION subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	4 / 80 (5.00%) 4	4 / 127 (3.15%) 4
Metabolism and nutrition disorders INCREASED APPETITE subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	2 / 80 (2.50%) 2	2 / 127 (1.57%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2017	Key changes included: <ul style="list-style-type: none">- Included specific changes for subjects in Japan to account for the participation of subjects in Japan.- Updated language regarding the SVR12 efficacy analysis to clarify the criteria that will establish when the Wilson's score method will be used as opposed to the normal approximation to the binomial distribution in determination of the confidence interval as per FDA Biometric comment.
09 March 2018	Key changes included: <ul style="list-style-type: none">- Provided dosing details about the GLE/PIB pediatric formulation to be used in Part 2 for subjects 3 to 11 years old.- Updated the proposed doses for 3 to 11 year old subjects (proposed dosing for each age group and weight range were added based on the current knowledge of the GLE and PIB exposures).- Included retreatment study information clarifying subjects in Part 1 who met the virologic failure criteria in the PT period have the option to enroll into Study M15-942 for retreatment of their virologic failure.- Included information on Study M17-142 results for pediatric formulation to support the proposed pediatric formulation dosing.- Updated the recommendations for use of pravastatin or rosuvastatin dose to clarify the timing of statin management.- Updated the statistical analysis section to clarify the number of planned analyses and to align the description of endpoints with the approved PIP.
22 March 2019	Key changes included: <ul style="list-style-type: none">- Updated the proposed doses for ≥ 3 to < 12 year old subjects based on current PK and safety knowledge of the pediatric doses for GLE and PIB.- Updated total number of subjects to be enrolled from 110 to 125 subjects, due to change in dosing and need for additional subject enrollment.- Details on the waived pediatric requirement for children < 3 years were added.- Update to the product identity with proposed doses and storage requirements, including a reference to the interchangeable nomenclature of pellets and granules.- The Suspected Unexpected Serious Adverse Reaction reporting process was added per company guidance.- Clarification on the use of the eCRF questionnaire added that would require completion in the event of active Hepatitis B.- Clarification provided on the lab draw procedures for the coagulation panel and addition of collection of HCV resistance samples.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported