Clinical trial results:
A Phase IIb Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chronic Hepatitis C Infection

Summary

EudraCT number	2015-003006-16
Trial protocol	DE SE PL Outside EU/EEA
Global end of trial date	23 July 2020

Results information

Result version number	v1
This version publication date	24 October 2020
First version publication date	24 October 2020

Trial information

Trial identification

Sponsor protocol code	5172-079

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03379506
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NC, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001604-PIP01-13
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	23 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the pharmacokinetics (PK), safety, and efficacy of oral MK-5172 (a fixed dose combination [FDC] tablet containing elbasvir [EBR] 50 mg and grazoprevir [GZR] 100 mg) and EBR/GZR (varying doses) pediatric granules in pediatric hepatitis C virus (HCV)-infected participants who are 3 to <18 years of age. Within each age cohort (Cohort 1: 12 to <18 years of age; Cohort 2: 7 to <12 years of age; and Cohort 3: 3 to <7 years of age), a Mini Cohort of 7 participants will be enrolled first. For the oldest cohort (Cohort 1), the Mini Cohort will assess ability to swallow a placebo tablet prior to administering active FDC tablets. Participants in Cohorts 2 and 3 will take pediatric granules instead of a tablet.

The present results disclosure includes the sustained virologic response 12 weeks after completing treatment (SVR12) endpoint data with a cutoff date of 10 April 2020. Study results will be updated once the final data analysis has completed.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	57
EEA total number of subjects	34

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)	35
Adolescents (12-17 years)	22
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female participants 3 to <18 years of age with chronic hepatitis C virus (HCV) genotype 1 (GT1) or GT4 were enrolled at 14 global study sites.

Pre-assignment

Screening details:

The present results include data up through the sustained virologic response 12 weeks after completing therapy (SVR12) endpoint cutoff date of 10 April 2020, and will be updated once the final dataset has been analyzed.

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	Age Cohort 1: 12 to <18 Years: Mini and Expanded

Arm description:

Pediatric participants 12 to <18 years of age received elbasvir (EBR) 50 mg / grazoprevir (GZR) 100 mg fixed dose combination (FDC) tablets once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	EBR/GZR Fixed Dose Combination
Investigational medicinal product code	
Other name	MK-5172; ZEPATIER®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who are 12 to <18 years of age will receive oral FDC tablets with EBR 50 mg/GZR 100 mg once daily.

Arm title	Age Cohort 2: 7 to <12 Years: Mini and Expanded

Arm description:

Participants who are 7 to <12 years of age received EBR/GZR 30 mg/60 mg pediatric granules once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	EBR/GZR Fixed Dose Combination
Investigational medicinal product code	
Other name	MK-5172; ZEPATIER®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who are 3 to <12 years of age will receive oral granules in a soft food vehicle (not to exceed EBR/GRZ 50 mg/100 mg) once daily.

Arm title	Age Cohort 3: 3 to <7 Years: Mini

Arm description:

Participants who are 3 to <7 years of age received a pediatric formulation of EBR/GZR (weight-based dosing) once daily for 12 weeks. The Mini cohort consists of the first 7 participants enrolled into Age Cohort 3. Participants <20 kg received EBR/GZR 15 mg/30 mg, and participants ≥20 kg received EBR/GZR 15 mg/50 mg.

Arm type	Experimental

Investigational medicinal product name	EBR/GZR Fixed Dose Combination
Investigational medicinal product code	
Other name	MK-5172; ZEPATIER®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who are 3 to <12 years of age will receive oral granules in a soft food vehicle (not to exceed EBR/GRZ 50 mg/100 mg) once daily.

Arm title	Age Cohort 3: 3 to <7 Years: Expanded

Arm description:

Participants who are 3 to <7 years of age received a pediatric formulation of EBR/GZR 25 mg/50 mg once daily for 12 weeks. The Expanded cohort consists of 11 participants enrolled after the Mini Cohort of 7 participants.

Arm type	Experimental
Investigational medicinal product name	EBR/GZR Fixed Dose Combination
Investigational medicinal product code	
Other name	MK-5172; ZEPATIER®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who are 3 to <12 years of age will receive oral granules in a soft food vehicle (not to exceed EBR/GRZ 50 mg/100 mg) once daily.

Number of subjects in period 1	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini
Started	22	17	7
Completed	22	8	7
Not completed	0	9	0
Ongoing in study	-	9	-

Number of subjects in period 1	Age Cohort 3: 3 to <7 Years: Expanded
Started	11
Completed	0
Not completed	11
Ongoing in study	11

Baseline characteristics

Reporting groups	
Reporting group title	Age Cohort 1: 12 to <18 Years: Mini and Expanded
Reporting group description:	
Pediatric participants 12 to <18 years of age received elbasvir (EBR) 50 mg / grazoprevir (GZR) 100 mg fixed dose combination (FDC) tablets once daily for 12 weeks.	
Reporting group title	Age Cohort 2: 7 to <12 Years: Mini and Expanded
Reporting group description:	
Participants who are 7 to <12 years of age received EBR/GZR 30 mg/60 mg pediatric granules once daily for 12 weeks.	
Reporting group title	Age Cohort 3: 3 to <7 Years: Mini
Reporting group description:	
Participants who are 3 to <7 years of age received a pediatric formulation of EBR/GZR (weight-based dosing) once daily for 12 weeks. The Mini cohort consists of the first 7 participants enrolled into Age Cohort 3. Participants <20 kg received EBR/GZR 15 mg/30 mg, and participants ≥20 kg received EBR/GZR 15 mg/50 mg.	
Reporting group title	Age Cohort 3: 3 to <7 Years: Expanded
Reporting group description:	
Participants who are 3 to <7 years of age received a pediatric formulation of EBR/GZR 25 mg/50 mg once daily for 12 weeks. The Expanded cohort consists of 11 participants enrolled after the Mini Cohort of 7 participants.	

Reporting group values	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini
Number of subjects	22	17	7
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	17	7
Adolescents (12-17 years)	22	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	14.1	8.7	3.7
standard deviation	± 1.9	± 1.2	± 0.8
Sex: Female, Male Units: Participants			
Female	11	7	3
Male	11	10	4
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	21	17	7
More than one race	1	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	2	1
Not Hispanic or Latino	19	14	6
Unknown or Not Reported	0	1	0

Reporting group values	Age Cohort 3: 3 to <7 Years: Expanded	Total	
Number of subjects	11	57	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	11	35	
Adolescents (12-17 years)	0	22	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	4.8		
standard deviation	± 1.3	-	
Sex: Female, Male			
Units: Participants			
Female	8	29	
Male	3	28	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	11	56	
More than one race	0	1	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	6	
Not Hispanic or Latino	11	50	
Unknown or Not Reported	0	1	

End points

End points reporting groups

Reporting group title	Age Cohort 1: 12 to <18 Years: Mini and Expanded
Reporting group description:	
Pediatric participants 12 to <18 years of age received elbasvir (EBR) 50 mg / grazoprevir (GZR) 100 mg fixed dose combination (FDC) tablets once daily for 12 weeks.	
Reporting group title	Age Cohort 2: 7 to <12 Years: Mini and Expanded
Reporting group description:	
Participants who are 7 to <12 years of age received EBR/GZR 30 mg/60 mg pediatric granules once daily for 12 weeks.	
Reporting group title	Age Cohort 3: 3 to <7 Years: Mini
Reporting group description:	
Participants who are 3 to <7 years of age received a pediatric formulation of EBR/GZR (weight-based dosing) once daily for 12 weeks. The Mini cohort consists of the first 7 participants enrolled into Age Cohort 3. Participants <20 kg received EBR/GZR 15 mg/30 mg, and participants ≥20 kg received EBR/GZR 15 mg/50 mg.	
Reporting group title	Age Cohort 3: 3 to <7 Years: Expanded
Reporting group description:	
Participants who are 3 to <7 years of age received a pediatric formulation of EBR/GZR 25 mg/50 mg once daily for 12 weeks. The Expanded cohort consists of 11 participants enrolled after the Mini Cohort of 7 participants.	

Primary: Area Under the Plasma Concentration-Time Curve from Dosing to 24 Hours Postdose (AUC0-24hr) of EBR at Steady State

End point title	Area Under the Plasma Concentration-Time Curve from Dosing to 24 Hours Postdose (AUC0-24hr) of EBR at Steady State[1]
End point description:	
The AUC0-24hr of EBR at steady state (Week 4) was determined in each cohort. All randomized and treated participants who complied with the protocol sufficiently to ensure that their pharmacokinetic (PK) data was likely to exhibit the effects of treatment, according to the underlying scientific model, are included.	
End point type	Primary
End point timeframe:	
Week 4: Predose and 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours postdose	

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: Per protocol, only descriptive statistics are presented.

End point values	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini	Age Cohort 3: 3 to <7 Years: Expanded
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	17	7	11
Units: µM*hr				
geometric mean (confidence interval 95%)	2.41 (1.97 to 2.94)	2.79 (2.31 to 3.37)	1.71 (1.36 to 2.15)	3.15 (2.52 to 3.96)

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Plasma Concentration (Cmax) of EBR

End point title	Maximum Plasma Concentration (Cmax) of EBR[2]

End point description:

The Cmax of EBR at steady state (Week 4) was determined in each cohort. All randomized and treated participants who complied with the protocol sufficiently to ensure that their pharmacokinetic (PK) data was likely to exhibit the effects of treatment, according to the underlying scientific model, are included.

End point type	Primary

End point timeframe:

Week 4: Predose and 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours postdose

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per protocol, only descriptive statistics are presented.

End point values	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini	Age Cohort 3: 3 to <7 Years: Expanded
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	17	7	11
Units: µM				
geometric mean (confidence interval 95%)	0.19 (0.15 to 0.23)	0.21 (0.17 to 0.25)	0.14 (0.11 to 0.19)	0.28 (0.22 to 0.36)

Statistical analyses

No statistical analyses for this end point

Primary: Steady State Predose Drug Concentration (Ctrough) of EBR

End point title	Steady State Predose Drug Concentration (Ctrough) of EBR[3]

End point description:

The Ctrough of EBR at steady state (Week 4) was determined at steady state prior to dosing in each cohort. All randomized and treated participants who complied with the protocol sufficiently to ensure that their PK data was likely to exhibit the effects of treatment, according to the underlying scientific model, are included. One participant in Age Cohort 2: 7 to <12 Years: Mini and Expanded had missing Ctrough data.

End point type	Primary

End point timeframe:

Week 4: Predose

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per protocol, only descriptive statistics are presented.

End point values	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini	Age Cohort 3: 3 to <7 Years: Expanded
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	16	7	11
Units: nM				
geometric mean (confidence interval 95%)	59.76 (47.20 to 75.67)	59.43 (48.67 to 72.58)	34.61 (28.00 to 42.77)	68.92 (54.32 to 87.44)

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Clearance (CL/F) of EBR at Steady State

End point title	Apparent Clearance (CL/F) of EBR at Steady State[4]

End point description:

The CL/F of EBR at steady state (Week 4) was determined in each cohort. All randomized and treated participants who complied with the protocol sufficiently to ensure that their PK data was likely to exhibit the effects of treatment, according to the underlying scientific model, are included.

End point type	Primary

End point timeframe:

Week 4: Predose and 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours postdose

Notes:

[4] - 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: Per protocol, only descriptive statistics are presented.

End point values	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini	Age Cohort 3: 3 to <7 Years: Expanded
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	17	7	11
Units: L/hr				
geometric mean (confidence interval 95%)	23.53 (19.25 to 28.75)	12.21 (10.10 to 14.75)	9.94 (7.89 to 12.53)	8.98 (7.16 to 11.27)

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-24hr of GZR at Steady State

End point title	AUC0-24hr of GZR at Steady State[5]

End point description:

The AUC0-24hr of GZR at steady state (Week 4) was determined in each cohort. All randomized and treated participants who complied with the protocol sufficiently to ensure that their PK data was likely to exhibit the effects of treatment, according to the underlying scientific model, are included.

End point type	Primary

End point timeframe:

Week 4: Predose and 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours postdose

Notes:

[5] - 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: Per protocol, only descriptive statistics are presented.

End point values	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini	Age Cohort 3: 3 to <7 Years: Expanded
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	17	7	11
Units: µM*hr				
geometric mean (confidence interval 95%)	1.45 (1.08 to 1.94)	1.42 (1.00 to 2.02)	0.77 (0.48 to 1.23)	1.66 (1.16 to 2.39)

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of GZR

End point title	Cmax of GZR[6]

End point description:

The Cmax of GZR at steady state (Week 4) was determined in each cohort. All randomized and treated participants who complied with the protocol sufficiently to ensure that their PK data was likely to exhibit the effects of treatment, according to the underlying scientific model, are included.

End point type	Primary

End point timeframe:

Week 4: Predose and 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours postdose

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: Per protocol, only descriptive statistics are presented.

End point values	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini	Age Cohort 3: 3 to <7 Years: Expanded
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	17	7	11
Units: µM				
geometric mean (confidence interval 95%)	0.25 (0.17 to 0.35)	0.19 (0.12 to 0.31)	0.09 (0.05 to 0.18)	0.29 (0.18 to 0.47)

Statistical analyses

No statistical analyses for this end point

Primary: Ctrough of GZR

End point title	Ctrough of GZR[7]

End point description:

The Ctrough of GZR at steady state (Week 4) was determined at steady state prior to dosing in each cohort. All randomized and treated participants who complied with the protocol sufficiently to ensure that their PK data was likely to exhibit the effects of treatment, according to the underlying scientific model, are included. One participant in Age Cohort 2: 7 to <12 Years: Mini and Expanded had missing Ctrough data.

End point type	Primary

End point timeframe:

Week 4: Predose

Notes:

[7] - 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: Per protocol, only descriptive statistics are presented.

End point values	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini	Age Cohort 3: 3 to <7 Years: Expanded
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	16	7	11
Units: nM				
geometric mean (confidence interval 95%)	16.20 (12.27 to 21.38)	16.27 (11.97 to 22.10)	13.79 (9.55 to 19.90)	16.17 (12.78 to 20.45)

Statistical analyses

No statistical analyses for this end point

Primary: CL/F of GZR at Steady State

End point title	CL/F of GZR at Steady State[8]

End point description:

The CL/F of GZR at steady state (Week 4) was determined in each cohort. No participants are included in the analysis as the CL/F of GZR was not calculable due to nonlinear PK.

End point type	Primary

End point timeframe:

Week 4: Predose and 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours postdose

Notes:

[8] - 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: Per protocol, only descriptive statistics are presented.

End point values	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini	Age Cohort 3: 3 to <7 Years: Expanded
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[9]	0[10]	0[11]	0[12]
Units: L/hr				
geometric mean (geometric coefficient of variation)	()	()	()	()

Notes:

[9] - CL/F of GZR was not calculable due to nonlinear PK.

[10] - CL/F of GZR was not calculable due to nonlinear PK.

[11] - CL/F of GZR was not calculable due to nonlinear PK.

[12] - CL/F of GZR was not calculable due to nonlinear PK.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with ≥1 Adverse Event (AE)

End point title	Percentage of Participants with ≥1 Adverse Event (AE)

End point description:

The percentage of participants with ≥1 AE is reported in each cohort. An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. All randomized participants who received ≥1 dose of study drug are included.

End point type	Secondary

End point timeframe:

Up to 14 weeks (12 weeks of treatment + first 14 days of follow-up)

End point values	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini	Age Cohort 3: 3 to <7 Years: Expanded
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	17	7	11
Units: Percentage of Participants				
number (not applicable)	77.3	76.5	85.7	63.6

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Discontinuing Study Treatment due to an AE

End point title	Percentage of Participants Discontinuing Study Treatment due to an AE

End point description:

The percentage of participants discontinuing study therapy due to an AE is reported in each cohort. An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. All randomized participants who received ≥1 dose of study drug are included.

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini	Age Cohort 3: 3 to <7 Years: Expanded
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	17	7	11
Units: Percentage of Participants				
number (not applicable)	0.0	0.0	0.0	0.0

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants With Sustained Virologic Response 12 Weeks After Completing Treatment (SVR12)

End point description:

The percentage of participants achieving SVR12, defined as hepatitis C virus (HCV) ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks after completing study therapy, was determined in each cohort. All randomized participants who received ≥1 dose of study treatment are included.

End point type	Secondary

End point timeframe:

Week 24

End point values	Age Cohort 1: 12 to <18 Years: Mini and Expanded	Age Cohort 2: 7 to <12 Years: Mini and Expanded	Age Cohort 3: 3 to <7 Years: Mini	Age Cohort 3: 3 to <7 Years: Expanded
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	17	7	11
Units: Percentage of Participants				
number (confidence interval 95%)	100.0 (84.6 to 100.0)	100.0 (80.5 to 100.0)	100.0 (59.0 to 100.0)	100.0 (71.5 to 100.0)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 36 weeks (up to approximately 21 months for all-cause mortality)	
Adverse event reporting additional description:	
All participants who received ≥1 dose of study drug are included.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Age Cohort 1: 12 to <18 years
Reporting group description:	
Pediatric participants 12 to <18 years of age received elbasvir (EBR) 50 mg / grazoprevir (GZR) 100 mg fixed dose combination (FDC) tablets once daily for 12 weeks.	
Reporting group title	Age Cohort 2: 7 to <12 years
Reporting group description:	
Participants who are 7 to <12 years of age received EBR/GZR 30 mg/60 mg pediatric granules once daily for 12 weeks.	
Reporting group title	Age Cohort 3 Mini: 3 to <7 years
Reporting group description:	
Participants who are 3 to <7 years of age received a pediatric formulation of EBR/GZR (weight-based dosing) once daily for 12 weeks. The Mini cohort consists of the first 7 participants enrolled into Age Cohort 3. Participants <20 kg received EBR/GZR 15 mg/30 mg, and participants ≥20 kg received EBR/GZR 15 mg/50 mg.	
Reporting group title	Age Cohort 3 Expanded: 3 to <7 years
Reporting group description:	
Participants who are 3 to <7 years of age received a pediatric formulation of EBR/GZR 25 mg/50 mg once daily for 12 weeks. The Expanded cohort consists of 11 participants enrolled after the Mini Cohort of 7 participants.	

Serious adverse events	Age Cohort 1: 12 to <18 years	Age Cohort 2: 7 to <12 years	Age Cohort 3 Mini: 3 to <7 years
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dyspepsia			

subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Age Cohort 3 Expanded: 3 to <7 years		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 11 (9.09%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 11 (9.09%)		
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	Age Cohort 1: 12 to <18 years	Age Cohort 2: 7 to <12 years	Age Cohort 3 Mini: 3 to <7 years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 22 (72.73%)	13 / 17 (76.47%)	6 / 7 (85.71%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood calcium decreased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Body temperature increased			
subjects affected / exposed	2 / 22 (9.09%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Animal bite			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Intentional overdose			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Post procedural discomfort			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Skin laceration			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Upper limb fracture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 22 (13.64%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Headache			
subjects affected / exposed	8 / 22 (36.36%)	2 / 17 (11.76%)	0 / 7 (0.00%)
occurrences (all)	14	4	0
General disorders and administration site conditions			

Energy increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	2 / 22 (9.09%)	2 / 17 (11.76%)	1 / 7 (14.29%)
occurrences (all)	2	2	1
Pyrexia			
subjects affected / exposed	3 / 22 (13.64%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 17 (5.88%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Abdominal pain upper			
subjects affected / exposed	3 / 22 (13.64%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	5	1	0
Constipation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)	1 / 17 (5.88%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Gastritis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	4 / 22 (18.18%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Vomiting			
subjects affected / exposed	3 / 22 (13.64%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	3	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 22 (4.55%)	1 / 17 (5.88%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Epistaxis			

subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 22 (4.55%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Sneezing			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	1 / 22 (4.55%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Behaviour disorder			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Provisional tic disorder			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Restlessness			

subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 22 (4.55%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	1 / 7 (14.29%)
occurrences (all)	0	1	2
Folliculitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis viral			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Herpes zoster			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	3 / 22 (13.64%)	1 / 17 (5.88%)	1 / 7 (14.29%)
occurrences (all)	6	2	1
Otitis media			

subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 22 (0.00%)	2 / 17 (11.76%)	1 / 7 (14.29%)
occurrences (all)	0	4	1
Rhinitis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Sinusitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 22 (0.00%)	3 / 17 (17.65%)	1 / 7 (14.29%)
occurrences (all)	0	3	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Age Cohort 3 Expanded: 3 to <7 years		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 11 (72.73%)		
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood calcium decreased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Body temperature increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Animal bite			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Intentional overdose			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	3		
Post procedural discomfort			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin laceration			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Upper limb fracture			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
General disorders and administration site conditions			
Energy increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Vomiting			

subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Sneezing			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Behaviour disorder			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Provisional tic disorder			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Restlessness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	3		
Herpes zoster			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Impetigo			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Influenza			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Otitis media			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pharyngitis streptococcal			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Rhinitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 August 2017	AM01: The primary purpose of the amendment was to reformat the original protocol into a new structure.
16 February 2018	AM02: The primary purpose of the amendment was to add an additional PK endpoint and modify dosing criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported