Clinical trial results:
A Long-Term Follow-up Study to Evaluate the Durability of Virologic Response and/or Viral Resistance Patterns of Subjects With Chronic Hepatitis C Who Have Been Previously Treated with MK-5172 in a Prior Clinical Trial

Summary

EudraCT number	2012-002232-85
Trial protocol	DE FR IT SE GB DK HU ES FI NL LT EE CZ NO AT PL GR
Global end of trial date	31 March 2021

Results information

Result version number	v1 (current)
This version publication date	25 March 2022
First version publication date	25 March 2022

Trial information

Trial identification

Sponsor protocol code	5172-017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01667081
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, 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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2021
Global end of trial reached?	Yes
Global end of trial date	31 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a three-year (except for participants with chronic kidney disease [CKD] or cirrhosis) multicenter study to follow participants who received at least one dose of grazoprevir (MK-5172) in a previous study to determine whether they remain hepatitis C virus (HCV)-Ribonucleic acid (RNA) negative over time, and to determine if they have developed antiviral resistance. The study will also evaluate long-term adverse events in this population. Participants from MK-5172-052 (NCT02092350) with CKD or cirrhosis will be followed for five years.

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	17 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	Australia: 41
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 99
Country: Number of subjects enrolled	Czechia: 45
Country: Number of subjects enrolled	Denmark: 96
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 206
Country: Number of subjects enrolled	Germany: 67
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Israel: 209
Country: Number of subjects enrolled	Italy: 39

Country: Number of subjects enrolled	Korea, Republic of: 88
Country: Number of subjects enrolled	Lithuania: 28
Country: Number of subjects enrolled	Malaysia: 10
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	New Zealand: 21
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Romania: 18
Country: Number of subjects enrolled	Russian Federation: 109
Country: Number of subjects enrolled	Spain: 110
Country: Number of subjects enrolled	Sweden: 56
Country: Number of subjects enrolled	Switzerland: 10
Country: Number of subjects enrolled	Taiwan: 120
Country: Number of subjects enrolled	Thailand: 25
Country: Number of subjects enrolled	Turkey: 19
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	United States: 882
Country: Number of subjects enrolled	Viet Nam: 5
Worldwide total number of subjects	2435
EEA total number of subjects	764

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	2207
From 65 to 84 years	228
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 2438 adult Hepatitis C Virus (HCV)-infected participants who were previously treated in 18 prior clinical trials, enrolled in this study.

Pre-assignment

Screening details:

Of the 2438 participants, three participants were excluded from all analyses. Two participants enrolled in error failed to receive at least 1 dose of Grazoprevir (GZR) in a prior study (each received a comparator regimen in a prior base study) and 1 participant had insufficient long-term follow-up data (participant withdrew consent on Day 27).

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	GZR 100 mg + EBR 50 mg +/- Ribavirin (RBV)

Arm description:

Participants previously received grazoprevir (GZR) 100mg + Elbasvir (EBR) 50mg with or without RBV in a prior study.

Arm type	non-interventional
Investigational medicinal product name	Grazoprevir (GZR)
Investigational medicinal product code	
Other name	MK-5172
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants previously received study treatment with grazoprevir in a prior clinical trial, at the dose and frequency specified in the study protocol. Grazoprevir was not administered to participants in the course of this follow-up study.

Arm title	Other GZR regimen

Arm description:

Participants previously received at least one dose of GZR in a prior study

Arm type	non-interventional

No investigational medicinal product assigned in this arm

Number of subjects in period 1	GZR 100 mg + EBR 50 mg +/- Ribavirin (RBV)	Other GZR regimen
Started	1909	526
Completed	132	169
Not completed	1777	357
Adverse event, serious fatal	43	3
Physician decision	16	2

Consent withdrawn by subject	90	35
amendment 3 modified the follow up criteria	1529	269
Lost to follow-up	99	48

Baseline characteristics

Reporting groups	
Reporting group title	GZR 100 mg + EBR 50 mg +/- Ribavirin (RBV)
Reporting group description:	
Participants previously received grazoprevir (GZR) 100mg + Elbasvir (EBR) 50mg with or without RBV in a prior study.	
Reporting group title	Other GZR regimen
Reporting group description:	
Participants previously received at least one dose of GZR in a prior study	

Reporting group values	GZR 100 mg + EBR 50 mg +/- Ribavirin (RBV)	Other GZR regimen	Total
Number of subjects	1909	526	2435
Age categorical Units: Participants			
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	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1712	495	2207
From 65-84 years	197	31	228
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	51.9	49.7	
standard deviation	± 11.0	± 11.4	-
Sex: Female, Male Units: Participants			
Female	785	238	1023
Male	1124	288	1412
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	5	2	7
Asian	283	12	295
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	253	35	288
White	1345	470	1815
More than one race	21	6	27
Unknown or Not Reported	1	0	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	135	68	203
Not Hispanic or Latino	1730	444	2174
Unknown or Not Reported	44	14	58

End points

End points reporting groups

Reporting group title	GZR 100 mg + EBR 50 mg +/- Ribavirin (RBV)
Reporting group description:	
Participants previously received grazoprevir (GZR) 100mg + Elbasvir (EBR) 50mg with or without RBV in a prior study.	
Reporting group title	Other GZR regimen
Reporting group description:	
Participants previously received at least one dose of GZR in a prior study	
Subject analysis set title	GZR 100 mg + EBR 50 mg +/- RBV
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants previously received GZR 100mg +EBR 50mg with or without RBV in a prior study.	
Subject analysis set title	EBR/GZR +/- RBV: NS3 RASs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants previously received EBR and GZR with or without RBV in a prior study and had treatment-emergent NS3 RASs	
Subject analysis set title	EBR/GZR +/- RBV: NS5A RASs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants previously received EBR and GZR with or without RBV in a prior study and had treatment-emergent NS5A RASs	
Subject analysis set title	EBR/GZR +/-RBV: Both NS3 and NS5A RASs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants previously received EBR and GZR with or without RBV in a prior study and had both treatment-emergent NS3 and NS5A RASs	
Subject analysis set title	GZR + pegylated interferon/ribavirin (PR): NS3 RASs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants previously received GZR and PR for 12 weeks in a prior study and had treatment-emergent NS3 RASs	
Subject analysis set title	EBR/GZR+/- RBV: NS3 RASs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants previously received EBR and GZR with or without RBV in a prior study and had treatment-emergent NS3 RASs	
Subject analysis set title	EBR/GZR +/- RBV: NS5A RASs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants previously received EBR and GZR with or without RBV in a prior study and had treatment-emergent NS5A RASs	
Subject analysis set title	EBR/GZR +/-RVB: Both NS3 and NS5A RASs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants previously received EBR and GZR with or without RBV in a prior study and had both treatment-emergent NS3 and NS5A RASs	
Subject analysis set title	GZR + RBV or PR: NS3 RASs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants previously received GZR and RBV or PR for 12 weeks in a prior study and had treatment-	

emergent NS3 RASs

Subject analysis set title	EBR/GZR: NS3 RASs
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants previously received EBR and GZR in a prior study and had treatment-emergent NS3 RASs

Subject analysis set title	EBR/GZR: NS5A RASs
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants previously received EBR and GZR in a prior study and had treatment-emergent NS5A RASs

Subject analysis set title	EBR/GZR: Both NS3 and NS5A RASs
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants previously received EBR and GZR in a prior study and had both treatment-emergent NS3 and NS5A RASs

Primary: Time to Viral Relapse

End point title	Time to Viral Relapse[1]

End point description:

Viral relapse is defined as any participant who has confirmed HCV Ribonucleic acid (RNA) ≥ Lower limit of quantification (LLoQ) of 15 IU/mL and had achieved sustained virologic response (SVR) in the follow up in the prior treatment study. Time to relapse is defined as the time from last dose of study therapy taken in the prior treatment study until the date where HCV RNA is ≥LLoQ. A value of 9999 indicates that median time to viral relapse and interquartile range were not reached due to the low rate of late virologic relapse. The analysis population included all participants who achieved SVR during the follow-up period of the prior treatment study and did not start any new HCV therapy between the end of the prior treatment study and entry in this study.

End point type	Primary

End point timeframe:

Up to ~60 months after enrollment in this study

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 statistical analysis was planned for this endpoint

End point values	GZR 100 mg + EBR 50 mg +/- Ribavirin (RBV)	Other GZR regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1837	495		
Units: Months				
median (inter-quartile range (Q1-Q3))	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Primary: Persistence of Treatment-Emergent Nonstructural Protein (NS)3 and NS5A Resistance-associated Substitutions (RASs) in Participants with HCV Genotype (GT) 1a infections

End point title	Persistence of Treatment-Emergent Nonstructural Protein (NS)3 and NS5A Resistance-associated Substitutions (RASs) in Participants with HCV Genotype (GT) 1a infections[2]

End point description:

In adult participants with HCV RNA ≥1000 IU/mL at entry or during the study period, HCV sequence analysis was performed to evaluate the presence of RASs and the persistence of RASs over time. The analysis population included participants who met the criteria of virologic failure either in the prior base study or had HCV RNA Target detected, quantifiable [TD(q)] at entry in current study. Participants did not receive new HCV therapy between the end of the prior base study and entry into this study. Only HCV genotype infections that had adequate reference information were included.

End point type	Primary

End point timeframe:

Up to ~60 months after enrollment in this study

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: No statistical analysis was planned for this endpoint

End point values	EBR/GZR +/- RBV: NS3 RASs	EBR/GZR +/- RBV: NS5A RASs	EBR/GZR +/- RBV: Both NS3 and NS5A RASs	GZR + pegylated interferon/ribavirin (PR): NS3 RASs
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	31	31	16
Units: Participants				
Failure	22	25	18	11
24 weeks (wk) post failure	10	25	8	2
48 weeks post failure (N analyzed=30, 30, 30, 16)	6	22	4	2
96 weeks post failure (N analyzed=21, 21, 21, 15)	4	15	3	1
≥144 weeks post failure (N analyzed=17, 17, 17, 8)	2	11	1	1

Statistical analyses

No statistical analyses for this end point

Primary: Persistence of Treatment-Emergent NS3 and NS5A RASs in Participants with HCV Genotype 1b Infections

End point title	Persistence of Treatment-Emergent NS3 and NS5A RASs in Participants with HCV Genotype 1b Infections[3]

End point description:

In adult participants with HCV RNA ≥1000 IU/mL at entry or during the study period, HCV sequence analysis was performed to evaluate the presence of RASs and the persistence of RASs over time. The analysis population included participants who met the criteria of virologic failure either in the prior base study or had HCV RNA TD(q) at entry in current study. Participants did not receive new HCV therapy between the end of the prior base study and entry into this study. Only HCV genotype infections that had adequate reference information were included.

End point type	Primary

End point timeframe:

Up to ~60 months after enrollment in this study

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: No statistical analysis was planned for this endpoint

End point values	EBR/GZR+/- RBV: NS3 RASs	EBR/GZR +/- RBV: NS5A RASs	EBR/GZR +/- RVB: Both NS3 and NS5A RASs	GZR + RBV or PR: NS3 RASs
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	9	5
Units: Participants				
Failure	4	7	2	3
24 weeks post failure	2	7	0	1
48 weeks post failure (N analyzed=6, 6, 6, 4)	1	5	0	1
96 weeks post failure (N analyzed=4, 4, 4, 4)	1	3	0	1
≥144 weeks post failure (N analyzed=3, 3, 3, 4)	0	3	0	1

Statistical analyses

No statistical analyses for this end point

Primary: Persistence of Treatment-Emergent NS3 and NS5A RASs in Participants with Genotype 4 Infections

End point title	Persistence of Treatment-Emergent NS3 and NS5A RASs in Participants with Genotype 4 Infections[4]

End point description:

In adult participants with HCV RNA ≥1000 IU/mL at entry or during the study period, HCV sequence analysis was performed to evaluate the presence of RASs and the persistence of RASs over time. The analysis population included participants who met the criteria of virologic failure either in the prior base study or had HCV RNA TD(q) at entry in current study. Participants did not receive new HCV therapy between the end of the prior base study and entry into this study. Only HCV genotype infections that had adequate reference information were included.

End point type	Primary

End point timeframe:

Up to ~60 months after enrollment in this study

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: No statistical analysis was planned for this endpoint

End point values	EBR/GZR: NS3 RASs	EBR/GZR: NS5A RASs	EBR/GZR: Both NS3 and NS5A RASs	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5	5	5	
Units: Participants				
Failure	2	4	2	
24 weeks post failure	1	3	1	
48 weeks post failure	1	2	1	
96 weeks post failure	1	2	1	
≥144 weeks post failure	1	2	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced a Drug-Related Adverse Event (AE) During the Long-Term Follow-Up

End point title	Number of Participants Who Experienced a Drug-Related Adverse Event (AE) During the Long-Term Follow-Up[5]

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The study investigator determined whether the adverse event was drug-related. The analysis population included all participants treated with GZR in a prior study. Three participants were excluded from analysis; two participants enrolled in error failed to receive at least one dose of GZR in a prior study (each received a comparator regimen in a prior base study) and one participant had insufficient long-term follow-up data (participant withdrew consent on Day 27).

End point type	Primary

End point timeframe:

Up to ~ 60 months after enrollment in this study

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: No statistical analysis was planned for this endpoint

End point values	GZR 100 mg + EBR 50 mg +/- Ribavirin (RBV)	Other GZR regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1909	526		
Units: Participants	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced a Drug-Related Serious Adverse Event (SAE) During the Long-Term Follow-Up

End point title	Number of Participants Who Experienced a Drug-Related Serious Adverse Event (SAE) During the Long-Term Follow-Up[6]

End point description:

An SAE is any adverse experience occurring at any dose that either results in death, is life threatening, results in a persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalization, is a congenital anomaly/birth defect, is a cancer, is an overdose, or other important medical events that may be considered an SAE when the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously. The study investigator determined whether the adverse event was drug-related. The analysis population included all participants treated with GZR in a prior study. Three participants were excluded from analysis; two participants enrolled in error failed to receive at least one dose of GZR in a prior study (each received a comparator regimen in a prior base study) and one participant had insufficient long-term follow-up data.

End point type	Primary

End point timeframe:

Up to ~60 months after enrollment in this study

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 statistical analysis was planned for this endpoint

End point values	GZR 100 mg + EBR 50 mg +/- Ribavirin (RBV)	Other GZR regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1909	526		
Units: Participants	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced an Event of Clinical Interest (ECI) During the Long-Term Follow-Up

End point title	Number of Participants Who Experienced an Event of Clinical Interest (ECI) During the Long-Term Follow-Up[7]

End point description:

An ECI includes spontaneous bacterial peritonitis, variceal bleeding, ascites, encephalopathy, hepatorenal syndrome, hepatocellular carcinoma, liver transplant, cardiovascular disease limited to angina and myocardial infarction, neurologic disorders limited to transient ischemic attack (TIA) or stroke, graft rejection in participants who have undergone liver or kidney transplant, or one of the following in participants from the MK-5172-052 (NCT02092350) base study: kidney transplant, decreased estimated glomerular filtration rate (eGFR), new onset diabetes, cryoglobulinemia, or post transplantation glomerulonephritis. The analysis population included all participants treated with GZR in a prior study. Three participants were excluded from analysis; two participants enrolled in error failed to receive at least one dose of GZR in a prior study (each received a comparator regimen in a prior base study) and one participant had insufficient long-term follow-up data.

End point type	Primary

End point timeframe:

Up to ~60 months after enrollment in this study

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: No statistical analysis was planned for this endpoint

End point values	GZR 100 mg + EBR 50 mg +/- Ribavirin (RBV)	Other GZR regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1909	526		
Units: Participants	98	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From first visit in follow-up (Screening/Baseline) up to ~60 months after enrollment in this study

Adverse event reporting additional description:

The all-cause mortality population includes all enrolled participants treated with GZR in a prior study (n=2436). The AE population excludes 3 enrolled participants- two enrolled in error who received a comparator regimen in a prior base study and one participant had insufficient long-term follow up data (participant withdrew consent on day 27).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Other GZR Regimen
Reporting group description: -	
Reporting group title	GZR 100 mg + EBR 50 mg +/- RBV
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Non-serious adverse events did not meet the frequency threshold of 5% for reporting

Serious adverse events	Other GZR Regimen	GZR 100 mg + EBR 50 mg +/- RBV	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 526 (0.76%)	100 / 1909 (5.24%)	
number of deaths (all causes)	3	44	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 526 (0.19%)	12 / 1909 (0.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 12	
deaths causally related to treatment / all	0 / 1	0 / 3	

Lung neoplasm malignant			
subjects affected / exposed	0 / 526 (0.00%)	2 / 1909 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Non-small cell lung cancer			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatic carcinoma			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 526 (0.00%)	8 / 1909 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 8	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden death			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Kidney transplant rejection			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory arrest			
subjects affected / exposed	1 / 526 (0.19%)	0 / 1909 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 526 (0.00%)	5 / 1909 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Overdose			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transplant dysfunction			

subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 526 (0.00%)	2 / 1909 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 526 (0.00%)	4 / 1909 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 4	
Cardiac failure			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			

subjects affected / exposed	0 / 526 (0.00%)	3 / 1909 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 526 (0.00%)	2 / 1909 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulseless electrical activity			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 526 (0.00%)	2 / 1909 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	0 / 526 (0.00%)	2 / 1909 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	1 / 526 (0.19%)	0 / 1909 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 526 (0.19%)	0 / 1909 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 526 (0.00%)	3 / 1909 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 526 (0.00%)	2 / 1909 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Chronic hepatic failure			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			

subjects affected / exposed	1 / 526 (0.19%)	0 / 1909 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 526 (0.00%)	7 / 1909 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	0 / 526 (0.00%)	17 / 1909 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 1	
Glomerulonephritis chronic			
subjects affected / exposed	0 / 526 (0.00%)	2 / 1909 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 526 (0.00%)	6 / 1909 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
subjects affected / exposed	0 / 526 (0.00%)	2 / 1909 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related sepsis			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peritonitis			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 526 (0.00%)	2 / 1909 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sepsis			
subjects affected / exposed	0 / 526 (0.00%)	2 / 1909 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Septic shock			
subjects affected / exposed	0 / 526 (0.00%)	2 / 1909 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Wound infection			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	0 / 526 (0.00%)	1 / 1909 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Other GZR Regimen	GZR 100 mg + EBR 50 mg +/- RBV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 526 (0.00%)	0 / 1909 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2013	AM 01: Updated definitions of relapse criteria to be consistent with the FDA assay label.
16 December 2014	AM 02: Added 4 visits to collect outcome data over a longer period of time in patients with CKD from the P052 base study and patients with advanced liver disease from the P059 base study.
04 July 2016	AM 03: The protocol was amended to align with updated HCV treatment data. Late relapse of HCV is rare in patients treated with direct-acting antivirals (DAAs). Participants who achieved SVR in their base protocol were no longer enrolled in this study and current participants who entered this study with undetectable HCV RNA were discontinued at their next study visit. Participants with CKD remained in the study regardless of prior virologic response. In addition, participants who failed due to reinfection or were retreated for HCV were discontinued at the next study visit. Participants from the P059 study were no longer followed for >3 years.
21 May 2018	AM 04: Updated to include enrollment of pediatric participants who experienced virologic failure associated with ≥1 treatment-emergent RASs in the P079 base study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30038064