Clinical trial results:
A Multi-Site, Open-Label, Partially Randomized Trial of the Efficacy and Safety of Fixed Dose Elbasvir/Grazoprevir (EBR/GZR) Based Regimens in French Subjects with Chronic Hepatitis C Virus (HCV) Genotype 4 Infection

Summary

EudraCT number	2016-001159-37
Trial protocol	FR
Global end of trial date	15 October 2018

Results information

Result version number	v2 (current)
This version publication date	29 November 2019
First version publication date	04 October 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MK-5172-096

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03111108
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	15 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy of 8 and 12 weeks of treatment with a fixed dose combination (FDC) of elbasvir (EBR) 50 mg + grazoprevir (GZR) 100 mg (i.e., MK-5172A) as assessed by the percentage of participants with hepatitis C virus (HCV) genotype (GT) 4 infection that achieve sustained virologic response (HCV ribonucleic acid [RNA] < Lower Limit of Quantification [LLOQ]) 12 weeks after the end of study therapy (SVR12). This study also evaluated the safety and tolerability of EBR/GZR.

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	20 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 117
Worldwide total number of subjects	117
EEA total number of subjects	117

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)	102
From 65 to 84 years	15

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adult male and female participants with chronic hepatitis C virus (HCV) genotype 4 (GT4) infection were enrolled at 12 study centers in France.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1: EBR/GZR for 8 Weeks

Arm description:

Treatment-naïve HCV GT4 participants with stage 0-2 fibrosis (F0-F2) received elbasvir/grazoprevir (EBR/GZR) fixed dose combination (FDC) [50 mg/100 mg] for 8 weeks, followed by 24 weeks of follow-up.

Arm type	Experimental
Investigational medicinal product name	Elbasvir/Grazoprevir 50 mg/100 mg Fixed Dose Combination (FDC)
Investigational medicinal product code	
Other name	MK-5172A
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One EBR/GZR FDC tablet taken by mouth once daily.

Arm title	Arm 2: EBR/GZR for 12 Weeks

Arm description:

Treatment-naïve HCV GT4 participants with F0-F2 stage fibrosis, treatment-naïve participants with F3-F4 stage fibrosis, and treatment-experienced participants with F0-F4 stage fibrosis received EBR/GZR FDC (50 mg/100 mg) for 12 weeks, followed by 24 weeks of follow-up.

Arm type	Experimental
Investigational medicinal product name	Elbasvir/Grazoprevir 50 mg/100 mg Fixed Dose Combination (FDC)
Investigational medicinal product code	
Other name	MK-5172A
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One EBR/GZR FDC tablet taken by mouth once daily.

Number of subjects in period 1	Arm 1: EBR/GZR for 8 Weeks	Arm 2: EBR/GZR for 12 Weeks
Started	53	64
Completed	52	63
Not completed	1	1
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1: EBR/GZR for 8 Weeks
Reporting group description:	
Treatment-naïve HCV GT4 participants with stage 0-2 fibrosis (F0-F2) received elbasvir/grazoprevir (EBR/GZR) fixed dose combination (FDC) [50 mg/100 mg] for 8 weeks, followed by 24 weeks of follow-up.	
Reporting group title	Arm 2: EBR/GZR for 12 Weeks
Reporting group description:	
Treatment-naïve HCV GT4 participants with F0-F2 stage fibrosis, treatment-naïve participants with F3-F4 stage fibrosis, and treatment-experienced participants with F0-F4 stage fibrosis received EBR/GZR FDC (50 mg/100 mg) for 12 weeks, followed by 24 weeks of follow-up.	

Reporting group values	Arm 1: EBR/GZR for 8 Weeks	Arm 2: EBR/GZR for 12 Weeks	Total
Number of subjects	53	64	117
Age categorical Units: Subjects			
Im Utero	0	0	0
Pre-term newborn - gestational age <37 weeks	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
Adults (18-64 years)	46	56	102
From 65-84 years	7	8	15
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	51.5	56.0	
standard deviation	± 12.9	± 9.7	-
Sex: Female, Male Units: Subjects			
Female	29	32	61
Male	24	32	56
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	20	29	49
White	28	29	57
More than one race	1	0	1
Unknown or Not Reported	3	6	9

End points

End points reporting groups

Reporting group title	Arm 1: EBR/GZR for 8 Weeks

Reporting group description:

Treatment-naïve HCV GT4 participants with stage 0-2 fibrosis (F0-F2) received elbasvir/grazoprevir (EBR/GZR) fixed dose combination (FDC) [50 mg/100 mg] for 8 weeks, followed by 24 weeks of follow-up.

Reporting group title	Arm 2: EBR/GZR for 12 Weeks

Reporting group description:

Treatment-naïve HCV GT4 participants with F0-F2 stage fibrosis, treatment-naïve participants with F3-F4 stage fibrosis, and treatment-experienced participants with F0-F4 stage fibrosis received EBR/GZR FDC (50 mg/100 mg) for 12 weeks, followed by 24 weeks of follow-up.

Primary: Percentage of Participants Achieving Sustained Virologic Response 12 Weeks After End of Treatment (SVR12)

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

End point description:

The percentage of participants to achieve SVR12 was determined for each arm (SVR12 was defined as HCV ribonucleic acid [RNA] < lower limit of quantification [LLOQ] at 12 weeks after the end of all study therapy). Plasma HCV RNA was measured using the COBAS™ AmpliPrep/COBAS™ TaqMan HCV Test, v2.0®, which has a LLOQ of 15 IU/mL. All randomized participants who received ≥1 dose of study treatment are included.

End point type	Primary

End point timeframe:

12 weeks after completing study treatment (Arm 1: Week 20 / Arm 2: Week 24)

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	Arm 1: EBR/GZR for 8 Weeks	Arm 2: EBR/GZR for 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	64		
Units: Percentage of Participants				
number (confidence interval 95%)	94.3 (84.3 to 98.8)	95.3 (86.9 to 99.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With ≥ 1 Adverse Events (AEs)

End point title	Number of Participants With ≥ 1 Adverse Events (AEs)[2]

End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All

randomized participants who received ≥1 dose of study treatment are included, classified according to treatment duration actually received.

End point type	Primary

End point timeframe:

Up to Week 14 (up to 14 days after completing treatment)

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	Arm 1: EBR/GZR for 8 Weeks	Arm 2: EBR/GZR for 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	64		
Units: Number of Participants	33	46		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Discontinued from Study Treatment Due to an AE

End point title	Number of Participants Who Discontinued from Study Treatment Due to an AE[3]

End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All randomized participants who received ≥1 dose of study treatment are included, classified according to treatment duration actually received.

End point type	Primary

End point timeframe:

Up to Week 12

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	Arm 1: EBR/GZR for 8 Weeks	Arm 2: EBR/GZR for 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	64		
Units: Number of Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Sustained Virologic Response 24

Weeks After End of Treatment (SVR24)

End point title	Percentage of Participants Achieving Sustained Virologic Response 24 Weeks After End of Treatment (SVR24)

End point description:

The percentage of participants to achieve SVR24 was determined for each arm (SVR24 was defined as HCV RNA < LLOQ at 24 weeks after the end of all study therapy). Plasma HCV RNA was measured using the COBAS™ AmpliPrep/COBAS™ TaqMan HCV Test, v2.0®, which has a LLOQ of 15 IU/mL. All randomized participants who received ≥1 dose of study treatment are included.

End point type	Secondary

End point timeframe:

24 weeks after completing study treatment (Arm 1: Week 32 / Arm 2: Week 36)

End point values	Arm 1: EBR/GZR for 8 Weeks	Arm 2: EBR/GZR for 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	64		
Units: Percentage of Participants				
number (confidence interval 95%)	94.3 (84.3 to 98.8)	93.8 (84.8 to 98.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Prevalence of Baseline NS3 Resistance-Associated Substitutions (RASs) to EBR or GZR

End point title	Prevalence of Baseline NS3 Resistance-Associated Substitutions (RASs) to EBR or GZR

End point description:

Blood samples for viral resistance assays were collected at Baseline (Day 1) and analyzed for substitutions in the NS3 gene region. Results are pooled for all participants with baseline sequencing data available, and the number of participants with RASs is reported according HCV genotype. Resistance-associated substitutions are defined as amino acid substitutions that confer reduced susceptibility to a direct-acting antiviral (DAA) and may contribute to virologic failure. The prevalence of baseline substitutions in participants infected with HCV GT4 subtypes was assessed by evaluating amino acid substitutions in NS3. All randomized participants with baseline sequencing data for NS3 are included.

End point type	Secondary

End point timeframe:

Day 1

End point values	Arm 1: EBR/GZR for 8 Weeks	Arm 2: EBR/GZR for 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	59		
Units: Number of Participants				
GT4	5	6		
GT4d	3	3		
GT4-Other	6	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Prevalence of Baseline NS5A RASs to EBR or GZR

End point title	Prevalence of Baseline NS5A RASs to EBR or GZR

End point description:

Blood samples for viral resistance assays were collected at Baseline (Day 1) and analyzed for substitutions in the NS5A gene region. Results are pooled for all participants with baseline sequencing data available, and the number of participants with RASs is reported according HCV genotype. Resistance-associated substitutions are defined as amino acid substitutions that confer reduced susceptibility to a DAA and may contribute to virologic failure. The prevalence of baseline substitutions in participants infected with HCV GT4 subtypes was assessed by evaluating amino acid substitutions in NS5A. All randomized participants with baseline sequencing data for NS5A are included.

End point type	Secondary

End point timeframe:

Day 1

End point values	Arm 1: EBR/GZR for 8 Weeks	Arm 2: EBR/GZR for 12 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	63		
Units: Number of Participants				
GT4	3	2		
GT4d	10	16		
GT4-Other	13	21		

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 24 weeks after completing study treatment)	
Adverse event reporting additional description:	
All participants who received ≥1 dose of study medication are included.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Arm 1: EBR/GZR for 8 Weeks
Reporting group description:	
Treatment-naïve HCV GT4 participants with stage 0-2 fibrosis (F0-F2) received EBR/GZR fixed dose combination (FDC) [50 mg/100 mg] for 8 weeks, followed by 24 weeks of follow-up.	
Reporting group title	Arm 2: EBR/GZR for 12 Weeks
Reporting group description:	
Treatment-naïve HCV GT4 participants with F0-F2 stage fibrosis, treatment-naïve participants with F3-F4 stage fibrosis, and treatment-experienced participants with F0-F4 stage fibrosis received EBR/GZR FDC (50 mg/100 mg) for 12 weeks, followed by 24 weeks of follow-up.	

Serious adverse events	Arm 1: EBR/GZR for 8 Weeks	Arm 2: EBR/GZR for 12 Weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 53 (3.77%)	2 / 64 (3.13%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Nervous system disorders			
Cerebellar stroke			
subjects affected / exposed	0 / 53 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Post procedural infection			

subjects affected / exposed	1 / 53 (1.89%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 53 (1.89%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm 1: EBR/GZR for 8 Weeks	Arm 2: EBR/GZR for 12 Weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 53 (50.94%)	38 / 64 (59.38%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 53 (5.66%)	1 / 64 (1.56%)	
occurrences (all)	4	1	
Headache			
subjects affected / exposed	9 / 53 (16.98%)	16 / 64 (25.00%)	
occurrences (all)	10	16	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 53 (22.64%)	14 / 64 (21.88%)	
occurrences (all)	12	14	
Fatigue			
subjects affected / exposed	1 / 53 (1.89%)	4 / 64 (6.25%)	
occurrences (all)	1	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 53 (0.00%)	4 / 64 (6.25%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	3 / 53 (5.66%)	3 / 64 (4.69%)	
occurrences (all)	4	4	
Nausea			

subjects affected / exposed	4 / 53 (7.55%)	4 / 64 (6.25%)	
occurrences (all)	4	5	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 53 (3.77%)	4 / 64 (6.25%)	
occurrences (all)	2	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 53 (3.77%)	5 / 64 (7.81%)	
occurrences (all)	2	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 53 (5.66%)	1 / 64 (1.56%)	
occurrences (all)	3	1	
Back pain			
subjects affected / exposed	3 / 53 (5.66%)	1 / 64 (1.56%)	
occurrences (all)	3	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 53 (5.66%)	1 / 64 (1.56%)	
occurrences (all)	3	1	
Influenza			
subjects affected / exposed	2 / 53 (3.77%)	4 / 64 (6.25%)	
occurrences (all)	2	4	
Nasopharyngitis			
subjects affected / exposed	1 / 53 (1.89%)	5 / 64 (7.81%)	
occurrences (all)	1	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2016	AM01: The primary purpose of the amendment was to change the drug supply from 16-count bottles to 14-count blister cards.
12 December 2016	AM02: The primary purpose of this amendment was to correct typographical errors.
26 January 2018	AM03: The primary purpose of the amendment was to increase the target for enrollment of treatment-naïve participants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported