Clinical trial results:
A Phase II Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172 + MK-8742 + Ribavirin (R) in Subjects with Chronic Hepatitis C Virus Infection Who Failed Prior Direct Acting Antiviral Therapy

Summary

EudraCT number	2013-004213-41
Trial protocol	ES AT
Global end of trial date	04 May 2015

Results information

Result version number	v1 (current)
This version publication date	06 March 2016
First version publication date	06 March 2016

Trial information

Trial identification

Sponsor protocol code	MK-5172-048

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02105454
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	04 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2015
Global end of trial reached?	Yes
Global end of trial date	04 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In this study, participants with hepatitis C virus (HCV) genotype 1 (GT1) who failed prior direct-acting antiviral (DAA) therapy will receive Grazoprevir (MK-5172) + Elbasvir (MK-8742) + Ribavirin (RBV) to evaluate sustained virologic response (SVR) using this drug combination.

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	23 May 2014
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	Austria: 9
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	79
EEA total number of subjects	39

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)	68

From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Following 12 weeks of treatment with grazoprevir (GZR), elbasvir (EBR) and ribavirin (RBV), participants were followed-up for an additional 24 weeks.

Period 1

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

Arms

Arm title	GZR 100 mg + EBR 50 mg + RBV for 12 weeks

Arm description:

Participants receive grazoprevir 100 mg once per day (QD), elbasvir 50 mg QD, and RBV 800 - 1400 mg total daily dose divided twice per day (based on body weight) for 12 weeks

Arm type	Experimental
Investigational medicinal product name	Grazoprevir (GZR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg oral tablet (total daily dose)

Investigational medicinal product name	Ribavirin (RBV)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

200 mg oral capsule (total daily dose = 4-7 capsules)

Investigational medicinal product name	Elbasvir (EBR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10 mg oral capsule (total daily dose = 5 capsules)

Number of subjects in period 1	GZR 100 mg + EBR 50 mg + RBV for 12 weeks
Started	79
Completed	78
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	GZR 100 mg + EBR 50 mg + RBV for 12 weeks
Reporting group description:	
Participants receive grazoprevir 100 mg once per day (QD), elbasvir 50 mg QD, and RBV 800 - 1400 mg total daily dose divided twice per day (based on body weight) for 12 weeks	

Reporting group values	GZR 100 mg + EBR 50 mg + RBV for 12 weeks	Total	
Number of subjects	79	79	
Age categorical Units: Subjects			
Age Continuous | Units: years			
arithmetic mean	54.4		
standard deviation	± 9.6	-	
Gender, Male/Female Units: Participants			
Female	33	33	
Male	46	46	

End points

End points reporting groups

Reporting group title	GZR 100 mg + EBR 50 mg + RBV for 12 weeks

Reporting group description:

Participants receive grazoprevir 100 mg once per day (QD), elbasvir 50 mg QD, and RBV 800 - 1400 mg total daily dose divided twice per day (based on body weight) for 12 weeks

Primary: Percentage of participants achieving sustained virologic response (SVR) at 12 weeks after the end of all study therapy (SVR12)

End point title	Percentage of participants achieving sustained virologic response (SVR) at 12 weeks after the end of all study therapy (SVR12)[1]

End point description:

SVR12 is defined as participants having hepatitis C virus ribonucleic acid (HCV RNA) level lower than the limit of quantification (LLoQ, <15 IU/mL in plasma), either target detected and unquantifiable or undetectable 12 weeks after the end of all study therapy. Per protocol population excludes participants due to important deviations from the protocol that may substantially affect the results of the primary and key secondary efficacy endpoints.

End point type	Primary

End point timeframe:

Up to 24 weeks

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 between-group statistical analyses were performed for this endpoint.

End point values	GZR 100 mg + EBR 50 mg + RBV for 12 weeks			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: Percentage of participants				
number (confidence interval 95%)	97.1 (90.1 to 99.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants experiencing adverse events

End point title	Percentage of participants experiencing adverse events[2]

End point description:

Adverse event is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the Sponsor's product, whether or not considered related to the use of the product. All participants as treated population defined as all participants who received at least one dose of study medication.

End point type	Primary

End point timeframe:

Up to 40 weeks (from Day 1 [post-dose] through 24 [-12/+4] weeks following last dose of study drug)

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: There was no plan to perform a statistical analysis for this endpoint.

End point values	GZR 100 mg + EBR 50 mg + RBV for 12 weeks			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Percentage of participants				
number (not applicable)	79.7			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants discontinuing study drug due to an adverse event

End point title	Percentage of participants discontinuing study drug due to an adverse event[3]

End point description:

Adverse event is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the Sponsor's product, whether or not considered related to the use of the product. All participants as treated population defined as all participants who received at least one dose of study medication.

End point type	Primary

End point timeframe:

Up to 12 weeks

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: There was no plan to perform a statistical analysis for this endpoint.

End point values	GZR 100 mg + EBR 50 mg + RBV for 12 weeks			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Percentage of participants				
number (not applicable)	1.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving SVR12 by prior direct-acting antiviral (DAA) therapy

End point title	Percentage of participants achieving SVR12 by prior direct-acting antiviral (DAA) therapy

End point description:

SVR12 is defined as participants having HCV RNA level lower than the LLoQ (<15 IU/mL in plasma), either target detected and unquantifiable or undetectable 12 weeks after the end of all study therapy. Prior DAA therapy regimen included boceprevir, telaprevir, simeprevir, or sofosbuvir taken concomitantly with peginterferon and ribavirin. Below categories specify with or without resistance-associated variants (RAVs) of the hepatitis C virus. Per protocol population excludes participants due to important deviations from the protocol that may substantially affect the results of the primary and key secondary efficacy endpoints.

End point type	Secondary

End point timeframe:

Up to 24 weeks

End point values	GZR 100 mg + EBR 50 mg + RBV for 12 weeks			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: Percentage of participants				
number (confidence interval 95%)				
Boceprevir with signature baseline RAVs, n=9	88.9 (51.8 to 99.7)			
Boceprevir without signature baseline RAVs, n=16	100 (79.4 to 100)			
Telaprevir with signature baseline RAVs, n=18	94.4 (72.7 to 99.9)			
Telaprevir without signature baseline RAVs, n=22	100 (84.6 to 100)			
Simeprevir with signature baseline RAVs, n=4	100 (39.8 to 100)			
Simeprevir without signature baseline RAVs, n=1	100 (2.5 to 100)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 40 weeks (including 24-week follow-up [-12/+4 weeks])

Adverse event reporting additional description:

All participants as treated population defined as all participants who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1, 18.0

Reporting groups

Reporting group title	GZR 100 mg + EBR 50 mg + RBV for 12 weeks

Reporting group description:

Participants receive grazoprevir 100 mg once per day (QD), elbasvir 50 mg QD, and RBV 800 - 1400 mg total daily dose divided twice per day (based on body weight) for 12 weeks

Serious adverse events	GZR 100 mg + EBR 50 mg + RBV for 12 weeks		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 79 (7.59%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis bacterial			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 79 (1.27%)		
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	GZR 100 mg + EBR 50 mg + RBV for 12 weeks		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 79 (59.49%)		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 79 (18.99%)		
occurrences (all)	16		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	6		
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	12 / 79 (15.19%)		
occurrences (all)	12		
Fatigue			
subjects affected / exposed	22 / 79 (27.85%)		
occurrences (all)	24		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	11		
Nausea			
subjects affected / exposed	9 / 79 (11.39%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2014	Amendment 1: exclusionary lab criteria were updated to include creatinine clearance, and several other exclusionary criteria were updated for the safety of subjects on a ribavirin containing regimen.
21 October 2014	Amendment 2: updated to include guidance on P-gp substrates with narrow therapeutic ranges and known hepatotoxic drugs; and updated INR requirements for treatment discontinuation criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported