Clinical trial results:
A Phase III Open-Label Clinical Trial to Study the Efficacy and Safety of the Combination Regimen Grazoprevir (GZR) and Elbasvir (EBR) in Treatment-Naïve Subjects with Chronic HCV GT1, GT4, and GT6 Infection who are Co-Infected with HIV

Summary

EudraCT number	2014-000342-30
Trial protocol	DK ES
Global end of trial date	22 May 2015

Results information

Result version number	v1 (current)
This version publication date	26 February 2016
First version publication date	26 February 2016

Trial information

Trial identification

Sponsor protocol code	5172-061

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02105662
WHO universal trial number (UTN)	-
Other trial identifiers	MK-5172-061: Merck Registration

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	22 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 May 2015
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 efficacy and safety of grazoprevir (MK-5172) 100 mg in combination with elbasvir (MK-8742) 50 mg in the treatment of chronic hepatitis C virus (HCV) in participants who are co-infected with human immunodeficiency virus (HIV). The primary hypothesis is that the percentage of participants who receive grazoprevir + elbasvir and achieve Sustained Virologic Response after 12 weeks of therapy (SVR12) will be greater than 70%.

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	03 June 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 83
Worldwide total number of subjects	218
EEA total number of subjects	107

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)	212
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

218 participants were enrolled and treated on study, 212 participants completed 24 weeks of follow-up.

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	Grazoprevir+Elbasvir

Arm description:

Participants received a fixed-dose combination (FDC) of grazoprevir 100 mg plus elbasvir 50 mg once daily for 12 weeks and were followed-up for 24 weeks.

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

Dosage and administration details:

MK5172A FDC tablet: MK5172 (100 mg)/MK8742 (50 mg)

Number of subjects in period 1	Grazoprevir+Elbasvir
Started	218
Completed	212
Not completed	6
Consent withdrawn by subject	1
Lost to follow-up	5

Baseline characteristics

Reporting groups	
Reporting group title	Grazoprevir+Elbasvir
Reporting group description:	
Participants received a fixed-dose combination (FDC) of grazoprevir 100 mg plus elbasvir 50 mg once daily for 12 weeks and were followed-up for 24 weeks.	

Reporting group values	Grazoprevir+Elbasvir	Total	
Number of subjects	218	218	
Age categorical Units: Subjects			

Age Continuous | Units: years			
arithmetic mean	48.7		
standard deviation	± 8.9	-	
Gender, Male/Female Units: participants			
Female	35	35	
Male	183	183	

End points

End points reporting groups

Reporting group title	Grazoprevir+Elbasvir

Reporting group description:

Participants received a fixed-dose combination (FDC) of grazoprevir 100 mg plus elbasvir 50 mg once daily for 12 weeks and were followed-up for 24 weeks.

Primary: Percentage of participants achieving Sustained Virologic Response 12 weeks after the end of all study therapy (SVR12)

End point title	Percentage of participants achieving Sustained Virologic Response 12 weeks after the end of all study therapy (SVR12)[1]

End point description:

Blood was drawn from each participant to assess Hepatitis C Virus ribonucleic acid (HCV RNA) plasma levels using the Roche COBAS™ Taqman™ HCV Test, v2.0 (High Pure System). The Roche COBAS Taqman HCV Test, v2.0 assay (High Pure System) had a lower limit of quantification of 15 IU/mL and a limit of detection of 9.3 IU/mL (in plasma). SVR12 was defined as HCV RNA less than the Lower Limit of Quantitation (<LLOQ) at 12 weeks after the end of all study therapy.

End point type	Primary

End point timeframe:

12 weeks after end of all therapy (Study 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: "There was no statistical analysis performed on the updated SVR12 data."

End point values	Grazoprevir+Elbasvir			
Subject group type	Reporting group			
Number of subjects analysed	218[2]			
Units: percentage of participants				
number (confidence interval 95%)	96.3 (92.9 to 98.4)			

Notes:

[2] - Full Analysis Set (FAS); all allocated participants who received ≥1 dose of study treatment.

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants experiencing adverse events (AEs) during the treatment period and first 14 follow-up days

End point title	Percentage of participants experiencing adverse events (AEs) during the treatment period and first 14 follow-up days[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. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol -specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor’s product, is also an AE.

End point type	Primary

End point timeframe:

Treatment Period plus first 14 follow-up days (up to 14 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: No formal hypothesis testing was planned for this safety endpoint, and there were no between-group statistical comparisons performed in this single-arm study.

End point values	Grazoprevir+Elbasvir			
Subject group type	Reporting group			
Number of subjects analysed	218[4]			
Units: percentage of participants				
number (confidence interval 95%)	73.9 (67.5 to 79.6)			

Notes:

[4] - All Subjects as Treated (ASaT) Population; participants who received ≥1 dose of study treatment.

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants discontinuing study therapy due to AEs during the treatment period

End point title	Percentage of participants discontinuing study therapy due to AEs during the treatment period[5]

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. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol -specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an AE.

End point type	Primary

End point timeframe:

Treatment Period (up to 12 weeks)

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 formal hypothesis testing was planned for this safety endpoint, and there were no between-group statistical comparisons performed in this single-arm study.

End point values	Grazoprevir+Elbasvir			
Subject group type	Reporting group			
Number of subjects analysed	218[6]			
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 1.7)			

Notes:

[6] - ASaT Population; all participants who received ≥1 dose of study treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving Sustained Virologic Response 24 weeks after the end of all study therapy (SVR24)

End point title	Percentage of participants achieving Sustained Virologic Response 24 weeks after the end of all study therapy (SVR24)

End point description:

Blood was drawn from each participant to assess HCV RNA plasma levels using the Roche COBAS™ Taqman™ HCV Test, v2.0 (High Pure System). The Roche COBAS Taqman HCV Test, v2.0 assay (High Pure System) had a lower limit of quantification of 15 IU/mL and a limit of detection of 9.3 IU/mL (in plasma). SVR24 was defined as HCV RNA <LLOQ at 24 weeks after the end of all study therapy.

End point type	Secondary

End point timeframe:

24 weeks after end of all therapy (Study Week 36)

End point values	Grazoprevir+Elbasvir			
Subject group type	Reporting group			
Number of subjects analysed	218[7]			
Units: percentage of participants				
number (confidence interval 95%)	93.1 (88.9 to 96.1)			

Notes:

[7] - FAS; all allocated participants who received ≥1 dose of study treatment.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 week treatment period plus 24 week follow-up period (up to 36 weeks)

Adverse event reporting additional description:

ASaT Population; all participants who received at least one dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Grazoprevir + Elbasvir

Reporting group description:

Participants received a FDC of grazoprevir 100 mg plus elbasvir 50 mg once daily for 12 weeks and were followed-up for 24 weeks.

Serious adverse events	Grazoprevir + Elbasvir		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 218 (3.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of the tongue			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ulna fracture			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis bacterial			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 218 (0.46%)		
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	Grazoprevir + Elbasvir		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 218 (48.62%)		
Nervous system disorders			

Headache			
subjects affected / exposed	27 / 218 (12.39%)		
occurrences (all)	33		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	29 / 218 (13.30%)		
occurrences (all)	31		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	11 / 218 (5.05%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	18 / 218 (8.26%)		
occurrences (all)	19		
Nausea			
subjects affected / exposed	20 / 218 (9.17%)		
occurrences (all)	20		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	16 / 218 (7.34%)		
occurrences (all)	16		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 218 (6.42%)		
occurrences (all)	14		
Upper respiratory tract infection			
subjects affected / exposed	17 / 218 (7.80%)		
occurrences (all)	18		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2014	Protocol amendment 1 (AM1) added urinalysis to specified study visits and revised some eligibility criteria for HIV-co-infected participants.
08 September 2014	AM2 indicated that participants infected with HCV GT5 were no longer eligible for enrollment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported