Clinical trial results:
A Phase III Double Blind Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172 and MK-8742 in Subjects With Chronic HCV GT1, GT4 and GT6 Infection With Inherited Blood Disorders With and Without HIV Co-Infection

Summary

EudraCT number	2014-002356-27
Trial protocol	DE IT GB GR
Global end of trial date	14 June 2016

Results information

Result version number	v1 (current)
This version publication date	15 June 2017
First version publication date	15 June 2017

Trial information

Trial identification

Sponsor protocol code	5172-065

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02252016
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	14 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a randomized, multi-site, placebo-controlled trial of a fixed dose combination (FDC) of grazoprevir (MK-5172) 100 mg + elbasvir (MK-8742) 50 mg in participants with chronic Hepatitis C Virus (HCV) genotype (GT) 1, GT4 or GT6 with inherited blood disorders. The primary hypothesis is that the proportion of participants treated with grazoprevir+elbasvir achieving Sustained Virologic Response (SVR) 12 weeks after the end of all study therapy (SVR12) will be greater than the reference rate of 40%.

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	22 October 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	Australia: 13
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	159
EEA total number of subjects	90

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)	154
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult participants with hepatitis C virus (HCV) genotypes (GT)1, GT4, and GT6 with inherited blood disorders and with or without human immunodeficiency virus (HIV) co-infection were recruited at study centers around the world.

Pre-assignment

Screening details:

The screening period lasted up to 45 days.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Immediate Treatment

Arm description:

Participants took grazoprevir 100 mg + elbasvir 50 mg once daily (q.d.) during the initial 12-week treatment period, followed by a 24-week safety monitoring period.

Arm type	Experimental
Investigational medicinal product name	Grazoprevir 100 mg + Elbasvir 50 mg
Investigational medicinal product code	MK-5172A; MK-5172 + MK-8742
Other name	ZEPATIER
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single FDC tablet containing grazoprevir 100 mg + Elbasvir 50 mg taken once daily by mouth.

Arm title	Deferred Treatment

Arm description:

Participants took placebo tablets q.d. during the initial 12-week treatment period, and then underwent a 4-week safety monitoring follow-up period. Next, participants took open-label grazoprevir 100 mg + elbasvir 50 mg q.d. for 12 weeks, followed by a 24-week safety monitoring period.

Arm type	Experimental
Investigational medicinal product name	Grazoprevir 100 mg + Elbasvir 50 mg
Investigational medicinal product code	MK-5172A; MK-5172 + MK-8742
Other name	ZEPATIER
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single FDC tablet containing grazoprevir 100 mg + Elbasvir 50 mg taken once daily by mouth.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet matched to MK-5172A taken once daily by mouth.

Number of subjects in period 1	Immediate Treatment	Deferred Treatment
Started	107	52
Completed	104	49
Not completed	3	3
Physician decision	1	-
Consent withdrawn by subject	-	2
Lost to follow-up	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Immediate Treatment
Reporting group description:	
Participants took grazoprevir 100 mg + elbasvir 50 mg once daily (q.d.) during the initial 12-week treatment period, followed by a 24-week safety monitoring period.	
Reporting group title	Deferred Treatment
Reporting group description:	
Participants took placebo tablets q.d. during the initial 12-week treatment period, and then underwent a 4-week safety monitoring follow-up period. Next, participants took open-label grazoprevir 100 mg + elbasvir 50 mg q.d. for 12 weeks, followed by a 24-week safety monitoring period.	

Reporting group values	Immediate Treatment	Deferred Treatment	Total
Number of subjects	107	52	159
Age categorical			
Units: Subjects			
Adults (18 to 64 years of age)	102	52	154
From 65 to 84 years of age	5	0	5
Age Continuous			
Units: Years			
arithmetic mean	44.2	42.5	
standard deviation	± 11.2	± 9.8	-
Gender, Male/Female			
Units: Subjects			
Female	27	13	40
Male	80	39	119

End points

End points reporting groups

Reporting group title	Immediate Treatment

Reporting group description:

Participants took grazoprevir 100 mg + elbasvir 50 mg once daily (q.d.) during the initial 12-week treatment period, followed by a 24-week safety monitoring period.

Reporting group title	Deferred Treatment

Reporting group description:

Participants took placebo tablets q.d. during the initial 12-week treatment period, and then underwent a 4-week safety monitoring follow-up period. Next, participants took open-label grazoprevir 100 mg + elbasvir 50 mg q.d. for 12 weeks, followed by a 24-week safety monitoring period.

Primary: Percentage of participants achieving sustained virologic response 12 weeks after completing study therapy (SVR12)

End point title	Percentage of participants achieving sustained virologic response 12 weeks after completing study therapy (SVR12)[1]

End point description:

The percentage of participants in the both arms achieving SVR12 (i.e., HCV riboncleic acid [RNA] level below the lower limit of quantification [LLoQ] 12 weeks after completing study therapy) was determined. HCV RNA levels were measured using the Roche COBAS™ Taqman™ HCV Test v2.0 (High Pure System), which has a LLoQ of <15 IU/mL. All randomized participants who received at least one dose of study treatment and had available data were analyzed. Data for the Deferred Treatment Arm was reported after participants received open-label active treatment.

End point type	Primary

End point timeframe:

12 weeks after completing study therapy (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: No statistical comparisons between experimental arms were performed for this endpoint.

End point values	Immediate Treatment	Deferred Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	49		
Units: Percentage of participants				
number (confidence interval 95%)	93.5 (87 to 97.3)	91.8 (80.4 to 97.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants experiencing an adverse event (AE)

End point title	Percentage of participants experiencing an adverse event (AE)

End point description:

An AE is any untoward medical occurrence which does not necessarily have to have a causal relationship with this treatment. All participants receiving ≥1 dose(s) of study drug were analyzed. For the Deferred Treatment arm, data indicate results obtained during the initial 12-week placebo treatment period.

End point type	Primary
End point timeframe:	
Up to Week 14	

End point values	Immediate Treatment	Deferred Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	52		
Units: Percentage of Participants				
number (not applicable)	72.9	65.4		

Statistical analyses

Statistical analysis title	Difference in Percentage
Statistical analysis description:	
The estimated difference (95% confidence interval [CI]) in percentage of participants experiencing an AE in the Immediate versus Deferred arms was determined.	
Comparison groups	Immediate Treatment v Deferred Treatment
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	23.3

Primary: Percentage of participants discontinuing from study treatment due to an AE(s)

End point title	Percentage of participants discontinuing from study treatment due to an AE(s)
End point description:	
An AE is any untoward medical occurrence which does not necessarily have to have a causal relationship with this treatment. All participants receiving ≥1 dose(s) of study drug were analyzed. For the Deferred Treatment arm, data indicate results obtained during the initial 12-week placebo treatment period.	
End point type	Primary
End point timeframe:	
Up to Week 12	

End point values	Immediate Treatment	Deferred Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	52		
Units: Percentage of Participants				
number (not applicable)	0	1.9		

Statistical analyses

Statistical analysis title	Difference in Percentage
Statistical analysis description:	
The estimated difference (95% confidence interval [CI]) in percentage of participants discontinuing due to an AE(s) in the Immediate versus Deferred arms was determined.	
Comparison groups	Immediate Treatment v Deferred Treatment
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.155
Method	Miettinen & Nurminen method
Parameter estimate	Mean difference (final values)
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	1.6

Secondary: Percentage of participants achieving sustained virologic response 24 weeks after completing study therapy (SVR24)

End point title	Percentage of participants achieving sustained virologic response 24 weeks after completing study therapy (SVR24)
End point description:	
The percentage of participants in both arms achieving SVR24 (i.e., HCV RNA level below the LLoQ 24 weeks after completing study therapy) was determined. HCV RNA levels were measured using the Roche COBAS™ Taqman™ HCV Test v2.0 (High Pure System), which has a LLoQ of <15 IU/mL. All randomized participants who received at least one dose of study treatment and had available data were analyzed. Data for the Deferred Treatment Arm was reported after participants received open-label active treatment.	
End point type	Secondary
End point timeframe:	
24 weeks after completing study therapy (Week 36)	

End point values	Immediate Treatment	Deferred Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	49		
Units: Percentage of participants				
number (confidence interval 95%)	90.7 (83.5 to 95.4)	91.8 (80.4 to 97.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 52 weeks.

Adverse event reporting additional description:

An AE is any untoward medical occurrence which does not necessarily have to have a causal relationship with this treatment. AEs were reported for all participants receiving ≥1 dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Deferred Treatment Group

Reporting group description:

Participants took placebo tablets q.d. during the initial 12-week treatment period, and then underwent a 4-week safety monitoring follow-up period. Next, participants took open-label grazoprevir 100 mg + elbasvir 50 mg q.d. for 12 weeks, followed by a 24-week safety monitoring period.

Reporting group title	Immediate Treatment Group

Reporting group description:

Participants took grazoprevir 100 mg + elbasvir 50 mg once daily (q.d.) during the initial 12-week treatment period, followed by a 24-week safety monitoring period.

Serious adverse events	Deferred Treatment Group	Immediate Treatment Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 52 (11.54%)	6 / 107 (5.61%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			

subjects affected / exposed	1 / 52 (1.92%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 52 (1.92%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 52 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sickle cell anaemia with crisis			
subjects affected / exposed	2 / 52 (3.85%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	0 / 52 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 52 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 52 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 52 (1.92%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Deferred Treatment Group	Immediate Treatment Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 52 (40.38%)	53 / 107 (49.53%)	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 52 (11.54%)	23 / 107 (21.50%)	
occurrences (all)	7	33	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 52 (3.85%)	8 / 107 (7.48%)	
occurrences (all)	2	11	
Fatigue			
subjects affected / exposed	4 / 52 (7.69%)	18 / 107 (16.82%)	
occurrences (all)	4	18	
Pyrexia			
subjects affected / exposed	0 / 52 (0.00%)	6 / 107 (5.61%)	
occurrences (all)	0	6	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 52 (5.77%)	2 / 107 (1.87%)	
occurrences (all)	4	2	
Abdominal pain			
subjects affected / exposed	2 / 52 (3.85%)	8 / 107 (7.48%)	
occurrences (all)	2	8	
Diarrhoea			
subjects affected / exposed	3 / 52 (5.77%)	4 / 107 (3.74%)	
occurrences (all)	3	5	
Nausea			
subjects affected / exposed	8 / 52 (15.38%)	9 / 107 (8.41%)	
occurrences (all)	9	9	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 52 (1.92%)	6 / 107 (5.61%)	
occurrences (all)	1	6	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	3 / 52 (5.77%)	7 / 107 (6.54%)	
occurrences (all)	4	8	
Haemarthrosis			
subjects affected / exposed	4 / 52 (7.69%)	4 / 107 (3.74%)	
occurrences (all)	8	13	
Pain in extremity			
subjects affected / exposed	4 / 52 (7.69%)	1 / 107 (0.93%)	
occurrences (all)	4	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 52 (3.85%)	7 / 107 (6.54%)	
occurrences (all)	2	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2015	AM2: The primary purposes of AM2 were to reduce target enrollment of participants with sickle cell anaemia and thalassemia, and to increase the pretreatment period to 12 weeks to more accurately collect safety events.
09 November 2015	AM3: The primary purposes of AM3 were to change the statistical methodology for efficacy analyses and to change the efficacy population of interest.
14 March 2016	AM4: The primary purpose of AM4 was to change the efficacy analysis population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported