Clinical trial results:
Full title of the trial: A Phase III Randomized Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172/MK-8742 in Treatment-Naïve Subjects with Chronic HCV GT1, GT4, and GT6 Infection Who are on Opiate Substitution Therapy

Summary

EudraCT number	2014-000343-32
Trial protocol	DE ES NL GB RO FR
Global end of trial date	04 December 2018

Results information

Result version number	v1 (current)
This version publication date	03 December 2019
First version publication date	03 December 2019

Trial information

Trial identification

Sponsor protocol code	5172-062

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02105688
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Registration: MK-5172-062

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 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 June 2015
Global end of trial reached?	Yes
Global end of trial date	04 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a 2-part study. The purpose of Part A was to assess the efficacy and safety of grazoprevir (MK-5172) 100 mg in combination with elbasvir (MK-8742) 50 mg for 12 weeks in the treatment of chronic Hepatitis C Virus (HCV) Genotype (GT)1, GT4, or GT6 infection in treatment-naïve participants who are on opiate substitution therapy. The primary hypothesis was that the percentage of participants who received grazoprevir/elbasvir fixed-dose combination (FDC) in the Immediate Treatment Arm (ITA) and achieved a Sustained Virologic Response 12 weeks after the end of all study therapy (SVR12) would be superior to 67%. In addition, participants who received at least 1 dose of grazoprevir/elbasvir in Part A were eligible to participate in Part B, which was a 3-year observational follow-up.

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	02 September 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
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: 51
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	New Zealand: 10
Country: Number of subjects enrolled	Norway: 9
Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	United States: 100

Worldwide total number of subjects	301
EEA total number of subjects	105

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)	298
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

301 participants were randomized to either the Immediate Treatment Arm or to the Deferred Treatment Arm during Part A. 199 participants who completed Part A were enrolled in Part B; of these, 142 participants completed the study.

Period 1

Period 1 title	Part A: Double-Blind
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Immediate Treatment Arm: Grazoprevir/Elbasvir

Arm description:

In Part A, participants received grazoprevir 100 mg plus elbasvir 50 mg FDC (MK-5172A) once daily for 12 weeks (blinded) and were followed-up for 24 weeks. In Part B, participants could enroll in a 3-year follow-up period where they were followed every 6 months for 3 years in an observational cohort (no treatment was administered during Part B).

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

Dosage and administration details:

Grazoprevir 100 mg/Elbasvir 50 mg fixed dose combination (FDC) tablet, taken once daily by mouth for 12 weeks.

Arm title	Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir

Arm description:

In Part A, participants received placebo to MK-5172A once daily for 12 weeks (blinded), followed by 4 weeks of follow-up. Afterwards, participants received 12 weeks of open-label treatment with the MK-5172A FDC and were followed-up for 24 weeks. In Part B, participants could enroll in a 3-year follow-up period where they were followed every 6 months for 3 years in an observational cohort (no treatment was administered during Part B).

Arm type	Placebo
Investigational medicinal product name	Placebo to Grazoprevir 100 mg/Elbasvir 50 mg FDC tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to Grazoprevir 100 mg/Elbasvir 50 mg FDC tablet, taken once daily by mouth for 12 weeks.

Investigational medicinal product name	Grazoprevir 100 mg/Elbasvir 50 mg FDC tablet
Investigational medicinal product code	
Other name	MK-5172A
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Grazoprevir 100 mg/Elbasvir 50 mg fixed dose combination (FDC) tablet, taken once daily by mouth for 12 weeks.

Number of subjects in period 1	Immediate Treatment Arm: Grazoprevir/Elbasvir	Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir
Started	201	100
Completed	181	83
Not completed	20	17
Adverse event, serious fatal	-	1
Consent withdrawn by subject	4	2
Physician decision	-	1
Adverse event, non-fatal	1	-
Status Unknown	-	2
Lost to follow-up	15	11

Period 2

Period 2 title	Part B: Observational Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Immediate Treatment Arm: Grazoprevir/Elbasvir

Arm description:

In Part A, participants received grazoprevir 100 mg plus elbasvir 50 mg FDC (MK-5172A) once daily for 12 weeks (blinded) and were followed-up for 24 weeks. In Part B, participants could enroll in a 3-year follow-up period where they were followed every 6 months for 3 years in an observational cohort (no treatment was administered during Part B).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir

Arm description:

In Part A, participants received placebo to MK-5172A once daily for 12 weeks (blinded), followed by 4 weeks of follow-up. Afterwards, participants received 12 weeks of open-label treatment with the MK-5172A FDC and were followed-up for 24 weeks. In Part B, participants could enroll in a 3-year follow-up period where they were followed every 6 months for 3 years in an observational cohort (no treatment was administered during Part B).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	Immediate Treatment Arm: Grazoprevir/Elbasvir	Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir
Started	131	68
Completed	94	48
Not completed	37	20
Adverse event, serious fatal	2	1
Consent withdrawn by subject	9	3
Physician decision	3	1
Lost to follow-up	23	15

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only participants who completed Part A and met Part B extension criteria were eligible to enter Part B.

Baseline characteristics

Reporting groups

Reporting group title	Immediate Treatment Arm: Grazoprevir/Elbasvir

Reporting group description:

In Part A, participants received grazoprevir 100 mg plus elbasvir 50 mg FDC (MK-5172A) once daily for 12 weeks (blinded) and were followed-up for 24 weeks. In Part B, participants could enroll in a 3-year follow-up period where they were followed every 6 months for 3 years in an observational cohort (no treatment was administered during Part B).

Reporting group title	Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir

Reporting group description:

In Part A, participants received placebo to MK-5172A once daily for 12 weeks (blinded), followed by 4 weeks of follow-up. Afterwards, participants received 12 weeks of open-label treatment with the MK-5172A FDC and were followed-up for 24 weeks. In Part B, participants could enroll in a 3-year follow-up period where they were followed every 6 months for 3 years in an observational cohort (no treatment was administered during Part B).

Reporting group values	Immediate Treatment Arm: Grazoprevir/Elbasvir	Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir	Total
Number of subjects	201	100	301
Age categorical Units: Subjects			
Adults (between 18 and 64 years)	198	100	298
From 65 to 84 years	3	0	3
Age Continuous Units: years			
arithmetic mean	47.4	46.4	
standard deviation	± 9.9	± 9.9	-
Sex: Female, Male Units: Subjects			
Female	48	23	71
Male	153	77	230

End points

End points reporting groups

Reporting group title	Immediate Treatment Arm: Grazoprevir/Elbasvir

Reporting group description:

In Part A, participants received grazoprevir 100 mg plus elbasvir 50 mg FDC (MK-5172A) once daily for 12 weeks (blinded) and were followed-up for 24 weeks. In Part B, participants could enroll in a 3-year follow-up period where they were followed every 6 months for 3 years in an observational cohort (no treatment was administered during Part B).

Reporting group title	Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir

Reporting group description:

In Part A, participants received placebo to MK-5172A once daily for 12 weeks (blinded), followed by 4 weeks of follow-up. Afterwards, participants received 12 weeks of open-label treatment with the MK-5172A FDC and were followed-up for 24 weeks. In Part B, participants could enroll in a 3-year follow-up period where they were followed every 6 months for 3 years in an observational cohort (no treatment was administered during Part B).

Reporting group title	Immediate Treatment Arm: Grazoprevir/Elbasvir

Reporting group description:

In Part A, participants received grazoprevir 100 mg plus elbasvir 50 mg FDC (MK-5172A) once daily for 12 weeks (blinded) and were followed-up for 24 weeks. In Part B, participants could enroll in a 3-year follow-up period where they were followed every 6 months for 3 years in an observational cohort (no treatment was administered during Part B).

Reporting group title	Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir

Reporting group description:

In Part A, participants received placebo to MK-5172A once daily for 12 weeks (blinded), followed by 4 weeks of follow-up. Afterwards, participants received 12 weeks of open-label treatment with the MK-5172A FDC and were followed-up for 24 weeks. In Part B, participants could enroll in a 3-year follow-up period where they were followed every 6 months for 3 years in an observational cohort (no treatment was administered during Part B).

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 HCV ribonucleic acid (RNA) plasma levels using the Roche COBAS® AmpliPrep/COBAS® Taqman HCV Test, v2.0 (lower limit of quantification = 15 IU/mL). SVR12 defined as HCV RNA below the lower limit of detection (<LLOQ) at 12 weeks after the end of all study therapy for baseline infection, or HCV RNA≥ LLOQ due to reinfection (after clearance of baseline infection). Clopper-Pearson method used to construct 95% confidence intervals for SVR12 rate. The primary efficacy analysis for Part A was the percentage of participants in the ITA who achieved SVR12. SVR12 was also calculated for the Deferred Treatment Arm (DTA).

All randomized participants receiving ≥1 dose of active study treatment and excluding participants for study discontinuation for reasons unrelated to treatment regimen, response to HCV treatment, or baseline GT2, GT3, or GT5 (modified FAS) were analysed. The primary efficacy hypothesis was evaluated within participants of the ITA.

End point type	Primary

End point timeframe:

12 weeks after end of all therapy (Study Week 24 for Immediate Treatment Arm and Study Week 40 for Deferred Treatment Arm)

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. A single-sided analysis (exact test) was used to test the null hypothesis, which was that the SVR12 rate for the Immediate Treatment Arm was less than 67% (historical reference rate derived from NCT01667731),

and is presented on ClinicalTrials.gov (NCT02105688).

End point values	Immediate Treatment Arm: Grazoprevir/Elbasvir	Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	88		
Units: Percentage of Participants				
number (confidence interval 95%)	95.5 (91.5 to 97.9)	96.6 (90.4 to 99.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants experiencing at least one Adverse Event (AE) during the Double-Blind (DB) treatment period and first 14 follow-up days

End point title	Percentage of participants experiencing at least one Adverse Event (AE) during the Double-Blind (DB) treatment period and first 14 follow-up days

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, 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 of a pre-existing condition that was temporally associated with the use of the Sponsor’s product, was also an AE. For this outcome measure, the primary safety analysis compared the percentage of participants experiencing an AE in the ITA during the DB active treatment period to that of the DTA during the DB placebo treatment period. All randomized participants who received at least one dose of study treatment during the Part A DB period were analysed.

End point type	Primary

End point timeframe:

DB Treatment period plus first 14 follow-up days (up to Study Week 14)

End point values	Immediate Treatment Arm: Grazoprevir/Elbasvir	Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	100		
Units: Percentage of Participants				
number (not applicable)	83.1	83.0		

Statistical analyses

Statistical analysis title	% Pts With ≥1 AE During DB+14 Days: ITA vs DTA

Statistical analysis description:

Categorical AE parameters were assessed via point estimates with 95% confidence intervals provided for between-treatment differences in the percentage of participants (pts) with events using the Miettinen and Nurminen method, an unconditional, asymptotic method.

Comparison groups	Immediate Treatment Arm: Grazoprevir/Elbasvir v Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentage
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	10

Primary: Percentage of participants discontinued from study therapy due to AEs during the DB treatment period

End point title	Percentage of participants discontinued from study therapy due to AEs during the DB treatment period

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, 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 of a pre-existing condition that was temporally associated with the use of the Sponsor's product, was also an AE. For this outcome measure, the primary safety analysis compared the percentage of participants discontinuing (DC) study therapy due to an AE in the ITA during the DB active treatment period to that of the DTA during the DB placebo treatment period. All randomized participants who received at least one dose of study treatment during the Part A DB period were analysed.

End point type	Primary

End point timeframe:

DB Treatment period (up to Study Week 12)

End point values	Immediate Treatment Arm: Grazoprevir/Elbasvir	Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	100		
Units: Percentage of Participants				
number (not applicable)	0.5	1.0		

Statistical analyses

Statistical analysis title	% Pts DC Due to AE During DB+14 Days: ITA vs DTA

Statistical analysis description:

Categorical AE parameters were assessed via point estimates with 95% confidence intervals provided for between-treatment differences in the percentage of participants (pts) with events using the Miettinen and Nurminen method, an unconditional, asymptotic method.

Comparison groups	Immediate Treatment Arm: Grazoprevir/Elbasvir v Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentage
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	1.9

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® AmpliPrep/COBAS® Taqman HCV Test, v2.0, which has an LLOQ of 15 IU/mL. SVR24 was defined as HCV RNA <LLOQ at 24 weeks after the end of all study therapy. The Clopper-Pearson method was used to construct 95% confidence intervals for the SVR24 rate. The secondary efficacy analysis for Part A evaluated the percentage of participants in the ITA who achieved SVR24. SVR24 was also calculated for the DTA.

All randomized participants receiving ≥1 dose of active study treatment and excluding participants for study discontinuation for reasons unrelated to treatment regimen, response to HCV treatment, or baseline genotype (GT)2, GT3, or GT5 (modified FAS) were analysed. The secondary efficacy analysis was evaluated within participants of the ITA.

End point type	Secondary

End point timeframe:

24 weeks after end of all therapy (Study Week 36 for Immediate Treatment Arm and Study Week 52 for Deferred Treatment Arm)

End point values	Immediate Treatment Arm: Grazoprevir/Elbasvir	Deferred Treatment Arm: Placebo > Grazoprevir/Elbasvir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	85		
Units: Percentage of Participants				
number (confidence interval 95%)	94.1 (89.7 to 97.0)	96.5 (90.0 to 99.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 4 years (Study Week 208)

Adverse event reporting additional description:

AEs reported for all randomized participants receiving ≥1 dose of study treatment. AEs were reported by the treatment that participants were receiving at the time of the event; AEs and deaths for Deferred Group reported separately for placebo (N=100) and active (N=95) treatment periods.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Immediate Treatment Arm: Grazoprevir/Elbasvir

Reporting group description:

In Part A, participants received grazoprevir 100 mg plus elbasvir 50 mg FDC (MK-5172A) once daily for 12 weeks (blinded) and were followed-up for 24 weeks. In Part B, participants could enroll in a 3-year follow-up period where they were followed every 6 months for 3 years in an observational cohort (no treatment was administered during Part B).

Reporting group title	Deferred Treatment Arm: Grazoprevir/Elbasvir

Reporting group description:

In Part A, participants received placebo to MK-5172A once daily for 12 weeks (blinded), followed by 4 weeks of follow-up. Afterwards, participants received 12 weeks of open-label treatment with the MK-5172A FDC and were followed-up for 24 weeks. In Part B, participants could enroll in a 3-year follow-up period where they were followed every 6 months for 3 years in an observational cohort (no treatment was administered during Part B).

Reporting group title	Deferred Treatment Arm: Placebo

Reporting group description:

In Part A, participants received placebo to MK-5172A once daily for 12 weeks (blinded), followed by 4 weeks of follow-up.

Serious adverse events	Immediate Treatment Arm: Grazoprevir/Elbasvir	Deferred Treatment Arm: Grazoprevir/Elbasvir	Deferred Treatment Arm: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 201 (7.96%)	7 / 95 (7.37%)	4 / 100 (4.00%)
number of deaths (all causes)	3	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer stage II			
subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			

subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	0 / 201 (0.00%)	1 / 95 (1.05%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 201 (0.00%)	1 / 95 (1.05%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 201 (0.00%)	0 / 95 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 201 (0.50%)	1 / 95 (1.05%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 201 (0.00%)	1 / 95 (1.05%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 201 (0.00%)	1 / 95 (1.05%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Left ventricular failure			
subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ruptured cerebral aneurysm			
subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 201 (0.00%)	0 / 95 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Emphysema			
subjects affected / exposed	0 / 201 (0.00%)	0 / 95 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural fibrosis			
subjects affected / exposed	0 / 201 (0.00%)	0 / 95 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 201 (0.00%)	1 / 95 (1.05%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar disorder			

subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 201 (0.00%)	1 / 95 (1.05%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug abuse			
subjects affected / exposed	1 / 201 (0.50%)	1 / 95 (1.05%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, auditory			
subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Personality disorder			
subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			

subjects affected / exposed	1 / 201 (0.50%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 201 (0.00%)	0 / 95 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 201 (0.50%)	1 / 95 (1.05%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 201 (0.00%)	0 / 95 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 201 (1.00%)	0 / 95 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 201 (0.00%)	0 / 95 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic candida			
subjects affected / exposed	0 / 201 (0.00%)	0 / 95 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Immediate Treatment Arm: Grazoprevir/Elbasvir	Deferred Treatment Arm: Grazoprevir/Elbasvir	Deferred Treatment Arm: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 201 (53.73%)	36 / 95 (37.89%)	46 / 100 (46.00%)
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	7 / 201 (3.48%)	5 / 95 (5.26%)	4 / 100 (4.00%)
occurrences (all)	7	5	5
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 201 (12.94%)	12 / 95 (12.63%)	14 / 100 (14.00%)
occurrences (all)	31	15	20
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	32 / 201 (15.92%)	13 / 95 (13.68%)	20 / 100 (20.00%)
occurrences (all)	32	14	22
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 201 (5.47%)	3 / 95 (3.16%)	4 / 100 (4.00%)
occurrences (all)	12	3	4
Constipation			
subjects affected / exposed	17 / 201 (8.46%)	2 / 95 (2.11%)	4 / 100 (4.00%)
occurrences (all)	17	2	5
Diarrhoea			
subjects affected / exposed	20 / 201 (9.95%)	8 / 95 (8.42%)	9 / 100 (9.00%)
occurrences (all)	22	8	11
Nausea			
subjects affected / exposed	23 / 201 (11.44%)	8 / 95 (8.42%)	9 / 100 (9.00%)
occurrences (all)	23	8	9
Vomiting			
subjects affected / exposed	8 / 201 (3.98%)	4 / 95 (4.21%)	7 / 100 (7.00%)
occurrences (all)	8	5	7
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 201 (6.47%)	0 / 95 (0.00%)	6 / 100 (6.00%)
occurrences (all)	13	0	6
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	8 / 201 (3.98%) 8	3 / 95 (3.16%) 3	6 / 100 (6.00%) 6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2014	Major changes of protocol amendment (AM) 1 included changes to the trial design with the addition of a deferred treatment arm enrolling 100 additional participants and the conversion from an open–label design to a double-blind design where a placebo control was added.
31 October 2014	Major changes of protocol AM 2 included changes to eligibility; participants who were infected with HCV GT5 were no longer eligible for enrollment.
18 May 2015	Major changes of protocol AM 3 included addition of a 3-year follow-up phase (Part B). Participants would no longer be enrolled in the MK-5172-017 long term follow-up study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported