Clinical trial results:
A Phase III, Open-Label Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172/MK-8742 versus Sofosbuvir/Pegylated Interferon/Ribavirin (PR) in Treatment-Naïve and PR Prior Treatment Failure Subjects with Chronic HCV GT1, 4 or 6 Infection

Summary

EudraCT number	2014-003836-38
Trial protocol	CZ LT ES NO HU DK PL
Global end of trial date	16 February 2016

Results information

Result version number	v1 (current)
This version publication date	17 February 2017
First version publication date	17 February 2017

Trial information

Trial identification

Sponsor protocol code	5172-077

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02358044
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	16 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a study comparing grazoprevir (MK-5172) plus elbasvir (MK-8742) treatment with sofosbuvir (SOF) plus Pegylated Interferon plus Ribavirin (RBV) [PR] treatment in treatment-naïve and prior PR treatment failure participants with chronic Hepatitis C Virus (HCV) genotype (GT)1, GT4, or GT6 infection. The primary objectives are to compare efficacy (assessed by the percentage of participants achieving sustained virologic response 12 weeks after ending study treatment [SVR12]) and safety between grazoprevir plus elbasvir and SOF plus PR treatment arms. The primary hypothesis is that the percentage of participants achieving SVR12 in the grazoprevir plus elbasvir arm is non-inferior to that in the SOF plus PR arm.

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	27 February 2015
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	Czech Republic: 40
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Hungary: 37
Country: Number of subjects enrolled	Lithuania: 38
Country: Number of subjects enrolled	Norway: 11
Country: Number of subjects enrolled	Poland: 45
Country: Number of subjects enrolled	Romania: 39
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Turkey: 20
Worldwide total number of subjects	257
EEA total number of subjects	237

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)	239
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 257 participants were randomized to treatment: 129 to Grazoprevir + Elbasvir arm and 128 to Sofosbuvir plus Pegylated Interferon/Ribavirin (SOF + PR) arm. Two participants in the SOF + PR arm withdrew from study prior to treatment.

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	Grazoprevir + Elbasvir

Arm description:

Participants receive a fixed-dose combination (FDC) tablet of 100 mg grazoprevir and 50 mg elbasvir for 12 weeks, followed by 24 weeks of follow-up.

Arm type	Experimental
Investigational medicinal product name	Grazoprevir + Elbasvir (100 mg/50 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:

FDC (100 mg/50 mg) taken orally (PO) every day (QD) for 12 weeks.

Arm title	SOF + PR

Arm description:

Participants receive SOF (400 mg) combined with PegIntron (1.5 mcg/kg) plus RBV (1000-1200 mg weight-based dose) for 12 weeks, followed by 24 weeks of follow-up.

Arm type	Experimental
Investigational medicinal product name	Sofosbuvir
Investigational medicinal product code	
Other name	Sovaldi
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg tablets taken PO QD for 12 weeks.

Investigational medicinal product name	Pegylated interferon alfa-2b
Investigational medicinal product code	
Other name	PegIntron™
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PegIntron™ administered as a subcutaneous (SC) injection every week (QW) at 1.5 µg/kg for 12 weeks.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Rebetol™
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsule and/or tablet administered PO twice daily (BID) based on weight (1000 - 1200 mg) for 12 weeks.

Number of subjects in period 1	Grazoprevir + Elbasvir	SOF + PR
Started	129	128
Treated	129	126
Completed	127	121
Not completed	2	7
Physician decision	-	1
Consent withdrawn by subject	-	4
Adverse event, non-fatal	-	1
Lost to follow-up	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Grazoprevir + Elbasvir
Reporting group description:	
Participants receive a fixed-dose combination (FDC) tablet of 100 mg grazoprevir and 50 mg elbasvir for 12 weeks, followed by 24 weeks of follow-up.	
Reporting group title	SOF + PR
Reporting group description:	
Participants receive SOF (400 mg) combined with PegIntron (1.5 mcg/kg) plus RBV (1000-1200 mg weight-based dose) for 12 weeks, followed by 24 weeks of follow-up.	

Reporting group values	Grazoprevir + Elbasvir	SOF + PR	Total
Number of subjects	129	128	257
Age categorical			
Units: Subjects			

Age Continuous			
All Randomized Participants			
Units: years			
arithmetic mean	47.6	48.4	
standard deviation	± 12.4	± 12.4	-
Gender, Male/Female			
All Randomized Participants			
Units: Subjects			
Female	74	64	138
Male	55	64	119

End points

End points reporting groups

Reporting group title	Grazoprevir + Elbasvir
Reporting group description:	
Participants receive a fixed-dose combination (FDC) tablet of 100 mg grazoprevir and 50 mg elbasvir for 12 weeks, followed by 24 weeks of follow-up.	
Reporting group title	SOF + PR
Reporting group description:	
Participants receive SOF (400 mg) combined with PegIntron (1.5 mcg/kg) plus RBV (1000-1200 mg weight-based dose) for 12 weeks, followed by 24 weeks of follow-up.	

Primary: Primary: Percentage of participants achieving Sustained Virologic Response at 12 Weeks after the end of all treatment (SVR12)

End point title	Primary: Percentage of participants achieving Sustained Virologic Response at 12 Weeks after the end of all treatment (SVR12)
End point description:	
Hepatitis C Virus ribonucleic acid (HCV-RNA) levels in plasma were measured using the Roche COBAS®AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 on blood samples drawn from each participant. SVR12 was defined as HCV RNA below the lower limit of quantification (<LLOQ) at 12 weeks after the end of all study therapy. The primary efficacy hypothesis for this study was that the percentage of participants achieving SVR12 in the grazoprevir plus elbasvir arm was non-inferior to the percentage in the SOF plus PR arm. A secondary statistical analysis was performed to determine whether the percentage of participants achieving SVR12 in the grazoprevir plus elbasvir arm was superior to the percentage in the SOF plus PR arm.	
End point type	Primary
End point timeframe:	
12 weeks after end of all therapy (Study Week 24)	

End point values	Grazoprevir + Elbasvir	SOF + PR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126[1]		
Units: percentage of participants				
number (not applicable)	99.2	90.5		

Notes:

[1] - 2 participants withdrew from study prior to treatment and were excluded from analysis.

Statistical analyses

Statistical analysis title	Non-Inferiority Efficacy Analyses: SVR12
Statistical analysis description:	
Primary Analysis Approach: Non-Inferiority Analyses of the percentage of participants achieving SVR12 was conducted using the Miettinen & Nurminen (M&N) method. The analysis was adjusted for genotype (1a vs. non-1a) and fibrosis stage (cirrhotic vs. non-cirrhotic). The adjusted differences (grazoprevir+elbasvir arm minus SOF+PR arm) in percentages along with the corresponding 95% confidence intervals (CIs) and p-values were provided.	
Comparison groups	Grazoprevir + Elbasvir v SOF + PR

Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Miettinen & Nurminen Method
Parameter estimate	Adjusted Difference in Percentage
Point estimate	8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.6
upper limit	15.3

Statistical analysis title	Superiority Efficacy Analysis: SVR12

Statistical analysis description:

Secondary Analysis Approach: Superiority Analyses of the percentage of participants achieving SVR12 was conducted using the M&N method. The analysis was adjusted for genotype (1a vs. non-1a) and fibrosis stage (cirrhotic vs. non-cirrhotic). The adjusted differences (grazoprevir +elbasvir arm minus SOF+PR arm) in percentages along with the corresponding 95% CIs and p-values were provided.

Comparison groups	Grazoprevir + Elbasvir v SOF + PR
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001
Method	Miettinen & Nurminen Method
Parameter estimate	Adjusted Difference in Percentage
Point estimate	8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.6
upper limit	15.3

Primary: Percentage of participants experiencing at least one adverse event (AE) during the treatment period plus first 14 follow-up days

End point title	Percentage of participants experiencing at least one adverse event (AE) during the treatment period plus 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 a causal relationship with this treatment. An AE could 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 of a preexisting condition that was temporally associated with the use of the Sponsor’s product, was also an AE. The percentage of participants who experienced at least one AE was reported for each treatment arm.

End point type	Primary

End point timeframe:

Treatment + First 14 days of follow-up (Up to Week 14)

End point values	Grazoprevir + Elbasvir	SOF + PR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126[2]		
Units: percentage of participants				
number (not applicable)	51.9	93.7		

Notes:

[2] - 2 participants withdrew from study prior to treatment and were excluded from analysis.

Statistical analyses

Statistical analysis title	Primary Safety Analysis: Tier 2 AEs

Statistical analysis description:

The percentage of participants with an event were assessed via point estimates with 95% CIs provided for between-group comparisons.

Comparison groups	Grazoprevir + Elbasvir v SOF + PR
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentage
Point estimate	-41.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.1
upper limit	-31.9

Primary: Percentage of participants discontinuing study treatment due to an AE

End point title	Percentage of participants discontinuing study treatment due to an AE[3]

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 a causal relationship with this treatment. An AE could 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 of a preexisting condition that was temporally associated with the use of the Sponsor’s product, was also an AE. The percentage of participants who discontinued study treatment due to an AE was reported for each treatment arm. Participants that discontinued study drug treatment due to an AE may have still continued on trial.

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: No between-group statistical comparison was planned for this endpoint.

End point values	Grazoprevir + Elbasvir	SOF + PR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126[4]		
Units: percentage of participants				
number (not applicable)	0.8	0.8		

Notes:

[4] - 2 participants withdrew from study prior to treatment and were excluded from analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants experiencing at least one Tier 1 safety event (key safety parameter) during the treatment period and first 14 follow-up days

End point title	Percentage of participants experiencing at least one Tier 1 safety event (key safety parameter) during the treatment period and first 14 follow-up days

End point description:

Tier 1 safety events were pre-specified by the protocol to evaluate safety and test the safety superiority hypothesis. Tier 1 safety events were chosen to assess broad tolerability, hematological side effects and liver-related laboratory abnormalities. For this study, Tier 1 safety events included: any serious drug-related AE, any drug-related AE leading to permanent discontinuation (DC) of all study drugs, neutrophil count <0.75 x 10^9/L, hemoglobin <10 g/dL, severe depression, hepatic events of clinical interest (defined by abnormal increases in alanine aminotransferase [ALT], aspartate aminotransferase [AST], or alkaline phosphatase [ALP]), or events meeting stopping rule criteria for DC from trial (due to abnormal increases of ALT, AST, or ALP with/without pre-specified related AEs). The percentage of participants who experienced each individual event that was defined as a Tier 1 safety event during the study treatment period was reported for each treatment arm.

End point type	Secondary

End point timeframe:

Treatment + First 14 days of follow-up (Up to Week 14)

End point values	Grazoprevir + Elbasvir	SOF + PR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126[5]		
Units: percentage of participants				
number (not applicable)				
Total Tier 1 AEs	0.8	27.8		
Tier 1 AE: Serious drug-related AE	0	2.4		
Tier 1 AE: DC due to drug-related AE	0	0.8		
Tier 1 AE: Neutrophil count <0.75 x 10^9/L	0	12.7		
Tier 1 AE: Hemoglobin <10 g/dL	0.8	14.3		
Tier 1 AE: Severe depression	0	0		
Tier 1 AE: Hepatic event of clinical interest	0	0		
Tier 1 AE: Trial DC due to stopping rule	0	0		

Notes:

[5] - 2 participants withdrew from study prior to treatment and were excluded from analysis.

Statistical analyses

Statistical analysis title	Total Tier 1 AEs

Statistical analysis description:

Total Tier 1 AEs: If, and only if the primary efficacy null hypothesis was rejected, the Tier 1 safety superiority hypothesis was tested at the 2-sided 5% alpha level. The safety superiority hypothesis was that the percentage of grazoprevir+elbasvir participants with ≥1 Tier 1 event is lower than the percentage of SOF+PR participants with ≥1 Tier 1 event.

Comparison groups	Grazoprevir + Elbasvir v SOF + PR
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [6]
Method	Miettinen & Nurminen Method
Parameter estimate	Difference in Percentage
Point estimate	-27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.5
upper limit	-19.6

Notes:

[6] - % of participants with ≥1 Tier 1 event = total number participants with ≥1 Tier 1 event ÷ total number ASaT participants within each treatment arm. M&N method used to calculate a 2-sided 95% CI for the treatment difference and corresponding p-value.

Statistical analysis title	Serious drug-related AEs

Statistical analysis description:

Serious drug-related AEs: If, and only if the primary efficacy null hypothesis was rejected, the Tier 1 safety superiority hypothesis was tested at the 2-sided 5% alpha level. The safety superiority hypothesis was that the percentage of grazoprevir+elbasvir participants with ≥1 Tier 1 event is lower than the percentage of SOF+PR participants with ≥1 Tier 1 event.

Comparison groups	Grazoprevir + Elbasvir v SOF + PR
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.078 [7]
Method	Miettinen & Nurminen Method
Parameter estimate	Difference in Percentage
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	0.6

Notes:

[7] - % of participants with ≥1 Tier 1 event = total number participants with ≥1 Tier 1 event ÷ total number ASaT participants within each treatment arm. M&N method used to calculate a 2-sided 95% CI for the treatment difference and corresponding p-value.

Statistical analysis title	DC due to drug-related AE

Statistical analysis description:

DC due to drug-related AE: If, and only if the primary efficacy null hypothesis was rejected, the Tier 1 safety superiority hypothesis was tested at the 2-sided 5% alpha level. The safety superiority hypothesis was that the percentage of grazoprevir+elbasvir participants with ≥1 Tier 1 event is lower than the percentage of SOF+PR participants with ≥1 Tier 1 event.

Comparison groups	Grazoprevir + Elbasvir v SOF + PR
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.312 [8]
Method	Miettinen & Nurminen Method
Parameter estimate	Difference in Percentage
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	2.1

Notes:

[8] - % of participants with ≥1 Tier 1 event = total number participants with ≥1 Tier 1 event ÷ total number ASaT participants within each treatment arm. M&N method used to calculate a 2-sided 95% CI for the treatment difference and corresponding p-value.

Statistical analysis title	Neutrophil count <0.75 x 10^9/L

Statistical analysis description:

Neutrophil count <0.75 x 10^9/L: If, and only if the primary efficacy null hypothesis was rejected, the Tier 1 safety superiority hypothesis was tested at the 2-sided 5% alpha level. The safety superiority hypothesis was that the percentage of grazoprevir+elbasvir participants with ≥1 Tier 1 event is lower than the percentage of SOF+PR participants with ≥1 Tier 1 event.

Comparison groups	Grazoprevir + Elbasvir v SOF + PR
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [9]
Method	Miettinen & Nurminen Method
Parameter estimate	Difference in Percentage
Point estimate	-12.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.7
upper limit	-8

Notes:

[9] - % of participants with ≥1 Tier 1 event = total number participants with ≥1 Tier 1 event ÷ total number ASaT participants within each treatment arm. M&N method used to calculate a 2-sided 95% CI for the treatment difference and corresponding p-value.

Statistical analysis title	Hemoglobin <10 g/dL

Statistical analysis description:

Hemoglobin <10 g/dL: If, and only if the primary efficacy null hypothesis was rejected, the Tier 1 safety superiority hypothesis was tested at the 2-sided 5% alpha level. The safety superiority hypothesis was that the percentage of grazoprevir+elbasvir participants with ≥1 Tier 1 event is lower than the percentage of SOF+PR participants with ≥1 Tier 1 event.

Comparison groups	Grazoprevir + Elbasvir v SOF + PR

Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [10]
Method	Miettinen & Nurminen Method
Parameter estimate	Difference in Percentage
Point estimate	-13.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.8
upper limit	-7.9

Notes:

[10] - % of participants with ≥1 Tier 1 event = total number participants with ≥1 Tier 1 event ÷ total number ASaT participants within each treatment arm. M&N method used to calculate a 2-sided 95% CI for the treatment difference and corresponding p-value.

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

End point title	Percentage of participants achieving sustained virologic response 24 weeks after ending study treatment (SVR24)

End point description:

HCV-RNA levels in plasma were measured using the Roche COBAS®AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 on blood samples drawn from each participant. 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	SOF + PR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126[11]		
Units: percentage of participants				
number (not applicable)	98.4	89.7		

Notes:

[11] - 2 participants withdrew from study prior to treatment and were excluded from analysis.

Statistical analyses

Statistical analysis title	SVR24

Statistical analysis description:

Analyses of the percentage of participants achieving SVR24 was conducted using the Miettinen & Nurminen (M&N) method. The analysis was adjusted for genotype (1a vs. non-1a) and fibrosis stage (cirrhotic vs. non-cirrhotic). The adjusted differences (grazoprevir+elbasvir arm minus SOF+PR arm) in percentages along with the corresponding 95% confidence intervals (CIs) and p-values were provided.

Comparison groups	Grazoprevir + Elbasvir v SOF + PR

Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	
Method	Miettinen & Nurminen Method
Parameter estimate	Adjusted Difference in Percentage
Point estimate	8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	15.7

Secondary: Percentage of participants achieving sustained virologic response 4 weeks after ending study treatment (SVR4)

End point title	Percentage of participants achieving sustained virologic response 4 weeks after ending study treatment (SVR4)

End point description:

HCV-RNA levels in plasma were measured using the Roche COBAS®AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 on blood samples drawn from each participant. SVR4 was defined as HCV RNA <LLOQ at 4 weeks after the end of all study therapy.

End point type	Secondary

End point timeframe:

4 weeks after end of all therapy (Study Week 16)

End point values	Grazoprevir + Elbasvir	SOF + PR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126[12]		
Units: percentage of participants				
number (confidence interval 95%)	99.2 (95.8 to 100)	92.1 (85.9 to 96.1)		

Notes:

[12] - 2 participants withdrew from study prior to treatment and were excluded from analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Follow-up Week 24

Adverse event reporting additional description:

ASaT population; all randomized participants who received at least one dose of study treatment. Two randomized participants in the SOF + PR arm withdrew from study prior to treatment and were excluded from analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Grazoprevir + Elbasvir

Reporting group description:

Participants receive a fixed-dose combination (FDC) tablet of 100 mg grazoprevir and 50 mg elbasvir for 12 weeks, followed by 24 weeks of follow-up.

Reporting group title	SOF + PR

Reporting group description:

Participants receive SOF (400 mg) combined with PegIntron (1.5 mcg/kg) plus RBV (1000-1200 mg weight-based dose) for 12 weeks, followed by 24 weeks of follow-up.

Serious adverse events	Grazoprevir + Elbasvir	SOF + PR	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 129 (0.78%)	6 / 126 (4.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 129 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 129 (0.00%)	1 / 126 (0.79%)	
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	0 / 129 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Proctitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Drug dependence			
subjects affected / exposed	0 / 129 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 129 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis infectious			
subjects affected / exposed	0 / 129 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			

subjects affected / exposed	1 / 129 (0.78%)	0 / 126 (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	Grazoprevir + Elbasvir	SOF + PR	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 129 (34.11%)	114 / 126 (90.48%)	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 129 (0.00%)	8 / 126 (6.35%)	
occurrences (all)	0	12	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 129 (3.10%)	7 / 126 (5.56%)	
occurrences (all)	5	10	
Headache			
subjects affected / exposed	17 / 129 (13.18%)	50 / 126 (39.68%)	
occurrences (all)	31	97	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 129 (0.78%)	15 / 126 (11.90%)	
occurrences (all)	1	15	
Neutropenia			
subjects affected / exposed	0 / 129 (0.00%)	11 / 126 (8.73%)	
occurrences (all)	0	15	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 129 (6.20%)	30 / 126 (23.81%)	
occurrences (all)	10	36	
Chills			
subjects affected / exposed	2 / 129 (1.55%)	21 / 126 (16.67%)	
occurrences (all)	4	27	
Fatigue			

subjects affected / exposed	9 / 129 (6.98%)	32 / 126 (25.40%)	
occurrences (all)	9	48	
Influenza like illness			
subjects affected / exposed	1 / 129 (0.78%)	23 / 126 (18.25%)	
occurrences (all)	1	40	
Pyrexia			
subjects affected / exposed	2 / 129 (1.55%)	68 / 126 (53.97%)	
occurrences (all)	2	191	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 129 (0.78%)	8 / 126 (6.35%)	
occurrences (all)	1	10	
Nausea			
subjects affected / exposed	8 / 129 (6.20%)	13 / 126 (10.32%)	
occurrences (all)	9	23	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 129 (0.00%)	13 / 126 (10.32%)	
occurrences (all)	0	27	
Dyspnoea			
subjects affected / exposed	3 / 129 (2.33%)	10 / 126 (7.94%)	
occurrences (all)	3	10	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 129 (0.78%)	18 / 126 (14.29%)	
occurrences (all)	1	18	
Pruritus			
subjects affected / exposed	2 / 129 (1.55%)	8 / 126 (6.35%)	
occurrences (all)	2	9	
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 129 (0.00%)	10 / 126 (7.94%)	
occurrences (all)	0	11	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	5 / 129 (3.88%)	14 / 126 (11.11%)	
occurrences (all)	5	25	
Back pain			
subjects affected / exposed	3 / 129 (2.33%)	8 / 126 (6.35%)	
occurrences (all)	4	8	
Myalgia			
subjects affected / exposed	4 / 129 (3.10%)	19 / 126 (15.08%)	
occurrences (all)	6	47	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 129 (0.78%)	16 / 126 (12.70%)	
occurrences (all)	1	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2015	Protocol amendment 1 (AM1) made several revisions to the Inclusion Criteria, Trial Design, Rationale for Dose Selection/Regimen, Trial Flow Chart footnotes, Future Biomedical Research, Assessing and Recording AEs, and Definition of Overdose sections.
26 November 2015	AM2 added language for reporting pregnancy of a male participant's female partner and clarified a footnote to the Trial Flow Chart regarding dosing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported