Clinical trial results:
A Phase II Randomized, Dose Ranging, Clinical Trial to Evaluate the Safety, Tolerability, and Efficacy of Different Doses of MK-5172 When Administered Concomitantly with Peginterferon alfa-2b and Ribavirin in Treatment Naïve Subjects with Chronic Hepatitis C Virus Infection

Summary

EudraCT number	2012-003333-42
Trial protocol	SE GB
Global end of trial date	29 January 2014

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	25 February 2015

Trial information

Trial identification

Sponsor protocol code	5172-038

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01710501
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	29 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a study designed to compare the safety and efficacy of 3 different doses of grazoprevir (MK-5172) combined with pegylated interferon alfa-2b (Peg-IFN) and ribavirin (RBV) in treatment-naïve participants with genotype 1 chronic hepatitis. Participants will receive 12 weeks of treatment with grazoprevir combined with Peg-IFN and RBV, and depending on response at Week 4 may go on to receive an additional 12 weeks of treatment with Peg-IFN and RBV.

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.

The following additional measure defined for this individual study was in place for the protection of trial subjects:

Boceprevir in combination with Peg-IFN and RBV as rescue therapy was offered (i.e. not mandatory) to any participant who met the virologic failure criterion of relapse. Participants were encouraged to start on rescue as soon as possible or within 4 months from the time of completing therapy for participants who did not achieve SVR12 or within 4 months from SVR12 for participants who did achieve SVR12.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	07 December 2012
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	Sweden: 10
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	United States: 56
Worldwide total number of subjects	87
EEA total number of subjects	18

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

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 136 screened participants, 87 were randomized to treatment at 19 sites worldwide.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Grazoprevir 25 mg + PEG-IFN + RBV

Arm description:

After a maximum of a 45 day screening window, randomized participants received 25 mg grazoprevir in combination with PEG-IFN and RBV for 12 weeks followed by 24 weeks of follow-up.

Arm type	Experimental
Investigational medicinal product name	Grazoprevir
Investigational medicinal product code	
Other name	MK-5172
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg once daily (QD), 50 mg QD, or 100 mg QD depending on randomization, administered orally without regard to food.

Investigational medicinal product name	PEG-IFN
Investigational medicinal product code	
Other name	PegIntron
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1.5 µg/kg/week administered as weekly subcutaneous (SC) injection.

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

Dosage and administration details:

Administered as twice-daily oral doses, at a total daily dose of 800 to 1400 mg based on the participant's weight on Day 1. Per product label, RBV was to be taken with food.

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

Dosage and administration details:

Placebo to match grazoprevir tablets to maintain dose blinding

Arm title	Grazoprevir 50 mg + PEG-IFN + RBV

Arm description:

After a maximum of a 45 day screening window, randomized participants received 50 mg grazoprevir in combination with PEG-IFN and RBV for 12 weeks followed by 24 weeks of follow-up.

Arm type	Experimental
Investigational medicinal product name	Grazoprevir
Investigational medicinal product code	
Other name	MK-5172
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg once daily (QD), 50 mg QD, or 100 mg QD depending on randomization, administered orally without regard to food.

Investigational medicinal product name	PEG-IFN
Investigational medicinal product code	
Other name	PegIntron
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1.5 µg/kg/week administered as weekly subcutaneous (SC) injection.

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

Dosage and administration details:

Administered as twice-daily oral doses, at a total daily dose of 800 to 1400 mg based on the participant's weight on Day 1. Per product label, RBV was to be taken with food.

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

Dosage and administration details:

Placebo to match grazoprevir tablets to maintain dose blinding

Arm title	Grazoprevir 100 mg + PEG-IFN + RBV

Arm description:

After a maximum of a 45 day screening window, randomized participants received 100 mg grazoprevir in combination with PEG-IFN and RBV for 12 weeks followed by 24 weeks of follow-up.

Arm type	Experimental
Investigational medicinal product name	Grazoprevir
Investigational medicinal product code	
Other name	MK-5172
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg once daily (QD), 50 mg QD, or 100 mg QD depending on randomization, administered orally without regard to food.

Investigational medicinal product name	PEG-IFN
Investigational medicinal product code	
Other name	PegIntron
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:	
1.5 µg/kg/week administered as weekly subcutaneous (SC) injection.	
Investigational medicinal product name	RBV
Investigational medicinal product code	
Other name	Rebetol™
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Administered as twice-daily oral doses, at a total daily dose of 800 to 1400 mg based on the participant's weight on Day 1. Per product label, RBV was to be taken with food.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Placebo to match grazoprevir tablets to maintain dose blinding	

Number of subjects in period 1	Grazoprevir 25 mg + PEG-IFN + RBV	Grazoprevir 50 mg + PEG-IFN + RBV	Grazoprevir 100 mg + PEG-IFN + RBV
Started	29	28	30
Completed	27	28	30
Not completed	2	0	0
Lost to follow-up	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Grazoprevir 25 mg + PEG-IFN + RBV
Reporting group description:	
After a maximum of a 45 day screening window, randomized participants received 25 mg grazoprevir in combination with PEG-IFN and RBV for 12 weeks followed by 24 weeks of follow-up.	
Reporting group title	Grazoprevir 50 mg + PEG-IFN + RBV
Reporting group description:	
After a maximum of a 45 day screening window, randomized participants received 50 mg grazoprevir in combination with PEG-IFN and RBV for 12 weeks followed by 24 weeks of follow-up.	
Reporting group title	Grazoprevir 100 mg + PEG-IFN + RBV
Reporting group description:	
After a maximum of a 45 day screening window, randomized participants received 100 mg grazoprevir in combination with PEG-IFN and RBV for 12 weeks followed by 24 weeks of follow-up.	

Reporting group values	Grazoprevir 25 mg + PEG-IFN + RBV	Grazoprevir 50 mg + PEG-IFN + RBV	Grazoprevir 100 mg + PEG-IFN + RBV
Number of subjects	29	28	30
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	52	48.5	46.4
standard deviation	± 7.9	± 12.5	± 13.3
Gender categorical			
Units: Subjects			
Female	8	18	15
Male	21	10	15

Reporting group values	Total		
Number of subjects	87		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	41		
Male	46		

End points

End points reporting groups

Reporting group title	Grazoprevir 25 mg + PEG-IFN + RBV

Reporting group description:

After a maximum of a 45 day screening window, randomized participants received 25 mg grazoprevir in combination with PEG-IFN and RBV for 12 weeks followed by 24 weeks of follow-up.

Reporting group title	Grazoprevir 50 mg + PEG-IFN + RBV

Reporting group description:

After a maximum of a 45 day screening window, randomized participants received 50 mg grazoprevir in combination with PEG-IFN and RBV for 12 weeks followed by 24 weeks of follow-up.

Reporting group title	Grazoprevir 100 mg + PEG-IFN + RBV

Reporting group description:

After a maximum of a 45 day screening window, randomized participants received 100 mg grazoprevir in combination with PEG-IFN and RBV for 12 weeks followed by 24 weeks of follow-up.

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

End point title	Percentage of participants achieving Sustained Virologic Response (SVR) at 12 weeks (SVR12) after the end of treatment[1]

End point description:

HCV RNA was measured using the Roche COBAS™ Taqman™ HCV Test, v2.0® assay, which has a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. SVR12 was defined as Hepatitis C Virus (HCV) ribonucleic acid (RNA) <25 IU/mL 12 weeks after the end of all study therapy.

End point type	Primary

End point timeframe:

12 weeks after end of treatment (up to 36 weeks total)

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 formal efficacy hypothesis testing conducted in this study.

End point values	Grazoprevir 25 mg + PEG-IFN + RBV	Grazoprevir 50 mg + PEG-IFN + RBV	Grazoprevir 100 mg + PEG-IFN + RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24[2]	25[3]	26[4]	
Units: percentage of participants				
number (confidence interval 95%)	54.2 (32.8 to 74.4)	84 (63.9 to 95.5)	88.5 (69.8 to 97.6)	

Notes:

[2] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation
[3] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation
[4] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants experiencing at least one adverse event (AE)

End point title	Number of participants experiencing at least one adverse event (AE)[5]

End point description:

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event 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 adverse event.

End point type	Primary

End point timeframe:

Fourteen days following last dose of study drug (up to 26 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: There was no formal efficacy hypothesis testing conducted in this study.

End point values	Grazoprevir 25 mg + PEG-IFN + RBV	Grazoprevir 50 mg + PEG-IFN + RBV	Grazoprevir 100 mg + PEG-IFN + RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[6]	28[7]	30[8]	
Units: participants	28	28	28	

Notes:

[6] - All randomized participants who received at least one dose of study treatment.

[7] - All randomized participants who received at least one dose of study treatment.

[8] - All randomized participants who received at least one dose of study treatment.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants discontinued from study treatment due to AEs

End point title	Number of participants discontinued from study treatment due to AEs[9]

End point description:

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event 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 adverse event.

End point type	Primary

End point timeframe:

up to 24 weeks

Notes:

[9] - 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 formal efficacy hypothesis testing conducted in this study.

End point values	Grazoprevir 25 mg + PEG-IFN + RBV	Grazoprevir 50 mg + PEG-IFN + RBV	Grazoprevir 100 mg + PEG-IFN + RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[10]	28[11]	30[12]	
Units: participant	1	1	1	

Notes:

[10] - All randomized participants who received at least one dose of study treatment.

[11] - All randomized participants who received at least one dose of study treatment.

[12] - All randomized participants who received at least one dose of study treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving undetectable HCV RNA by time point

End point title	Percentage of participants achieving undetectable HCV RNA by time point

End point description:

HCV RNA levels in plasma were measured using the Roche COBAS™ Taqman™ HCV Test, v2.0® assay on blood samples drawn from each participant at Week 2, Week 4, Week 12, and at end of treatment. The assay has a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. Undetectable HCV RNA was defined as below the limit of detection of 9.3 IU/mL.

End point type	Secondary

End point timeframe:

From Week 2 through end of treatment (up to 24 weeks)

End point values	Grazoprevir 25 mg + PEG-IFN + RBV	Grazoprevir 50 mg + PEG-IFN + RBV	Grazoprevir 100 mg + PEG-IFN + RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[13]	26[14]	29[15]	
Units: percentage of participants				
number (confidence interval 95%)				
Week 2 (n=29, 25, 29)	34.5 (17.9 to 54.3)	32 (14.9 to 53.5)	55.2 (35.7 to 73.6)	
Week 4 (n=28, 26, 29)	82.1 (63.1 to 93.9)	76.9 (56.4 to 91)	89.7 (72.6 to 97.8)	
Week 12 (n=28, 26, 28)	96.4 (81.7 to 99.9)	92.3 (74.9 to 99.1)	100 (87.7 to 100)	
End of All Therapy (n=26, 25, 26)	92.3 (74.9 to 99.1)	92 (74 to 99)	100 (86.8 to 100)	

Notes:

[13] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

[14] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

[15] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving HCV RNA <25 IU/mL by time point

End point title	Percentage of participants achieving HCV RNA <25 IU/mL by time point

End point description:

HCV RNA levels in plasma were measured using the Roche COBAS™ Taqman™ HCV Test, v2.0® assay on blood samples drawn from each participant at Week 2, Week 4, Week 12, and at end of treatment. The assay has a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL.

End point type	Secondary

End point timeframe:

From Week 2 through end of treatment (up to 24 weeks)

End point values	Grazoprevir 25 mg + PEG-IFN + RBV	Grazoprevir 50 mg + PEG-IFN + RBV	Grazoprevir 100 mg + PEG-IFN + RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[16]	26[17]	29[18]	
Units: percentage of participants				
number (confidence interval 95%)				
Week 2 (n=29, 25, 29)	86.2 (68.3 to 96.1)	88 (68.8 to 97.5)	96.6 (82.2 to 99.9)	
Week 4 (n=28, 26, 29)	96.4 (81.7 to 99.9)	100 (86.8 to 100)	100 (88.1 to 100)	
Week 12 (n=28, 26, 28)	96.4 (81.7 to 99.9)	100 (86.8 to 100)	100 (87.7 to 100)	
End of all Therapy (n=26, 25, 26)	92.3 (74.9 to 99.1)	100 (86.3 to 100)	100 (86.8 to 100)	

Notes:

[16] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

[17] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

[18] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving SVR 4 weeks after the end of all study therapy (SVR4)

End point title	Percentage of participants achieving SVR 4 weeks after the end of all study therapy (SVR4)

End point description:

HCV RNA was measured using the Roche COBAS™ Taqman™ HCV Test, v2.0® assay, which has a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. SVR4 was defined as HCV RNA <25 IU/mL 4 weeks after the end of all study therapy.

End point type	Secondary

End point timeframe:

4 weeks after end of treatment (up to 28 weeks total)

End point values	Grazoprevir 25 mg + PEG-IFN + RBV	Grazoprevir 50 mg + PEG-IFN + RBV	Grazoprevir 100 mg + PEG-IFN + RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26[19]	25[20]	26[21]	
Units: percentage of participants				
number (confidence interval 95%)	76.9 (56.4 to 91)	88 (68.8 to 97.5)	92.3 (74.9 to 99.1)	

Notes:

[19] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

[20] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

[21] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

HCV RNA was measured using the Roche COBAS™ Taqman™ HCV Test, v2.0® assay, which has a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. SVR24 was defined as HCV RNA <25 IU/mL 24 weeks after the end of all study therapy.

End point type	Secondary

End point timeframe:

24 weeks after end of treatment (up to 48 weeks total)

End point values	Grazoprevir 25 mg + PEG-IFN + RBV	Grazoprevir 50 mg + PEG-IFN + RBV	Grazoprevir 100 mg + PEG-IFN + RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24[22]	25[23]	26[24]	
Units: percentage of participants				
number (confidence interval 95%)	54.2 (32.8 to 74.4)	84 (63.9 to 95.5)	84.6 (65.1 to 95.6)	

Notes:

[22] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

[23] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

[24] - All randomized participants receiving ≥1 dose of study treatment and no important protocol deviation

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants developing post-baseline antiviral resistance to grazoprevir among participants not achieving SVR24 Response

End point title	Number of participants developing post-baseline antiviral

	resistance to grazoprevir among participants not achieving SVR24 Response

End point description:

Post-baseline resistance associated variants (RAV) analysis was conducted by comparing the amino acid sequences at the time of virologic failure to those at baseline (BL): Day 1, pre-dose. A post-BL variant was defined as an amino acid substitution within HCV protease (NS3/4A) that was present after the first dose at virologic failure and follow-up visits but not at BL. Post-BL variant analysis was conducted for participants who did not achieve SVR24 and had sequence data available.

End point type	Secondary

End point timeframe:

From Day 1 up to Follow-up Week 24 (up to 48 weeks total)

End point values	Grazoprevir 25 mg + PEG-IFN + RBV	Grazoprevir 50 mg + PEG-IFN + RBV	Grazoprevir 100 mg + PEG-IFN + RBV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12[25]	7[26]	4[27]	
Units: participants	9	5	3	

Notes:

[25] - Treated non-SVR24 participants with BL and post-BL samples sequenced for RAVs.

[26] - Treated non-SVR24 participants with BL and post-BL samples sequenced for RAVs.

[27] - Treated non-SVR24 participants with BL and post-BL samples sequenced for RAVs.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From 1st day of treatment (Day 1) through Follow-up Week 24 (up to 48 weeks)	
Adverse event reporting additional description:	
All randomized participants who received at least one dose of study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Grazoprevir 25 mg + PEG-IFN + RBV
Reporting group description:	
After a maximum of a 45 day screening window, randomized participants received 25 mg grazoprevir in combination with PEG-IFN and RBV for 12 weeks followed by 24 weeks of follow-up.	
Reporting group title	Grazoprevir 100 mg + PEG-IFN + RB
Reporting group description:	
After a maximum of a 45 day screening window, randomized participants received 100 mg grazoprevir in combination with PEG-IFN and RBV for 12 weeks followed by 24 weeks of follow-up.	
Reporting group title	Grazoprevir 50 mg + PEG-IFN + RBV
Reporting group description:	
After a maximum of a 45 day screening window, randomized participants received 50 mg grazoprevir in combination with PEG-IFN and RBV for 12 weeks followed by 24 weeks of follow-up.	

Serious adverse events	Grazoprevir 25 mg + PEG-IFN + RBV	Grazoprevir 100 mg + PEG-IFN + RB	Grazoprevir 50 mg + PEG-IFN + RBV
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	2 / 28 (7.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 28 (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

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

Non-serious adverse events	Grazoprevir 25 mg + PEG-IFN + RBV	Grazoprevir 100 mg + PEG-IFN + RB	Grazoprevir 50 mg + PEG-IFN + RBV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 29 (96.55%)	27 / 30 (90.00%)	28 / 28 (100.00%)
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Asthenia			
subjects affected / exposed	2 / 29 (6.90%)	3 / 30 (10.00%)	2 / 28 (7.14%)
occurrences (all)	2	3	2
Chills			
subjects affected / exposed	13 / 29 (44.83%)	13 / 30 (43.33%)	12 / 28 (42.86%)
occurrences (all)	14	13	12
Fatigue			
subjects affected / exposed	18 / 29 (62.07%)	18 / 30 (60.00%)	17 / 28 (60.71%)
occurrences (all)	18	19	17
Influenza like illness			
subjects affected / exposed	6 / 29 (20.69%)	7 / 30 (23.33%)	7 / 28 (25.00%)
occurrences (all)	6	7	7
Feeling cold			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Injection site erythema			
subjects affected / exposed	9 / 29 (31.03%)	7 / 30 (23.33%)	8 / 28 (28.57%)
occurrences (all)	9	7	8
Irritability			
subjects affected / exposed	8 / 29 (27.59%)	7 / 30 (23.33%)	2 / 28 (7.14%)
occurrences (all)	8	8	2

Malaise			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	2 / 28 (7.14%)
occurrences (all)	1	0	2
Pain			
subjects affected / exposed	3 / 29 (10.34%)	6 / 30 (20.00%)	2 / 28 (7.14%)
occurrences (all)	5	6	2
Pyrexia			
subjects affected / exposed	10 / 29 (34.48%)	11 / 30 (36.67%)	7 / 28 (25.00%)
occurrences (all)	12	11	7
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 29 (13.79%)	5 / 30 (16.67%)	3 / 28 (10.71%)
occurrences (all)	4	6	3
Dysphonia			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	0 / 28 (0.00%)
occurrences (all)	2	1	0
Dyspnoea			
subjects affected / exposed	5 / 29 (17.24%)	5 / 30 (16.67%)	5 / 28 (17.86%)
occurrences (all)	5	5	5
Dyspnoea exertional			
subjects affected / exposed	3 / 29 (10.34%)	4 / 30 (13.33%)	3 / 28 (10.71%)
occurrences (all)	3	4	3
Oropharyngeal pain			
subjects affected / exposed	2 / 29 (6.90%)	2 / 30 (6.67%)	1 / 28 (3.57%)
occurrences (all)	2	3	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	2 / 28 (7.14%)
occurrences (all)	1	1	2
Depression			
subjects affected / exposed	3 / 29 (10.34%)	1 / 30 (3.33%)	3 / 28 (10.71%)
occurrences (all)	3	2	3
Insomnia			
subjects affected / exposed	5 / 29 (17.24%)	4 / 30 (13.33%)	3 / 28 (10.71%)
occurrences (all)	5	5	3
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 29 (3.45%)	3 / 30 (10.00%)	1 / 28 (3.57%)
occurrences (all)	1	3	2
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 29 (3.45%)	2 / 30 (6.67%)	1 / 28 (3.57%)
occurrences (all)	1	2	3
Blood bilirubin increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	2 / 28 (7.14%)
occurrences (all)	0	1	4
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 29 (3.45%)	3 / 30 (10.00%)	0 / 28 (0.00%)
occurrences (all)	1	4	0
Red cell distribution width increased			
subjects affected / exposed	1 / 29 (3.45%)	2 / 30 (6.67%)	0 / 28 (0.00%)
occurrences (all)	1	2	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	4 / 29 (13.79%)	1 / 30 (3.33%)	4 / 28 (14.29%)
occurrences (all)	4	1	4
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	2 / 28 (7.14%)
occurrences (all)	1	1	2
Dizziness			
subjects affected / exposed	6 / 29 (20.69%)	2 / 30 (6.67%)	5 / 28 (17.86%)
occurrences (all)	7	2	6
Dysgeusia			
subjects affected / exposed	2 / 29 (6.90%)	4 / 30 (13.33%)	2 / 28 (7.14%)
occurrences (all)	2	4	2
Headache			
subjects affected / exposed	10 / 29 (34.48%)	13 / 30 (43.33%)	17 / 28 (60.71%)
occurrences (all)	13	17	19
Lethargy			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	2	0

Sinus headache			
subjects affected / exposed	1 / 29 (3.45%)	2 / 30 (6.67%)	0 / 28 (0.00%)
occurrences (all)	1	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 29 (27.59%)	11 / 30 (36.67%)	11 / 28 (39.29%)
occurrences (all)	11	11	11
Leukopenia			
subjects affected / exposed	3 / 29 (10.34%)	3 / 30 (10.00%)	0 / 28 (0.00%)
occurrences (all)	3	5	0
Monocytosis			
subjects affected / exposed	1 / 29 (3.45%)	3 / 30 (10.00%)	0 / 28 (0.00%)
occurrences (all)	1	3	0
Neutropenia			
subjects affected / exposed	9 / 29 (31.03%)	7 / 30 (23.33%)	4 / 28 (14.29%)
occurrences (all)	9	12	5
Thrombocytopenia			
subjects affected / exposed	2 / 29 (6.90%)	2 / 30 (6.67%)	1 / 28 (3.57%)
occurrences (all)	2	3	3
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	2 / 28 (7.14%)
occurrences (all)	1	1	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	4 / 28 (14.29%)
occurrences (all)	1	1	4
Aphthous stomatitis			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	0 / 28 (0.00%)
occurrences (all)	2	1	0
Constipation			
subjects affected / exposed	2 / 29 (6.90%)	3 / 30 (10.00%)	3 / 28 (10.71%)
occurrences (all)	2	3	4
Diarrhoea			

subjects affected / exposed	2 / 29 (6.90%)	5 / 30 (16.67%)	7 / 28 (25.00%)
occurrences (all)	2	5	8
Dry mouth			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	3 / 28 (10.71%)
occurrences (all)	0	1	3
Dyspepsia			
subjects affected / exposed	1 / 29 (3.45%)	2 / 30 (6.67%)	1 / 28 (3.57%)
occurrences (all)	1	2	1
Haemorrhoids			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	3 / 28 (10.71%)
occurrences (all)	1	0	4
Nausea			
subjects affected / exposed	11 / 29 (37.93%)	9 / 30 (30.00%)	17 / 28 (60.71%)
occurrences (all)	11	10	18
Vomiting			
subjects affected / exposed	3 / 29 (10.34%)	6 / 30 (20.00%)	1 / 28 (3.57%)
occurrences (all)	3	6	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 29 (6.90%)	3 / 30 (10.00%)	3 / 28 (10.71%)
occurrences (all)	2	3	3
Dry skin			
subjects affected / exposed	2 / 29 (6.90%)	3 / 30 (10.00%)	5 / 28 (17.86%)
occurrences (all)	2	3	6
Pruritus			
subjects affected / exposed	5 / 29 (17.24%)	5 / 30 (16.67%)	8 / 28 (28.57%)
occurrences (all)	5	5	9
Pruritus generalised			
subjects affected / exposed	1 / 29 (3.45%)	3 / 30 (10.00%)	0 / 28 (0.00%)
occurrences (all)	1	3	0
Rash			
subjects affected / exposed	5 / 29 (17.24%)	4 / 30 (13.33%)	5 / 28 (17.86%)
occurrences (all)	7	5	6
Rash maculo-papular			
subjects affected / exposed	1 / 29 (3.45%)	2 / 30 (6.67%)	0 / 28 (0.00%)
occurrences (all)	2	2	0

Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 29 (17.24%)	1 / 30 (3.33%)	8 / 28 (28.57%)
occurrences (all)	6	1	8
Back pain			
subjects affected / exposed	1 / 29 (3.45%)	4 / 30 (13.33%)	2 / 28 (7.14%)
occurrences (all)	1	5	2
Muscle spasms			
subjects affected / exposed	0 / 29 (0.00%)	3 / 30 (10.00%)	0 / 28 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal pain			
subjects affected / exposed	0 / 29 (0.00%)	3 / 30 (10.00%)	2 / 28 (7.14%)
occurrences (all)	0	3	2
Myalgia			
subjects affected / exposed	11 / 29 (37.93%)	9 / 30 (30.00%)	6 / 28 (21.43%)
occurrences (all)	12	10	7
Infections and infestations			
Folliculitis			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Sinusitis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Urinary tract infection			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	2 / 28 (7.14%)
occurrences (all)	2	0	6
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed occurrences (all)	12 / 29 (41.38%) 12	14 / 30 (46.67%) 14	7 / 28 (25.00%) 7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2013	Several changes were made in amendment 1 including revision of text regarding dosing duration modification, revision of clinical criteria for early termination, revision of text detailing rescue medications and supportive care, clarification of eligibility and withdrawal/discontinuation criteria, redefinition of several endpoints, and definition of viral rebound.
27 May 2013	Amendment 2 added a prohibited drug pathway (OATP1B1 substrates) and examples of that pathway to the list of prohibited medications to reflect the results of recently completed drug interaction studies. It also clarified the drug pathway for OATP1B1 inhibitors, providing guidance on which are prohibited and which may be permitted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported