Clinical trial results:
Study of Efficacy and Safety of Grazoprevir (MK-5172) + Elbasvir (MK-8742) with or Without Ribavirin for Participants with Hepatitis C Genotype 1, 4, or 6 Infections Who Have Failed Prior Treatment with Pegylated Interferon + Ribavirin

Summary

EudraCT number	2014-000824-12
Trial protocol	DK ES FI PL NL
Global end of trial date	19 June 2015

Results information

Result version number	v1 (current)
This version publication date	24 June 2016
First version publication date	24 June 2016

Trial information

Trial identification

Sponsor protocol code	5172-068

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02105701
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	19 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 June 2015
Global end of trial reached?	Yes
Global end of trial date	19 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an efficacy and safety study of grazoprevir (MK-5172) in combination with elbasvir (MK-8742) with or without ribavirin (RBV) in participants with chronic hepatitis C virus (HCV) genotype (GT) 1, 4, or 6 infections who have failed prior therapy with pegylated interferon and RBV. The primary study hypothesis is that in at least one of the study arms, the percentage of participants achieving sustained viral response 12 weeks after the end of all study treatment (SVR12) will be superior to 58%.

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	05 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Canada: 33
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	Israel: 24
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Malaysia: 10
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	New Zealand: 11
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Taiwan: 20
Country: Number of subjects enrolled	United States: 195
Worldwide total number of subjects	420
EEA total number of subjects	97

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)	363
From 65 to 84 years	57
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Female and male adult participants with HCV genotype (GT) 1, 4, or 6 were recruited.

Pre-assignment

Screening details:

The screening period lasted for up to 45 days.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Grazoprevir + Elbasvir 12 weeks

Arm description:

Participants received grazoprevir 100 mg/elbasvir 50 mg fixed dose combination (FDC) tablets once daily (q.d.) by mouth for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Grazoprevir + Elbasvir FDC
Investigational medicinal product code	
Other name	Zepatier®; MK-5172A
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants took a FDC tablet containing grazoprevir 100 mg + elbasvir 50 mg q.d. by mouth for 12 or 16 weeks depending on allocation.

Arm title	Grazoprevir + Elbasvir + RBV 12 weeks

Arm description:

Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth, along with RBV capsules twice daily (b.i.d.) by mouth (weight-based dosing; 800 to 1400 mg total daily dose), for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Rebetol®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants took 200 mg ribavirin capsules b.i.d. at a total daily dose of 800 mg to 1600 mg based on body weight for 12 or 16 weeks depending on allocation.

Investigational medicinal product name	Grazoprevir + Elbasvir FDC
Investigational medicinal product code	
Other name	Zepatier®; MK-5172A
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants took a FDC tablet containing grazoprevir 100 mg + elbasvir 50 mg q.d. by mouth for 12 or 16 weeks depending on allocation.

Arm title	Grazoprevir + Elbasvir 16 weeks

Arm description:

Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth for 16 weeks.

Arm type	Experimental
Investigational medicinal product name	Grazoprevir + Elbasvir FDC
Investigational medicinal product code	
Other name	Zepatier®; MK-5172A
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants took a FDC tablet containing grazoprevir 100 mg + elbasvir 50 mg q.d. by mouth for 12 or 16 weeks depending on allocation.

Arm title	Grazoprevir + Elbasvir + RBV 16 weeks

Arm description:

Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth, along with RBV capsules b.i.d. by mouth (weight-based dosing; 800 to 1400 mg total daily dose), for 16 weeks.

Arm type	Experimental
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Rebetol®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants took 200 mg ribavirin capsules b.i.d. at a total daily dose of 800 mg to 1600 mg based on body weight for 12 or 16 weeks depending on allocation.

Investigational medicinal product name	Grazoprevir + Elbasvir FDC
Investigational medicinal product code	
Other name	Zepatier®; MK-5172A
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants took a FDC tablet containing grazoprevir 100 mg + elbasvir 50 mg q.d. by mouth for 12 or 16 weeks depending on allocation.

Number of subjects in period 1	Grazoprevir + Elbasvir 12 weeks	Grazoprevir + Elbasvir + RBV 12 weeks	Grazoprevir + Elbasvir 16 weeks
Started	105	104	105
Completed	101	103	102
Not completed	4	1	3
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	2	1	-
Lost to follow-up	1	-	2
Protocol deviation	-	-	1

Number of subjects in period 1	Grazoprevir + Elbasvir + RBV 16 weeks
Started	106

Completed	104
Not completed	2
Adverse event, serious fatal	-
Consent withdrawn by subject	1
Lost to follow-up	1
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Grazoprevir + Elbasvir 12 weeks
Reporting group description:	
Participants received grazoprevir 100 mg/elbasvir 50 mg fixed dose combination (FDC) tablets once daily (q.d.) by mouth for 12 weeks.	
Reporting group title	Grazoprevir + Elbasvir + RBV 12 weeks
Reporting group description:	
Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth, along with RBV capsules twice daily (b.i.d.) by mouth (weight-based dosing; 800 to 1400 mg total daily dose), for 12 weeks.	
Reporting group title	Grazoprevir + Elbasvir 16 weeks
Reporting group description:	
Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth for 16 weeks.	
Reporting group title	Grazoprevir + Elbasvir + RBV 16 weeks
Reporting group description:	
Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth, along with RBV capsules b.i.d. by mouth (weight-based dosing; 800 to 1400 mg total daily dose), for 16 weeks.	

Reporting group values	Grazoprevir + Elbasvir 12 weeks	Grazoprevir + Elbasvir + RBV 12 weeks	Grazoprevir + Elbasvir 16 weeks
Number of subjects	105	104	105
Age categorical Units: Subjects			
Adults (18-64 years)	88	92	89
From 65-84 years	17	12	16
Age Continuous | Units: Years			
arithmetic mean	55.71	55.46	54.91
standard deviation	± 9.81	± 8.26	± 9.79
Gender, Male/Female Units: Participants			
Female	39	32	36
Male	66	72	69

Reporting group values	Grazoprevir + Elbasvir + RBV 16 weeks	Total	
Number of subjects	106	420	
Age categorical Units: Subjects			
Adults (18-64 years)	94	363	
From 65-84 years	12	57	
Age Continuous | Units: Years			
arithmetic mean	54.98		
standard deviation	± 9.61	-	
Gender, Male/Female Units: Participants			
Female	42	149	

Male	64	271	

End points

End points reporting groups

Reporting group title	Grazoprevir + Elbasvir 12 weeks
Reporting group description:	
Participants received grazoprevir 100 mg/elbasvir 50 mg fixed dose combination (FDC) tablets once daily (q.d.) by mouth for 12 weeks.	
Reporting group title	Grazoprevir + Elbasvir + RBV 12 weeks
Reporting group description:	
Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth, along with RBV capsules twice daily (b.i.d.) by mouth (weight-based dosing; 800 to 1400 mg total daily dose), for 12 weeks.	
Reporting group title	Grazoprevir + Elbasvir 16 weeks
Reporting group description:	
Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth for 16 weeks.	
Reporting group title	Grazoprevir + Elbasvir + RBV 16 weeks
Reporting group description:	
Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth, along with RBV capsules b.i.d. by mouth (weight-based dosing; 800 to 1400 mg total daily dose), for 16 weeks.	

Primary: Percentage of participants achieving undetectable HCV RNA 12 weeks after completing study therapy (SVR12)

End point title	Percentage of participants achieving undetectable HCV RNA 12 weeks after completing study therapy (SVR12)[1]
End point description:	
HCV RNA was measured using the Roche COBAS® Taqman® HCV Test, v2.0 assay.	
End point type	Primary
End point timeframe:	
12 weeks after the end of all study treatment (up to 28 weeks)	

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: Statistical 1-sided comparisons to a historical control SVR rate of 58% were performed but cannot be represented in EudraCT. See complete statistical analyses reported on clinicaltrials.gov (NCT02105701).

End point values	Grazoprevir + Elbasvir 12 weeks	Grazoprevir + Elbasvir + RBV 12 weeks	Grazoprevir + Elbasvir 16 weeks	Grazoprevir + Elbasvir + RBV 16 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105	104	105	106
Units: Percentage of participants				
number (confidence interval)	92.4 (85.5 to 96.7)	94.2 (87.9 to 97.9)	92.4 (85.5 to 96.7)	98.1 (93.4 to 99.8)

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants experiencing adverse events (AE)

End point title	Number of participants experiencing adverse events (AE)[2]

End point description:

An AE 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. The number of participants experiencing at least 1 AE during the treatment period was reported.

End point type	Primary

End point timeframe:

Up to 18 weeks

Notes:

[2] - 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 hypothesis testing planned for this endpoint, and there were no between-group statistical comparisons performed.

End point values	Grazoprevir + Elbasvir 12 weeks	Grazoprevir + Elbasvir + RBV 12 weeks	Grazoprevir + Elbasvir 16 weeks	Grazoprevir + Elbasvir + RBV 16 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105	104	105	106
Units: Number of participants	74	85	77	95

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

An AE 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.

End point type	Primary

End point timeframe:

Up to 16 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no formal hypothesis testing planned for this endpoint, and there were no between-group statistical comparisons performed.

End point values	Grazoprevir + Elbasvir 12 weeks	Grazoprevir + Elbasvir + RBV 12 weeks	Grazoprevir + Elbasvir 16 weeks	Grazoprevir + Elbasvir + RBV 16 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105	104	105	106
Units: Number of participants	1	1	0	5

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving undetectable HCV RNA 24 weeks after the end of all treatment (SVR24)

End point title	Percentage of participants achieving undetectable HCV RNA 24 weeks after the end of all treatment (SVR24)

End point description:

HCV RNA was measured using the Roche COBAS® Taqman® HCV Test, v2.0 assay.

End point type	Secondary

End point timeframe:

24 weeks after the end of all study treatment (up to 40 weeks)

End point values	Grazoprevir + Elbasvir 12 weeks	Grazoprevir + Elbasvir + RBV 12 weeks	Grazoprevir + Elbasvir 16 weeks	Grazoprevir + Elbasvir + RBV 16 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105	104	105	106
Units: Percentage of participants				
number (confidence interval)	91.4 (84.4 to 96)	94.2 (87.9 to 97.9)	89.5 (82 to 94.7)	95.3 (89.3 to 98.5)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Week 40.	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	GZR/EBR 12 Weeks
Reporting group description:	
Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth for 12 weeks.	
Reporting group title	GZR/EBR + RBV 16 Weeks
Reporting group description:	
Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth, along with RBV capsules b.i.d. by mouth (weight-based dosing; 800 to 1400 mg total daily dose), for 16 weeks.	
Reporting group title	GZR/EBR 16 Weeks
Reporting group description:	
Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth for 16 weeks.	
Reporting group title	GZR/EBR + RBV 12 Weeks
Reporting group description:	
Participants received grazoprevir 100 mg/elbasvir 50 mg FDC tablets q.d. by mouth, along with RBV capsules b.i.d. by mouth (weight-based dosing; 800 to 1400 mg total daily dose), for 12 weeks.	

Serious adverse events	GZR/EBR 12 Weeks	GZR/EBR + RBV 16 Weeks	GZR/EBR 16 Weeks
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 105 (5.71%)	6 / 106 (5.66%)	4 / 105 (3.81%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic marginal zone lymphoma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	1 / 105 (0.95%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Femoral artery occlusion			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	0 / 105 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	0 / 105 (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
Overdose			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	1 / 105 (0.95%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	0 / 105 (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
Tibia fracture			

subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	0 / 105 (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
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	0 / 105 (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
Coronary artery disease			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	0 / 105 (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			
Loss of consciousness			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	1 / 105 (0.95%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	0 / 105 (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
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	0 / 105 (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
Colitis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	0 / 105 (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
Diarrhoea			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal angioedema			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	0 / 105 (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
Varices oesophageal			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	0 / 105 (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
Infections and infestations			
Herpes simplex oesophagitis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	0 / 105 (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
Infectious colitis			

subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	0 / 105 (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
Post procedural infection			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	1 / 105 (0.95%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	GZR/EBR + RBV 12 Weeks		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 104 (7.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic marginal zone lymphoma			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Femoral artery occlusion			

subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			

subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	0 / 104 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 104 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal angioedema				
subjects affected / exposed	0 / 104 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varices oesophageal				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Nephrolithiasis				
subjects affected / exposed	0 / 104 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Herpes simplex oesophagitis				
subjects affected / exposed	0 / 104 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infectious colitis				

subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parotitis			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural infection			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	GZR/EBR 12 Weeks	GZR/EBR + RBV 16 Weeks	GZR/EBR 16 Weeks
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 105 (52.38%)	84 / 106 (79.25%)	58 / 105 (55.24%)
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 105 (0.00%)	7 / 106 (6.60%)	0 / 105 (0.00%)
occurrences (all)	0	7	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	3 / 105 (2.86%)	14 / 106 (13.21%)	1 / 105 (0.95%)
occurrences (all)	3	23	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 105 (6.67%)	6 / 106 (5.66%)	5 / 105 (4.76%)
occurrences (all)	7	8	10
Headache			

subjects affected / exposed	21 / 105 (20.00%)	20 / 106 (18.87%)	21 / 105 (20.00%)
occurrences (all)	23	22	23
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 105 (0.00%)	17 / 106 (16.04%)	0 / 105 (0.00%)
occurrences (all)	0	19	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 105 (7.62%)	10 / 106 (9.43%)	9 / 105 (8.57%)
occurrences (all)	9	10	10
Fatigue			
subjects affected / exposed	20 / 105 (19.05%)	32 / 106 (30.19%)	17 / 105 (16.19%)
occurrences (all)	21	33	18
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 105 (5.71%)	3 / 106 (2.83%)	1 / 105 (0.95%)
occurrences (all)	6	3	1
Constipation			
subjects affected / exposed	1 / 105 (0.95%)	5 / 106 (4.72%)	7 / 105 (6.67%)
occurrences (all)	1	5	8
Diarrhoea			
subjects affected / exposed	5 / 105 (4.76%)	9 / 106 (8.49%)	8 / 105 (7.62%)
occurrences (all)	5	9	9
Dyspepsia			
subjects affected / exposed	3 / 105 (2.86%)	7 / 106 (6.60%)	0 / 105 (0.00%)
occurrences (all)	3	9	0
Nausea			
subjects affected / exposed	9 / 105 (8.57%)	18 / 106 (16.98%)	4 / 105 (3.81%)
occurrences (all)	10	20	4
Vomiting			
subjects affected / exposed	2 / 105 (1.90%)	9 / 106 (8.49%)	1 / 105 (0.95%)
occurrences (all)	2	10	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 105 (5.71%)	10 / 106 (9.43%)	4 / 105 (3.81%)
occurrences (all)	6	10	4

Dyspnoea			
subjects affected / exposed	1 / 105 (0.95%)	10 / 106 (9.43%)	1 / 105 (0.95%)
occurrences (all)	1	10	1
Dyspnoea exertional			
subjects affected / exposed	1 / 105 (0.95%)	8 / 106 (7.55%)	0 / 105 (0.00%)
occurrences (all)	1	8	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 105 (0.95%)	11 / 106 (10.38%)	6 / 105 (5.71%)
occurrences (all)	1	11	6
Rash			
subjects affected / exposed	3 / 105 (2.86%)	8 / 106 (7.55%)	1 / 105 (0.95%)
occurrences (all)	3	10	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 105 (4.76%)	10 / 106 (9.43%)	7 / 105 (6.67%)
occurrences (all)	5	10	7
Irritability			
subjects affected / exposed	4 / 105 (3.81%)	8 / 106 (7.55%)	2 / 105 (1.90%)
occurrences (all)	6	8	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 105 (3.81%)	4 / 106 (3.77%)	7 / 105 (6.67%)
occurrences (all)	4	5	8
Myalgia			
subjects affected / exposed	2 / 105 (1.90%)	7 / 106 (6.60%)	8 / 105 (7.62%)
occurrences (all)	2	7	8
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 105 (2.86%)	5 / 106 (4.72%)	6 / 105 (5.71%)
occurrences (all)	3	6	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 105 (1.90%)	6 / 106 (5.66%)	1 / 105 (0.95%)
occurrences (all)	2	6	1

Non-serious adverse events	GZR/EBR + RBV 12 Weeks		

Total subjects affected by non-serious adverse events subjects affected / exposed	72 / 104 (69.23%)		
Investigations Haemoglobin decreased subjects affected / exposed occurrences (all)	1 / 104 (0.96%) 1		
Injury, poisoning and procedural complications Accidental overdose subjects affected / exposed occurrences (all)	15 / 104 (14.42%) 22		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	8 / 104 (7.69%) 8 21 / 104 (20.19%) 23		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	12 / 104 (11.54%) 13		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	11 / 104 (10.58%) 13 28 / 104 (26.92%) 32		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea	3 / 104 (2.88%) 3 3 / 104 (2.88%) 3		

subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	4 / 104 (3.85%) 4 4 / 104 (3.85%) 4 15 / 104 (14.42%) 19 7 / 104 (6.73%) 8		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Dyspnoea exertional subjects affected / exposed occurrences (all)	 10 / 104 (9.62%) 10 9 / 104 (8.65%) 11 3 / 104 (2.88%) 4		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 11 / 104 (10.58%) 13 4 / 104 (3.85%) 4		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all)	 11 / 104 (10.58%) 12 5 / 104 (4.81%) 5		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	3 / 104 (2.88%) 4 6 / 104 (5.77%) 7		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 104 (1.92%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2014	AM1: The primary purpose of this amendment was to add hormonal contraceptive as a birth control option.
15 July 2014	AM2: The primary purpose of this amendment was to clarify the urinalysis schedule and, for HIV co-infected participants, to adjust the length of time for dose modifications or changes to antiretroviral therapy (ART) from 8 weeks to 4 weeks.
29 September 2014	AM3: The primary purpose was to remove GT5 participants from eligibility.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported