Clinical trial results:
A Phase II/III Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172 and MK-8742 in Subjects with Chronic Hepatitis C Virus Infection with Advanced Cirrhosis and Child-Pugh (CP) -B Hepatic Insufficiency

Summary

EudraCT number	2014-000672-25
Trial protocol	LT ES NL EE PL IT GB
Global end of trial date	09 September 2015

Results information

Result version number	v1 (current)
This version publication date	16 April 2016
First version publication date	16 April 2016

Trial information

Trial identification

Sponsor protocol code	5172-059

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02115321
WHO universal trial number (UTN)	-
Other trial identifiers	MK-5172-059: Merck Protocol Number

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 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 September 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study is being done to evaluate the efficacy and safety of the drug combination grazoprevir (GZR; MK-5172) + elbasvir (EBR; MK-8742) taken once daily (q.d.) in participants with chronic hepatitis C virus (HCV) genotype (GT) 1, 4, or 6 infection and who have cirrhosis and Child-Pugh (CP) score 7-9 moderate hepatic insufficiency (CP-B). The primary hypothesis is that the percentage of HCV-infected participants with hepatic insufficiency (the CP-B population) achieving sustained viral response (SVR) 12 weeks after the end of all treatment (SVR12) will be greater than 60%. Additionally, ten non-cirrhotic (NC) HCV-infected GT1 participants will also be given GZR + EBR at the beginning of the study; this will be done for the purpose of collecting plasma pharmacokinetic (PK) data in HCV GT1-infected participants who do not have hepatic insufficiency.

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	09 May 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	United States: 40
Worldwide total number of subjects	40
EEA total number of subjects	0

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)	34
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was halted after enrolling participants in the two Part A arms, as the current clinical development plan is focused on a fixed-dose combination (FDC) product containing grazoprevir (GZR) 100 mg and elbasvir (EBR) 50 mg. No participants were enrolled in Parts B or C.

Pre-assignment

Screening details:

The screening period lasted for 60 days.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: CP-B GZR 50 mg + EBR 50 mg

Arm description:

CP-B participants take GZR 50 mg + EBR 50 mg q.d. by mouth for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Elbasvir
Investigational medicinal product code	
Other name	MK-8742
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

EBR 50 mg was supplied as either EBR tablets or contained in the MK-5172A FDC and was taken q.d. by mouth.

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:

GZR was supplied as two 25 mg tablets in the Part A CP-B arm, or as either one GZR 100 mg tablet or one fixed-dose combination (FDC) tablet containing GZR 100 mg + EBR 50 mg in a single tablet (MK-5172A) in the Part A NC arm. GZR was taken once daily (q.d.) by mouth.

Arm title	Part A: NC GZR 100 mg + EBR 50 mg

Arm description:

NC participants take GZR 100 mg + EBR 50 mg q.d. by mouth for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Elbasvir
Investigational medicinal product code	
Other name	MK-8742
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

EBR 50 mg was supplied as either EBR tablets or contained in the MK-5172A FDC and was taken q.d. by mouth.

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:

GZR was supplied as two 25 mg tablets in the Part A CP-B arm, or as either one GZR 100 mg tablet or one FDC tablet containing GZR 100 mg + EBR 50 mg in a single tablet (MK-5172A) in the Part A NC arm. GZR was taken q.d. by mouth.

Number of subjects in period 1	Part A: CP-B GZR 50 mg + EBR 50 mg	Part A: NC GZR 100 mg + EBR 50 mg
Started	30	10
Completed	29	10
Not completed	1	0
Adverse event, serious fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Part A: CP-B GZR 50 mg + EBR 50 mg
Reporting group description:	
CP-B participants take GZR 50 mg + EBR 50 mg q.d. by mouth for 12 weeks.	
Reporting group title	Part A: NC GZR 100 mg + EBR 50 mg
Reporting group description:	
NC participants take GZR 100 mg + EBR 50 mg q.d. by mouth for 12 weeks.	

Reporting group values	Part A: CP-B GZR 50 mg + EBR 50 mg	Part A: NC GZR 100 mg + EBR 50 mg	Total
Number of subjects	30	10	40
Age categorical Units: Subjects			
Adults (18-64 years)	26	8	34
From 65-84 years	4	2	6
Age Continuous | Units: Years			
arithmetic mean	58.3	60.4	
standard deviation	± 7	± 5.3	-
Gender, Male/Female Units: Participants			
Female	13	5	18
Male	17	5	22

End points

End points reporting groups

Reporting group title	Part A: CP-B GZR 50 mg + EBR 50 mg
Reporting group description: CP-B participants take GZR 50 mg + EBR 50 mg q.d. by mouth for 12 weeks.	
Reporting group title	Part A: NC GZR 100 mg + EBR 50 mg
Reporting group description: NC participants take GZR 100 mg + EBR 50 mg q.d. by mouth for 12 weeks.	

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

End point title	Percentage of participants achieving sustained viral response 12 weeks after completing study therapy (SVR12)[1]
End point description: SVR12 was defined as hepatitis C virus (HCV) ribonucleic acid (RNA) levels below the lower limit of quantification (LLoQ) 12 weeks after completing study therapy. HCV RNA was measured with the COBAS™ AmpliPrep/COBAS™ Taqman™ HCV Test, v2.0 ® assay which has a LLoQ of 15 IU/mL and a limit of detection of 15 IU/mL.	
End point type	Primary
End point timeframe: Week 24 (Follow-up [FU] Week 12)	

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: Per protocol, only descriptive statistics are presented.

End point values	Part A: CP-B GZR 50 mg + EBR 50 mg	Part A: NC GZR 100 mg + EBR 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	10		
Units: Percentage of participants				
number (confidence interval 95%)	90 (73.5 to 97.9)	100 (69.2 to 100)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants experiencing an adverse event (AE) during treatment and first 14 follow-up days

End point title	Number of participants experiencing an adverse event (AE) during treatment and first 14 follow-up days[2]
End point description: An AE is defined as any untoward medical occurrence in a participant 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 14 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: Per protocol, only descriptive statistics are presented.

End point values	Part A: CP-B GZR 50 mg + EBR 50 mg	Part A: NC GZR 100 mg + EBR 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	10		
Units: Number of participants	25	8		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

An AE is defined as any untoward medical occurrence in a participant 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 12 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: Per protocol, only descriptive statistics are presented.

End point values	Part A: CP-B GZR 50 mg + EBR 50 mg	Part A: NC GZR 100 mg + EBR 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	10		
Units: Number of participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Model for End-Stage Liver Disease (MELD) scores in CP-B participants

End point title	Mean change from baseline in Model for End-Stage Liver Disease (MELD) scores in CP-B participants

End point description:

The MELD score provides an objective and granular assessment of liver improvement as a continuous variable. The calculation of MELD score is based on three biochemical variables (serum bilirubin, creatinine and international normalized ratio [INR] of prothrombin time). The MELD equation is as

follows: 9.57 x ln(creatinine mg/dL) +3.78 x ln (bilirubin mg/dL) + 11.2 x ln(INR) + 6.43. Scores are multiplied by 10 and rounded to the nearest whole number and range from 6 (less ill) to 40 (gravely ill). MELD scores were determined at Baseline (Day 1) and again at Week 12, FU Week 12 (Week 24), and FU Week 24 (Week 36). Change from baseline in MELD score = Post-baseline MELD score - baseline MELD score.

End point type	Secondary

End point timeframe:

Baseline and Weeks 12, 24, and 36

End point values	Part A: CP-B GZR 50 mg + EBR 50 mg	Part A: NC GZR 100 mg + EBR 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	0[4]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=30)	-0.67 (± 1.35)	()		
FU Week 12 (Week 24) [n=29]	-0.38 (± 1.74)	()		
FU Week 24 (Week 36) [n=29]	-0.34 (± 3.15)	()		

Notes:

[4] - MELD scores are not applicable to NC participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with HCV RNA undetectable at Weeks 2, 4, and 12

End point title	Percentage of participants with HCV RNA undetectable at Weeks 2, 4, and 12

End point description:

HCV RNA was measured with the COBAS™ AmpliPrep/COBAS™ Taqman™ HCV Test, v2.0 ® assay which has a LLoQ of 15 IU/mL and a limit of detection of 15 IU/mL.

End point type	Secondary

End point timeframe:

Week 2, 4, and 12

End point values	Part A: CP-B GZR 50 mg + EBR 50 mg	Part A: NC GZR 100 mg + EBR 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: Percentage of participants				
number (confidence interval)	(to)	(to)		

Notes:

[5] - This was to be determined in Part C; enrollment was halted after Part A and no data are available.

[6] - This was to be determined in Part C; enrollment was halted after Part A and no data are available.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with HCV RNA <LLoQ at Weeks 2, 4, and 12

End point title	Percentage of participants with HCV RNA <LLoQ at Weeks 2, 4, and 12

End point description:

HCV RNA was measured with the COBAS™ AmpliPrep/COBAS™ Taqman™ HCV Test, v2.0 ® assay which has a LLoQ of 15 IU/mL and a limit of detection of 15 IU/mL.

End point type	Secondary

End point timeframe:

Weeks 2, 4, and 12

End point values	Part A: CP-B GZR 50 mg + EBR 50 mg	Part A: NC GZR 100 mg + EBR 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Percentage of participants				
number (confidence interval)	(to)	(to)		

Notes:

[7] - This was to be determined in Part C; enrollment was halted after Part A and no data are available.

[8] - This was to be determined in Part C; enrollment was halted after Part A and no data are available.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving sustained viral response 4 weeks after completing study therapy (SVR4)

End point title	Percentage of participants achieving sustained viral response 4 weeks after completing study therapy (SVR4)

End point description:

SVR4 was defined as HCV RNA levels <LLoQ 4 weeks after completing study therapy. HCV RNA was measured with the COBAS™ AmpliPrep/COBAS™ Taqman™ HCV Test, v2.0 ® assay which has a LLoQ of 15 IU/mL and a limit of detection of 15 IU/mL.

End point type	Secondary

End point timeframe:

Week 16

End point values	Part A: CP-B GZR 50 mg + EBR 50 mg	Part A: NC GZR 100 mg + EBR 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	10		
Units: Percentage of participants				
number (confidence interval 95%)	93.3 (77.9 to 99.2)	100 (69.2 to 100)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of participants achieving sustained viral response 24 weeks after completing study therapy (SVR24)

End point description:

SVR24 was defined as HCV RNA levels <LLoQ 24 weeks after completing study therapy. HCV RNA was measured with the COBAS™ AmpliPrep/COBAS™ Taqman™ HCV Test, v2.0 ® assay which has a LLoQ of 15 IU/mL and a limit of detection of 15 IU/mL.

End point type	Secondary

End point timeframe:

Week 36

End point values	Part A: CP-B GZR 50 mg + EBR 50 mg	Part A: NC GZR 100 mg + EBR 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	10		
Units: Percentage of participants				
number (confidence interval 95%)	90 (73.5 to 97.9)	100 (69.2 to 100)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 36 weeks.

Adverse event reporting additional description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Part A: CP-B GZR 50 mg + EBR 50 mg

Reporting group description:

CP-B participants take GZR 50 mg + EBR 50 mg q.d. by mouth for 12 weeks.

Reporting group title	Part A: NC GZR 100 mg + EBR 50 mg

Reporting group description:

NC participants take GZR 100 mg + EBR 50 mg q.d. by mouth for 12 weeks.

Serious adverse events	Part A: CP-B GZR 50 mg + EBR 50 mg	Part A: NC GZR 100 mg + EBR 50 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 30 (16.67%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 30 (3.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Peritonitis bacterial			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Malnutrition			
alternative dictionary used:			

MedDRA 18.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 10 (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	Part A: CP-B GZR 50 mg + EBR 50 mg	Part A: NC GZR 100 mg + EBR 50 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 30 (66.67%)	8 / 10 (80.00%)	
General disorders and administration site conditions			
Chills			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 30 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Fatigue			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	9 / 30 (30.00%)	3 / 10 (30.00%)	
occurrences (all)	11	3	
Feeling abnormal			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pyrexia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 30 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 30 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Oropharyngeal pain			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Sinus congestion			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Affect lability			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Insomnia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 30 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Investigations			
Blood creatine phosphokinase increased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Ligament sprain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Muscle strain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 30 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Headache			

alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 30 (10.00%)	5 / 10 (50.00%)	
occurrences (all)	3	6	
Sinus headache			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Increased tendency to bruise			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear discomfort			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Eye disorders			
Retinal detachment			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 30 (3.33%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Abdominal pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 30 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Abdominal pain upper			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Diarrhoea			

alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 30 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Nausea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 30 (10.00%)	2 / 10 (20.00%)	
occurrences (all)	3	2	
Vomiting			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 30 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Constipation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	5 / 30 (16.67%)	2 / 10 (20.00%)	
occurrences (all)	5	3	
Myalgia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 30 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Influenza			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 30 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Tooth infection			

alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Urinary tract infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 30 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Pneumonia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2014	Amendment 1: Updated the laboratory exclusion criterion (EC) of platelets from < 40 x 10^3/µL to < 30 x 10^3/µL for CP-B participants and added the laboratory EC of creatinine clearance <30 mL/min for both populations.
16 April 2014	Amendment 2: Modified to indicate study will be discontinued if 3 or more CP-B participants in Part A have alanine transaminase (ALT) or aspartate transaminase (AST) elevations >5 times the upper limit of normal (ULN) after treatment week (TW) 4.
04 August 2014	Amendment 3: Modified laboratory EC for CP-B participants including (1) albumin changed from <2.8 grams/deciliter [g/dL] to <2.2 g/dL; and (2) hemoglobin changed from <10.5 g/dL to <9.5 g/dL.
02 March 2015	Amendment 4: An exploratory objective was added to evaluate improvement in neurocognitive function from Day 1 to end of treatment (EOT), follow-up (FU) Week 12, and FU Week 24 in Part C (Part C was not conducted).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 September 2015	Because the current development program is focused on a fixed dose combination product of 100 mg GZR + 50 mg EBR, it was decided not to proceed with the rest of the study. The study was terminated upon completion of Part A; no participants were enrolled in Parts B or C.	-

Notes:

Limitations and caveats

None reported