

**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: $9.57 \times \ln(\text{creatinine mg/dL}) + 3.78 \times \ln(\text{bilirubin mg/dL}) + 11.2 \times \ln(\text{INR}) + 6.43$. 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 | | | |

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

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

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

| | | | |
|---|-----------------|-----------------|--|
| 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 $< 40 \times 10^3/\mu\text{L}$ to $< 30 \times 10^3/\mu\text{L}$ for CP-B participants and added the laboratory EC of creatinine clearance $< 30 \text{ mL/min}$ 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 $< 2.8 \text{ grams/deciliter [g/dL]}$ to $< 2.2 \text{ g/dL}$; and (2) hemoglobin changed from $< 10.5 \text{ g/dL}$ to $< 9.5 \text{ g/dL}$. |
| 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