



Clinical trial results:

A multi-centre, double-blind, parallel-group, randomised, placebo-controlled phase IIa study to investigate safety, tolerability, pharmacodynamics, and pharmacokinetics of different doses of orally administered BI 1467335 during a 12-week treatment period compared to placebo in patients with clinical evidence of NASH

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2016-000499-83 |
| Trial protocol | NL BE DE IE GB ES |
| Global end of trial date | 14 June 2019 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 24 December 2020 |
| First version publication date | 24 June 2020 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set Addition of NCT Number in section Trial Information / Additional Trial Identifier. |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | 1386-0004 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03166735 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, |
| Public contact | Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.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 | 26 July 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 June 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 June 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The key objectives of this trial were the proof of mechanism, support of dose finding, and safety evaluation of different doses of BI 1467335 compared to placebo in patients with clinical evidence of non-alcoholic steato-hepatitis (NASH).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all subjects as required.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 06 June 2017 |
| 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 | Belgium: 12 |
| Country: Number of subjects enrolled | Canada: 4 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Germany: 20 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Spain: 7 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | United States: 58 |
| Worldwide total number of subjects | 113 |
| EEA total number of subjects | 51 |

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) | 96 |
| From 65 to 84 years | 17 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study is a multi-centre, double-blind, parallel-group, randomised, placebo-controlled phase IIa study to investigate safety, tolerability, pharmacodynamics, and pharmacokinetics of different doses of orally administered BI 1467335 (for 12-weeks) compared to placebo in patients with clinical evidence of Non-alcoholic steato-hepatitis (NASH).

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Matching placebo taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated placebo tablets were supplied. For blinding reasons, all patients took 5 tablets placebo daily.

| | |
|--|--------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Matching placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Matching placebo taken daily for 12 weeks. Tablets taken orally with water in the morning before breakfast. Film-coated placebo tablets were supplied. For blinding reasons, all patients took 5 tablets placebo daily.

| | |
|------------------|-----------------------------|
| Arm title | BI 1467335 1 milligram (mg) |
|------------------|-----------------------------|

Arm description:

1 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 1467335 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily.

| | |
|------------------|-----------------------------|
| Arm title | BI 1467335 3 milligram (mg) |
|------------------|-----------------------------|

Arm description:

3 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 1467335 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

3 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily.

| | |
|------------------|-----------------------------|
| Arm title | BI 1467335 6 milligram (mg) |
|------------------|-----------------------------|

Arm description:

6 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 1467335 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

6 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily.

| | |
|------------------|------------------------------|
| Arm title | BI 1467335 10 milligram (mg) |
|------------------|------------------------------|

Arm description:

10 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 1467335 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily.

| Number of subjects in period 1 | Placebo | BI 1467335 1 milligram (mg) | BI 1467335 3 milligram (mg) |
|---------------------------------------|---------|-----------------------------|-----------------------------|
| Started | 32 | 16 | 16 |
| Completed | 32 | 13 | 13 |
| Not completed | 0 | 3 | 3 |
| Consent withdrawn by subject | - | - | 1 |

| | | | |
|------------------------------------|---|---|---|
| follow-up not completed as planned | - | 1 | 1 |
| Lost to follow-up | - | 2 | 1 |

| Number of subjects in period 1 | BI 1467335 6 milligram (mg) | BI 1467335 10 milligram (mg) |
|---------------------------------------|--------------------------------|---------------------------------|
| Started | 17 | 32 |
| Completed | 16 | 28 |
| Not completed | 1 | 4 |
| Consent withdrawn by subject | 1 | 2 |
| follow-up not completed as planned | - | 1 |
| Lost to follow-up | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--|------------------------------|
| Reporting group title | Placebo |
| Reporting group description: Matching placebo taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated placebo tablets were supplied. For blinding reasons, all patients took 5 tablets placebo daily. | |
| Reporting group title | BI 1467335 1 milligram (mg) |
| Reporting group description: 1 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily. | |
| Reporting group title | BI 1467335 3 milligram (mg) |
| Reporting group description: 3 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily. | |
| Reporting group title | BI 1467335 6 milligram (mg) |
| Reporting group description: 6 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily. | |
| Reporting group title | BI 1467335 10 milligram (mg) |
| Reporting group description: 10 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily. | |

| Reporting group values | Placebo | BI 1467335 1 milligram (mg) | BI 1467335 3 milligram (mg) |
|---|---------|-----------------------------|-----------------------------|
| Number of subjects | 32 | 16 | 16 |
| Age categorical | | | |
| Treated Set (TS): All patients who signed the informed consent and were treated with at least one dose of the trial medication. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 26 | 12 | 12 |
| From 65-84 years | 6 | 4 | 4 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Treated Set (TS): All patients who signed the informed consent and were treated with at least one dose of the trial medication. | | | |
| Units: years | | | |
| arithmetic mean | 51.8 | 52.6 | 53.9 |
| standard deviation | ± 12.3 | ± 13.3 | ± 11.5 |

| | | | |
|---|------------|------------|------------|
| Sex: Female, Male | | | |
| Treated Set (TS): All patients who signed the informed consent and were treated with at least one dose of the trial medication. | | | |
| Units: Participants | | | |
| Female | 13 | 10 | 8 |
| Male | 19 | 6 | 8 |
| Race (NIH/OMB) | | | |
| Treated Set (TS): All patients who signed the informed consent and were treated with at least one dose of the trial medication. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 1 | 1 | 0 |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 30 | 14 | 16 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 11 | 5 | 5 |
| Not Hispanic or Latino | 21 | 11 | 11 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Plasma amine oxidase copper-containing 3 (AOC3) baseline concentration | | | |
| Plasma amine oxidase copper-containing 3 (AOC3) baseline concentration. Treated Set (TS): All patients who signed the informed consent and were treated with at least one dose of the trial medication. | | | |
| Units: microgram per liter (µg/l) | | | |
| arithmetic mean | 471.4063 | 537.7143 | 498.0000 |
| standard deviation | ± 165.6802 | ± 204.4100 | ± 141.0225 |

| Reporting group values | BI 1467335 6 milligram (mg) | BI 1467335 10 milligram (mg) | Total |
|---|-----------------------------|------------------------------|-------|
| Number of subjects | 17 | 32 | 113 |
| Age categorical | | | |
| Treated Set (TS): All patients who signed the informed consent and were treated with at least one dose of the trial medication. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 17 | 29 | 96 |
| From 65-84 years | 0 | 3 | 17 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Treated Set (TS): All patients who signed the informed consent and were treated with at least one dose of the trial medication. | | | |
| Units: years | | | |
| arithmetic mean | 48.2 | 49.8 | |

| | | | |
|--------------------|--------|--------|---|
| standard deviation | ± 10.1 | ± 14.0 | - |
|--------------------|--------|--------|---|

| | | | |
|---|------------|------------|-----|
| Sex: Female, Male | | | |
| Treated Set (TS): All patients who signed the informed consent and were treated with at least one dose of the trial medication. | | | |
| Units: Participants | | | |
| Female | 9 | 18 | 58 |
| Male | 8 | 14 | 55 |
| Race (NIH/OMB) | | | |
| Treated Set (TS): All patients who signed the informed consent and were treated with at least one dose of the trial medication. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 2 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 2 |
| Black or African American | 0 | 0 | 0 |
| White | 17 | 32 | 109 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 4 | 8 | 33 |
| Not Hispanic or Latino | 13 | 24 | 80 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Plasma amine oxidase copper-containing 3 (AOC3) baseline concentration | | | |
| Plasma amine oxidase copper-containing 3 (AOC3) baseline concentration. Treated Set (TS): All patients who signed the informed consent and were treated with at least one dose of the trial medication. | | | |
| Units: microgram per liter (µg/l) | | | |
| arithmetic mean | 527.2941 | 516.1613 | |
| standard deviation | ± 142.3722 | ± 144.0727 | - |

End points

End points reporting groups

| | |
|--|------------------------------|
| Reporting group title | Placebo |
| Reporting group description: Matching placebo taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated placebo tablets were supplied. For blinding reasons, all patients took 5 tablets placebo daily. | |
| Reporting group title | BI 1467335 1 milligram (mg) |
| Reporting group description: 1 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily. | |
| Reporting group title | BI 1467335 3 milligram (mg) |
| Reporting group description: 3 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily. | |
| Reporting group title | BI 1467335 6 milligram (mg) |
| Reporting group description: 6 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily. | |
| Reporting group title | BI 1467335 10 milligram (mg) |
| Reporting group description: 10 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily. | |

Primary: Plasma amine oxidase copper-containing 3 (AOC3) activity after 12 weeks of treatment, relative to baseline in percent

| | |
|--|---|
| End point title | Plasma amine oxidase copper-containing 3 (AOC3) activity after 12 weeks of treatment, relative to baseline in percent |
| End point description: The patient-specific plasma AOC3 activity at time t (24 hours after the last dose in week 12) relative to baseline in percentage was calculated as follows: $\%AOC3at = [(AOC3at - AOC3at,back) / (AOC3abase - AOC3abase,back)] * 100$ with AOC3at the AOC3 activity measured at time t, AOC3at,back the background noise at time t, AOC3abase the AOC3 activity measured at baseline and AOC3abase,back the background noise at baseline. A dose-response relationship was analysed using a non-linear regression model to estimate the daily dosage needed to reach 10% of AOC3 activity (i.e. 90% inhibition) 12 weeks after treatment. Per Protocol Set (PPS): patients who signed informed consent, were treated with at least one dose of the trial medication, without any important protocol deviations leading to exclusion and who had non-missing baseline and at least one non-missing post-baseline and on-treatment measurement on any primary, secondary or further biomarker endpoint. | |
| End point type | Primary |
| End point timeframe: Day 1 (baseline), day 15, 29, 43, 57 and 85 (time t) 24 hours after the last dose of BI 1467335. | |

| End point values | Placebo | BI 1467335 1 milligram (mg) | BI 1467335 3 milligram (mg) | BI 1467335 6 milligram (mg) |
|--|-------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 30 ^[1] | 12 ^[2] | 14 ^[3] | 11 ^[4] |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard deviation) | 102 (± 13.0) | 24.0 (± 11.9) | 13.1 (± 10.4) | 8.27 (± 5.19) |

Notes:

[1] - PPS

[2] - PPS

[3] - PPS

[4] - PPS

| End point values | BI 1467335 10 milligram (mg) | | | |
|--|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 ^[5] | | | |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard deviation) | 2.06 (± 3.62) | | | |

Notes:

[5] - PPS

Statistical analyses

| Statistical analysis title | Estimated dose reaching ≤10% activity |
|--|--|
| Statistical analysis description: | |
| D10: Estimated dose reaching ≤10% activity the first time. | |
| Comparison groups | Placebo v BI 1467335 1 milligram (mg) v BI 1467335 3 milligram (mg) v BI 1467335 6 milligram (mg) v BI 1467335 10 milligram (mg) |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| Method | non-linear regression |
| Parameter estimate | Predicted mean daily dose in mg |
| Point estimate | 3.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9999 |
| upper limit | 99999 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.1 |

Notes:

[6] - The model fit used power of mean variance estimates (POM) to account for heterogeneity.

0.9999 & 99999 stand for 'not applicable'.

Secondary: Percentage of participants with drug-related adverse events (AEs)

| | |
|-----------------|---|
| End point title | Percentage of participants with drug-related adverse events (AEs) |
|-----------------|---|

End point description:

Percentage of participants with drug-related adverse events (AEs). Percentages are calculated using total number of patients per treatment as the denominator.

Treated Set (TS): All patients who signed the informed consent and were treated with at least one dose of the trial medication.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Start of treatment till end of treatment + 28 days, up to 113 days.

| End point values | Placebo | BI 1467335 1 milligram (mg) | BI 1467335 3 milligram (mg) | BI 1467335 6 milligram (mg) |
|-----------------------------------|-------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 ^[7] | 16 ^[8] | 16 ^[9] | 17 ^[10] |
| Units: Percentage of participants | | | | |
| number (not applicable) | 25.0 | 31.3 | 12.5 | 11.8 |

Notes:

[7] - TS

[8] - TS

[9] - TS

[10] - TS

| End point values | BI 1467335 10 milligram (mg) | | | |
|-----------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 32 ^[11] | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 25.0 | | | |

Notes:

[11] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Alanine aminotransaminase (ALT) after 12 weeks of treatment, relative to baseline in percent

| | |
|-----------------|--|
| End point title | Alanine aminotransaminase (ALT) after 12 weeks of treatment, relative to baseline in percent |
|-----------------|--|

End point description:

Alanine aminotransaminase (ALT) after 12 weeks of treatment, relative to baseline in percent. Number analyzed lower than N in PPS if there is missing data for specific timepoints.

The unit of measure is: percentage relative to baseline = [post baseline (time t)/baseline]*100%

Statistical analyses description: A Mixed effects Model for Repeated Measurements (MMRM) over time including fixed effects for 'base', 'treatment', 'time', 'base*time' interaction, and 'treatment*time' interaction was performed. The MMRM estimates for the treatment effects at Week 12 and the corresponding covariance matrix were used to analyse the dose-response relationship using the Multiple contrast test (MCPMod). A test for non-flat dose-response relationship was first performed. If this relationship could be shown, the best fitting model out of a set of candidate models (Sigmoidal Emax, Logistic, Quadratic, Linear, Exponential, Linear logistic, Emax and Betamod) was to be selected and fitted.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 (baseline), day 15, 29, 43, 57 and 85 (time t) 24 hours after the last dose of BI 1467335.

| End point values | Placebo | BI 1467335 1 milligram (mg) | BI 1467335 3 milligram (mg) | BI 1467335 6 milligram (mg) |
|--|--------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 28 ^[12] | 12 ^[13] | 13 ^[14] | 14 ^[15] |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard error) | 92.66 (± 106.55) | 97.32 (± 110.13) | 87.49 (± 109.79) | 80.61 (± 109.43) |

Notes:

[12] - PPS

[13] - PPS

[14] - PPS

[15] - PPS

| End point values | BI 1467335 10 milligram (mg) | | | |
|--|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 ^[16] | | | |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard error) | 77.57 (± 106.66) | | | |

Notes:

[16] - PPS

Statistical analyses

| Statistical analysis title | MCPMod Sigmoidal Emax model fit |
|--|--|
| Statistical analysis description: | |
| Model assumptions: 30% of the maximum effect is achieved at 3 mg and 90% of the maximum effect is achieved at 7 mg of BI 1467335. MCPMod = multiple comparison procedures and modelling. | |
| Comparison groups | Placebo v BI 1467335 1 milligram (mg) v BI 1467335 3 milligram (mg) v BI 1467335 6 milligram (mg) v BI 1467335 10 milligram (mg) |
| Number of subjects included in analysis | 94 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0212 ^[17] |
| Method | MCPMod Sigmoidal Emax model fit. |

Notes:

[17] - p<0.05 is a significant test result (rejecting the null hypothesis of a flat dose–response curve) with alpha 0.05, one–sided.

Secondary: Aspartate aminotransferase (AST) after 12 weeks of treatment, relative to baseline in percent

| | |
|-----------------|---|
| End point title | Aspartate aminotransferase (AST) after 12 weeks of treatment, relative to baseline in percent |
|-----------------|---|

End point description:

Aspartate aminotransferase (AST) after 12 weeks of treatment, relative to baseline in percent. Number analyzed lower than N in PPS if there is missing data for specific timepoints.

The unit of measure is: percentage relative to baseline = [post baseline (time t)/baseline]*100%

Statistical analyses description: A Mixed effects Model for Repeated Measurements (MMRM) over time including fixed effects for 'base', 'treatment', 'time', 'base*time' interaction, and 'treatment*time' interaction was performed. The MMRM estimates for the treatment effects at Week 12 and the corresponding covariance matrix were used to analyse the dose-response relationship using the Multiple contrast test (MCPMod). A test for non-flat dose-response relationship was first performed. If this relationship could be shown, the best fitting model out of a set of candidate models (Sigmoidal Emax, Logistic, Quadratic, Linear, Exponential, Linear logistic, Emax and Betamod) was to be selected and fitted.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 (baseline), day 15, 29, 43, 57 and 85 (time t) 24 hours after the last dose of BI 1467335.

| End point values | Placebo | BI 1467335 1 milligram (mg) | BI 1467335 3 milligram (mg) | BI 1467335 6 milligram (mg) |
|--|--------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 27 ^[18] | 12 ^[19] | 13 ^[20] | 14 ^[21] |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard error) | 93.77 (± 105.91) | 105.17 (± 108.93) | 90.09 (± 108.72) | 84.12 (± 108.34) |

Notes:

[18] - PPS

[19] - PPS

[20] - PPS

[21] - PPS

| End point values | BI 1467335 10 milligram (mg) | | | |
|--|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 ^[22] | | | |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard error) | 87.83 (± 106.26) | | | |

Notes:

[22] - PPS

Statistical analyses

| Statistical analysis title | MCPMod Sigmoidal Emax model fit |
|----------------------------|---------------------------------|
|----------------------------|---------------------------------|

Statistical analysis description:

Model assumptions: 30% of the maximum effect is achieved at 3 mg and 90% of the maximum effect is achieved at 7 mg of BI 1467335.

| | |
|---|--|
| Comparison groups | Placebo v BI 1467335 1 milligram (mg) v BI 1467335 3 milligram (mg) v BI 1467335 6 milligram (mg) v BI 1467335 10 milligram (mg) |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.127 ^[23] |
| Method | MCPMod Sigmoidal Emax model fit. |

Notes:

[23] - p<0.05 is a significant test result (rejecting the null hypothesis of a flat dose-response curve) with alpha 0.05, one-sided.

Secondary: Alkaline phosphatase (AP) after 12 weeks of treatment, relative to baseline in percent

| | |
|-----------------|--|
| End point title | Alkaline phosphatase (AP) after 12 weeks of treatment, relative to baseline in percent |
|-----------------|--|

End point description:

Alkaline phosphatase (AP) after 12 weeks of treatment, relative to baseline in percent. Number analyzed lower than N in PPS if there is missing data for specific timepoints.

The unit of measure is: percentage relative to baseline = [post baseline (time t)/baseline]*100%

Statistical analyses description: A Mixed effects Model for Repeated Measurements (MMRM) over time including fixed effects for 'base', 'treatment', 'time', 'base*time' interaction, and 'treatment*time' interaction was performed. The MMRM estimates for the treatment effects at Week 12 and the corresponding covariance matrix were used to analyse the dose-response relationship using the Multiple contrast test (MCPMod). A test for non-flat dose-response relationship was first performed. If this relationship could be shown, the best fitting model out of a set of candidate models (Sigmoidal Emax, Logistic, Quadratic, Linear, Exponential, Linear logistic, Emax and Betamod) was to be selected and fitted.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 (baseline), day 15, 29, 43, 57 and 85 (time t) 24 hours after the last dose of BI 1467335.

| End point values | Placebo | BI 1467335 1 milligram (mg) | BI 1467335 3 milligram (mg) | BI 1467335 6 milligram (mg) |
|--|--------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 ^[24] | 12 ^[25] | 13 ^[26] | 14 ^[27] |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard error) | 96.62 (± 102.31) | 97.58 (± 103.56) | 100.52 (± 103.45) | 98.47 (± 103.34) |

Notes:

[24] - PPS

[25] - PPS

[26] - PPS

[27] - PPS

| End point values | BI 1467335 10 milligram (mg) | | | |
|--|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 ^[28] | | | |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard error) | 94.71 (± 102.34) | | | |

Notes:

[28] - PPS

Statistical analyses

| | |
|----------------------------|------------------------------|
| Statistical analysis title | MCPMod exponential model fit |
|----------------------------|------------------------------|

Statistical analysis description:

Model assumptions: 90% of the maximum effect is achieved at 7 mg of BI 1467335.

| | |
|-------------------|--|
| Comparison groups | Placebo v BI 1467335 1 milligram (mg) v BI 1467335 3 milligram (mg) v BI 1467335 6 milligram (mg) v BI 1467335 10 milligram (mg) |
|-------------------|--|

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3324 [29] |
| Method | MCPMod exponential model fit. |

Notes:

[29] - $p < 0.05$ is a significant test result (rejecting the null hypothesis of a flat dose–response curve) with alpha 0.05, one–sided.

Secondary: Gamma-glutamyltransferase (GGT) after 12 weeks of treatment, relative to baseline in percent

| | |
|-----------------|--|
| End point title | Gamma-glutamyltransferase (GGT) after 12 weeks of treatment, relative to baseline in percent |
|-----------------|--|

End point description:

Gamma-glutamyltransferase (GGT) after 12 weeks of treatment, relative to baseline in percent. Number analyzed lower than N in PPS if there is missing data for specific timepoints.

The unit of measure is: percentage relative to baseline = $[\text{post baseline (time t)}/\text{baseline}] * 100\%$

Statistical analyses description: A Mixed effects Model for Repeated Measurements (MMRM) over time including fixed effects for 'base', 'treatment', 'time', 'base*time' interaction, and 'treatment*time' interaction was performed. The MMRM estimates for the treatment effects at Week 12 and the corresponding covariance matrix were used to analyse the dose-response relationship using the Multiple contrast test (MCPMod). A test for non-flat dose-response relationship was first performed. If this relationship could be shown, the best fitting model out of a set of candidate models (Sigmoidal Emax, Logistic, Quadratic, Linear, Exponential, Linear logistic, Emax and Betamod) was to be selected and fitted.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 (baseline), day 15, 29, 43, 57 and 85 (time t) 24 hours after the last dose of BI 1467335.

| End point values | Placebo | BI 1467335 1 milligram (mg) | BI 1467335 3 milligram (mg) | BI 1467335 6 milligram (mg) |
|--|-----------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 ^[30] | 12 ^[31] | 13 ^[32] | 14 ^[33] |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard error) | 91.37 (\pm 105.24) | 99.42 (\pm 108.25) | 92.44 (\pm 108.09) | 99.51 (\pm 107.71) |

Notes:

[30] - PPS

[31] - PPS

[32] - PPS

[33] - PPS

| End point values | BI 1467335 10 milligram (mg) | | | |
|--|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 ^[34] | | | |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard error) | 83.70 (\pm 105.40) | | | |

Notes:

[34] - PPS

Statistical analyses

| | |
|---|--|
| Statistical analysis title | MCPMod exponential model fit |
| Statistical analysis description: | |
| Model assumptions: 90% of the maximum effect is achieved at 7 mg of BI 1467335. | |
| Comparison groups | Placebo v BI 1467335 1 milligram (mg) v BI 1467335 3 milligram (mg) v BI 1467335 6 milligram (mg) v BI 1467335 10 milligram (mg) |
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.129 ^[35] |
| Method | MCPMod exponential model fit. |

Notes:

[35] - $p < 0.05$ is a significant test result (rejecting the null hypothesis of a flat dose–response curve) with alpha 0.05, one–sided.

Secondary: Caspase-cleaved cytokeratin 18 (CK-18 caspase) after 12 weeks of treatment, relative to baseline in percent

| | |
|-----------------|---|
| End point title | Caspase-cleaved cytokeratin 18 (CK-18 caspase) after 12 weeks of treatment, relative to baseline in percent |
|-----------------|---|

End point description:

Caspase-cleaved cytokeratin 18 (CK-18 caspase) after 12 weeks of treatment, relative to baseline in percent. Number analyzed lower than N in PPS if there is missing data for specific timepoints.

The unit of measure is: percentage relative to baseline = $[\text{post baseline (time t)}/\text{baseline}] \times 100\%$

Statistical analyses description: A MMRM over time including fixed effects for 'base', 'treatment', 'time', 'base*time' interaction, and 'treatment*time' interaction was performed. The MMRM estimates for the treatment effects at Week 12 and the corresponding covariance matrix were used to analyse the dose-response relationship using the Multiple contrast test (MCPMod). A test for non-flat dose-response relationship was first performed. If this relationship could be shown, the best fitting model out of a set of candidate models (Sigmoidal Emax, Logistic, Quadratic, Linear, Exponential, Linear logistic, Emax and Betamod) was to be selected and fitted.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 (baseline), day 15, 29, 43, 57 and 85 (time t) 24 hours after the last dose of BI 1467335.

| End point values | Placebo | BI 1467335 1 milligram (mg) | BI 1467335 3 milligram (mg) | BI 1467335 6 milligram (mg) |
|--|--------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 ^[36] | 12 ^[37] | 12 ^[38] | 14 ^[39] |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard error) | 101.35 (± 111.15) | 155.04 (± 117.61) | 96.87 (± 117.54) | 80.51 (± 116.32) |

Notes:

[36] - PPS

[37] - PPS

[38] - PPS

[39] - PPS

| End point values | BI 1467335 10 milligram (mg) | | | |
|-----------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 26 ^[40] | | | |

| | | | | |
|--|------------------|--|--|--|
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard error) | 78.08 (± 111.59) | | | |

Notes:

[40] - PPS

Statistical analyses

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | MCPMod Sigmoidal Emax model fit |
|-----------------------------------|---------------------------------|

Statistical analysis description:

Model assumptions: 30% of the maximum effect is achieved at 3 mg and 90% of the maximum effect is achieved at 7 mg of BI 1467335.

| | |
|---|--|
| Comparison groups | Placebo v BI 1467335 1 milligram (mg) v BI 1467335 3 milligram (mg) v BI 1467335 6 milligram (mg) v BI 1467335 10 milligram (mg) |
| Number of subjects included in analysis | 93 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0042 [41] |
| Method | MCPMod Sigmoidal Emax model fit. |

Notes:

[41] - $p < 0.05$ is a significant test result (rejecting the null hypothesis of a flat dose-response curve) with alpha 0.05, one-sided.

Secondary: Total cytokeratin 18 (CK-18 total) after 12 weeks of treatment, relative to baseline in percent

| | |
|-----------------|---|
| End point title | Total cytokeratin 18 (CK-18 total) after 12 weeks of treatment, relative to baseline in percent |
|-----------------|---|

End point description:

total cytokeratin 18 (CK-18 total) after 12 weeks of treatment, relative to baseline in percent. Number analyzed lower than N in PPS if there is missing data for specific timepoints.

The unit of measure is: percentage relative to baseline = $[\text{post baseline (time t)}/\text{baseline}] * 100\%$

Statistical analyses description: A Mixed effects Model for Repeated Measurements (MMRM) over time including fixed effects for 'base', 'treatment', 'time', 'base*time' interaction, and 'treatment*time' interaction was performed. The MMRM estimates for the treatment effects at Week 12 and the corresponding covariance matrix were used to analyse the dose-response relationship using the Multiple contrast test (MCPMod). A test for non-flat dose-response relationship was first performed. If this relationship could be shown, the best fitting model out of a set of candidate models (Sigmoidal Emax, Logistic, Quadratic, Linear, Exponential, Linear logistic, Emax and Betamod) was to be selected and fitted.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 (baseline), day 15, 29, 43, 57 and 85 (time t) 24 hours after the last dose of BI 1467335.

| End point values | Placebo | BI 1467335 1 milligram (mg) | BI 1467335 3 milligram (mg) | BI 1467335 6 milligram (mg) |
|--|--------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 28 ^[42] | 11 ^[43] | 13 ^[44] | 14 ^[45] |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard error) | 92.44 (± 109.13) | 128.33 (± 114.64) | 99.56 (± 113.78) | 94.74 (± 113.10) |

Notes:

[42] - PPS

[43] - PPS

[44] - PPS

[45] - PPS

| | | | | |
|--|------------------------------|--|--|--|
| End point values | BI 1467335 10 milligram (mg) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 26 ^[46] | | | |
| Units: Percentage relative to baseline | | | | |
| arithmetic mean (standard error) | 81.47 (± 109.35) | | | |

Notes:

[46] - PPS

Statistical analyses

| | |
|--|--|
| Statistical analysis title | MCPMod exponential model fit |
| Statistical analysis description: | |
| Model assumptions: 90% of the maximum effect is achieved at 7 mg of BI 1467335 | |
| Comparison groups | Placebo v BI 1467335 1 milligram (mg) v BI 1467335 3 milligram (mg) v BI 1467335 6 milligram (mg) v BI 1467335 10 milligram (mg) |
| Number of subjects included in analysis | 92 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0728 ^[47] |
| Method | MCPMod exponential model fit. |

Notes:

[47] - $p < 0.05$ is a significant test result (rejecting the null hypothesis of a flat dose–response curve) with alpha 0.05, one–sided.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

start of treatment till end of treatment + 28 days, up to 113 days.

Adverse event reporting additional description:

Adverse events are reported based on the Treated Set (all patients who signed the informed consent and were treated with at least one dose of the trial medication).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Matching placebo taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated placebo tablets were supplied. For blinding reasons, all patients took 5 tablets placebo daily.

| | |
|-----------------------|-----------------------------|
| Reporting group title | BI 1467335 1 milligram (mg) |
|-----------------------|-----------------------------|

Reporting group description:

1 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily.

| | |
|-----------------------|-----------------------------|
| Reporting group title | BI 1467335 3 milligram (mg) |
|-----------------------|-----------------------------|

Reporting group description:

3 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily.

| | |
|-----------------------|-----------------------------|
| Reporting group title | BI 1467335 6 milligram (mg) |
|-----------------------|-----------------------------|

Reporting group description:

6 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily.

| | |
|-----------------------|------------------------------|
| Reporting group title | BI 1467335 10 milligram (mg) |
|-----------------------|------------------------------|

Reporting group description:

10 milligram (mg) BI 1467335 taken daily for 12 weeks. Tablets taken orally with water in the morning, fasted, 1 hour before breakfast. Film-coated tablets were supplied as 1 mg and 5 mg dose strengths. For blinding reasons, all patients took 5 tablets verum or placebo daily.

| | |
|-----------------------|------------------|
| Reporting group title | Total BI 1467335 |
|-----------------------|------------------|

Reporting group description:

Sum of all BI 1467335 arms

| Serious adverse events | Placebo | BI 1467335 1 milligram (mg) | BI 1467335 3 milligram (mg) |
|---|----------------|-----------------------------|-----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal septum deviation | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 16 (0.00%) | 0 / 16 (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 |
| Infections and infestations | | | |
| H1N1 influenza | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 16 (0.00%) | 0 / 16 (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 |

| Serious adverse events | BI 1467335 6 milligram (mg) | BI 1467335 10 milligram (mg) | Total BI 1467335 |
|---|-----------------------------|------------------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 2 / 81 (2.47%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal septum deviation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 0 / 81 (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 |
| Infections and infestations | | | |
| H1N1 influenza | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 0 / 81 (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 |

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

| Non-serious adverse events | Placebo | BI 1467335 1 milligram (mg) | BI 1467335 3 milligram (mg) |
|---|------------------|-----------------------------|-----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 32 (56.25%) | 12 / 16 (75.00%) | 12 / 16 (75.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| Anogenital warts subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Vascular disorders | | | |
| Orthostatic hypotension subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Subclavian steal syndrome subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Chest pain subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Early satiety subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Influenza like illness subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Immune system disorders | | | |
| Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry throat | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Paranasal sinus discomfort | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinus pain | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Weight increased | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Post-traumatic neck syndrome | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth fracture | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular procedure complication | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 16 (6.25%) | 2 / 16 (12.50%) |
| occurrences (all) | 0 | 1 | 2 |
| Headache | | | |
| subjects affected / exposed | 4 / 32 (12.50%) | 3 / 16 (18.75%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 5 | 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Tension headache | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 2 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Eye disorders Vision blurred subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 1 / 16 (6.25%) 2 | 0 / 16 (0.00%) 0 |
| Abdominal pain lower subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 16 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | 1 / 16 (6.25%) 1 | 1 / 16 (6.25%) 1 |
| Dry mouth subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 16 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Flatulence subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Gastrooesophageal reflux disease | | | |

| | | | |
|--|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 4 / 16 (25.00%) 4 | 1 / 16 (6.25%) 1 |
| Pouchitis subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Toothache subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 2 | 0 / 16 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 2 / 16 (12.50%) 2 | 0 / 16 (0.00%) 0 |
| Hepatobiliary disorders Hepatic pain subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Rash erythematous subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Rash papular subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 2 | 2 / 16 (12.50%) 2 | 1 / 16 (6.25%) 1 |

| | | | |
|---|---------------------|----------------------|----------------------|
| Muscular weakness subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Neck pain subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 2 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 3 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Gastroenteritis bacterial subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Influenza subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 2 / 16 (12.50%) 3 | 0 / 16 (0.00%) 0 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 4 | 3 / 16 (18.75%) 3 | 2 / 16 (12.50%) 2 |
| Otitis media subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Sinusitis subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Tooth abscess subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Tooth infection | | | |

| | | | |
|---|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 2 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 2 | 2 / 16 (12.50%) 2 | 0 / 16 (0.00%) 0 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Diabetes mellitus inadequate control subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Hyperlipidaemia subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |
| Type 2 diabetes mellitus subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 16 (0.00%) 0 |

| Non-serious adverse events | BI 1467335 6 milligram (mg) | BI 1467335 10 milligram (mg) | Total BI 1467335 |
|--|--------------------------------|---------------------------------|---------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 13 / 17 (76.47%) | 17 / 32 (53.13%) | 54 / 81 (66.67%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Anogenital warts subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Vascular disorders | | | |

| | | | |
|---|---------------------|----------------------|---------------------|
| Orthostatic hypotension subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Subclavian steal syndrome subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Chest pain subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Early satiety subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 5 / 32 (15.63%) 5 | 6 / 81 (7.41%) 6 |
| Influenza like illness subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Pain subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 2 / 32 (6.25%) 3 | 2 / 81 (2.47%) 3 |
| Immune system disorders | | | |
| Hypersensitivity subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 1 / 32 (3.13%) 1 | 3 / 81 (3.70%) 3 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 32 (3.13%) 1 | 2 / 81 (2.47%) 2 |
| Dry throat subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 32 (0.00%) 0 | 2 / 81 (2.47%) 2 |

| | | | |
|--|----------------|----------------|----------------|
| Epistaxis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 2 / 81 (2.47%) |
| occurrences (all) | 1 | 0 | 2 |
| Paranasal sinus discomfort | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 1 | 0 | 1 |
| Sinus pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 1 | 0 | 1 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 2 / 81 (2.47%) |
| occurrences (all) | 1 | 0 | 2 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 2 / 81 (2.47%) |
| occurrences (all) | 1 | 0 | 2 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |

| | | | |
|---------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 1 | 0 | 1 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 32 (3.13%) | 2 / 81 (2.47%) |
| occurrences (all) | 0 | 1 | 2 |
| Post-traumatic neck syndrome | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 1 | 0 | 1 |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 1 | 0 | 1 |
| Tooth fracture | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 1 | 0 | 1 |
| Vascular procedure complication | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 32 (9.38%) | 6 / 81 (7.41%) |
| occurrences (all) | 0 | 3 | 6 |
| Headache | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 2 / 32 (6.25%) | 9 / 81 (11.11%) |
| occurrences (all) | 5 | 2 | 12 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Tension headache | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 32 (3.13%) 1 | 2 / 81 (2.47%) 2 |
| Eye disorders | | | |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 1 / 32 (3.13%) 1 | 3 / 81 (3.70%) 4 |
| Abdominal pain lower subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 2 | 3 / 32 (9.38%) 3 | 7 / 81 (8.64%) 7 |
| Dry mouth subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 32 (0.00%) 0 | 2 / 81 (2.47%) 2 |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 2 / 32 (6.25%) 2 | 3 / 81 (3.70%) 3 |
| Flatulence subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 32 (3.13%) 2 | 2 / 81 (2.47%) 3 |
| Nausea | | | |

| | | | |
|--|---------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 5 / 32 (15.63%) 5 | 10 / 81 (12.35%) 10 |
| Pouchitis subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Toothache subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 0 / 81 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 2 / 81 (2.47%) 2 |
| Hepatobiliary disorders Hepatic pain subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 2 / 32 (6.25%) 2 | 2 / 81 (2.47%) 2 |
| Rash erythematous subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Rash papular subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 32 (3.13%) 1 | 4 / 81 (4.94%) 4 |
| Muscular weakness subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 81 (1.23%) 1 |

| | | | |
|-----------------------------------|-----------------|-----------------|------------------|
| Neck pain | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 32 (0.00%) | 2 / 81 (2.47%) |
| occurrences (all) | 2 | 0 | 2 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastroenteritis bacterial | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Influenza | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 2 / 81 (2.47%) |
| occurrences (all) | 0 | 0 | 3 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 5 / 32 (15.63%) | 11 / 81 (13.58%) |
| occurrences (all) | 1 | 5 | 11 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 2 / 81 (2.47%) |
| occurrences (all) | 1 | 0 | 2 |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 1 | 0 | 1 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 2 / 81 (2.47%) |
| occurrences (all) | 1 | 0 | 2 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 32 (3.13%) | 3 / 81 (3.70%) |
| occurrences (all) | 0 | 1 | 3 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 32 (3.13%) | 2 / 81 (2.47%) |
| occurrences (all) | 0 | 1 | 2 |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 32 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 0 | 0 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 12 September 2018 | Global Amendment 5 (dated 12 Sep 2018): Sample size reduction from 147 to 108 randomised patients due to a lower expected variability for ALT based on new external and blinded internal data |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported