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	v1
This version publication date	24 June 2020
First version publication date	24 June 2020

Trial information

Trial identification

Sponsor protocol code	1386-0004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 strenghts. 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 strenghts. 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 strenghts. 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 strenghts. 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 = [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[30]	12[31]	13[32]	14[33]
Units: Percentage relative to baseline				
arithmetic mean (standard error)	91.37 (± 105.24)	99.42 (± 108.25)	92.44 (± 108.09)	99.51 (± 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 (± 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 = [post baseline (time t)/baseline]*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 = [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[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 strenghts. 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 strenghts. 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 strenghts. 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 strenghts. 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	0 / 32 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Subclavian steal syndrome			
subjects affected / exposed	0 / 32 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Early satiety			
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	3 / 32 (9.38%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1
Influenza like illness			
subjects affected / exposed	0 / 32 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	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	0 / 32 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	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	0 / 32 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 32 (6.25%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 32 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	1 / 32 (3.13%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Abdominal pain lower			
subjects affected / exposed	0 / 32 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	3 / 32 (9.38%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	3	1	1
Dry mouth			
subjects affected / exposed	1 / 32 (3.13%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Dyspepsia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Gastrooesophageal reflux disease			

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

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

subjects affected / exposed	0 / 32 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 32 (6.25%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Urinary tract infection			
subjects affected / exposed	2 / 32 (6.25%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	2	2	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 32 (3.13%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 32 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Hyperlipidaemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 32 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	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	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Vascular disorders			

Orthostatic hypotension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Subclavian steal syndrome			
subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	1 / 81 (1.23%)
occurrences (all)	1	0	1
Early satiety			
subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 17 (0.00%)	5 / 32 (15.63%)	6 / 81 (7.41%)
occurrences (all)	0	5	6
Influenza like illness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	1 / 81 (1.23%)
occurrences (all)	1	0	1
Pain			
subjects affected / exposed	0 / 17 (0.00%)	2 / 32 (6.25%)	2 / 81 (2.47%)
occurrences (all)	0	3	3
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 17 (5.88%)	1 / 32 (3.13%)	3 / 81 (3.70%)
occurrences (all)	1	1	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	2 / 81 (2.47%)
occurrences (all)	0	1	2
Dry throat			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	2 / 81 (2.47%)
occurrences (all)	1	0	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	0 / 17 (0.00%)	1 / 32 (3.13%)	2 / 81 (2.47%)
occurrences (all)	0	1	2
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 32 (3.13%)	3 / 81 (3.70%)
occurrences (all)	1	1	4
Abdominal pain lower			
subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	1 / 81 (1.23%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	2 / 17 (11.76%)	3 / 32 (9.38%)	7 / 81 (8.64%)
occurrences (all)	2	3	7
Dry mouth			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	2 / 81 (2.47%)
occurrences (all)	1	0	2
Dyspepsia			
subjects affected / exposed	1 / 17 (5.88%)	2 / 32 (6.25%)	3 / 81 (3.70%)
occurrences (all)	1	2	3
Flatulence			
subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	2 / 81 (2.47%)
occurrences (all)	0	2	3
Nausea			

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